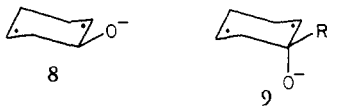
character. If it is envisioned in a reasonable conformation, as a pseudo-chair **8**, then the anionic oxygen can assume either an equatorial or axial position. If the usual conformational rules apply, the alkoxide functionality in the secondary system should prefer a pseudo-equatorial orientation as in **8**, while for the tertiary



8 9

system with both a methyl and an alkoxide group present on C-3, **9** with the anionic group in an axial orientation should compete in energy with the equatorial alkoxide conformer. Such positional dependence has been observed in the Cope rearrangement of 3,4-dimethyl-1,5-hexadiene, where the methyls prefer being equatorial in the chair-like transition state relative to the axial positions by 9:1.[2c] The mechanism by which an axial oxyanion should result in a more favorable transition state than an equatorial one is not immediately evident, but presumably it would involve some sort of secondary orbital interaction. Most of the solution-phase examples of this reaction are capable of such a conformation, and this postulate is testable by design of conformationally locked systems, with the oxyanion alternately axial and equatorial.

Other MNDO calculations have been performed on these systems which shed further light on the nature of the rearrangement. Geometry optimization using MNDO calculations on **1a**, arranged with a starting geometry in a chair-like form, results in a structure where the C1–C2 double bond has rotated about the C2–C3 bond approximately 120° into a pseudo-exo geometry, presumably to avoid steric interactions with the C6 carbon. The interesting point is that the C3–C4 single bond (the bond that is broken in the BB intermediate) has appreciably lengthened to 1.613 Å, and the C1–C2–C3–O atoms (the enone in the BB intermediate) are coplanar. The optimized structure thus resembles a planar enone with an allylic moeity near it. The negative charge remains primarily on the oxygen We are not aware of any crystal structures to verify such a large bond lengthening in a homoallylic alkoxide, but the fact that the lengthening does not occur for the C2–C3 bond, rather only for the bond leading to the most stable components, would seem to indicate that the reactive nature of the alkoxide is reflected in its structure. If the BM intermediate **3** is arranged in a chair conformation, geometry optimization with the MNDO method results in the product enolate **4** being the most stable structure located, irrespective of whether the oxyanion is axial or equatorial. Since semi-empirical calculations are strictly parameterized only for minima on potential energy surfaces, one must be careful in interpreting them for other parts of the surface. Nevertheless, qualitatively this indicates that the BM intermediate is on the product side of the reaction coordinate. A similar optimization of a planar enone and allyl moeties arranged to mimic a BB transition state results in relaxation to either the reactant alkoxide or product enolate, depending on small changes in the starting geometry.

In conclusion, we find that the acceleration of the Cope rearrangement due to the presence of an anionic group on C3 occurs in the gas phase as well as in solution. Alkyl substitution at C3 results in an apreciable rate difference between the prototypical anionic Cope rearrangement systems **2a** and **2b** in both the gas and condensed phases, ascribable to an intrinsic structural effect and not to relative ion-pairing or solvation effects. The question of whether this change is due to methyl stabilization of the intermediate or to a stereoelectronic conformational effect should be amenable to testing by suitably designed models with conformationally locked anionic substituents.

Acknowledgment. We thank the National Science Foundation, Grant No, 79-19528, for support of this work and Professors J. J. Gajewski, D. A. Evans, and W. v. E. Doering for helpful discussions.

Registry No. 1a, 924-41-4; **1b**, 5903-40-2; **1c**, 17123-61-4.

Complete Kinetic Analysis of Thermal Stereomutations among the Eight 2,3-Dideuterio-2-(methoxymethyl)spiro[cyclopropane-1,1′-indenes]

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Abstract: Two isomeric cyclopropanes with stereochemical labels at each of three ring carbons, (−)-(1*S*,2*S*,3*S*)-*trans*,-*trans*-2,3-dideuterio-*cis*-2-(methoxymethyl)spiro[cyclopropane-1,1′-indene] and (+)-(1*R*,2*S*,3*R*)-*cis*,*trans*-2,3-dideuterio-*trans*-2-(methoxymethyl)spiro[cyclopropane-1,1′-indene], were synthesized in optically pure form and pyrolysed at 198.9 °C. The relative concentrations of stereoisomers in product mixtures were determined as a function of time by using a combination of analytical techniques: vapor phase chromatography, polarimetry, NMR spectroscopy, and NMR spectroscopy in the presence of an optically active lanthanide shift reagent. The stereochemical reaction kinetics reveal that the Smith mechanism is not a plausible model for one-center epimerization; two trimethylenes, produced through two distinct cyclopropane C-C bond cleavages, are implicated, since all three possible one-center epimerizations are seen: from the cis isomer, k_1, k_2, and k_3 ($\times 10^5$ s) are 0.95, 2.34, and 0.17, while from the trans isomer, k_1', k_2', and k_3' ($\times 10^5$ s) are 0.32, 0.80, and 0.19.

The energy gap between molecules having either a tetrahedral or a planar tetracoordinate carbon is diminished if that atom resides in a cyclopropane ring or at C(5) of a cyclopentadiene ring.[1] These conclusions have been drawn from early theoretical analyses based on single-determinant calculations[1] and from later studies employing configuration interaction.[2] When both structural features are present, as in a spiro[2.4]hepta-4,6-diene system, the energy-gap reducing influences are in large part cumulative: for the series methane, cyclopropane, cyclopentadiene, and spiro-

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(2) Crans, D. C.; Snyder, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7152–7154. See also: Collins, J. B.; Dill, J. D.; Jemmis, E. D.; Apeloig, Y.; Schleyer, P. R.; Seeger, R.; Pople, J. A. *Ibid.* **1976**, *98*, 5419–5427 and references therein.

