viation less than 25° for any single ϕ torsion estimated from the $J_{NH-H\alpha}$ coupling constants.

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Supplementary Material Available: Experimental descriptions for syntheses of **1a**, **1b**, **2a**, and **2b**, as well as physical properties and analytical data for several intermediate protected linear and cyclic hexapeptides; Supplemental Scheme 1 for preparation of **1a** and **1b**; Supplemental Scheme 2 for synthesis of the peptides **V-VIII**; X-ray structural data for threo N-acetyl β-MeTrp-OH; tables of chemical shifts, $J_{NH-H\alpha}$ vicinal coupling constants, and calculated ϕ torsions for analogs containing side chain variations at positions 7 and 11 (16 pages); observed and calculated structure factors for $C_{14}H_{16}N_2O_3$ (11 pages). Ordering information is given on any current masthead page.

Syntheses of Racemic and Both Chiral Forms of Cyclopropane-*1,2-d*$_2$ and Cyclopropane-*1*-^{13}*C-1,2,3-d*$_3$

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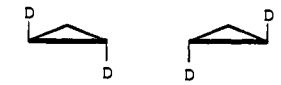
Abstract: The racemic and both chiral forms of cyclopropane-*1,2-d*$_2$ and cyclopropane-*1*-^{13}*C-1,2,3-d*$_3$ have been prepared efficiently through sequences based on *trans*-1,2-bis(methoxycarbonyl)cyclopropanes. These diesters have been prepared in racemic form with 1,2-d_2 labeling and with 3-^{13}C-1,2,3-d_3 labeling. The labeled diesters have been resolved to provide both chiral forms, and the racemic or resolved diesters have been converted to the corresponding specifically labeled racemic or chiral cyclopropanes through a two-step sequence involving reduction and decarbonylation. The chemical, isotopic, geometrical, and chiral quality of the labeled cyclopropanes in both sets of isomers is estimated to be quite high and strictly comparable.

The geometrical isomerization of the cis and trans forms of cyclopropane-*1,2-d*$_2$ was discovered by Rabinovitch, Schlag, and Wiberg in 1958,[1] and the optical isomerization interconverting directly the two chiral trans-1,2-*d*$_2$ cyclopropanes was demonstrated by Berson and Pedersen in 1975.[2] These stereomutation reactions result from one-center or two-center epimerization processes and are thought to be mediated by singlet trimethylene diradical structures.[3]

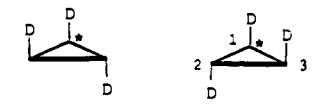
Between 1975 and 1990 these reactions were not subject to further experimental study. Theoretical efforts to understand these stereomutations were sustained, and experimental investigations with cyclopropanes substituted with functional groups or with functional groups and deuterium labels were pursued.[3,4] But kinetic studies with isotopically substituted cyclopropanes, the systems most likely to provide a meaningful link between theory and experiment, were not conducted, in spite of the fact that the fundamental experimentally accessible characteristic of these reactions—the relative kinetic significance of one-center versus two-center epimerization events[5]—remained uncertain.

This hiatus in experimental activity may have been due to perceived synthetic limitations, for without efficient routes to selected isotopically labeled and chiral cyclopropanes, the information they could provide through kinetic studies remained unavailable. Or this hiatus may have been consequent to a conceptual limitation: just how one might gain experimental access to the k_1/k_{12} ratio by following the thermal stereomutations of a suitably selected isotopically labeled cyclopropane was not immediately obvious. Or, possibly, some might have imagined that the experimental problem had been solved.

This paper reports in full detail efficient preparations of racemic and both optically active forms of cyclopropane-*1,2-d*$_2$, **1**-*d*$_2$, (*rac*-**1**-*d*$_2$), (*S,S*)-**1**-*d*$_2$, and (*R,R*)-**1**-*d*$_2$, and of racemic and both optically active forms of cyclopropane-*1*-^{13}*C-1,2,3-d*$_3$, **1**-^{13}*C,d*$_3$, (2*R*,3*R*)-**1**-^{13}*C,d*$_3$, and (2*S*,3*S*)-**1**-^{13}*C,d*$_3$. The d_2 cyclopropanes



(*S, S*)-1-d_2 (*R, R*)-1-d_2



(2*R, 3R*)-1-^{13}C, d_3 (2*S, 3S*)-1-^{13}C, d_3

have been used to confirm[6] the experimental findings (the relative magnitures of rate constants for geometrical isomerization, k_i, and for racemization, k_a) reported in 1975 by Berson and Pedersen,[2] while the chiral cyclopropane-*1*-^{13}*C-1,2,3-d*$_3$ compounds have permitted access to an experimentally determined measure of one-center versus two-center epimerizations. These modes of thermal stereomutation are of comparable kinetic importance: for this isotopically labeled system at 407 °C, k_1/k_{12} is (0.95 ± 0.09)/1.[7]

The credibility of this experimental result has recently been questioned,[8] on the basis of a theoretical analysis of possible isotope effects and of reported kinetic data for both 1,2-d_2 and 1-^{13}C-

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1,2,3-d_3 cyclopropanes.[2,6,7] The stark conclusion attained through this theoretical effort, "there is no apparent way to reconcile the experimental results obtained for [cyclopropane-*1,2-d*$_2$], which indicate a clear preference for double rotation, with those obtained for [cyclopropane-*1*-^{13}*C-1,2,3-d*$_3$], which indicate that single and double methylene group rotations proceed at essentially equal rates",[8] implies that there may be some serious shortcoming in the synthetic or kinetic aspects of our experimental studies. Our view is quite the opposite: we consider our synthetic and analytical work to be sound and the experimental data for the thermal stereomutations shown by both sets of isotopically labeled cyclopropanes, interpreted through a sound treatment of kinetic isotope effects, to be fully consistent with k_1 and k_{12}, being of comparable magnitude in both sets of isomers.[9]

To entertain the possibility that the compounds or the techniques used to follow the reaction kinetics—FTIR spectroscopy, tunable diode laser spectroscopy,[10] and vibrational circular dichroism[11]—may have been faulty, one must posit selective errors. One must imagine that the synthetic methods and purifications of labeled cyclopropanes were successful when used to make chiral cyclopropane-*1,2-d*$_2$ compounds but not when used to prepare the 1-^{13}C-1,2,3-d_3 kinetic substrates or that the three analytical techniques we employed to follow reaction kinetics were indeed reliable when the Berson–Pedersen experiments were reproduced but not when these same three techniques were applied to study the 1-^{13}C-1,2,3-d_3 isomers, when an experimental result was uncovered ($k_1/k_{12} \approx 0.95/1$)[7] at odds with the Berson–Pedersen conclusion ($k_1/k_{12} \approx 2/98$)[2] based on insufficient experimental data (two kinetic observables to interpret kinetic behavior dependent on four unknown k_j and k_{jl} rate constants).

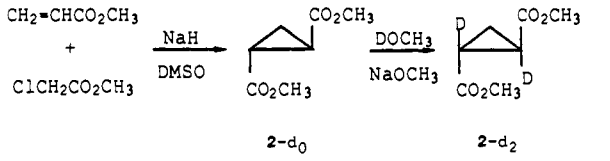
This paper addresses the expressed doubts[8] related to the synthetic aspects of our work with labeled chiral cyclopropanes. Sufficient detail is provided to permit informed judgments as to whether the syntheses, purifications, and characterizations of the labeled cyclopropanes **1**-d_2, (*S,S*)-**1**-d_2, (*R,R*)-**1**-d_2, **1**-^{13}*C,d*$_3$, (2*R*,3*R*)-**1**-^{13}*C,d*$_3$, and (2*S*,3*S*)-**1**-^{13}*C,d*$_3$ may have given substrates for kinetic studies sufficiently different in purity, isotopic incorporation, geometrical definition, or optical purity to render the isomeric forms of **1**-d_2 appropriate and the isomeric forms of **1**-^{13}*C,d*$_3$ unsuited for reliable kinetic experiments.

Synthetic Results

Only one chiral isotopically labeled cyclopropane, (*S,S*)-**1**-d_2, had been reported when the present effort was initiated, but that synthesis[2] offered little directly helpful guidance for the present work. A more direct, efficient, and inexpensive route was required, one that would provide access to racemic and both mirror image forms of **1**-d_2 and **1**-^{13}*C,d*$_3$. Further, it was hoped that reaction sequences having the final several steps in common could be devised: one would gain thereby an efficiency in developmental synthetic efforts and would have at the end labeled cyclopropanes of comparable quality.

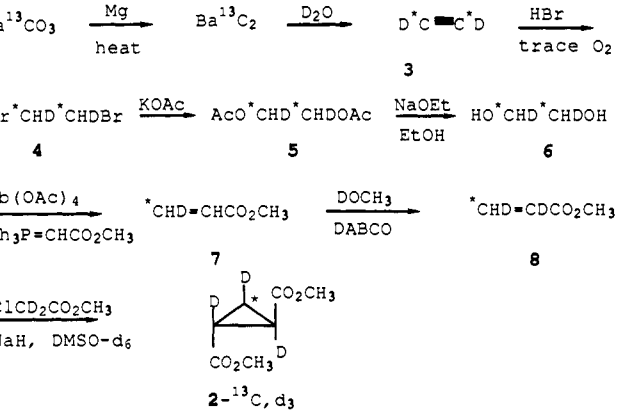
Several schemes and strategies for resolutions and for appropriate functional group manipulations were explored before *trans*-1,2-bis(methoxycarbonyl)cyclopropane was selected as a key intermediate. The synthetic requirements were then subdivided into three tasks: preparation of this diester in racemic form with the required d_2 or ^{13}C,d_3 labeling; resolution of these diesters to give both mirror image forms of each; and, finally, conversion of each isotopically labeled racemic or chiral diester through highly stereoselective ester to hydrogen functional group modifications to produce the corresponding cyclopropane. The presentation now and the Experimental Section of this paper follow this three-objective synthetic plan.

