Stereochemical Kinetics of the Thermal Stereomutations Interconverting Achiral Isomers of 1-Phenyl-1,2,3-trideuteriocyclopropane

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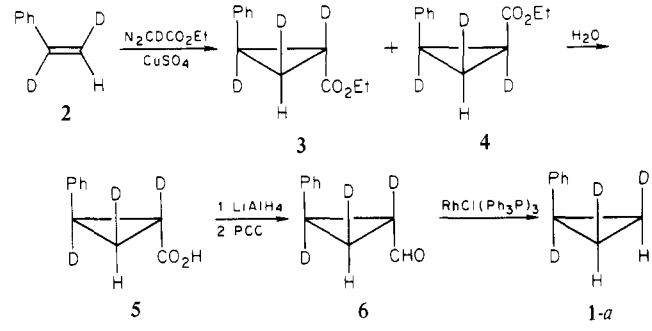
Abstract: All three achiral forms of 1-phenyl-1,2,3-trideuteriocyclopropane have been synthesized with high stereochemical integrity, and the thermal stereomutations among them have been followed at 309.3 °C in the gas phase by Raman and ^{1}H NMR spectroscopy. The combinations of rate constants for one-center and two-center epimerizations derived from this kinetic study are $(k_1 + k_{23}) = 0.36 \times 10^{-5}$ s^{-1} and $(k_2 + k_{12}) = 1.07 \times 10^{-5}$ s^{-1}. The substantial magnitude of $(k_1 + k_{23})$ is particularly noteworthy in light of prior work and generally accepted theory.

The thermal stereomutations of cyclopropanes have attracted considerable attention from theoreticians and experimentalists over the past 25 years.[1] From a theoretical perspective, the reaction has seemed both approachable through modern computation techniques and significantly relevant to an understanding of one of the simplest of diradical entities, trimethylene.[2] From the experimental side, the goal has been to measure all of the distinguishable one-center (k_i) and two-center (k_{ij}) stereomutation rate constants for representative cyclopropanes; from the pattern of observed rate constants, one may gain an experimentally based comprehension of the interconversions between cyclopropanes and trimethylenes and grounds for discriminating among alternative theoretical models for the stereomutation processes.

In the last few years, values for all of the stereomutation rate constants for several substituted cyclopropanes have been reported.[3-8] The limits of the "most substituted bond hypothesis" have been defined,[6-8] and the Smith mechanism[9] has been shown to be an implausible model for one-center epimerizations.[8]

Of most direct relevance to the present work, the complete kinetic analyses of thermal stereomutations among the eight 1-cyano-2-methyl-1,2,3-trideuteriocyclopropanes[7] and among the eight 2,3-dideuterio-2-(methoxymethyl)spiro[cyclopropane-1,1′-indenes][8] have given insights on the behavior of cyclopropane methylene units flanked by a carbon substituted with a relatively effective radical-stabilizing substituent. For both of these cyclopropane systems, k_1 is substantial, k_{23} is zero, and k_3 is comparable to or larger than k_{13}. Stereomutations in these systems, most readily interpreted as involving two distinct bond cleavages and two distinct trimethylene diradicals, may not be subdivided into component parts: some one-center epimerization at C(1) may occur through either C(1)–C(2) or C(1)–C(3) bond cleavage, but the experimentally accessible k_1 rate constant includes both. To overcome this limitation, a more symmetrical cyclopropane must be examined: a monosubstituted cyclopropane, phenylcyclopropane, has been our choice.

Scheme I



The stereomutations of three monosubstituted cyclopropanes have been studied with the aid of deuterium labeling, but no complete kinetic analysis has yet been achieved. Setzer and Rabinovitch[10] followed the interconversions of 1-methyl-2,3-dideuteriocyclopropanes and were able to secure values for the combination of rate constants $(k_1 + k_2 + k_{12} + k_{23})$ as a function of temperature. Willcott and Cargle[11] followed the cis–trans isomerization of 1-vinyl-2-deuteriocyclopropane and the stereomutations of the achiral 1-vinyl-2,3-dideuteriocyclopropanes; they found $(k_1 + k_{23}) \cong (k_2 + k_{12})$. Berson and co-workers have worked on deuterated phenylcyclopropanes; they concluded from their experiments with 1-phenyl-2-deuteriocyclopropanes that $k_{12}:k_1 > 96:4$ and $(k_2 + k_{23}) < k_{12}$, results suggesting that rotation at C(1) is strongly coupled to rotation at C(2).[12] A study of the racemization of (+)-1-phenyl-*trans*-2,3-dideuteriocyclopropane provided additional evidence on the stereomutations, but did not make possible a complete kinetic analysis.[13]

We sought an approach to the stereomutation kinetics of a monosubstituted cyclopropane that would afford a complete solution, reliable experimental values for k_1, k_2, k_{12}, and k_{23}. New synthetic routes, analytical techniques, and conceptual tactics were clearly needed.

Earlier work on deuterium-labeled monosubstituted cyclopropanes[10-13] prepared and utilized mixtures of stereoisomers and mixtures of isotopic variants of substrates. All isomers were not available in high stereochemical and labeling integrity; thus the range of kinetic analyses which could be performed, the rate constant combinations which could be deduced from observational data, and the accuracy of the parameters deduced were all restricted.

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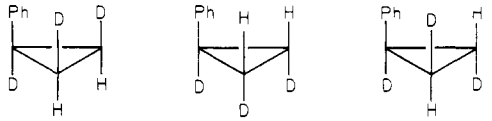
This manuscript presents one solution to these synthetic problems and reports the kinetics of stereomutations of the achiral 1-phenyl-1,2,3-trideuteriocyclopropanes as determined by both NMR and Raman spectroscopic analyses. A following paper on chiral and carbon-13 labeled 1-phenyl-1,2,3-trideuteriocyclopropanes completes the full stereochemical kinetic analysis of the stereomutations.

The spectroscopic techniques to be used for following the stereomutations among the achiral anti (**1**-*a*), syn (**1**-*s*), and trans



1-*a* **1**-*s* **1**-*t*

(**1**-*t*) isomers of 1-phenyl-1,2,3-trideuteriocyclopropane required authentic samples of each, with the highest achievable stereochemical integrity and as isotopically pure as possile.

The structural representation for **1**-*t* shown is appropriate to the (+)-isomer,[12] but throughout this paper the trans isomer of concern is the racemic form.