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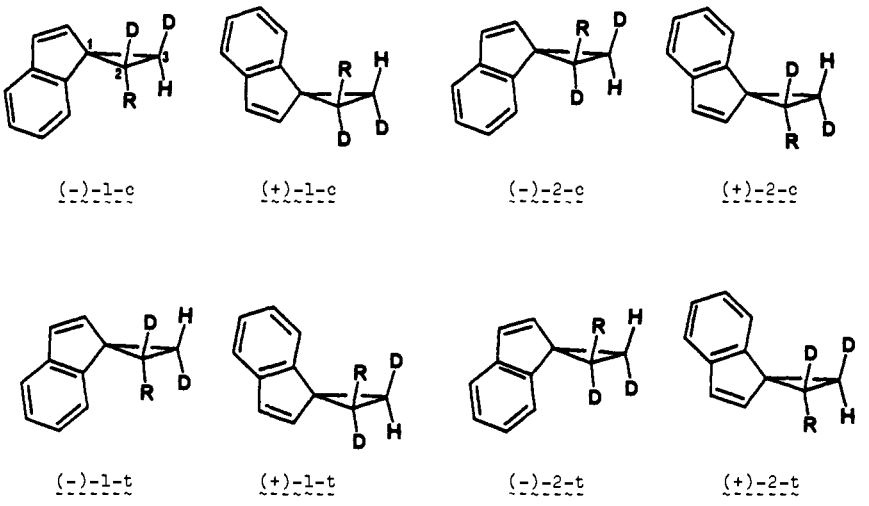
Chart I



[2.4]hepta-4,6-diene, one recent series of calculations estimated energy differences between tetrahedral and planar geometries as 225, 176, 168, and 125 kcal/mol.[2] Other calculations have resulted in far different and generally smaller numerical values for these energy differences,[3] but all seem in qualitative agreement: a planar methane transition state for one-center thermal epimerization in a cyclopropane is energetically much more accessible than in an acyclic methane, and it is favored considerably more in spiro-[2.4]hepta-4,6-dienes. If the Smith mechanism[4] for one-center thermal epimerizations is generally accessible for substituted cyclopropanes, then this pathway for stereomutation should be dramatically enhanced in spiroheptadienes. The thermal stereomutations of spiroheptadienes should be dominated by one-center epimerization at the spirocyclic carbon.

To put this proposition to a rigorous experimental test requires measuring individual rate constants for all one-center and two-center epimerizations in a suitable spiroheptadiene system. Earlier studies with chiral and deuterium-labeled variants of 1-methylspiro[2.4]hepta-4,6-diene provided suggestive but incomplete evidence on the matter: an upper limit for the rate of one-center epimerization at the spirocyclic carbon was deduced, and it was definitely not prominent.[5]

Subsequent work with other systems has demonstrated that thermal interconversions among as many as eight isomeric cyclopropanes may be subjected to complete kinetic analyses and all kinetic parameters found;[6,7] encouraged by these precedents for successful negotiation of the complexities inherent in such stereochemical kinetic studies, we sought a complete treatment of the stereomutations of a spiro[2.4]hepta-4,6-diene system.[8]

Experimental Design

To secure a complete kinetic description of the thermal stereomutations shown by a set of substituted cyclopropanes, there must be a stereochemical label at each ring carbon. The three chiral centers in such a cyclopropane define a set of eight potentially interconvertible stereoisomers. Thus the experimental task involves stereoselective synthesis of at least one and preferably more than one optically active triply labeled cyclopropane, development of analytical techniques sufficient to measure the relative concentrations of stereoisomers in a thermolysis reaction mixture, and derivation of all kinetic parameters from the concentration vs. time data acquired.

The set of eight cyclopropanes studied in this work is presented in Chart I: two of these cyclopropanes, (-)-**1**-**c** and (+)-**2**-**c**, were synthesized and used as substrates for the kinetic determinations.

The symbolism adopted here utilizes a three-component label: (+) or (-) refers to the sign of rotation, and the spatial representations of structures give absolute stereochemistry; **1** stands for the isomer in which indenyl and methoxymethyl groups are cis, while in **2** they are trans; and **c** and **t** give the cis or trans stereochemical disposition of the C(3) proton relative to the reference indenyl moiety at C(1).

The spiroindenyl group, a benzoannulated cyclopentadiene, is capable of delocalizing electron density in a p orbital at C(1) in the hypothetical Smith mechanism planar transition state, yet the indenyl unit, it was anticipated, would impede 1,5 shifts that intrude upon the thermal stereomutation chemistry of spiro-[2.4]hepta-4,6-dienes.[5,9]

The methoxymethyl group was chosen to provide minimal activation and a site of Lewis basicity, a requirement for part of the analytical work involved in the kinetic analysis. A second activating substituent such as phenyl or cyano would so bias the system in favor of C(1)–C(2) bond cleavage that stereomutations dependent upon thermolysis of the C(1)–C(3) bond would not be in evidence.

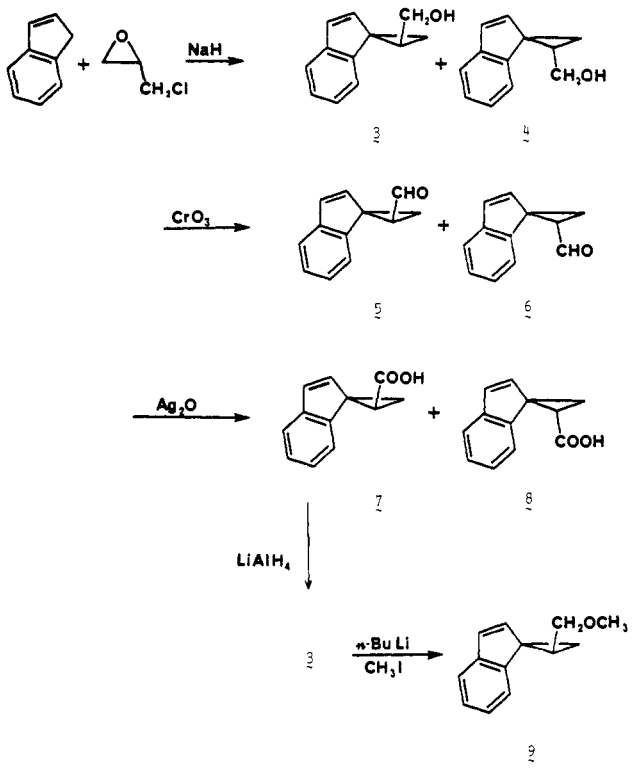
Deuterium substitution at C(3) gives chirality at that center and yet is thermodynamically unperturbing. Neglecting the differences in secondary deuterium isotope effects attendant upon different stereochemical dispositions in the compounds of Chart I preserves sufficient symmetry in the kinetic situation to vastly simplify analysis.