Scheme I



2-d_0 2-d_2

Scheme II



2-^{13}C, d_3

Racemic Isotopically Labeled Diesters. The dideutereio racemic diester **2**-d_2 was made from *trans*-1,2-bis(methoxycarbonyl)-cyclopropane through five sodium methoxide-catalyzed exchanges with *O*-deuteriomethanol (Scheme I). The deuterium incorporation at C(1) and C(2) in **2**-d_2 was judged by ^{1}H NMR spectroscopy to be 96% complete.

The ^{13}C,d_3-labeled racemic diester **2**-^{13}*C,d*$_3$ was prepared through the sequence outlined in Scheme II. Labeled barium carbonate (98.3% ^{13}C) was heated with magnesium powder under argon to give barium carbide-$^{13}C_2$, which was in turn treated with D_2O to provide ethyne-$^{13}C_2$,d_2 (**3**).[12] Acetylene **3** was then combined with anhydrous hydrogen bromide along with a small amount of air[13] to produce the labeled ethylene dibromide **4** in 60% overall yield from barium carbonate. Mass spectral analysis of this dibromide revealed 98% ^{13}C and 99% d_2 incorporation.

Treating dibromide **4** with potassium acetate afforded the diacetate **5** which, when treated with sodium ethoxide in refluxing ethanol,[13] gave the $^{13}C_2$,d_2-labeled ethylene glycol **6**. Glycol **6** was then converted in an efficient one-pot transformation, combining glycol cleavage and Wittig condensation of the formaldehyde-^{13}*C,d* generated in situ, to produce acrylate **7** (80% yield of GC pure material). Mass spectral analysis showed **7** to be 99% d_1, while ^{13}C{^{1}H} NMR spectra showed only one triplet, indicating that all of the ^{13}C label was in the C(3) position. Modification of a method reported by Mathias and Colletti[14] produced the triply labeled methyl acrylate **8** through an exchange of the C(2) proton catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) in the presence of *O*-deuteriomethanol. Mass spectrometric and proton NMR analyses indicated 99% deuterium incorporation at C(2).

Synthesis of methyl chloroacetate-*2,2-d*$_2$ was accomplished by first reacting acetic acid-d_4 with thionyl chloride in the presence of *N*-chlorosuccinimide and then treating the resulting acid chloride with methanol to produce the labeled chloro ester; it contained 99% d_2 at C(2) as evidenced by mass spectral and ^{1}H NMR analyses. Finally, the condensation reaction of methyl chloroacetate–*2,2-d*$_2$ and the ^{13}C,d_2-labeled acrylate **8** in the presence of NaH in DMSO-d_6 produced, in 61% isolated yield, racemic **2**-^{13}*C,d*$_3$ that was 99% trans, 96% d each at C(1) and at C(2), and 99% d_1 at C(3), as estimated by ^{1}H NMR analyses.

Resolved Chiral Isotopically Labeled Diesters. The resolution of diesters **2**-d_2 and **2**-^{13}*C,d*$_3$ was accomplished in two stages:

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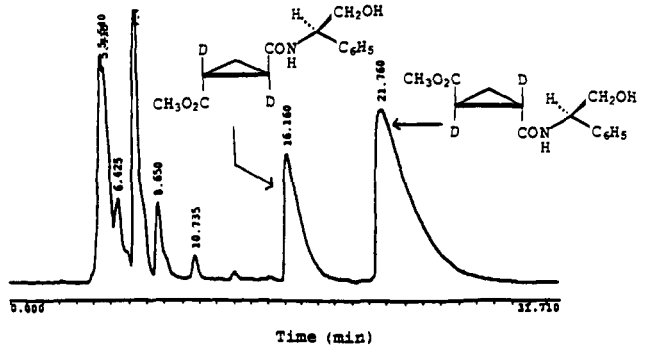
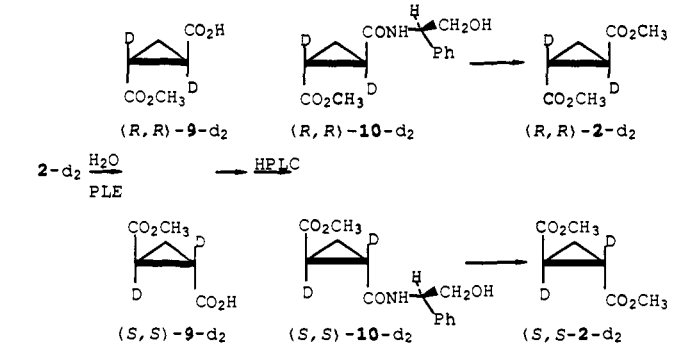


Figure 1. Preparative HPLC separation of the diastereomeric amides (*R,R*)-**10**-d_2 and (*S,S*)-**10**-d_2.

Scheme III



selective hydrolysis catalyzed by pig liver esterase, followed by chromatographic separation of diastereomeric amides prepared from (−)-(*R*)-2-phenylglycinol. The resolution process is outlined for racemic diester **2**-d_2 in Scheme III.

Selective hydrolysis of *trans*-1,2-bis(methoxycarbonyl)-3,3-dimethylcyclopropane in the presence of pig liver esterase gives 97% of an acid ester having 96% ee.[15] Encouraged by this precedent, we conducted the selective hydrolysis of racemic diester **2**-d_2 under these enzyme-catalyzed conditions. The acid ester obtained was enriched in the *S,S* isomer;[16] conversion of this product to the dimethyl ester using diazomethane, followed by ^{1}H NMR analysis using the chiral shift reagent Eu(hfc)$_3$, showed that it was about 50% ee. The unreacted diester was also about 50% ee and was *R,R*-enriched.[16] This selective hydrolysis thus gave a useful entry into the resolution process, but it was by itself insufficient.

The partially resolved acid ester (*S,S*)-**9**-d_2 was converted to a mixture of the diastereomeric amides (*R,R*)-**10**-d_2 and (*S,S*)-**10**-d_2 derived from (−)-(*R*)-2-phenylglycinol in 90% yield, following a number of relevant precedents.[17] Large scale separation of the diasteromeric amides was easily accomplished on a 6-cm diameter column using 425 g of silica gel with 2–3-g loadings to afford diastereomerically pure amides after one recycling process. Later resolutions utilized preparative HPLC which achieved beautiful base-line separation of the amides, thus eliminating the need for recycling (Figure 1). Analytical HPLC and ^{1}H NMR showed these amides to be diastereomerically pure.

After hydrolyses to the corresponding diacids[18] and conversion to the dimethyl esters, ^{1}H-NMR analyses using the chiral shift reagent Eu(hfc)$_3$ showed these diesters (*R,R*)-**2**-d_2 and (*S,S*)-**2**-d_2 to be enantiomerically pure (Figure 2). The unlabeled diester from the early eluting d_0-amide had $[\alpha]_{578}$ −233° (MeOH) and thus is of *R,R* configuration (lit.[16] $[\alpha]_{578}$ −232°). Proton NMR

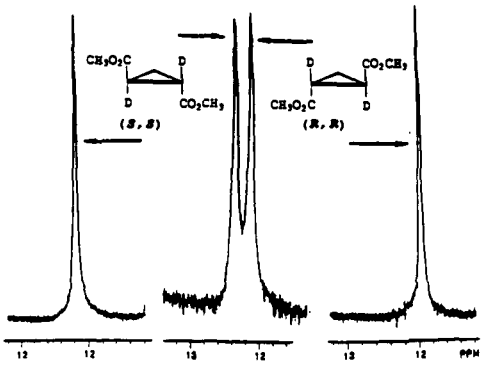
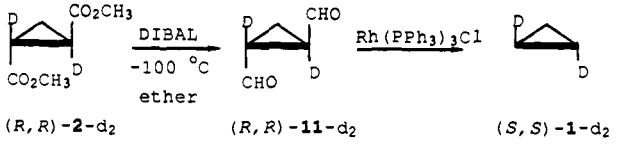


Figure 2. ^{1}H NMR spectra of the enantiotopic methyl groups of (left to right) (*S,S*)-**2**-d_2, *rac*-**2**-d_2, and (*R,R*)-**2**-d_2 in the presence of the chiral shift reagent Eu(hfc)$_3$.

Scheme IV



analyses of the dimethyl esters (*R,R*)-**2**-d_2 and (*S,S*)-**2**-d_2 showed no detectable loss of deuterium incorporation when compared to racemic **2**-d_2.

The ^{13}C-1,2,3-d_3-labeled trans diester **2**-$^{13}C,d_3$ was resolved in the same way through selective hydrolysis, conversion to a mixture of diasteromeric amides, chromatographic separation of the two amides, hydrolysis, and esterification, as outlined in Scheme III for the d_2-labeled trans diesters.