Results

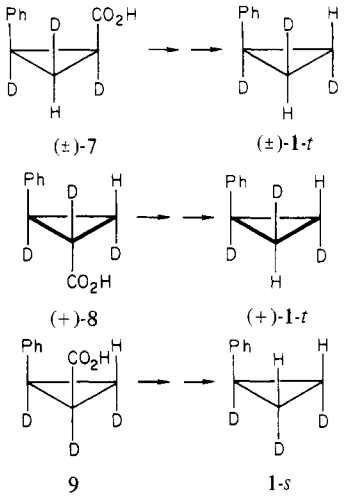
Syntheses. Preparation of **1**-*a* followed in part a synthetic sequence developed in earlier work.[6,14] *trans*-Dideuteriostyrene (98% trans-d_2 by ^{1}H NMR) was condensed with ethyl α-deuteriodiazoacetate (99% d_1) with the aid of a copper(II) catalyst (Scheme I). Saponification gave a mixture of cis and trans carboxylic acids which could be separated conveniently by fractional recrystallizations. The racemic trans acid was obtained as fine needles from water while the cis isomer was secured as colorless prisms from hexanes.

Reduction of trans acid **5** with lithium aluminum hydride, followed by oxidation using pyridinium chlorochromate,[15] gave the trans aldehyde **6**. This aldehyde was reacted with slightly more than 1 equiv of Wilkinson's catalyst,[16] chlorotris(triphenylphosphine)rhodium(I), in benzene at reflux. Under these conditions decarbonylation proved highly stereoselective,[17] giving **1**-*a* and carbonylchlorobis(triphenylphosphine)rhodium(I).

The ratio of ^{1}H NMR signal intensities for protons anti to phenyl (downfield) vs. syn to phenyl was 96:4. Most of the upfield protons turned out (see below) to be derived from small amounts of syn and trans d_3 isomers, rather than from d_2 species.

Simple variants of the route outlined in Scheme I provided the other substrates required. Although the present work required only the racemic form of **1**-*t*, a single antipode would serve equally well, and both (+)-**1**-*t* and (±)-**1**-*t* were prepared. The racemic cis acid (±)-**7** from ester **4** (Scheme I) led to (±)-**1**-*t*. From the reaction of *cis*-α,β-dideuteriostyrene (greater than 96% stereochemically pure) and menthyl α-deuteriodiazoacetate in the presence of a chiral copper(II) catalyst[18] was secured a 15:85 mixture of cis and trans esters, each about 90% optically pure. A resolution by way of quinine salts[19] gave trans acid (+)-(1*S*,2*S*,3*R*)-**8** in optically pure form,[20] and cis isomer **9** of high diastereomeric and optical purity was obtained by way of low-pressure column chromatography of a mixture of methyl esters of **8** and **9**.

The three-step procedure for stereoselective replacement of the carboxylic acid function by a hydrogen gave (+)-**1**-*t* from (+)-**8**



(±)-**7** (±)-**1**-*t*

(+)-**8** (+)-**1**-*t*

9 **1**-*s*

and **1**-*s* from **9**. The nearly racemic residue remaining after the quinine resolution of (+)-**8** gave a large sample of almost racemic **1**-*t* after the reduction, oxidation, and decarboxylation sequence. This sample was heated at 309.3 °C in the gas phase for 140 h to give an equilibrium mixture of anti:syn:trans isomers (1:1:2) to serve as a standard for spectroscopic analyses.

Gas-Phase Pyrolyses. Samples of two different isomeric 1-phenyl-1,2,3-trideuteriocyclopropanes were heated at 309.3 °C in a 300-mL quartz bulb mounted in a thermostated aluminum block.[21] The first series of runs used about 30 μL of **1**-*a* and 100 μL of dry pentane, added to ensure sufficient pressure to bring the stereomutation reactions above the Lindemann low-pressure rate-constant fall-off region.[22] To demonstrate that the reactions were conducted at a sufficiently high pressure, the second series of runs was performed with 100 μL samples of **1**-*t* and 150 μL of pentane; no changes in the stereomutation rate constants were apparent. At the end of a reaction period, the cyclopropanes were transferred from the bulb to a collection vessel on a vacuum line. After purification by preparative vapor-phase chromatography on an Apiezon L column, kinetic samples were analyzed for **1**-*a*, **1**-*s*, and **1**-*t* by two analytical methods.

Analysis by ^{1}H NMR. The ^{1}H NMR spectra of **1**-*a*, **1**-*s*, and **1**-*t* in the upfield region are extremely simple. The anti and syn isomers show singlets, while the trans isomer has the anticipated AB pattern with J = 6.26 Hz (Figure 1).[23] The spectra of the individual isomers speak for the high degree of stereochemical and isotopic labeling integrity in these compounds achieved through the syntheses employed. Without such a high degree of stereochemical control and of incorporation for all three deuterium labels, the kinetic work to be performed would have been seriously compromised.

In mixtures of all three isomers, such as in the equilibrium 1:1:2 mixture or in a pyrolysis sample derived from **1**-*a* (Figure 2), the accuracy of the analytical technique is restricted by two factors: At low conversions, when one must compare the relative intensities of absorptions having very different magnitudes and very similar chemical shifts (**1**-*a* plus downfield AB absorptions to **1**-*s* plus upfield AB lines), slight uncertainties in integral ratios convert to larger uncertainties in mol percent concentrations. Secondly, the separation of the three components in either group cannot be done with very high precision, for the three absorptions are not fully resolved at the baseline.[24] Nevertheless, the NMR analytical technique provides a very useful tool, qualitatively and quantitatively, and it makes perfectly clear that the stereomutations one wants to follow are just what one is following.

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(21) The Pyrex bulb, kinetic bath, and vacuum line used in the thermolyses have been described in detail;[7] temperature measurements were made with a Hewlett-Packard Model 2802A digital thermometer.
(22) Cf. Robinson, P. J.; Holbrook, K. A. "Unimolecular Reactions"; Wiley-Interscience: London, 1972; p 15–25.
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(24) Without ^{2}H decoupling, the required separation could not be attained.