Kinetic isotope effects themselves are not neglected. All of the kinetic work is done with compounds possessing a constant complement of isotopic labels. No assumptions as to the relative rates of deuterium-labeled and unlabeled versions of the spiro[cyclopropane-1,1′-indenes] are ever employed. The deuterium at C(2) is not a stereochemical label, but rather serves to simplify ^{1}H NMR spectra.

Any one of the eight stereoisomers of Chart I has six possible direct epimerization processes available: three one-center epimerizations (k_1, k_2, and k_3) and three two-center epimerizations (k_{12}, k_{13}, and k_{23}). Each of these processes creates a unique stereoisomeric product. The last stereoisomer in the set of eight is enantiomeric to the starting isomer and could only be produced

(3) For example: Kollmar, H. *J. Am. Chem. Soc.* **1973**, *95*, 966–967.
(4) Smith, F. T. *J. Phys. Chem.* **1958**, *29*, 235–236.
(5) Gilbert, K. E.; Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1593–1595.
(6) Baldwin, J. E.; Carter, C. G. *J. Am. Chem. Soc.* **1978**, *100*, 3942–3944. See also: Doering, W. von E.; Barsa, E. A. *Tetrahedron Lett.* **1978**, 2495–2498; Doering, W. von E.; Barsa, E. A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2355–2357.
(7) Baldwin, J. E.; Carter, C. G. *J. Am. Chem. Soc.* **1982**, *104*, 1362–1368.
(8) For recent work on the structure of spiro[2.4]hepta-4,6-diene see: Harmony, M. D.; Mathur, S. N.; Choe, J.-I.; Kattija-Ari, M.; Howard, A. E.; Staley, S. W. *J. Am. Chem. Soc.* **1981**, *103*, 2961–2966 and references therein.
(9) Clark, R. A.; Hayles, W. J.; Youngs, D. S. *J. Am. Chem. Soc.* **1975**, *97*, 1966–1967.

Scheme I



directly by a simultaneous three-center epimerization (k_{123}), a process that has no experimental or theoretical support.

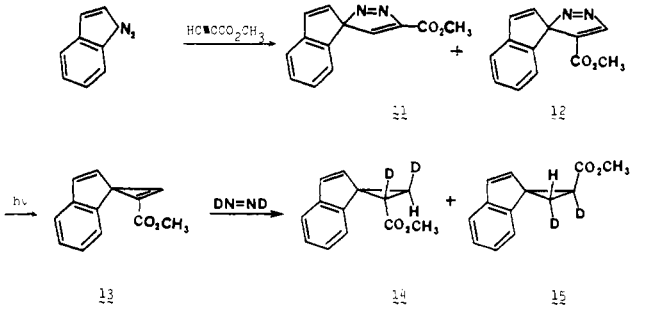
The kinetic situation, then, is defined by 48 unimolecular rate constants. Thanks to the deuterium at C(3) and the principle of microscopic reversibility, these 48 rate constants may be derived from just nine independent variables: eight stereochemically distinct rate constants and one equilibrium constant. Four of these rate constants describe different paths for the conversion of **1** to **2** (k_1, k_2, k_{13}, and k_{23}), two define interconversions among **1** isomers (k_{12} and k_3), and two describe interconversions among **2** isomers (k'_{12} and k'_3). All other rate constants can be calculated from these eight rate constants and the equilibrium constant. In this study primed rate constants denote processes that begin from one of the isomers **2**.

Results

Syntheses. Unlabeled racemic versions of the desired substrates were approached by two routes, the second of which proved amenable to stereoselective introduction of deuterium labels and the required optical resolutions.

Ready access to spiro[cyclopropane-1,1'-indenes] was achieved as outlined in Scheme I. Condensation of the indenyl anion with epichlorohydrin[10] in tetrahydrofuran gave a 2:1 mixture of alcohols **3** and **4** in 74% yield after Kugelrohr distillation. Oxidation to the corresponding carboxylic acids was accomplished in two steps so as to avoid acidic conditions. Collins oxidation[11] to the aldehydes **5** and **6** produced an oil (82%) which was then oxidized further with silver(I) oxide[12] to give a 2:1 mixture of acids **7** and **8** in 87% yield. Recrystallization of the mixture resulted in separation of the diastereomers. Trans acid **7** crystallized preferentially in 97% isomeric purity. Reduction of acid **7** with lithium aluminum hydride in diethyl ether gave alcohol **3** which was immediately alkylated. One equivalent of *n*-butyllithium in dimethyl sulfoxide gave the anion of **3**, which was quenched with excess iodomethane to give the trans methyl ether **9** in 95% yield from the acid **7**.

Scheme II



An optical resolution of the trans acid **7** was accomplished by way of the quinine salts. Three or four recrystallizations of the diastereomeric salts from hot absolute ethanol and hexanes yielded, after hydrolysis of the salt, optically pure trans acid, (+)-**7**, $[\alpha]_{546}$ 873° ($CHCl_3$). Optical purity was confirmed in this case as well as in later resolutions by converting the acid to the methyl ester and using ^1H NMR in the presence of an optically active shift reagent. In the presence of tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III), Eu(hfc)$_3$, in benzene-d_6, the signal for methyl ester of (±)-**7**, (±)-**10**, as well as the signal for one of the cyclopropyl ring protons moved downfield to about δ 9.5 and 3.5, respectively. By this point they had both split into enantiotopic signals. Ester (+)-**10** obtained from (+)-**7** showed only one signal in each of these regions of the NMR spectrum and was thus considered to be optically pure.

During the resolution of **7**, the trans isomer being resolved was freed of diasteromeric impurity. About 3% of the cis isomer (±)-**8** had contaminated the trans isomer (±)-**7**; this isomeric impurity was efficiently concentrated in the mother liquor during the resolution. The (+)-**7** obtained appeared to be entirely free of the diastereomeric cis isomer **8**, within the limits of detectability by NMR analysis. Preliminary experiments indicated that the opposite antipode, (−)-**7**, could be secured through three or four recrystallizations of the (−)-α-methylbenzylamine salt of (±)-**7** from chloroform and diethyl ether.