Isotopically Labeled Cyclopropanes. The conversion of isotopically labeled *trans*-1,2-bis(methoxycarbonyl)cyclopropanes to the corresponding racemic or chiral labeled cyclopropanes was accomplished through the two-step route shown for one specific example of the process in Scheme IV. Reduction of the dimethyl ester (*R,R*)-**2**-d_2 in ether at −100 °C with diisobutylaluminum hydride (DIBAL) afforded the corresponding dialdehyde (*R,R*)-**11**-d_2 in 76–84% yield, and then complete decarbonylation of the intermediate dialdehyde with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) provided the cyclopropane (*R,R*)-**1**-d_2. With other diesters, this two-step procedure gave the other labeled cyclopropanes **1**-d_2, (*S,S*)-**1**-d_2, **1**-$^{13}C,d_3$, (2*R*,3*R*)-**1**-$^{13}C,d_3$, and (2*S*,3*S*)-**1**-$^{13}C,d_3$.

The decarbonylation reaction presented some initial problems. The reported yield for this transformation in toluene is less than 4%.[19] A slight modification of this procedure using unlabeled dialdehyde produced a 10% yield of isolated and gas chromatographically purified cyclopropane-d_0. Further study of this reaction showed that a relatively stable intermediate, cyclopropanecarboxaldehyde, was produced within an hour. Further decarbonylation of the monoaldehyde to give cyclopropane and propylene in a ~10:1 ratio was very much slower.

Since decarbonylation reactions promoted by Wilkinson's catalyst[20] may be sensitive to solvent, a search for a better solvent was conducted. The use of 1,2-dichloroethane, the solvent employed for decarbonylation reactions of *trans*-1,3-cyclobutanedicarboxaldehyde in yields of up to 60%,[21] increased the yield from unlabeled dialdehyde to cyclopropane to 23%. Further trials determined that decarbonylation reactions in 1,2-dichloropropane provided still higher yields of cyclopropane. In this solvent, under the reaction conditions developed, yields of isolated GC-pure cyclopropane as high as 47% from monoaldehyde and 42% from dialdehyde were realized.

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Table I. Stereochemical Integrity and Estimated Deuterium Content for Isotopically Labeled Cyclopropanes

cyclopropane	% cis	% anti	% d_i[a]
rac-**1**-d_2	5.5[b]		96% d_2
(*S*,*S*)-**1**-d_2	5.4[c]		96% d_2
rac-**1**-$^{13}C,d_3$		94.7[c]	97% d_3
(2*S*,3*S*)-**1**-$^{13}C,d_3$		94.7[c]	97% d_3

[a] Estimated using ^{1}H NMR of the (resolved) dimethyl ester precursor (assumes no deuterium lost in the reduction of the diester and subsequent decarbonylation of the dialdehyde). [b] Judged by TDL spectroscopy.[10] [c] Determined by FTIR spectroscopy.[6,7]

Characterizations of Labeled Cyclopropanes. The labeled cyclopropanes prepared, purified by preparative gas chromatography and carefully degassed and freed of water vapor, were of high chemical, isotopic, and stereochemical purity as judged by several criteria.

First, chemical purity: the samples were free of contamination by other compounds, according to capillary GC analyses on two columns known to give decisive resolution of cyclopropane and the most likely contaminant, propene. Other possible contaminants would differ more substantially in molecular weight and volatility and would be even easier to detect. None was seen.

Second, label incorporation: the estimates of deuterium incorporation derived primarily by ^{1}H NMR analyses of synthetic precursors are summarized in Table I. Whenever mass spectrometric data could be utilized, they reinforced the NMR indications. The carbon-13 incorporation in **2**-$^{13}C,d_3$, (2*R*,3*R*)-**2**-$^{13}C,d_3$, and (2*S*,3*S*)-**2**-$^{13}C,d_3$ was as good as the starting carbon carbonate employed (98.3%), for no isotopic dilutions were incorporated into the syntheses of $^{13}C,d_3$-cyclopropanes.

Third, geometrical specificity: analyses of the labeled cyclopropanes by FTIR[6,7] and by tunable diode laser spectroscopy[10] suggested that they were of high but not completely uniform geometrical disposition (Table I). The analyses of Table I suggest that some stereochemical integrity was lost during the conversion of labeled diesters to cyclopropanes according to Scheme IV. It may be that the relatively slow decarbonylation of cyclopropanecarboxaldehyde allows a small amount of some normally kinetically insignificant stereochemical scrambling to occur, for faster decarbonylation reactions of substituted cyclopropanecarboxaldehydes show no detectable loss of stereochemical integrity.[22] At any rate, the extent of loss of geometrical specificity is relatively small, about 5.5% as estimated for both trans-d_2 and anti-d_3 products, using spectroscopic measures and independently synthesized reference samples of *rac*-**1**, cyclopropane-*cis*-*1*,*2*-d_2, and syn and anti isomers of cyclopropane-*1*,*2*,*3*-d_3.[6,7,10]

Finally, chiral purity: the resolved labeled diesters utilized as precursors for the cyclopropanes were judged to be optically pure according to chiral NMR shift reagent analyses (Figure 2). The loss of stereochemical integrity in the last two synthetic steps (Scheme IV) is estimated to be about 5.5% (Table I) and is most probably associated with the second decarbonylation step being unusually slow. Thus, it seems highly unlikely that the reduction and decarbonylation chemistry involves net enantiomerization in addition to the slight loss of geometrical integrity, and the chiral trans-d_2- and anti-$^{13}C,d_3$ cyclopropanes prepared are viewed as being essentially optically pure, contaminated only with about 5.5% of achiral geometrical isomers. The pairs of mirror-image forms (*S*,*S*)-**1**-d_2 versus (*R*,*R*)-**1**-d_2 and (2*R*,3*R*)-**1**-$^{13}C,d_3$ versus (2*S*,3*S*)-**1**-$^{13}C,d_3$ give strong mirror-image related vibrational circular dichroism spectra, establishing that they are of comparable optical purity and related as enantiomers.[6,7,11,23]

Fortunately, the small extent to which these labeled cyclopropanes lack complete geometrical isomeric purity and lack perfect optical purity is not of consequence in kinetic experiments following first-order reactions. They are sufficiently well-defined geometrically and optically that the thermal reactions they show begin well away from equilibrium and may be followed over a significant range of variations in (relative) optical purity and of (relative) geometrical purity with high precision and verified accuracy.[6,7,10,11]

Conclusions

The efficient syntheses of isotopically labeled racemic and chiral cyclopropanes reported here in detail provided the substrates for kinetic investigations that have solved a long troublesome problem in basic hydrocarbon thermal chemistry.[7,9] The cyclopropanes prepared have high chemical, isotopic, geometrical, and optical purity and are all of strictly comparable quality. There is no apparent reason to suggest that the **1**-d_2 isomers are suitable but that the **1**-$^{13}C,d_3$ isomers are unsuitable as substrates for kinetic experiments.

Experimental Section

Analytical gas chromatographic (GC) analyses used two 0.2-mm i.d. × 25-m Hewlett-Packard (HP) ultraperformance fused silica capillary columns (cross-linked dimethyl silicone and cross-linked 5% phenyl methyl silicone) connected to a single injection port through a two-holed graphite ferrule on an HP 5790 instrument equipped with dual flame ionization detectors and dual HP 3392A reporting integrators. Gas chromatographic/mass spectral (GC/MS) analyses were secured with HP 5890 GC, 5970 mass selective detector (ionizing voltage = 70 eV), and 9836 instruments and computer. Nuclear magnetic resonance spectra were obtained on a General Electric GN 300 MHz for ^{1}H (75.46 MHz for ^{13}C) spectrometer using $CDCl_3$ as the solvent.

Preparative gas chromatographic separations were accomplished using a Varian Aerograph A90-P3 instrument, using either a $^1/_4$-in. o.d. (6.4-mm) × 3.7-m aluminum column containing 20% SE-30 on 60–80-mesh Chromosorb W NAW that had been treated with hexamethyldisilazane (column A) or a $^1/_4$-in. o.d. × 2.6-m column packed with 10% FFAP on Chromosorb W (column B). Preparative high-pressure liquid chromatography was accomplished using a Rainin HPLC system based on two Rainin Rabbit HBX pumping units and a Gilson 112 UV/vis detector, interfaced with an Apple Macintosh Plus computer. A custom-made 20-mm × 25-cm Machery–Nagel Nucleosil 50-5 column was used for preparative separators.

Infrared (IR) spectra were recorded on a Nicolet 7199 instrument equipped with a TGS detector and a 1180 series computer. The sample cell used for analyzing gaseous samples had a 5-cm path length and ~20 mL volume and was equipped with a high-vacuum stopcock, cold finger, and 25- × 2-mm KBr disks. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a standard 1-mL microcell (path length 100 mm). Spinning-band distillations utilized either a B/R Instrument Corporation 800 Micro spinning band column or a B/R 36T column interfaced with a B/R 8500 microprocessor controller.

Either dimethyl sulfoxide (DMSO) was dried over CaH_2 and distilled at reduced pressure or commercial anhydrous DMSO (Aldrich Chemical Co.) was used. Diethyl ether was distilled from Na metal and benzophenone. 1,2-Dichloropropane was distilled at aspirator vacuum immediately prior to use.

Microanalyses were performed by E & R Microanalytical Laboratory, Inc. of Corona, NY.