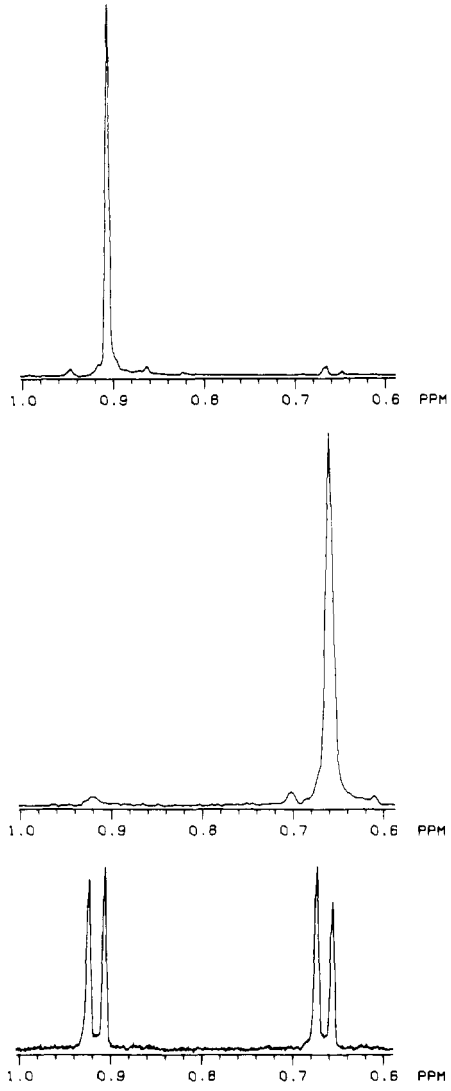

Figure 1. Upfield ^{2}H-decoupled 360 MHz ^{1}H NMR spectra for synthetic samples of anti, syn, and trans isomers of **1**.

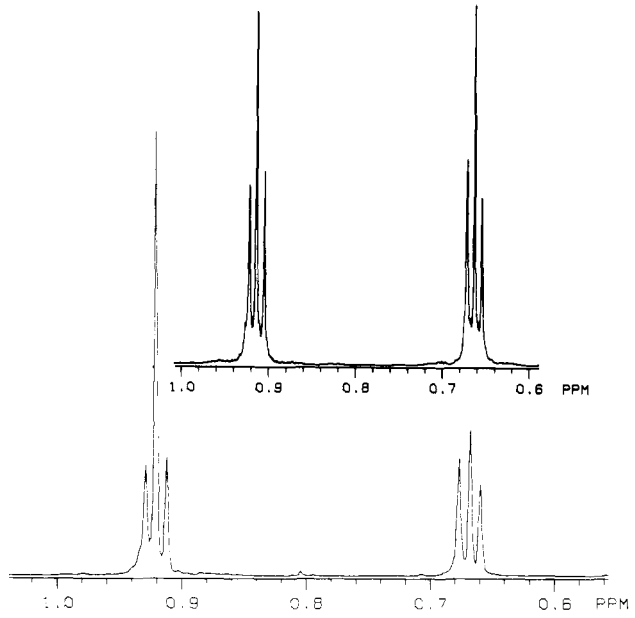

Figure 2. Upfield ^{2}H-decoupled 360 MHz ^{1}H NMR spectra for an equilibrium mixture of **1**-*a*, **1**-*s*, and **1**-*t* (above) and of a pyrolysis mixture from **1**-*a* after 900 min at 309.3 °C.

Analyses by Raman Spectroscopy.[25] Raman spectra of the anti, syn, and trans forms of 1-phenyl-1,2,3-trideuteriocyclopropane

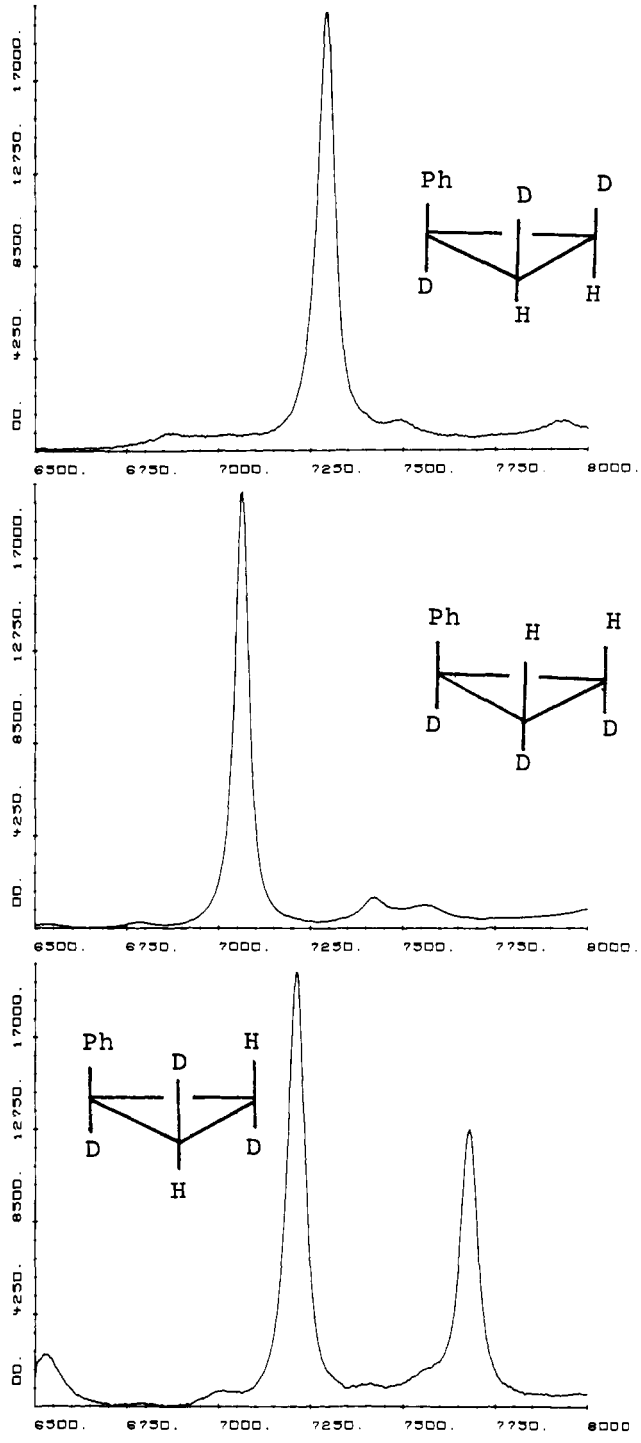

Figure 3. Raman spectra in the region 650–800 cm^{-1} for anti, syn, and trans isomers of **1**.