Extension of the synthetic route of Scheme I to provide dideuterio chiral isomers **1** and **2** with high stereoselectivity proved impracticable. The addition of bromine to *trans*-2,3-dideuterioallyl alcohol[13,14] seemed to give clean trans addition; the resultant erythro stereoisomer of 2,3-dideuterio-2,3-dibromopropanol was converted with 1 N aqueous KOH in a mixture of ether and water to the corresponding stereoisomer of epibromohydrin,[15] which was in turn reacted with the indenyl anion. Continuing with the route of Scheme I, dideuterio analogues of acids **7** and **8** were secured and examined by ^1H NMR spectroscopy. It was evident that the deuterium labels had been partially scrambled at one or more points during the synthetic sequence. Insufficiently high regioselectivity in the condensation of indene with epibromohydrin, a likely source of the problem,[16] was not circumvented in reactions of indenyl anion with various hydroxyl-protected derivatives of *erythro*-2,3-dideuterio-2,3-dibromopropanol.

Successful syntheses of unlabeled methyl ether (±)-**17** and the two deuterium labeled compounds (−)-**1-c** and (+)-**2-c** all began with the series of reactions outlined in Scheme II. Diazoindene prepared from indene and tosyl azide[17] was isolated and an impure red oil containing unreacted indene and a small amount of *N,N*-

(10) Bangert, K.; Boekelheide, V. *Tetrahedron Lett.* **1963**, *14*, 1119–1121. Staley, S. W.; Fox, M. A.; Hirzel, T. K. *J. Am. Chem. Soc.* **1976**, *98*, 3910–3916.

(11) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, *30*, 3363–3366.

(12) Campaigne, E.; Le Suer, W. M. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, 919–921.

(13) Baldwin, J. E.; Black, K. A. *J. Org. Chem.* **1983**, *48*, 2778–2779.

(14) Kornprobst, J. M.; Dubois, J. E. *Tetrahedron Lett.* **1974**, *25*, 2203–2206. Jones, M. F. German Patent; *Chem. Abstr.* **1973**, *79*, 136773t. See also: Movsumzade, M. M.; Shabanov, A. L.; Gurbanov, P. A.; Muradova, Sh. S. *J. Org. Chem. USSR Engl. Trans.* **1972**, *8*, 2074–2076.

(15) Hiskey, C. F.; Slates, H. L.; Wendler, N. L. *J. Org. Chem.* **1956**, *21*, 429–433.

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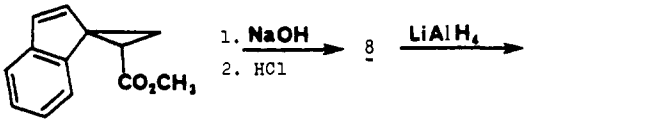
(17) Regitz, M.; Hocker, J.; Liedhegener, A. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, 179–183.

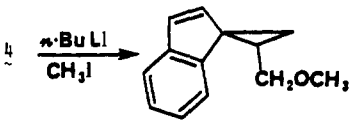
diethyl-*p*-toluenesulfonamide.[18] These contaminants posed no problems in subsequent reactions and were conveniently removed in later purifications. The 1,3-dipolar addition of diazoindene and methyl propiolate[19] proceeded smoothly at room temperature in 18–40 h and gave a mixture of the two isomeric pyrazoles **11** and **12**, typically in 70% yield after chromatography. Although one of these regioisomers could be obtained as red needles, mp 78–81 °C dec, no separation was done since the isomeric distinction was lost in the next step and both regioisomers were equally suited for the synthesis.

The photolysis of spiroindenylpyrazoles to give spiroindenylcyclopropenes is well precedented, but often only low yields attributed to secondary photoreactions such as di-π-methane rearrangements have been realized. Higher yields have been achieved through greater selectivity in irradiation frequencies.[20,21] For the photolysis of Scheme II a 450-W medium-pressure mercury arc lamp and a filter solution[21] ($BiCl_3$ in aqueous HCl, 50% transmittance at $\lambda = 356$ nm) were used, which allowed only irradiation of the intense $n \rightarrow \pi^*$ absorption band (log $\epsilon = 4.23$, $\lambda_{max} = 364$ nm) of pyrazoles **11** and **12**. In this manner irradiation of **11** and **12** in benzene at 15 °C gave cyclopropene **13** in quantitative yield.

Solutions of the cyclopropene **13** proved to be reasonably stable, though it did decompose slowly in solution at room temperature and was therefore photochemically generated immediately before use in the next reaction. Reduction of **13** with diimide proceeded almost entirely from the less hindered side of the double bond; the cis methyl ester **16** and its trans isomer **10** were produced in a 96:4 ratio. Hydrolysis of ester **16** in 10% aqueous sodium hydroxide gave the cis acid **8** in 45% yield from the pyrazoles. This acid was then reduced and alkylated as previously described to give the cis methyl ether **17** in nearly quantitative yield.



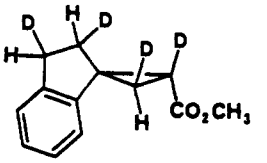
16



17

Reduction of cyclopropene **13** with dideuteriodiimide[22] generated from a solution of potassium azodicarboxylate in dioxane and acetic acid-*d* gave adequate levels of deuterium incorporation in products **14** and **15** (Scheme III) only after special care was employed to remove all proton sources. Benzene solutions of **13** were dried over freshly activated 4-A molecular sieves for 4–5 h in the dark,[23] the dioxane was heated at reflux over sodium for several weeks,[23] and the potassium azodicarboxylate salt, synthesized from azodicarboxamide in aqueous potassium hydroxide,[22] was washed extensively with absolute alcohol, stored over P_2O_5 at 0.01 Torr for over a month, powdered, treated with ethanol-*d*,[24] and stored again over P_2O_5 under vacuum. With these precautions 96% deuterium incorporation was realized. Since the reduction employed 4.5 equiv of acetic acid-*d* (99% deuterium content), a higher than 96% deuterium incorporation in **14** and **15** could hardly be expected.