Dimethyl Cyclopropane-*trans*-*1*,*2*-dicarboxylate (2). A mixture of methyl chloroacetate (40 g, 0.37 mol) and methyl acrylate (31.7 g, 0.37 mol) was added dropwise over a 45-min period with occasional water bath cooling to a mixture of dry DMSO (200 mL) and sodium hydride (18 g of a 60% dispersion in mineral oil, 0.45 mol). The reaction mixture became warm and turned yellow at the onset of the addition. The mixture was stirred for 12 h and then cooled in an ice bath. Ice-cold 5 N HCl (100 mL) was added cautiously, the mixture was allowed to stir for 10 min, and then 100 mL of H_2O was added. The mixture was extracted with three 100-mL portion of ether. The combined ethereal extracts were washed first with 100 mL of saturated aqueous $NaHCO_3$ and then with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated. Kugelrohr distillation (70–80 °C bath temperature, 16 Torr) afforded 43.2 g of a clear liquid that was estimated by GC to be 92% of the diester (39.7 g, 68% estimated yield, 98% trans diester, 2% cis diester by GC): ^{1}H NMR δ 1.44 (t, 2 H), 2.18 (t, 2 H), 3.69 (s, 6 H).

***trans*-1,2-Bis(methoxycarbonyl)cyclopropane-*1*,*2*-d_2 (2-d_2).** Sodium methoxide (3.4 g, 0.063 mol) was dissolved in 35 mL of methanol-*d* (Aldrich, 99.5+ atom % ^{2}H). The dimethyl ester **2** (20 g, 0.126 mol) was added, and the resulting pale yellow solution was heated at reflux for 4 days and then cooled in an ice bath; 2 mL of D_2O was added, followed by 35 mL of ice-cold 2 N HCl. The mixture was stirred for 10

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min and extracted with ether (4 × 75 mL). The aqueous layer was acidified to pH 2.0 and extracted with ether to recover hydrolyzed material, which was subsequently esterified with ethereal CH_2N_2 and recycled. The ethereal extracts were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated; the residue was distilled to give 15.8 g (79% recovery) of partially deuterated **2**-d_2. This procedure was repeated until the product diester **2**-d_2 was 96% deuterated at the trans-1,2 positions (a total of 5 equilibrations): ^{1}H NMR δ 1.44 (s, 2 H), 2.18 (residual apparent triplet (dd, J = 2 Hz[81]) 0.08 H), 3.69 (s, 6 H).

Ethyne-$^{13}C_2$,d_2 (3). Barium carbonate-^{13}C (98.7% ^{13}C, Isotec Inc., 25 g, 0.126 mol) and magnesium powder (50 mesh, 60 g, 2.47 mol) were ground in a mortar and pestle to a fine powder. The powder was placed in a stainless steel bomb.[12] The bomb was sealed, flushed with a stream of argon for 1 h, and then heated at the base with a grid-top high-temperature burner while still under a slow stream of argon until the vessel got red hot (~5 min); the outlet tubing had a small piece of glass wool in line before the bubbler to trap postreaction particulate matter. During this time, a puff of black powder was emitted through the outlet tubing, giving visual evidence of reaction. Heating was continued for an additional 10 min, and the bomb was allowed to cool to room temperature. The reaction vessel was opened in a drybox under argon, and the greyish-black solid was scraped out and ground with mortar and pestle. This solid was added in small portions to 75 g of D_2O (99.96% D, Aldrich) with stirring. After the addition, the reaction mixture was slowly heated to reflux for 1–2 h. The evolved gas was carried in a stream of helium through a H_2SO_4 bubbler into a liquid nitrogen trap.

1,2-Dibromoethane-$^{13}C_2$-*1,2*-d_2 (4). A thick-walled graduated tube equipped with a 14/20 female joint and septum was flushed with helium and then cooled in a −78 °C bath. Anhydrous HBr (Matheson lecture bottle) was blown through the tube via a large-bore syringe needle inlet from the HBr tank and a large-bore syringe needle outlet to a bubbler. The inlet and outlet tubing was Nalgene clear plastic tubing. When the desired amount of liquid HBr was collected, the septum was quickly replaced with a vacuum stopcock equipped with a 14/20 male joint and tubing adapter. The tube was then removed from the −78 °C bath and quickly cooled in a liquid nitrogen bath. The tube was degassed and the anhydrous HBr (3.7 mL, 10.2 g, 0.126 mol) was vacuum transferred to a 5-L flask (equipped with a three-way vacuum stopcock and a cold finger protrusion on the bottom of the flask). The collected acetylene **3** prepared above was vacuum transferred to the 5-L flask immediately following the vacuum transfer of HBr. The flask was then allowed to come to room temperature, and a small amount of air was introduced into the vessel by quickly opening and closing the stopcock; the reaction did not proceed in the absence of air. Liquid began to form on the walls of the flask within a few minutes, and the flask was allowed to stand overnight. The vessel was then rinsed with 150 mL of CH_2Cl_2. The CH_2Cl_2 solution was washed with two 100-mL portions of 0.14 M K_2CO_3 followed by 100 mL of brine and then was dried over K_2CO_3, filtered, and concentrated. The concentrate was distilled (bp 40–50 °C, ~20 Torr) to give 7.2 g of **4** (60% yield from $Ba^{13}CO_3$). Two-dimensional GC analysis showed that this material had retention data identical with those of an authentic commercial sample of unlabeled 1,2-dibromoethane.

A total of 100 g of $Ba^{13}CO_3$ possessing an average of 98.3% ^{13}C (Isotec Inc.) was used giving a total of 26.7 g of GC pure **4** estimated to be 98.5% $^2H_2$ by GC/MS (55% overall yield from $Ba^{13}CO_3$): ^{1}H NMR δ 3.38 (s, m), 3.88 (s, m); ^{13}C NMR δ 29.16 (t, J = 23.3 Hz), 29.00 (apparent t), 29.32 (apparent t); mass spectrum m/e 194 (2.4), 193 (0.1), 192 (4.8), 191 (0.19), 190 (2.6), 189 (0.09), 113 (96.2), 112 (2.9), 111 (100), 110 (3.3).

Ethylene Glycol Diacetate-*1,2*-$^{13}C_2$-*1,2*-d_2 (5). 1,2-Dibromoethane-$^{13}C_2$-1,2-d_2 (26.7 g, 0.139 mol), potassium acetate (31.23 g, 0.318 mol), and 4 mL of acetic acid were combined in a 100-mL flask and heated to reflux for 3.5 h.[13] The condenser was then replaced with a short-path distillation head, and the mixture was distilled first at atmospheric pressure and then at 16 Torr at a bath temperature of 140 °C. The distillate was then heated at a bath temperature of 140 °C to distill off traces of acetic acid, leaving a colorless still-pot residue of crude product (17.4 g, 83% yield): ^{1}H NMR δ 2.09 (s, 6 H), 400 (s), 4.49 (s).

Ethylene Glycol-$^{13}C_2$-*1,2*-d_2 (6). Sodium metal (0.3 g) was dissolved in 100 mL of absolute ethanol. Crude ethylene glycol diacetate-*1,2*-$^{13}C_2$-*1,2*-d_2 (17.4 g, 0.12 mol) was added, and the mixture was brought to reflux for 6 h.[13] The reaction mixture was concentrated at atmospheric pressure, and the residue was Kugelrohr distilled (100 °C bath temp, ~16 Torr) to give 8.8 g of material that was contaminated with 8% of ethanol, according to capillary GC estimates. The identity of the product was confirmed by capillary GC comparisons with authentic unlabeled ethylene glycol.

Methyl Propenoate-*3*-^{13}C-*3*-*d* (7). The reagent $Pb(OAc)_4$ (26.85 g, 60.6 mmol) was added to 200 mL of anhydrous DMSO (Aldrich) to give a light orange solution. (A dark brown solution at this point indicated wet DMSO and presaged a low yield.) Diol **6** (4.35 g of the above 92% solution, 60.5 mmol) was added dropwise with stirring to this solution. The reaction mixture became light yellow after the addition and was warmed to 55 °C with an oil bath. The solution was still yellow, indicating that not all of the $Pb(OAc)_4$ had been consumed (on the basis of earlier experimentation using commercial ethylene glycol). An additional 10 drops of the ethylene glycol-$^{13}C_2$-*1,2*-d_2 solution was added, and the reaction mixture became colorless. The oil bath was removed (total time on oil bath ~7 min), and methyl (triphenylphosphoranylidene)acetate (40.62 g, 0.121 mol) was added all at once followed by a crystal of 4-methoxyphenol as a polymerization inhibitor, and the mixture was allowed to stir for 24 h. Methyl propenoate-*3*-^{13}C-*3*-*d* (8.45 g, 80% yield, 98% GC pure) was collected in a −78 °C trap (glass coil) by vacuum distillation (~16 Torr), first at room temperature and then while heating the reaction mixture to 100 °C. A second reaction produced 7.35 g of **7** from 4.0 g of the starting solution (74% yield): ^{1}H NMR δ 3.76 (s), 5.55 (d), 6.14 (m), 6.66 (d); ^{13}C NMR δ 130.44 (t); mass spectrum m/e 55 (2.2), 57 (100), 58 (3.4), 86 (4.0), 87 (7.9), 88 (1.1), 89 (6.3). For unlabeled methyl acrylate: MS m/e 53 (3.9), 55 (100), 56 (4.1), 85 (17.0), 86 (1.8), 87 (0.8).