in the region 650–800 cm^{-1} showed marked differences; mixtures of these isomers could be analyzed then by treating observed spectra in this region as weighted linear combinations of the spectra of each distinct stereochemical form. The equilibrium 1:1:2 mixture of anti:syn:trans isomers provided the requisite scaling factors, and Raman spectra for stereochemically pure versions of the isomers could be calculated even though the synthetic materials were not perfectly defined stereochemically; computer-assisted analysis of observed spectra for starting materials treated as linear combinations of spectra of stereochemically pure isomers gave through an iterative best-fit approach the spectra

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Table I. Observed and Calculated[a] Mole Percent Concentrations of Anti, Syn, and Trans Isomers of 1-Phenyl-1,2,3-trideuteriocyclopropane

T (min)	1-a	1-s	1-t
0	94.8	1.2	4.1
150	74.1 (76.8)	5.2 (4.4)	20.7 (18.7)
300	66.6 (63.6)	6.8 (7.6)	26.6 (28.7)
500	50.5 (51.2)	12.4 (11.5)	37.1 (37.3)
0	2.2	1.3	96.4
200	11.7 (11.4)	11.0 (10.8)	77.2 (77.8)
200	12.5 (11.4)	11.7 (10.8)	75.8 (77.8)
400	17.0 (16.9)	16.3 (16.5)	66.6 (66.6)
800	21.6 (22.1)	21.0 (21.9)	57.4 (55.9)

[a] According to the parameters $(k_1 + k_{23}) = 0.36 \times 10^{-5}$ s^{-1}, $(k_2 + k_{12}) = 1.07 \times 10^{-5}$ s^{-1}, and the kinetic treatment of Scheme II. Calculated values are in parentheses.

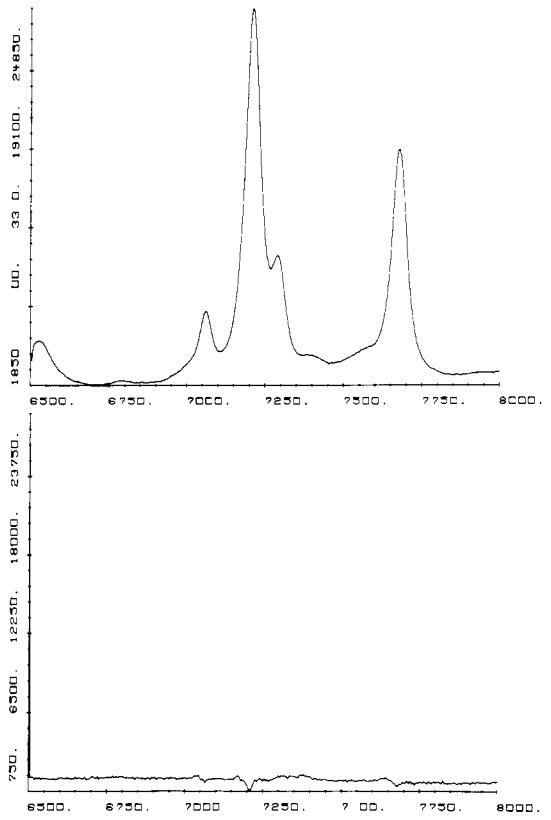


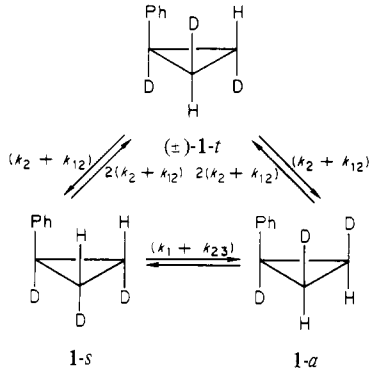
Figure 4. Raman spectrum for isomers of **1** after pyrolysis of **1-t** for 200 min at 309.3 °C (above); the difference between the observed spectrum and the spectrum calculated for a 12.3:11.7:75.8 mixture of **1-a**, **1-s**, and **1-t**.

of Figure 3 and the time = 0 concentration data of Table I.

A Raman spectrum for the isomers of **1** obtained after pyrolysis of **1-t** at 309.3 °C for 200 min is shown in Figure 4, together with the difference spectrum, i.e., the difference between the spectrum calculated for a 12.5:11.7:75.8 mixture of **1-a**, **1-s**, and **1-t** and the experimentally observed spectrum. The relatively featureless difference spectrum implies that the purified kinetic samples do not contain substantial structural or isotopic contaminants; the entire spectrum observed may be reproduced as a linear combination of the spectra from Figure 3. The reproducibility of the Raman method is demonstrated by the two 200-min kinetic points. Two separate samples of **1-t** were heated for 200 min each at 309.3 °C. As nearly as possible, both were treated identically and analyzed individually by Raman spectroscopy with the results shown in Table I. The experimentally measured concentrations for the two 200-min kinetic points were in fair agreement, with 1.4% the maximum discrepancy.

Data Analysis. The observed concentrations as a function of time for the two kinetic runs, as determined by Raman spectroscopy, are summarized in Table I. Following the kinetics of

Scheme II



stereomutations by NMR or by Raman spectroscopy gave very similar results. For the 500-min point starting from **1-a**, for instance, the NMR and Raman spectroscopic analyses for anti:syn:trans isomers were 50.6:10.8:38.6 and 50.5:12.4:37.1 mol percent; the values calculated from the rate constants eventually derived were 51.2:11.5:37.3. Such close agreement from two distinct analytical methods, each subject to different sources of systematic and random errors, lends enhanced reliability to the kinetic study.