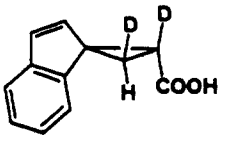
Reduction of **13** with dideuteriodiimide was much slower than reduction with diimide due to primary deuterium kinetic isotope effects; even after 30 h of stirring some of the dicarboxylate salt was still present. The relative slowness of the reaction caused two problems: the yield of the cyclopropyl ester was substantially reduced (30% after chromatographic purification), presumably because more of the cyclopropene decomposed before reduction could occur, and some reduction of the indenyl double bond took place, giving about 7% of the spiro[cyclopropane-1,1′-indane] compound **18**. The analogous reduction was not observed when undeuterated diimide was employed.



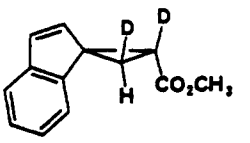
18

Separation of the spiroindenyl esters **14** and **15** from the overreduced material **18** proved difficult. Absorption, reverse phase, and silver nitrate impregnated chromatographic materials were not helpful. After hydrolysis of a sample of this ester mixture, the corresponding carboxylic acids and various amine salts were recrystallized to no avail. Vapor-phase chromatography employing several different liquid phases was only moderately effective; one liquid phase, however, diethylene glycol succinate (DEGS), did show promise. With a 60-cm × 6.2-cm 20% DEGS column the overreduced compound **18** had a retention time of just under one half of that for the desired ester **14**. The needed separation was finally accomplished by exploiting this observation: partition chromatography at low pressure using a liquid chromatography column packed with DEGS coated silica gel (20% by weight) with 3% ethyl acetate in hexanes as the eluent did not quite resolve the two compounds, but, by recycling overlap material, we obtained **14** containing less than 0.3% of the overreduced compound **18**. This chromatographic purification did not remove trans methyl ester **15** from the major isomer **14**.

Hydrolysis of the 96:4 mixture of isomeric esters **14** and **15** in 10% aqueous sodium hydroxide gave the corresponding acid **19** and its stereoisomer, in 97% yield. An optical resolution of cis isomer (±)-**19** was developed; it proceeded again, as did the resolution of trans isomer (±)-**7**, by way of diastereomeric quinine salts. Three to four recrystallizations of the salts from hot absolute ethanol gave upon hydrolysis of the salt optically pure dextrorotatory cis acid (+)-**19**. Analysis of this material by NMR spectroscopy indicated that during the resolution process (+)-**19** had been completely freed of diastereomeric impurity. Several recrystallizations of the diastereomeric salts from a different solvent, absolute methanol, yielded after hydrolysis the opposite antipode, (−)-**19**, also in optically pure form.



(±)-19



(+)-20

Analysis by NMR of the (−)-**19** obtained by this procedure revealed the presence of approximately 2% of trans acid. The extent and nature of this diastereomeric impurity were determined

(18) Rewicki, D.; Tuchscherer, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 44–45.
(19) Wolf, V. *Chem. Ber.* **1953**, *86*, 735–737. Rhinesmith, H. S. *J. Org. Chem.* **1975**, *40*, 1773–1776.
(20) Dürr, H.; Ranade, A. C.; Halberstadt, I. *Synthesis* **1974**, 878–880. Dürr, H.; Ruge, B.; Weib, B. *Liebigs Ann. Chem.* **1974**, 1150–1161. Dürr, H.; Schmidt, W.; Sergio, R. *Ibid.* **1974**, 1132–1139. Dürr, H.; Schmidt, W. *Ibid.* **1974**, 1140–1149. Dürr, H.; Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 559–569 and references therein. Engel, P. S. *Chem. Rev.* **1980**, *80*, 99–150 and references therein.
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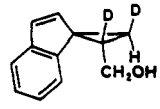
(24) Pasto, D. J.; Meyer, G. R. *J. Org. Chem.* **1968**, *33*, 1257.

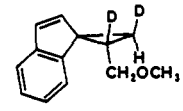
more precisely at the end of the synthetic sequence leading to the cis methyl ether (−)-**1-c**.

Optical purity for the two antipodes of acid **19** was confirmed by conversion of these acids to the corresponding methyl esters **20**, which were then analyzed by NMR in the presence of $Eu(hfc)_3$ in benzene-d_6. The signals for both the methyl group and the remaining cyclopropyl ring proton were split into well-resolved enantiotopic signals by the optically active shift reagent. No trace of the opposite antipode was evidenced in the NMR spectrum of either ester. At a wavelength of 546 nm the observed specific rotations of the methyl esters from (+)- and (−)-**19** were +126.6° and −125.5°, respectively.

Reduction of cis acid (−)-**19** with lithium aluminum hydride gave alcohol **21**, which was alkylated as previously described to give in nearly quantitative yield the optically pure dideuterio ether (−)-**1-c** ($[\alpha]_{546}$ −171.7° ($CHCl_3$)). This observed specific rotation



21

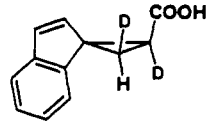


(−)-1-c

was measured on a sample that had been completely freed of diastereomeric impurity by preparative VPC.

The samples of (−)-**1-c** used as thermolysis starting material were purified on a shorter VPC column, and the diastereomeric impurity was not removed. Analysis by NMR at 360 MHz revealed 2.3% of **2-t** in this material, which had $[\alpha]_{546}$ −165.9° ($CHCl_3$). From these data and the measured specific rotation of optically pure trans methyl ether (+)-**2-c** ($[\alpha]_{546}$ +269.0° ($CHCl_3$)), this 2.3% isomeric impurity was calculated to be a 65:35 mixture of (+)-**2-t**:(−)-**2**-t. This impurity was accounted for explicitly in the kinetic analysis.

The synthesis of trans methyl ether (+)-**2-c** began from optically pure cis acid (+)-**19**, which was esterified by using diazomethane to give (+)-**20** in 95% yield. Treatment of the methyl ester with freshly sublimed potassium *tert*-butoxide[25] in *tert*-butyl alcohol-d[26] gave a mixture of six compounds. The acidic fraction (29%) was a 4:1 mixture of cis and trans acids. The neutral fraction was a mixture of four esters, with 86% of this mixture having the trans configuration; most of the trans material was the *tert*-butyl ester, a product of both epimerization and transesterification. Hydrolysis of the mixture of esters in 1,2-dimethoxyethane and 10% aqueous hydrochloric acid gave an 86:14 mixture of acids (+)-**22** and (+)-**19**.