Methyl Propenoate-*3*-^{13}C-*2,3*-d_2 (8). The labeled methyl acrylate **7** (15.35 g, 0.174 mol), 1,4-diazabicyclo[2.2.2]octane (DABCO, 19.55 g, 0.174 mol), CH_3OD (232.8 g, 7.04 mol), and a small crystal of 4-methoxyphenol were combined and stirred at room temperature for 5 h. (Longer reaction times led to significant amounts of labeled methyl 3-methoxypropanoate.) The reaction mixture was then cooled to −25 °C, and 755 mL of ice-cold CH_2Cl_2 was added. This solution was then washed consecutively with ice-cold 2 N HCl (2 × 200 mL), 200 mL of a saturated solution of $NaHCO_3$, and 200 mL of brine and then was dried over $CaCl_2$ and filtered. A small crystal of 4-methoxyphenol was added, and the solution was slowly concentrated by distillation using a 15-cm Vigreux column to give a 40% solution of **8** (12.89 g, 83% yield) in CH_2Cl_2. The deuterium incorporation was followed by GC/MS by monitoring m/e 57 (M − 31, loss of OCH_3) in methyl propenoate-*3*-^{13}C-*3*-*d* and m/e 58 (M − 31) in methyl propenoate-*3*-^{13}C-*2,3*-d_2: ^{1}H NMR δ 3.76 (s, 3 H), 5.54 (s, 0.25 H), 6.08 (t, 0.26 H), 6.11 (t, 0.26 H), 6.65 (t, 0.25 H); mass spectrum m/e 55 (1.8), 58 (100), 59 (8.0), 87 (4.7), 88 (8.0), 89 (1.1), 90 (0.6).

Methyl Chloroacetate-*2,2*-d_2. Acetic acid-d_4 (Aldrich 99.5% d_4, 30 g, 0.468 mol) was added dropwise to $SOCl_2$ (222.6 g, 1.87 mol) with stirring, and the reaction mixture was slowly brought to reflux for 1.5 h and then allowed to cool to room temperature. *N*-Chlorosuccinimide (125.1 g, 0.94 mol) was added all at once (10 mL of $SOCl_2$ was used to aid in the addition) along with 5 drops of 37% DCl in D_2O, and the mixture was heated to reflux for 2.5 h. Methanol (50 g) was cooled to −78 °C, and the warm reaction mixture was added to the cold methanol dropwise. After the addition, the solution was allowed to warm to room temperature and was stirred for 2 h while gaseous HCl evolved. The mixture was then heated to reflux for 2 h to remove dimethyl sulfite, cooled to room temperature, and taken up in 450 mL of CH_2Cl_2. This CH_2Cl_2 solution was washed consecutively with H_2O (2 × 150 mL), a saturated solution of $Na_2S_2O_3$ (2 × 150 mL), 150 mL of a saturated solution of $NaHCO_3$, and 150 mL of brine and then dried over $CaCl_2$, filtered, and concentrated. Spinning-band distillation gave 21.19 g of methyl chloroacetate-*2,2*-d_2 (41% yield, >99% $^2H_2$ by GC/MS): mass spectrum m/e 59 (100), 66 (15.5), 68 (4.9), 79 (37.1), 81 (11.8), 110 (8.3), 112 (2.7).

***trans*-1,2-Bis(methoxycarbonyl)cyclopropane-*3*-^{13}C-*1,2,3*-d_3 (2-^{13}C,d_3).** Methyl chloroacetate-*2,2*-d_2 (17.13 g, 0.155 mol) and the labeled methyl acrylate **8** (12.89 g, 0.145 mol) in 60 mL of DMSO-d_6 (99.9% d_6, Isotec Inc.) was slowly added dropwise with periodic ice bath cooling to a stirred slurry of NaH (6.1 g, 0.25 mol) in 110 mL of DMSO-d_6 at 25 °C. The yellow slurry was then allowed to stir for 23 h, and 14 g of ice-cold 37% DCl in D_2O was added dropwise followed by 100 mL of cold H_2O. This solution was extracted with ether (3 × 200 mL), and the organic extracts were washed with 200 mL of a saturated solution of $NaHCO_3$ and then with brine (2 × 200 mL) and then dried over $MgSO_4$, filtered, concentrated, and Kugelrohr distilled (80–100 °C bath temperature, ~16 Torr) to give 14.43 g (92% GC pure, 61% yield, 99% trans isomer by GC) of product: ^{1}H NMR δ 1.14 (s, 0.5 H), 1.70 (s, 0.5 H), 2.17 (residual d, 0.08 H), 3.70 (s, 6 H); ^{13}C NMR δ 14.90 (t).

Partially Resolved *trans*-2-(Methoxycarbonyl)cyclopropanecarboxylic Acid-*1,2*-d_2. A magnetically stirred solution of 0.1 M KH_2PO_4 buffer was adjusted to pH 7.0 with 1 M NaOH. Pig liver esterase (Sigma, 0.4 mL of a suspension that was approximately 11 mg/mL, 260 units/mg protein) was then added. The diester **2**-d_2 (12.1 g, 76 mmol) was added dropwise to the vigorously stirred solution. The pH was maintained at 7.0 by a pH-stat (a solenoid activated two-way stream switching valve

(Rainin 38-080) interfaced with an Orion Model 231 pH/mV/temperature meter through a millivolt-sensitive solenoid driver). Over an 8.5-h period, 55 mL of 1 N NaOH was added. The solution was saturated with NaCl and extracted with ether (4 × 100 mL). The combined ethereal extracts were washed with 100 mL of brine, dried over $MgSO_4$, filtered, concentrated, and Kugelrohr distilled to give 3.05 g (93%) of *R,R*-enriched diester.[16] This enriched diester was estimated to be of 50% ee using ^1H NMR and the chiral shift reagent Eu(hfc)$_3$; the enantiotopic methyl groups displayed resolved singlets when shifted to $\delta \geq 9$ ppm.

The aqueous layer was acidified to pH 2.0 with 2 N HCl followed by extraction with ether (3 × 100 mL). The aqueous layer was then continuously extracted with the combined etheral extracts for 20 h. The ethereal solution was dried over $MgSO_4$, filtered, concentrated, and Kugelrohr distilled (75–85 °C bath temp, 0.1 Torr) to afford 8.06 g (quantitative yield) of *S,S*-enriched acid ester:[16] ^1H NMR δ 1.48 (d, 2 H), 2.21 (m, 0.09 H), 3.72 (s, 3 H).

(1*R*,2*R*)- and (1*S*,2*S*)-*N*-(2-Hydroxy-1(*R*)-phenylethyl)-2-(methoxycarbonyl)cyclopropane-1-carboxamide-*1,2-d*$_2$ [(*R,R*)-10-*d*$_2$ and (*S,S*)-10-*d*$_2$]. Partially resolved acid ester **9** (8.06 g, 55 mmol) was dissolved in 250 mL of THF and cooled to −20 °C. *N*-Methylmorphine (5.56 g, 55 mmol) was added dropwise, and the reaction mixture was stirred for 5 min. Isobutyl chloroformate (7.81 g, 57 mmol) was added dropwise, and the solution was stirred for 10 min. Powdered (−)-(*R*)-phenylglycinol (7.85 g, 57 mmol; Aldrich, $[\alpha]_D$ −31.7° (*c* 0.76, 1 N HCl)) was then added all at once, and stirring was continued at −20 °C for 20 min and then at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in 250 mL of ethyl acetate/CH_2Cl_2 (85:15 v:v) and successively washed with H_2O, saturated $NaHCO_3$ solution, 2 N HCl, and brine (125 mL each). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 13.51 g (93% crude yield) of a white solid. A second run starting with 1.94 g of partially resolved acid ester **2**-*d*$_2$ gave 3.50 g (99% yield) of a crude mixture of (*R,R*)-**10**-*d*$_2$ and (*S,S*)-**10**-*d*$_2$, as evidenced by ^1H NMR.

The diastereomers (*R,R*)-**10**-*d*$_2$ and (*S,S*)-**10**-*d*$_2$ were chromatographed in 2–3-g portions on a 6-cm × 31-cm glass column using 425 g of Merck Lichoprep Si 60 (15–25 μm particle size). The mixture of (*R,R*)-**10**-*d*$_2$ and (*S,S*)-**10**-*d*$_2$ dissolved in ethyl acetate/CH_2Cl_2 (85:15 v:v) was loaded onto the column and eluted with ethyl acetate/petroleum ether (1.6:1 v:v). Starting from a total of 17.01 g of a crude mixture of amides, 5.14 g of (*R,R*)-**10**-*d*$_2$ and 6.56 g of (*S,S*)-**10**-*d*$_2$ were recovered >99% diastereomerically pure according to ^1H NMR analyses after rechromatographing mixed fractions (65% yield based on starting amount of acid ester). Later resolutions were accomplished by preparative HPLC under conditions giving base-line separation of the diasteromers, thus eliminating the need for recycling (Figure 1); amide (*R,R*)-**10**-*d*$_2$ was eluted first (Figure 1).

The isomer (*R,R*)-**10**-*d*$_2$ had mp 142–143 °C: ^1H NMR δ 1.33 (d, 1 H), 1.45 (d, 1 H), 2.45 (t, 1 H), 3.71 (s, 3 H), 3.90 (q, 2 H), 5.06 (q, 1 H), 6.42 (m, 1 H), 7.35 (m, 5 H). For the unlabeled analog (*R,R*)-**10**-*d*$_0$: Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.65; H, 6.74; N, 5.25.