The kinetic scheme appropriate to stereomutations of the achiral isomers **1-a**, **1-s**, and **1-t** is quite simple (Scheme II). Initial estimates of the two kinetic parameters were obtained from linear plots, for $\ln(|2[\mathbf{1}\text{-}t] - 1|) = -4(k_2 + k_{12})t$ starting from either **1-a** or **1-t**, and $\ln([\mathbf{1}\text{-}a] - [\mathbf{1}\text{-}s]) = -2(k_1 + k_2 + k_{12} + k_{23})t$ for points derived from pyrolyses of **1-a**, when concentrations in these equations are expressed as mol fractions. The best values for $(k_1 + k_{23})$ and $(k_2 + k_{12})$ were obtained from the initial estimates obtained in this fashion with the aid of a computer program[26] based on the exact integrated solutions for the differential equations descriptive of Scheme II and a modified Simplex optimization strategy:[27] $(k_1 + k_{23}) = 0.36 \times 10^{-5}$ s^{-1} and $(k_2 + k_{12}) = 1.07 \times 10^{-5}$ s^{-1} at 309.3 °C. These best values, as judged by a minimum in χ^2,[27] do not represent a false minimum or one of several equal minima; they were obtained whatever the initial values given to the Simplex program. When $(k_1 + k_{23})$ was restricted to 0, the best agreement of experimental and calculated concentrations over time gave a three-fold increase in χ^2.

Conclusions and Unresolved Questions

This study has provided syntheses of the isomeric 1-phenyl-1,2,3-trideuteriocyclopropanes having sufficiently high stereochemical and isotopic labeling specificity to permit quantitative kinetic investigations of the stereomutations they exhibit. Analysis of kinetic points of NMR and Raman spectroscopy gave concentration data in close agreement. The rate constants observed at 309.3 °C were $(k_1 + k_{23}) = 0.36 \times 10^{-5}$ s^{-1} and $(k_2 + k_{12}) = 1.07 \times 10^{-5}$ s^{-1}.

A following paper deals with experimental dissections of these two sums of two rate constants, and a detailed consideration of the mechanistic import of individual rate constants must be postponed now. The present results do heighten interest in the final resolution of this kinetic problem insofar as $(k_1 + k_{23})$ might have been expected to be negligibly small. Earlier kinetic work on chiral isomers of 1-phenyl-2-deuteriocyclopropanes[12] and chiral 1-phenyl-*trans*-2,3-dideuteriocyclopropanes[13] led to the conclusion that $k_1 = 0$ at 309.5 °C and there are substantial experimental precedents and thermochemical reasons to justify the anticipation that $k_{23} = 0$. Yet $(k_1 + k_{23})$ is not negligibly small: it is a substantial fraction of $(k_2 + k_{12})$.

Experimental Section

Infrared (IR) spectra were obtained as $CHCl_3$ solutions on a Sargent-Welch 3-200 infrared spectrophotometer. Standard ^{1}H NMR

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(27) Deming, S. N.; Morgan, S. L. *Anal. Chem.* **1973**, *45*, 278A–283A. Cooper, J. W. "Introduction to Pascal for Scientists"; Wiley-Interscience: New York, 1981; Chapter 18.

spectra were recorded for $CDCl_3$ solutions on a Varian XL-100 instrument; chemical shifts reported are relative to Me_4Si at 0.0 ppm. The ^2H-decoupled ^1H NMR spectra were determined on a Nicolet NT-360 instrument operating in the Fourier transform mode. The Nicolet NTCCAP deconvolution program was utilized to obtain NMR integral intensities from which the relative amounts of **1-*a***, **1-*s***, and **1-*t*** in each kinetic point were determined.[28] Elemental analyses were performed by Dr. Richard Wielesek at the University of Oregon. Melting points were taken in sealed capillary tubes and are uncorrected. Vapor-phase chromatography (VPC) was performed on a Varian Aerograph A90-P3. The gas chromatography columns used were 6.4-mm i.d. aluminum columns having the following lengths and packings: A, 2 m with 20% Carbowax 20 M on 60/80 mesh Chromasorb W-AWDMCS; B, 1.5 m with 30% Apiezon L on 60/80 mesh Chromasorb W-AWDMCS; C, 1.2 m with 10% Carbowax 20 M on 60/80 mesh Chromasorb W-AWDMCS; D, 2.5 m with 30% Apiezon L on 60/80 mesh Chromasorb W-AWDMCS; E, 2.5 m with 14% Apiezon L on 60/80 mesh Chromasorb G. Reactions were conducted under a nitrogen atmospehre in oven-dried or flame-dried glassware and were magnetically stirred. The benzene used for decarbonylations was purified by bubbling nitrogen through reagent grade benzene for 15 min followed by distillation, under nitrogen, from CaH_2 or sodium. Tetrahydrofuran (THF) was dried over sodium and benzophenone, and diethyl ether was dried over lithium aluminum hydride; each was distilled under a positive nitrogen pressure directly into reaction vessels as required. Dichloromethane was dried over activated 3-A molecular sieves. Organic solutions of crude products were generally dried over magnesium sulfate, filtered, and concentrated by rotary evaporation.

Raman spectra were obtained at 22 °C by using a Spex 1301 double monochromator operating with a spectral bandpass of <2 cm^{-1} and a 90° collection geometry. The light source was a Spectra Physics Model 165 Argon ion laser operating at the 514.5-nm line with an output power of approximately 100 mW. Both the monochromator stepping motor and the photon counting electronics were interfaced to a Varian 620i computer. In order to increase the signal to noise ratio of each spectrum, approximately 10–12 scans were gathered and then stored and summed by computer. All spectra were taken of neat samples in 1.5-mm i.d. glass capillaries with a monochromator step size of 0.5 cm^{-1}. Peticolas[29] has previously described the experimental apparatus in more detail.

***trans*-2-Phenylcyclopropanemethanol.** Lithium aluminum hydride (1.06 g, 27.9 mmol) was suspended in THF (90 mL) and a solution of the trans acid **5**-d_0 (3.00 g, 18.5 mmol, Aldrich) in THF (15 mL) was dripped in over 5 min. The reaction mixture was heated at reflux for 18 h, then cooled in ice and subjected to a standard[32] workup. Kugelrohr distillation at 70–90 °C and 0.3–0.5 torr gave 2.62 g (96%) of the alcohol as a colorless liquid: IR 3620, 3450, 3070, 3030, 3010, 2920, 2880, 1600, 1505 cm^{-1}; NMR δ 7.0–7.4 (m, 5 H), 3.60 (d, J = 6, 2 H), 1.70–1.90 (m, 1 H), 1.72 (s, 1 H), 1.20–1.60 (m, 1 H), 0.80–1.02 (m, 2 H).