(+)-22

Separation of these diastereomers was accomplished by recrystallization of the quinine salts from absolute ethanol. The (+)-**22** thus secured was reduced to the alcohol and alkylated as previously described to yield optically pure (+)-**2-c**, $[\alpha]_{546}$ +269.0° ($CHCl_3$). Analysis by NMR at 360 MHz showed a very small amount (0.4%) of cis isomer **1-c**, a consequence of incomplete separation of the diastereomeric acids (+)-**22** and (+)-**19**. It was accordingly treated as (+)-**1-c** and accounted for in the kinetic analyses.

Absolute Stereochemistry. Analyses of kinetic data require knowledge of the relative stereochemistry of all eight isomers of Scheme I. A correlation between chiral cis and trans ethers **1** and **2** was therefore required; it was obtained during the course of synthetic work, demonstrating that (+)-**1-c** and (+)-**2-c** are related by epimerization at C(2).

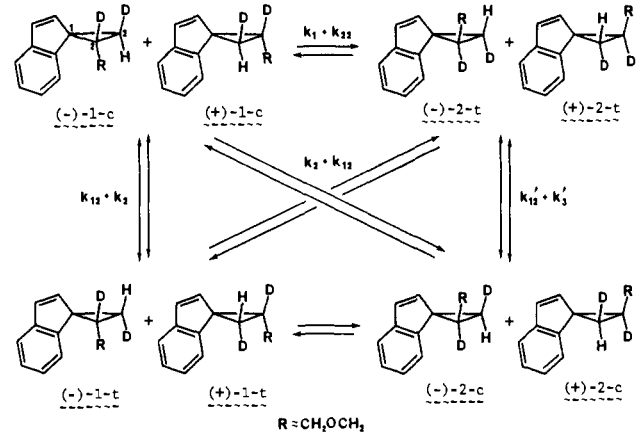
(25) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; p 911.
(26) Young, A. T.; Guthrie, R. D. *J. Org. Chem.* **1970**, *35*, 853.

Table I. Observed and Calculated[a] Mole-Percents of Isomers **1** and **2**

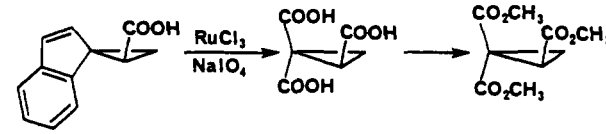
time, min	1	2
0	97.7	2.3
100	80.7 (80.8)	19.3 (19.2)
200	67.5 (67.8)	32.5 (32.2)
300	58.0 (57.9)	42.0 (42.1)
400	49.8 (50.3)	50.2 (49.7)
550	42.8 (42.1)	57.2 (57.9)
700	36.8 (36.6)	63.2 (63.4)
0	0.4	99.6
100	6.8 (6.2)	93.2 (93.8)
200	12.2 (10.7)	87.8 (89.3)
400	16.2 (16.8)	83.8 (83.2)
600	19.9 (20.3)	80.1 (79.7)

[a] According to the parameters $K_{eq} = 2.94$, and $(k_1 + k_2 + k_{13} + k_{23}) = 3.31 \times 10^{-5}\ s^{-1}$. Calculated values are in parentheses.

Scheme III



The absolute stereochemistry of the isomers of Scheme I was determined through a correlation with triester **24**. Oxidation of (−)-**7** ($[\alpha]_{546}$ −238.5°, ($CHCl_3$)) with ruthenium trichloride and sodium periodate following the procedure of Sharpless and coworkers[27] gave the tricarboxylic acid **22**, which was then esterified in methanol with excess ethereal diazomethane to give after VPC purification (−)-**24**, $[\alpha]_{546}$ −37.9° ($CHCl_3$), a compound of known absolute stereochemistry.[28]



(−)-7 23 (−)-24

Kinetic Data and Rate Constants. A complete kinetic analysis of the thermal stereomutations interconverting the isomers of Chart I was approached by working with four successive kinetic schemes. Ten kinetic points from thermolyses lasting from 100 to 700 min at 198.9 °C were obtained, six starting from (−)-**1-c** and four starting from (+)-**2-c**. Each sample (40–100 mg, toluene solution, sealed ampule) was thermolyzed in a molten salt bath and then analyzed by using a combination of analytical techniques, including vapor phase chromatography, polarimetry, and proton NMR spectroscopy, with and without the presence of an optically active lanthanide shift reagent.

(27) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
(28) Walborsky, H. M.; Pitt, C. G. *J. Am. Chem. Soc.* **1962**, *84*, 4831–4838. Saegusa, T.; Yonezawa, K.; Murase, I.; Konoike, T.; Tomita, S.; Ito, Y. *J. Org. Chem.* **1973**, *38*, 2319–2328. Chmurny, A. B.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4237–4244. Nishiyama, K.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3175–3176.

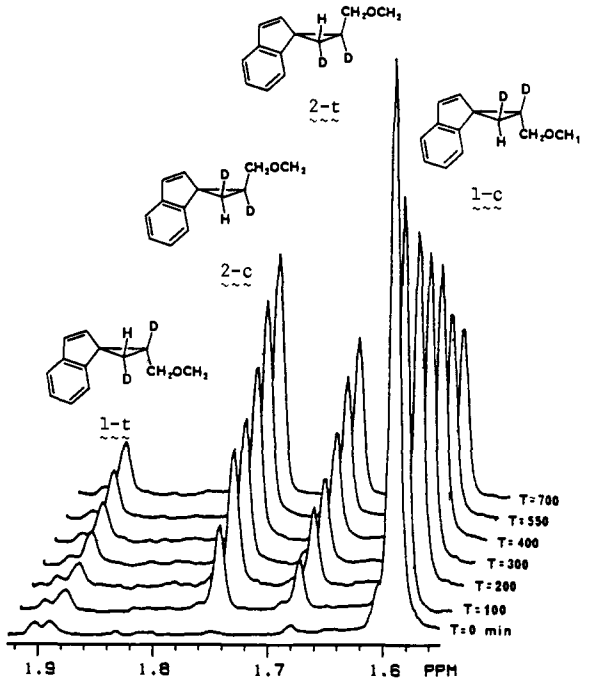


Figure 1. NMR spectra of C(3)–H for (−)-**1-c** and six thermolysis reaction mixtures.