Compound (*S,S*)-**10**-*d*$_2$ had mp 151–152 °C: ^1H NMR δ 1.36 (d, 1 H), 1.48 (d, 1 H), 2.44 (t, 1 H), 3.68 (s, 3 H), 3.90 (q, 2 H), 5.07 (q, 1 H), 6.39 (m, 1 H), 7.36 (m, 5 H). For the unlabeled analog (*S,S*)-**10**-*d*$_0$: Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.70; N, 5.32.

(−)-(*R,R*)-*trans*-1,2-Bis(methoxycarbonyl)cyclopropane-*1,2-d*$_2$ ((*R,R*)-2-*d*$_2$). The resolved amide (*R,R*)-**10**-*d*$_2$ (5.14 g, 19 mmol) was dissolved in a solution containing 13.3 mL of concentrated H_2SO_4 in 147 mL of 1:1 (v:v) THF:H_2O. The solution was heated to gentle reflux for 23 h, cooled to room temperature, diluted with 75 mL of brine, and extracted with ether (3 × 150 mL). The aqueous layer was continuously extracted with the combined organic extracts for 16 h. The resulting diacid in 200 mL of ether was esterified with CH_2N_2, dried over $MgSO_4$, filtered, stripped of solvents, and Kugelrohr distilled (bath temperature 75–100 °C, ~16 Torr) to give 2.7 g of diester (*R,R*)-**2**-*d*$_2$ (86% yield from amide (*R,R*)-**10**-*d*$_2$) as a waxy white solid. The diester was further purified by GC for chiral shift reagent analysis. The CH_3 singlet remained unsplit as it was shifted downfield to δ 12.0. Previous experiments with partially racemic material had shown that the enantiotopic methyl resonances were well separated at $\delta \geq 9.0$ (Figure 2). Diester (*R,R*)-**2**-*d*$_2$ had $[\alpha]_D$ −239° (*c* 0.65, $CDCl_3$): ^1H NMR δ 1.44 (s, 2 H), 2.18 (residual apparent triplet (d, J = 2 Hz,[24] 0.09 H), 3.69 (s, 6 H). The (*R,R*)-**2**-*d*$_0$ diester had $[\alpha]_D$ −233° (MeOH) (lit.[16] $[\alpha]_D$ −232° (MeOH)).

(+)-(*S,S*)-*trans*-1,2-Bis(methoxycarbonyl)cyclopropane-*1,2-d*$_2$ ((*S,S*)-2-*d*$_2$). According to the procedure above, resolved amide **29** (6.0 g, 23 mmol) gave 2.8 g (77% from amide) of (*S,S*)-**15**. The diester was purified by GC for chiral shift reagent analysis. The CH_3 singlet remained unsplit as it was shifted downfield to δ 12.5 (Figure 2). Diester (*S,S*)-**2**-*d*$_2$ had $[\alpha]_D$ +239° (*c* 0.69, $CDCl_3$), +236° (CCl_4) (lit.[25] $[\alpha]_D$ +236° (CCl_4)): ^1H NMR δ 1.44 (s, 2 H), 2.18 (residual triplet 0.08 H), 3.69 (s, 6 H).

Partially Resolved *trans*-2-(Methoxycarbonyl)cyclopropanecarboxylic Acid-*3*-^{13}*C-1,2,3-d*$_3$ (9-^{13}*C,d*$_3$). According to the procedure described for the formation of *S,S*-enriched 9-$^{13}C,d_3$, racemic 2-$^{13}C,d_3$ (5.0 g, 30.8 mmol) gave 2.14 g of distilled 9-$^{13}C,d_3$ (97% yield based on 50% hydrolysis) along with 2.4 g of unreacted diester.

(1*R*,2*R*)- and (1*S*,2*S*)-*N*-(2-Hydroxy-1(*R*)-phenylethyl)-2-(methoxycarbonyl)cyclopropane-1-carboxamide-*3*-^{13}*C-1,2,3-d*$_3$ ((*R,R*)-10-^{13}*C,d*$_3$ and (*S,S*)-10-^{13}*C,d*$_3$). According to the same procedure used for the d_2 compounds, the *S,S*-enriched sample of 9-$^{13}C,d_3$ (2.14 g, 14.4 mmol) was converted to 3.6 g (94% crude yield) of a white solid. This solid was chromatographed using the Nucleosil 50-5 column and the Rainin preparative HPLC system. The chromatographic procedure was as follows: the crude amides were dissolved in 35:65 2,2,4-trimethylpentane:ethyl acetate, and the solution was injected onto the column using a 5-mL injection loop. The amides were eluted with 35:65 2,2,4-trimethylpentane:ethyl acetate at a flow rate of 16 mL/min and were base-line resolved (Figure 1) and collected diasteromerically pure.

Amide (*R,R*)-10-$^{13}C,d_3$ eluted first: ^1H NMR δ 1.04 (s, 0.25 H), 1.15 (s, 0.25 H), 1.60 (s, 0.25 H), 1.72 (s, 0.25 H), 2.52 (t, 1 H), 3.71 (s, 3 H), 3.89 (t, 2 H), 5.06 (q, 1 H), 6.48 (d, 1 H), 7.32 (m, 5 H).

Amide (*S,S*)-10-$^{13}C,d_3$ eluted second: ^1H NMR δ 1.06 (s, 0.25 H), 1.18 (s, 0.25 H), 1.62 (s, 0.25 H), 1.74 (s, 0.25 H), 2.61 (t, 1 H), 3.67 (s, 3 H), 3.88 (t, 2 H), 5.05 (q, 1 H), 6.53 (br s, 1 H), 7.32 (m, 5 H); ^{13}C NMR δ 16.4 (t).

(+)-(*S,S*)-*trans*-1,2-Bis(methoxycarbonyl)cyclopropane-*3*-^{13}*C-1,2,3-d*$_3$ ((*S,S*)-2-^{13}*C,d*$_3$). The resolved amide (*S,S*)-10-$^{13}C,d_3$ (2.05 g, 7.7 mmol) was dissolved in a solution containing 5 mL of concentrated H_2SO_4 in 50 mL of 1:1 (v:v) THF:H_2O. The solution was heated to gentle reflux for 29 h, cooled to room temperature, diluted with 25 mL of brine, and extracted with ether (3 × 50 mL). The aqueous layer was continuously extracted with the combined organic extracts for 20 h. The ethereal solution was dried over $MgSO_4$, filtered, and concentrated to a volume of 20 mL. To this solution was added an ethereal solution of CH_2N_2 until the yellow color persisted. This mixture was then allowed to stand for 1 h. The solution was concentrated, and the still-pot material was Kugelrohr distilled (bath temperature 75–100 °C, ~16 Torr) to give 1.04 g (83% yield from amide) of a waxy white solid. The diester was further purified by GC on column A for ^1H NMR chiral shift reagent analysis. The CH_3 singlet remained unsplit as it was shifted downfield to δ 12.0. Diester (*S,S*)-**2**-$^{13}C,d_3$ had $[\alpha]_D$ +239° (*c* 0.55, $CDCl_3$): ^1H NMR δ 1.14 (s, 0.5 H), 1.70 (s, 0.5 H), 2.17 (residual d, 0.08 H), 3.70 (s, 6 H); ^{13}C NMR δ 14.91 (t).

(−)-(*R,R*)-*trans*-1,2-Bis(methoxycarbonyl)cyclopropane-*3*-^{13}*C-1,2,3-d*$_3$ ((*R,R*)-2-^{13}*C,d*$_3$). According to the above procedure, from (*R,R*)-10-$^{13}C,d_3$ (4.87 g, 18.2 mmol) was produced (*R,R*)-**2**-$^{13}C,d_3$ (2.74 g, 93% yield). ^1H NMR chiral shift reagent analysis showed that the CH_3 singlet remained unsplit as it was shifted downfield to δ 12.0. Diester (*R,R*)-**2**-$^{13}C,d_3$ had $[\alpha]_D$ −236° (*c* 0.50, $CDCl_3$): ^1H NMR δ 1.14 (s, 0.5 H), 1.70 (s, 0.5 H), 2.17 (residual d, 0.09 H), 3.70 (s, 6 H); ^{13}C NMR δ 14.91 (t).

Cyclopropane-*trans*-1,2-dicarboxaldehyde-*1,2-d*$_2$ (11-*d*$_2$). To the racemic diester **2**-*d*$_2$ (2.00 g, 12.5 mmol) in 150 mL of ether at −100 °C (internal temperature) was added dropwise with stirring at a rate of 30 mL/h via syringe pump (Sage Instruments, Model 352) diisobutylaluminum hydride (DIBAL, Ventron, 21.7 mL of a 1.15 M solution in hexane). A small aliquot of the reaction mixture was quenched with MeOH and analyzed by GC to check for incomplete reduction products: at an injection port temperature of 160 °C, an oven temperature of 90 °C, and a detector temperature of 300 °C, the diester **11**-*d*$_2$ had a retention time of 8.11 min, the ester aldehyde had a retention time of 4.53 min, and the dialdehyde eluted at 2.53 min on the cross-linked dimethyl silicone column. After the addition, 20 mL of HPLC grade MeOH was added at such a rate that the reaction temperature never rose above −96 °C. The mixture was then allowed to warm to room temperature. The resulting white globular solid was removed by filtration and washed thoroughly with 300 mL of ether. The ethereal solution was concentrated to afford crude dialdehyde **11**-*d*$_2$ (7.3 g of a solution that was 13% **11**-*d*$_2$ by GC; 0.95 g, 76% estimated yield). The dialdehyde was purified by preparative GC using column B at 80 °C (injection port, 100 °C; detector, 100 °C): ^1H NMR δ 1.67 (s, 2 H), 9.35 (s, 2 H). The residual proton signals at 2.54 ppm were not significantly above base-line noise.