***trans*-2-Phenylcyclopropanecarboxaldehyde (6-d_0).** Pyridinium chlorochromate (0.70 g, 3.3 mmol, Aldrich) was suspended in CH_2Cl_2 (5 mL) at room temperature. The alcohol prepared immediately above (0.30 g, 2.0 mmol) dissolved in CH_2Cl_2 (3 mL) was quickly added. The reaction mixture was stirred for 1.5 h, ether (10 mL) was added, and the dark solution was filtered through a short column of Florisil; additional ether was used to wash the pot residue and the column. After concentration by rotary evaporation to remove ether, 0.25 g (84%) of aldehyde **6**-d_0 was collected by flash distillation at 0.05 torr as an extremely oxygen-sensitive, colorless oil, >95% pure by VPC on column B at 190 °C. An analytical sample had: IR 3060, 3030, 2820, 2720, 1700, 1605 cm^{-1}; NMR δ 9.31 (d, J = 4, 1 H), 7.02–7.40 (m, 5 H), 2.50–2.70 (m, 1 H), 2.04–2.26 (m, 1 H), 1.38–1.80 (c, 2 H). Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.97; H, 6.99.

***trans*-α,β-Dideuteriostyrene**[6,7] prepared from phenylacetlene-d_1 and triphenyltin deuteride was judged to be 98% stereochemically pure by NMR analysis; signals at δ 5.66–5.72 (m) and 5.16 (t, J = 2 Hz) had relative intensities of 2:98. No signal from residual proton at C(α) was seen.

Ethyl α-deuteriodiazoacetate was prepared with better than 99% deuterium incorporation through phase transfer catalyst promoted exchanges with D_2O.[30]

Condensation of *trans*-α,β-Dideuteriostyrene with Ethyl α-Deuteriodiazoacetate.[31] The labeled styrene (9.76 g), anhydrous copper sulfate (1.8 g, Mallinckrodt), and 35 mL of cyclohexane were heated to about 80 °C. Neat ethyl α-deuteriodiazoacetate (8.4 mL, 9.2 g) in a 10-mL gas-tight syringe was added at 0.4 mL/h for 3 h, then at 0.6 mL/h for 12 h with the aid of a syringe pump (Sage Instruments, Model 352). The reaction mixture was cooled to 25 °C; the solid material was removed by suction filtration through Celite and washed thoroughly with ether (3 × 20 mL). Rotary evaporation and vacuum distillation of the residue at 0.02 torr (50–60 °C) gave 6.9 g of colorless liquid: analysis by VPC on column A at 180 °C showed that the distillate contained 4.1 g of esters **3** and **4** in a 63:37 ratio. A sample of trans ester **3** purified by VPC had NMR δ 7.00–7.36 (m, 5 H), 4.18 (q, J = 7, 2 H), 1.58 (s, 1 H), 1.30 (t, J = 7, 3 H); cis ester **4** had NMR δ 7.24 (s, 5 H), 3.85 (q, J = 7, 2 H), 1.26 (s, 1 H), 0.94 (t, J = 7, 3 H).

2-Phenyl-1,2,*t*-3-trideuteriocyclopropanecarboxylic Acids 5 and 7. A 3:1 mixture of esters **3** and **4** (2.95 g, 15.3 mmol) was combined with aqueous 10% NaOH (25 mL) and ethanol (10 mL), and the solution was heated at reflux for 14 h. The reaction mixture was cooled in an ice bath and acidified to pH 3 with concentrated HCl; the acids **5** and **7** were collected and dried (2.18 g). Another 0.45 g of the acids was recovered by reducing the volume of the filtrate by rotary evaporation by two-thirds and extracting the concentrate with CH_2Cl_2 (3 × 10 mL). Repeated recrystallizations from water gave a 0.426-g sample of pure **5**, mp 90–91 °C (lit.[31] mp 93 °C), which had NMR δ 10.4–11.4 (br s, 1 H), 7.00–7.40 (m, 5 H), 1.64 (br s, 1 H), 1.36 (br s, 3.7% of δ 1.64). As an independent check to confirm the total absence of **7** in the sample, a small portion was esterified with CH_2N_2. Only one methyl peak (δ 3.73) was observed in the NMR; the CH_3O singlet of **7** comes at δ 3.43.

The residue from the mother liquors remaining from the recrystallization of **5** was taken up in hot hexane and allowed to cool. Another recrystallization gave 0.70 g of pure acid (±)-**7** as colorless prisms having mp 104–106 °C (lit.[31] mp 106–107 °C): NMR δ 10.4–11.2 (br s, 1 H), 7.24 (s, 5 H), 1.62 (br s, 4.9% of δ 1.32), 1.32 (br s, 1 H).

***t*-2-Phenyl-1,2,*t*-3-trideuteriocyclopropanemethanol.** Following the procedure detailed above, pure **5** (0.54 g, 3.3 mmol) was reduced with $LiAlH_4$ (0.32 g, 8.4 mmol) to give 0.49 g (97%) of product alcohol as a colorless oil, >95% pure as judged by VPC on column C at 190 °C: IR 3610, 3440, 3060, 3030, 3010, 2930, 2880, 1605, 1500 cm^{-1}; NMR δ 7.0–7.4 (c, 5 H), 3.59 (br s, 2 H), 1.84 (br s, 1 H), 0.88 (br s, 1 H).

***t*-2-Phenyl-1,2,*t*-3-trideuteriocyclopropanecarboxaldehyde (6).** The trideuterio alcohol prepared immediately above (0.461, 3.0 mmol) was oxidized with pyridinium chlorochromate (1.13 g, 5.2 mmol) to give 0.416 g (91%) of aldehyde as a colorless liquid: NMR δ 9.32 (s, 1 H), 7.0–7.4 (m, 5 H), 1.68 and 1.45 (both br s, relative integration 96.6:3.4).

1-Phenyl-*r*-1,*t*-2,*t*-3-trideuteriocyclopropane (1-*a*). The aldehyde prepared immediately above (0.416 g, 2.79 mmol) was dissolved in benzene (30 mL) at room temperature. Fine, dark red crystals of chlorotris(triphenylphsophine)rhodium(I) (2.60 g, 2.89 mmol, Strem Chemicals) were added directly to the stirred solution and the reaction mixture was heated at reflux for 17 h. The orange reaction mixture and the yellow precipitate which had separated were cooled to room temperature and diluted with pentane (60 mL). The solids were removed by suction filtration and the filtrate was concentrated to about 5 mL by fractional distillation at atmospheric pressure. The residue was taken up in pentane and passed through a short column of neutral Al_2O_3; the column was washed thoroughly with more pentane. Once again the pentane was distilled. Purification of **1-*a*** was accomplished through VPC on column D at 170 °C to give 0.242 g (72%) of a colorless liquid. A minor hydrocarbon product from the decarbonylation, about 5% of α-methylstyrene-d_3, was identified through VPC and NMR spectroscopic comparisons with an authentic sample of α-methylstyrene.[33] Phenylcyclopropane **1-*a*** had IR ($CHCl_3$) 3090, 3060, 3030, 3010, 2360, 2330, 2270, 2240, 1605, 1500, 1450 cm^{-1} and NMR δ 7.0–7.4 (m, 5 H), 0.94 (skewed t, J = 2 Hz, 2 H), 0.71 (br s, 4.3% of δ 0.94).