The ratio of cis isomers **1** to trans isomers **2** was determined by VPC both for the ten thermolysis samples and for a sample heated to equilibrium. Standard least-squares analysis of these data for a reversible first-order interconversion **1** ⇌ **2** gave an equilibrium constant $K_{eq} = 2.98$ and the forward rate constant $(k_1 + k_2 + k_{13} + k_{23}) = 3.40 \times 10^{-5}\ s^{-1}$. Improved estimates of these parameters were obtained by using a program[29] to minimize the sum of the squares of differences between observed and calculated concentrations; this method gave $K_{eq} = 2.94$ and $(k_1 + k_2 + k_{13} + k_{23}) = 3.31 \times 10^{-5}\ s^{-1}$ with a standard deviation for the 20 comparisons of ±0.65% (Table I).

The second kinetic scheme to be solved (Scheme III) involved four interconverting pairs of enantiomers; the four pairs are interrelated by four different sums of two mechanistic rate constants. The concentration data required to solve Scheme III were obtained by proton NMR in conjunction with the ratio of **1**:**2** previously determined for each kinetic sample by VPC.

The ^1H NMR spectra were secured at 360 MHz; typically 24–100 acquisitions were collected with a pulse width of 8.5 μs and a 10-s pulse delay. Longer pulse delays did not alter relative signal intensities. In $CDCl_3$ solution the C(3) proton signal for each of the isomers **1-t**, **1-c**, **2-t**, and **2-c** comes at a unique chemical shift between δ 1.55 and 1.92, and at high field these signals are well separated. Traces of this region of NMR spectra for six kinetic samples starting from (−)-**1-c** are shown in Figure 1.

Preparative VPC was employed to separate cis and trans isomers; then the ratios **1-c**:**1-t** and **2-c**:**2-t** were obtained by NMR. Integration of the NMR spectra combined with the VPC-determined ratio of **1** to **2** provided the concentration data collected in Table II.

Best values for the sums of mechanistic rate constants appropriate to Scheme III were found by using a program based on the exact solution to the differential equations describing this kinetic situation.[29] Knowing K_{eq} and $(k_1 + k_{23} + k_2 + k_{13})$, the three parameters remaining were varied to achieve the best least-squares fit between observed and calculated concentrations. The sums so obtained are $(k_1 + k_{23}) = 0.95 \times 10^{-5}\ s^{-1}$, $(k_2 + k_{13}) = 2.36 \times 10^{-5}\ s^{-1}$, $(k_{12} + k_3) = 0.43 \times 10^{-5}\ s^{-1}$, and $(k'_{12} + k'_3) = 0.52 \times 10^{-5}\ s^{-1}$. The standard deviation between observed and calculated data sets is ±0.48% (Table II).

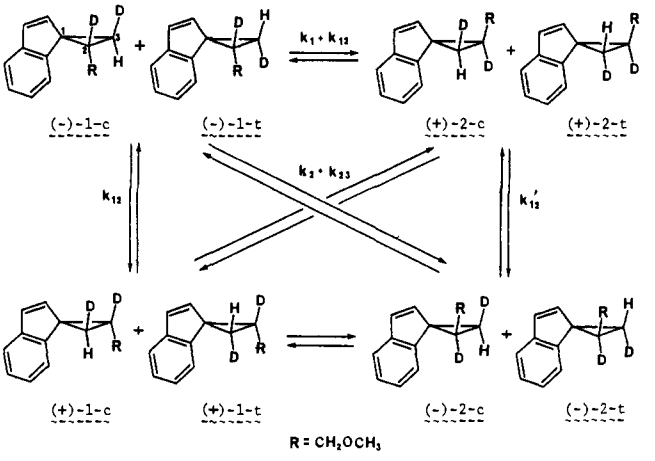
(29) Baldwin, J. E.; Carter, C. G.; Chang, G. E. C., unpublished results.

Table II. Observed and Calculated[a] Mole-Percents for Isomers of Scheme III

time, min	1-c	2-t	2-c	1-t
0	97.7	2.3	0	0
100	78.0 (78.5)	7.1 (7.2)	12.2 (12.0)	2.7 (2.3)
200	63.0 (63.6)	11.2 (11.3)	21.3 (20.9)	4.5 (4.2)
300	52.3 (52.3)	15.2 (14.7)	26.8 (27.3)	5.7 (5.7)
400	43.2 (43.5)	18.0 (17.7)	32.2 (32.0)	6.6 (6.8)
550	34.4 (33.9)	20.8 (21.3)	36.4 (36.6)	8.4 (8.2)
700	27.9 (27.4)	24.2 (24.2)	39.0 (39.2)	8.9 (9.2)
0	0.4	0	99.6	0
100	4.6 (4.5)	3.2 (3.1)	90.0 (90.7)	2.2 (1.8)
200	8.2 (7.4)	6.3 (6.0)	81.5 (83.2)	4.0 (3.3)
400	10.7 (11.2)	12.1 (11.5)	71.7 (71.8)	5.5 (5.6)
600	12.9 (13.1)	15.8 (16.2)	64.3 (63.5)	7.0 (7.3)

[a] According to the parameters $K_{eq} = 2.94$, $(k_1 + k_{23}) = 0.95 \times 10^{-5}\ s^{-1}$, $(k_2 + k_{13}) = 2.36 \times 10^{-5}\ s^{-1}$, $(k_{12} + k_3) = 0.43 \times 10^{-5}\ s^{-1}$, and $(k'_{12} + k'_3) = 0.52 \times 10^{-5}\ s^{-1}$. Calculated values are in parentheses.

Scheme IV



Here as well as in later analyses a more precise determination of rate constants was secured with data from two diastereomeric starting materials than would have been attainable from one only. Only one of the rate constants for interconverting different cis isomers or different trans isomers, $(k_{12} + k_3)$ and $(k'_{12} + k'_3)$, may be found with reasonable precision starting from only one isomer: the fit between observed and calculated concentrations for thermolysis product mixtures starting with **1-c**, for instance, is not very sensitive to the value of $(k'_{12} + k'_3)$ used in calculations, since $(k'_{12} + k'_3)$ corresponds in this case to a secondary reaction contributing little to the initial phase of the stereomutations.