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***trans*-1,2-Dideuteriocyclopropane (1-d_2).** Dialdehyde **11**-d_2 (0.272 g, 2.7 mmol, GC pure) was dissolved in 131 mL of 1,2-dichloropropane. The reagent $Rh(PPh_3)_3Cl$ (7.55 g, 8.2 mmol; Strem Chemical Co.) was added, and the reaction mixture was heated in a 65 °C oil bath and stirred for 20 min. The mixture was then allowed to stand without stirring for 5 days, while the temperature was maintained at 65 °C.

The reaction flask was a three-necked 250-mL flask (14/20 joints), fitted with a vacuum stopcock, connected to helium in one neck, a ground glass stopper in another neck, and a reflux condenser in the third. The top of the condenser was connected via a ground glass joint to an Ace-Thred threaded glass connecter with a FETFE O-ring (Ace glass, 5027-05, for 6–7-mm o.d. tubing) to which a Pyrex coil fitted with two Teflon brand vacuum stopcocks was attached. The coil was cooled in liquid nitrogen. At various intervals during the 5 days of reaction, the reaction flask was swept with a stream of helium while the coil was cooled in liquid N_2. Once each day during the 5-day reaction period, the coil was evacuated (with the stopcock to the reaction vessel closed) while still immersed in liquid nitrogen. The reaction vessel was left under a slight vacuum by quickly opening and closing the collection coil stopcock leading to the reaction vessel (with the coil still immersed in liquid nitrogen and with the stopcock to the vacuum closed).

At the end of the fifth day, a stream of helium flushed the reaction flask headspace into the collection coil. The helium inlet stopcock was then replaced with a sintered glass degassing tube connected to a thermometer adapter (Kontes K-179800-2114) that was immersed in the reaction mixture, and helium was bubbled through the solution with stirring. This helium flow removed all propylene (retention time 1.09 min) and cyclopropane (1.11 min), according to capillary GC analysis using the cross-linked dimethyl silicone column (injection port temperature, 160 °C; oven temperature, 30 °C; detector temperature, 300 °C; 1 μL of reaction mixture injected). The cyclopropane product was isolated by preparative GC on column A at room temperature using the injection loop assembly described below. This procedure afforded 29 mg (33% yield) of GC-pure racemic **1**-d_2, determined using a known-volume vacuum manifold and a MKS Instruments 1000-Torr capacitance monometer. The labeled cyclopropane was degassed and vacuum transferred to the known volume manifold, and the pressure of the sample was determined after allowing the sample to warm to room temperature. The sample was estimated to be 94.5% trans by TDL spectroscopy (Table I):[10] IR 3090, 3073, 3058, 3046, 3031, 2273, 2268, 1063, 1057, 1044, 1038, 1028, 862, 856, 852 cm^{-1}; mass spectrum *m/e* 45 (4.0), 44 (100), 43 (99.1), 42 (53.7), 41 (43.0), 40 (57.8), 39 (28.3). For cyclopropane-d_0 (Matheson, estimated by GC analysis to be 99.8% cyclopropane and 0.2% propene): ^1H NMR δ 0.23 (s, 6 H); mass spectrum *m/e* 43 (3.3), 42 (93.7), 41 (100), 40 (33.7), 39 (83.2), 38 (20.3), 37 (15.1). The sample of **1**-d_2 and other cyclopropanes were stored in Pyrex coils equipped with two vacuum stopcocks.

Preparative GC Isolation of Cyclopropane and of Isotopically Labeled Cyclopropanes. Small amounts (<50 mg) of propylene and cyclopropane were cleanly separated by preparative GC on column A. At a column temperature of 30 °C, a thermal conductivity detector temperature of 100 °C, and a flow rate of approximately 50 mL/min, propylene eluted at 3.0 min and cyclopropane at 4.5 min. Preparative GC separation and purification of these hydrocarbons was readily accomplished by using a modified Varian Aerograph A90-P3 instrument fitted with an eight-port injection valve assembly, based on a valve (internal bore of the valve assembly = 0.08 in.) purchased from Hach/Carle, connected with $^1/_8$-in. o.d. copper tubing (Figure 3).

The sample loop was filled with the valve in the backflush position, stopcocks A and C open, and stopcock B closed. A labeled cyclopropane contaminated with solvent and propene was degassed and vacuum transferred to the sample loop (a 7-in. length of $^1/_4$-in. i.d. aluminum tube bent in the shape of the letter U) which was immersed in a liquid nitrogen bath. If there was a significant amount of solvent present in the sample, then only a portion of the sample was transferred to the loop. Stopcock C was then closed, and untransferred sample was condensed back into the sample coil via a liquid nitrogen bath. The loop was then allowed to warm to room temperature and heated with a heat gun. The valve was then placed in the normal position and stopcock C was quickly opened. The labeled cyclopropanes were collected in a collection coil fitted with two vacuum stopcocks immersed in liquid nitrogen.

Prior to a collection procedure, a collection coil was evacuated, flushed with helium, immersed in liquid nitrogen, and further flushed with helium, leaving the coil under a slight positive pressure of helium. The outlet of the coil was attached to a calcium sulfate drying tube while a sample was collected. This procedure excluded carbon dioxide and a significant amount of water vapor from entering the coil during the actual collection. After the sample was collected, it was degassed and then vacuum transferred through 3A sieves. This procedure removed residual water vapor as evidenced by gas-phase FTIR spectroscopy.

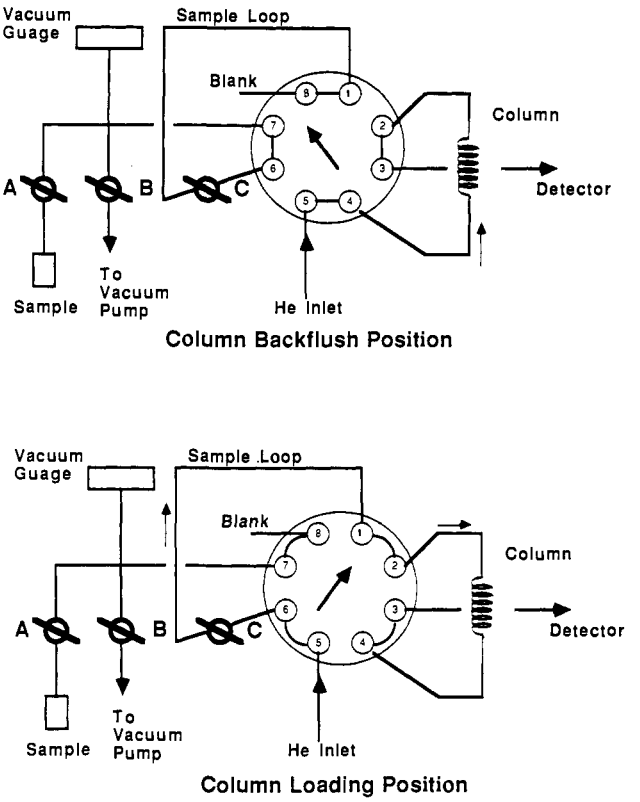

Figure 3. Preparative GC injection loop assembly.

(−)-(*R,R*)-Cyclopropane-*trans*-1,2-dicarboxaldehyde-*1,2*-d_2 ((*R,R*)-11-d_2). Diester (*R,R*)-**2**-d_2 (1.8 g, 11 mmol) was dissolved in 135 mL of ether, and the solution was cooled to −100 °C (internal temperature). Diisobutylaluminum hydride (DIBAL, Ventron, 20% in hexane) was added via syringe pump at a rate of 40 mL/h an internal reaction temperature of −100 °C was maintained. After 24 mL of DIBAL had been added, a small aliquot of the reaction mixture was worked up and analyzed by GC for underreduction products. Only the dialdehyde was detected. Methanol (24 mL) was then added to the reaction mixture dropwise at such a rate that the temperature never rose above −96 °C. After the addition, the cold bath was removed and the clear solution was allowed to warm to room temperature and was stirred for about 1 h until a white globular precipitate formed. The precipitate was filtered and washed extensively with 250 mL of ether. Concentration of the ethereal solution by spinning-band distillation afforded 6 g of a pale yellow oil. Analysis by GC indicated 0.87 g of (*R,R*)-**11**-d_2 (78% yield) present. The dialdehyde was purified by GC for polarimetry and had $[\alpha]_D$ −424° (*c* 0.37, $CDCl_3$): ^1H NMR δ 1.67 (s, 2 H), 2.54 (m, 0.05 H), 9.35 (s, 2 H).

(+)-(*S,S*)-Cyclopropane-*trans*-1,2-dicarboxaldehyde-*1,2*-d_2 ((*S,S*)-11-d_2). According to the procedure above, diester (*S,S*-**2**-d_2 gave dialdehyde (*S,S*)-**11**-d_2, which had $[\alpha]_D$ +423° (*c* 0.13, $CDCl_3$): ^1H NMR δ 1.67 (s, 2 H), 9.35 (s, 2 H). The residual protons at 2.54 ppm were not significantly above base-line noise.