***c*-2-Phenyl-1,2,*c*-3-trideuteriocyclopropanemethanol.** Acid (±)-**7** (0.684 g, 3.92 mmol) was reduced with lithium aluminum hydride (0.64 g, 16.9 mmol) in THF to give 0.550 g (92%) of product alcohol as a colorless oil after Kugelrohr distillation: NMR δ 7.26 (s, 5 H), 3.43 (d, J = 12 Hz, 1 H), 3.23 (d, J = 12 Hz, 1 H), 1.40 (br s, 1 H), 0.98 (br s, 1 H).

(±)-*c*-2-Phenyl-1,2,*c*-3-trideuteriocyclopropanecarboxaldehyde. The alcohol prepared above (0.515 g, 3.40 mmol) was oxidized with pyridinium chlorochromate (1.33 g, 6.2 mmol) in CH_2Cl_2 to afford 0.508 g (100%) of aldehyde as a colorless oil after solvent removal: NMR δ 8.68

(28) For a detailed treatment of peak height error in Fourier transform spectroscopy see Comisarow, M. B.; Melka, J. D. *Anal. Chem.* **1979**, *51*, 2198–2203.

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(s, 1 H), 7.30 (s, 5 H), 1.54 (br s, 1 H). Less than 0.5% of trans isomer was present, for its corresponding aldehyde singlet at δ 9.30 was barely detectable. Stereochemical purity was established as being greater than 95% by integration of the ring proton at δ 1.54 vs. a small singlet at δ 1.82.

1-Phenyl-*r*-1,*c*-2,*t*-3-trideuteriocyclopropane (1-*t*). The aldehyde prepared immediately above (0.51 g, 3.4 mmol) was decarbonylated with Wilkinson's catalyst (3.30 g, 3.6 mmol) in benzene (30 mL) under the conditions detailed above and was subjected to the distillation, chromatography, distillation workup previously described. The cyclopropane/styrene mixture was then separated from Ph_3P by vacuum transfer (0.1 torr) into a liquid nitrogen cooled receiving flask while the stillpot was kept below 25 °C. This additional step was found to greatly simplify the VPC purification and was made a part of the standard workup procedure in all subsequent decarbonylations. Purification by VPC on column E at 155 °C gave 0.229 g (55%) of (±)-1-*t*: NMR (100 MHz) δ 7.00–7.40 (m, 5 H), 0.90 (br d, J = 7 Hz, 1 H), 0.64 (br d, J = 7 Hz, 1 H).

***(dl)*-Menthyl 2-Phenyltrideuteriocyclopropanecarboxylates from *cis*-α,β-Dideuteriostyrene.** *cis*-α,β-Dideuteriostyrene[6,7] (4.3 g, 40.5 mmol, >96% cis by NMR analysis) and the chiral copper(II) catalyst described previously[7,18] (0.3 g, $[\alpha]_{546}$ +400° (*c* 0.12, EtOH) [lit.[7] $[\alpha]_{546}$ +465° (*c* 2.8, EtOH)]) in 100 mL of dry reagent grade cyclohexane was heated to 67 °C. Menthyl α-Deuteriodiazoacetate (10.0 mL, 44.4 mmol, >99% d_1 by NMR analysis) was added by syringe pump at 0.6 mL/h to the hot reaction mixture; upon completion of the addition, the mixture was cooled and filtered, and the filtrate was concentrated by rotary evaporation. Kugelrohr distillation at 0.05 torr and an oven temperature of 100 °C gave 9.2 g of colorless viscous oil; according to analysis by NMR spectroscopy, about 7.8 g (63%) of the 2-phenylcyclopropanecarboxylates was present, together with maleate and fumarate esters.

(+)-*t*-2-Phenyl-1,2,*c*-3-trideuteriocyclopropanecarboxylic Acid ((+)-8). The crude mixture of menthyl esters prepared immediately above (9.0 g, about 7.6 g of cyclopropanecarboxylates) was dissolved in 50 mL of methanol and 30 mL of 25% aqueous NaOH. The mixture was heated at reflux for 12.5 h, cooled, diluted with 60 mL of water, and extracted with ether (3 × 50 mL) and then with CH_2Cl_2 (3 × 20 mL). The aqueous phase was acidified with concentrated HCl and extracted with CH_2Cl_2 (4 × 20 mL). These extracts were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to leave 3.99 g (96%) of crude acids as a viscous oil. A small sample was esterified with diazomethane and the methyl esters were examined by NMR in C_6D_6. The CH_3O singlets for *cis*- and *trans*-methyl 2-phenylcyclopropanecarboxylates were in a 12:88 intensity ratio. With added chiral shift reagent Eu(hfbc)$_3$,[34] the enantiomeric CH_3O singlets were cleanly separated; each geometrical isomer was about 90% optically pure, with the downfield CH_3O predominating in each case.

A salt prepared from 3.84 g (23.2 mmol) of the mixture of acids and 7.53 g (23.2 mmol) of quinine was recrystallized systematically from 3:7 ethanol:hexanes. The salt of the cis acid tended to remain in the mother liquors, and resolution of the trans acid was completed. Combination of the appropriate crystalline fractions followed by hydrolysis gave 1.43 g (47%) of colorless oil: NMR δ 12.32 (s, 1 H), 7.0–7.4 (m, 5 H), 1.36 (br s, 1 H). A small sample of the methyl ester of this acid was analyzed by NMR; it contained about 2.3% cis ester and, in the presence of Eu(hfbc)$_3$, only one CH_3O singlet for the trans methyl ester could be detected under conditions known to separate the enantiotopic CH_3O peaks in racemic material. An additional 0.67 g of optically pure acid (+)-**8**, entirely free from the cis isomer, was obtained. The remaining fractions of quinine salts from the resolution were combined and hydrolyzed, and the resulting acids were esterified with CH_2N_2. Low-pressure liquid chromatography with 9:1 hexanes/ethyl acetate gave 1.52 g of the methyl ester of **8**, containing <1% of the corresponding cis ester as a contaminant. (A 0.251-g sample of the methyl ester of **9**, entirely free from the trans ester by NMR analysis, was also obtained.) Saponification with 10% aqueous NaOH (12.5 mL) resulted in a quantitative yield (1.40 g) of the corresponding acid **8**. Quinine resolution provided 0.67 g of optically pure acid (+)-**8**.