(*S,S*)-Cyclopropane-*1,2*-d_2 ((*S,S*)-1-d_2). According to the procedure used in the preparation of *rac*-**1**-d_2, GC pure dialdehyde (*R,R*)-**11**-d_2 (0.287 g, 2.9 mmol) gave 34 mg (27% yield) of GC pure (*S,S*)-**1**-d_2: mass spectrum *m/e* 45 (4.4), 44 (100), 43 (93.4), 42 (56.5), 41 (51.2), 40 (60.2), 39 (32.4); IR 3090, 3073, 3058, 3046, 3031, 2273, 2268, 1063, 1057, 1044, 1038, 1028, 862, 856, 852 cm^{-1}.

(*R,R*)-Cyclopropane-*1,2*-d_2 ((*R,R*)-1-d_2). According to a modification of the above procedure, dialdehyde (*S,S*)-**11**-d_2 (0.14 g, 1.4 mmol) gave 26 mg (42%) of GC pure (*R,R*)-**1**-d_2. Only two differences distinguished this from the previously employed procedure: (1) the $Rh(PPh_3)_3Cl$ reagent was first placed in the reaction flask and the flask was evaculated and purged with helium in an effort to exclude oxygen and (2) the solvent was vacuum distilled immediately prior to use. Repetitions of this reaction employing these precautions gave similar yields. (*R,R*)-**1**-d_2: mass spectrum *m/e* 45 (3.5), 44 (100), 43 (96.2), 42 (51.2), 41 (43.2), 40 (58.4), 39 (28.3); IR 3090, 3073, 3058, 3046, 3031, 2273, 2268, 1063, 1057, 1044, 1038, 1028, 862, 856, 852 cm^{-1}.

Cyclopropane-*trans*-1,2-dicarboxaldehyde-*3*-^{13}C-*1,2,3*-d_3 (*rac*-11-$^{13}C,d_3$). To the diester *rac*-**2**-$^{13}C,d_3$ (1.00 g, 6.2 mmol) in 75 mL of ether at −100 °C (internal temperature) was added dropwise with stirring at a rate of 30 mL/h via syringe pump diisobutylaluminum hydride (DI-

BAL, Aldrich, 14 mL of a 1 M solution in hexane). A small aliquot of the reaction mixture was quenched with MeOH and analyzed by GC to check for incomplete reduction products. After the addition, 14 mL of HPLC grade MeOH was added at such a rate that the reaction temperature never rose above -96 °C. The mixture was then allowed to warm to room temperature. The resulting white globular solid was filtered off and rigorously washed with 300 mL of ether. The ethereal solution was concentrated, and two layers formed. After being allowed to stand refrigerated at 4 °C for 5 days, the layers coalesced, resulting in an oil that was 70% enriched in the dialdehyde *rac*-**11**-$^{13}C,d_3$ (GC estimate: 0.53 g, 84% yield): ^{1}H NMR δ 1.37 (s, 0.5 H), 1.93 (s, 0.5 H), 2.53 (residual m, 0.05 H), 9.35 (s, 2 H); ^{13}C NMR δ 14.03 (t).

Cyclopropane-*1*-^{13}C-*trans*-*2,3*-d_2 (*rac*-1-$^{13}C,d_3$). The reagent Rh(PPh$_3$)$_3$Cl (8.09 g), freshly vacuum-distilled 1,2-dichloropropane (50 mL), and the crude dialdehyde reaction product described immediately above (*rac*-**11**-$^{13}C,d_3$, 0.29 g, 2.8 mmol) were allowed to react according to the procedure described above. The cyclopropane product *rac*-**1**-$^{13}C,d_3$ (50 mg, 38% yield) was isolated in pure form by preparative GC: mass spectrum *m/e* 47 (3.3), 46 (M, 100), 45 (80.4), 44 (58.2), 43 (34.4), 42 (55.5), 41 (45.9); IR 3090, 3061, 3045, 2272, 2155, 1075, 825, 750 cm^{-1}.

(+)-(*S,S*)-Cyclopropane-*trans*-1,2-dicarboxaldehyde-*3*-^{13}C-*1,2,3*-d_3 ((2*S*,3*S*)-11-$^{13}C,d_3$). According to the procedure for the reduction of *rac*-**2**-$^{13}C,d_3$, (2*S*,3*S*)-**2**-$^{13}C,d_3$ (0.98 g, 6.0 mmol) gave (2*S*,3*S*)-**11**-$^{13}C,d_3$ (0.49 g, 80% crude yield): ^{1}H NMR δ 1.37 (s, 0.5 H), 1.93 (s, 0.5 H), 2.57 (residual d, 0.08 H), 9.35 (s, 1 H); ^{13}C NMR δ 14.01 (t).

(-)-(*R,R*)-Cyclopropane-*trans*-1,2-dicarboxaldehyde-*3*-^{13}C-*1,2,3*-d_3 ((2*R*,3*R*)-11-$^{13}C,d_3$). According to the procedure for the reduction of *rac*-**2**-$^{13}C,d_3$, (2*R*,3*R*)-**2**-$^{13}C,d_3$ (0.5 g, 3.1 mmol) gave (2*R*,3*R*)-**11**-$^{13}C,d_3$ (0.23 g, 74% crude yield): ^{1}H NMR δ 1.37 (s, 0.5 H), 1.93 (s, 0.5 H), 2.57 (residual d, 0.08 H), 9.35 (s, 1 H); ^{13}C NMR δ 14.01 (t).

(2*S*,3*S*)-Cyclopropane-*1*-^{13}C,*d*-*trans*-*2,3*-d_2 ((2*S*,3*S*)-1-$^{13}C,d_3$). According to the procedure for the production of *rac*-**1**-$^{13}C,d_3$, (2*S*,3*S*)-**11**-$^{13}C,d_3$ (0.144 g, 1.4 mmol) produced 23 mg (35% yield) of GC-pure (2*S*,3*S*)-**1**-$^{13}C,d_3$: mass spectrum *m/e* 47 (3.2), 46 (M, 100), 45 (80.8), 44 (57.7), 43 (32.6), 42 (52.1), 41 (43.9); IR 3090, 3061, 3045, 2272, 2155, 1075, 825, 750 cm^{-1}.

(2*R*,3*R*)-Cyclopropane-*1*-^{13}C,*d*-*trans*-*2,3*-d_2 ((2*R*,3*R*)-1-$^{13}C,d_3$). According to the procedure for the production of *rac*-**1**-$^{13}C,d_3$, (2*R*,3*R*)-**11**-$^{13}C,d_3$ (0.12 g, 1.2 mmol) gave 13 mg (24% yield) of GC-pure (2*R*,3*R*)-**1**-$^{13}C,d_3$: mass spectrum *m/e* 47 (2.9), 46 (M, 100), 45 (81.8), 44 (58.5), 43 (36.6), 42 (57.4), 41 (50.9); IR 3090, 3061, 3045, 2272, 2155, 1075, 825, 750 cm^{-1}.

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Kinetics of Thermal Geometrical Isomerizations of Three Sets of Isotopically Labeled Cyclopropanes Followed by Tunable Diode Laser Spectroscopy

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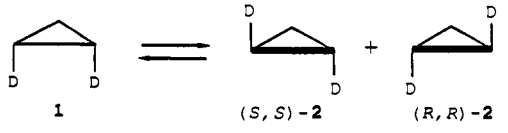
Abstract: First-order rate constants for the approach to equilibrium through thermal geometrical isomerizations have been secured using tunable diode laser spectroscopy for three sets of isotopically labeled cyclopropanes. For the cis and trans 1,2-d_2 cyclopropanes at 422.5 °C, $k_t(d_2) = (13.6 \pm 0.26) \times 10^{-5}$ s^{-1}. For the syn and anti isomers of cyclopropane-*1,2,3*-d_3 at 422.5 °C, $k_t(d_3) = (15.5 \pm 0.47) \times 10^{-5}$ s^{-1}. For the isomers of cyclopropane-*1*-^{13}C-*1,2,3*-d_3 at 407.0 °C, $k_t(^{13}C,d_3) = (4.63 \pm 0.20) \times 10^{-5}$ s^{-1}. These results are compared with independent determinations of two of these rate constants based on FTIR spectroscopy, and the relative advantages and limitations of the two spectroscopic techniques are compared.

The thermal interconversion of the cis and trans isomers of cyclopropane-*1,2*-d_2 (**1** and **2**) discovered by Rabinovitch, Schlag,



1 (*S, S*)-**2** (*R, R*)-**2**

and Wiberg in 1958[1] involves a net epimerization of one deuteriomethylene unit. This prototypical instance of a thermal reaction which may occur by way of trimethylene diradicals has been subjected to extensive theoretical scrutiny[2] but to relatively little experimental study.

Since 1958, thermal epimerizations exhibited by numerous more heavily substituted cyclopropanes have been followed at various levels of completeness and rigor.[3] Yet experimental studies of isotopically labeled but otherwise unsubstituted cyclopropanes, systems of most direct relevance to theoretical efforts to understand this fundamental type of thermal reaction, have been few, indeed.

Thermal interconversions of **1** and racemic **2**, each prepared from cyclopropane through stereoselective reductions, have been

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