(1*S*,2*S*,3*S*)-*t*-2-Phenyl-1,2,*c*-3-trideuteriocyclopropanemethanol. The first batch of resolved trideuterio acid (+)-**8** (1.01 g, 6.1 mmol) was reduced with lithium aluminum hydride (1.00 g, 26.4 mmol) in THF to give 0.88 g (96%) of colorless oil after Kugelrohr distillation: NMR δ 7.00–7.40 (m, 5 H), 3.63 (s, 1 H), 1.46 (br s, 1 H), 0.93 (br s, 1 H).

(1*S*,2*S*,3*S*)-*t*-2-Phenyl-1,2,*c*-3-trideuteriocyclopropanecarboxaldehyde. The chiral alcohol prepared immediately above (0.872 g, 5.77 mmol) was oxidized with pyridinium chlorochromate (2.28 g, 10.6 mmol) to give 0.775 g (90%) of the trans aldehyde as a colorless oil: NMR δ 9.32 (s, 1 H), 7.00–7.40 (m, 5 H), 1.48 (br s, 1 H). About 2.5% of the cis aldehyde was still present as evidenced by a small singlet at δ 8.69. Very small signals at δ 2.60 and 2.17 corresponding to residual protons at C(2) and C(1), respectively, confirmed that deuterium incorporation at these carbon atoms was at least 98%.

(2*R*,3*R*)-1-Phenyl-*r*-1,*c*-2,*t*-3-trideuteriocyclopropane ((+)-1-*t*). The chiral aldehyde described immediately above (0.775 g, 5.19 mmol) was decarbonylated with Wilkinson's catalyst (5.28 g, 5.7 mmol) in benzene (40 mL) to give 0.39 g (63%) of pure (+)-1-*t* after purification by VPC on column E at 155 °C. The NMR spectrum of this product was identical with that of (±)-1-*t*. The 0.67-g sample of acid (+)-**8** obtained from the second resolution was also converted to (+)-1-*t* through the reduction, oxidation, decarbonylation sequence just described. The material obtained (0.232 g, 47% yield from (+)-**8**) was combined with that already in hand giving a total of 0.628 g of hydrocarbon (+)-1-*t*.

***c*-2-Phenyl-1,2,*t*-3-trideuteriocyclopropanemethanol.** Lithium aluminum hydride (0.15 g, 4.0 mmol) was suspended in ether (10 mL). The methyl ester of cis acid **9** (0.251 g, 1.4 mmol) was added by syringe and the reaction solution was heated at reflux for 2.5 h. Standard workup[32] and Kugelrohr distillation at 0.15 torr and an oven temperature of ~65 °C gave 0.21 g (100%) of white crystals which were recrystallized from pentane to yield colorless needles: mp 56–57 °C;[35] NMR δ 7.27 (s, 5 H), 3.48 (br d, J = 11 Hz, 1 H), 3.27 (br d, J = 11 Hz, 1 H), 1.15 (br s, 1 H), 0.94 (br s, 1 H).

***c*-2-Phenyl-1,2,*t*-3-trideuteriocyclopropanecarboxaldehyde.** The alcohol prepared above (0.114 g, 0.75 mmol) was oxidized with pyridinium chlorochromate (0.30 g, 1.4 mmol) to provide 0.112 g (100%) of aldehyde as a colorless oil: NMR δ 8.69 (s, 1 H), 7.31 (s, 5 H), 1.83 (br s, 1 H). The complete absence of an absorption at δ 9.3 confirmed that none of the trans geometrical isomer was present. Stereochemical integrity at C(3) was greater than 96% as judged by the intensities of the signals at δ 1.83 and 1.50. Better than 98% deuterium incorporation at C(1) and C(2) was evident from the extremely weak signals at δ 2.75 and 2.05.

1-Phenyl-*r*-1,*c*-2,*c*-3-trideuteriocyclopropane (1-*s*). The entire sample of the aldehyde from above (0.112 g, 0.75 mmol) was decarbonylated with Wilkinson's catalyst (0.730 g, 0.79 mmol) in benzene (5 mL) to give 0.63 g (69%) of 1-*s* after purification by VPC at 155 °C on column E: NMR (100 MHz) δ 7.00–7.40 (m, 5 H), 0.70 (s, 2 H). Comparison of the primary absorption at δ 0.70 to the minor one at δ 0.92 demonstrated that the stereochemical purity of 1-*s* was greater than 97%.

Preparation of an Equilibrium 1:1:2 Mixture of 1-*a*, 1-*s*, and 1-*t*. The salts from the mother liquors of the second quinine resolution described above were combined and hydrolyzed to give 0.62 g of nearly racemic acid **8**. This sample of acid **8** (0.62 g, 3.75 mmol) was reduced with lithium aluminum hydride (0.50 g, 13.2 mmol) in THF (15 mL) giving 0.44 g (78%) of the corresponding alcohol, identical (by ^{1}H NMR) with that obtained by reduction of optically pure acid (+)-**8**. The alcohol (0.44 g, 2.9 mmol) was reoxidized with pyridinium chlorochromate (1.16 g, 5.4 mmol) to the carboxaldehyde (0.37 g, 86% yield), which was immediately decarbonylated with Wilkinson's catalyst (2.31 g, 2.5 mmol) in benzene (15 mL). Purification by VPC on column E at 155 °C gave 0.185 g (62%) of 1-*t*, spectroscopically identical with the completely racemic and optically pure forms synthesized earlier. A 165-mg sample of the material prepared immediately above was heated at 309.3 °C for 140 h. After recovery, a small portion of the pyrolysis mixture was repurified by VPC at 155 °C on column E for analysis by Raman spectroscopy and ^{1}H NMR.

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