The third kinetic scheme considered, Scheme IV, is just like Scheme III in form but is based on different criteria for pairing isomers. Here, pairs of isomers having the same absolute configuration at C(1) and C(2) are taken together. They rotate polarized light equally, and the required ratios (+)-**1**:(−)-**1** and (+)-**2**:(−)-**2** were determined by either NMR analysis in the presence of an optically active shift reagent or polarimetrically.

The ratio (+)-**2**:(−)-**2** was determined through portionwise addition of $Eu(hfc)_3$ to a benzene solution of **2**; when the olefinic C(3′)-H signal had been shifted downfield to approximately 10.4 ppm it appeared as two well-separated, though line-broadened, enantiotopic signals. The two representative spectra shown in Figure 2 are for the 550- and 400-min kinetic point products, starting from (−)-**1-c** and (+)-**2-c**, respectively.

The optical activity of the cis isomers isolated after a thermolysis of (−)-**1-c** was determined by using polarimetry. Optical rotations were measured at a wavelength of 546 nm on 11–20-mg samples dissolved in chloroform (4 mL).

Kinetic runs starting from (+)-**2-c** did not provide quantities of **1** sufficient for polarimetric measurements, and hence the kinetic solution, i.e., the determination of three unknown parameters, was

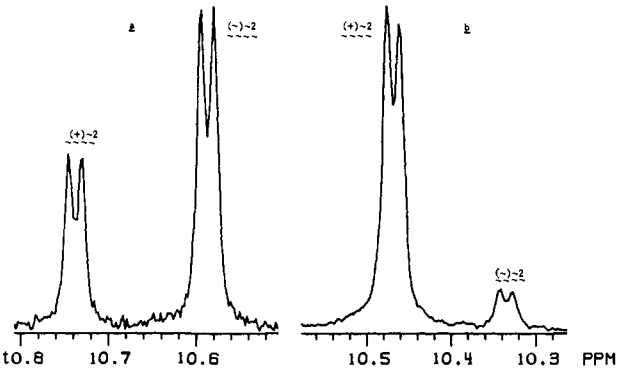


Figure 2. NMR spectra of the C(3′)–H signals of trans isomers **2** in the presence of Eu(hfc)$_3$: (*a*) 550-min thermolysis sample from (−)-**1-c**; (b) 400-min thermolysis sample from (+)-**2-c**.

Table III. Observed and Calculated[a] Mole-Percents for the Isomers of Scheme IV

time, min	(−)-**1**	(+)-2	(−)-2	(+)-**1**
0	97.7	1.5	0.8	0
100	78.2 (79.3)	6.8 (6.5)	12.5 (12.7)	2.5 (1.5)
200	64.1 (64.9)	10.9 (10.6)	21.6 (21.6)	3.4 (2.9)
300	54.0 (53.7)	14.1 (14.0)	27.9 (28.1)	4.0 (4.2)
400	44.6 (45.0)	17.2 (16.8)	33.0 (32.9)	5.2 (5.3)
550	36.3 (35.4)	19.5 (20.1)	37.7 (37.8)	6.5 (6.7)
700	29.2 (28.8)	22.6 (22.8)	40.6 (40.6)	7.6 (7.8)
0	0	99.6	0	0.4
100		90.6 (91.7)	2.6 (2.1)	
200		83.2 (85.0)	4.6 (4.3)	
400		74.7 (74.6)	9.1 (8.6)	
600		67.7 (66.9)	12.4 (12.8)	

[a] According to the parameters $K_{eq} = 2.94$, $(k_1 + k_{13}) = 0.97 \times 10^{-5}$ s^{-1}, $(k_2 + k_{23}) = 2.34 \times 10^{-5}$ s^{-1}, $k_{12} = 0.26 \times 10^{-5}$ s^{-1}, and $k'_{12} = 0.33 \times 10^{-5}$ s^{-1}. Calculated values are in parentheses.

based on 32 comparisons between calculated and observed concentrations, rather than on the full 40 which might have been accessible. The usual minimization of the sum of squares of differences between observed and calculated concentrations gave the parameters $(k_1 + k_{13}) = 0.97 \times 10^{-5}$ s^{-1}, $(k_2 + k_{23}) = 2.34 \times 10^{-5}$ s^{-1}, $k_{12} = 0.26 \times 10^{-5}$ s^{-1}, and $k'_{12} = 0.33 \times 10^{-5}$ s^{-1}. The mean and standard deviation for these 32 comparisons is −0.03 ± 0.60% (Table III).

By this point in the kinetic analysis, four of the eight mechanistic rate constants had been found, and four sums of pairs of mechanistic rate constants had been defined:

$$k_{12} = 0.26 \times 10^{-5}\ s^{-1} \qquad k_1 + k_{23} = 0.95 \times 10^{-5}\ s^{-1}$$

$$k'_{12} = 0.33 \times 10^{-5}\ s^{-1} \qquad k_2 + k_{13} = 2.36 \times 10^{-5}\ s^{-1}$$

$$k_3 = 0.17 \times 10^{-5}\ s^{-1} \qquad k_1 + k_{13} = 0.97 \times 10^{-5}\ s^{-1}$$

$$k'_3 = 0.19 \times 10^{-5}\ s^{-1} \qquad k_2 + k_{23} = 2.34 \times 10^{-5}\ s^{-1}$$

Although there are four sums of linearly dependent rate constants left to be resolved into the individual mechanistically significant one-center and two-center stereomutation components, there is but one unknown, or one parameter still to be found. Knowledge of any one of the constants k_1, k_2, k_{13}, or k_{23} would provide values of the others as well from the equations above.

To break these sums of rate constants, the concentrations of some of the individual isomers of Chart I had to be determined, and calculations based on the fully complex kinetic scheme of 8 interconverting isomers and 48 rate constants had to be performed.

To deduce the relative concentrations of all eight of the individual stereoisomers in a kinetic sample required that the ratio of any two cis isomers and the ratio of any two trans isomers be determined. For these distinctions NMR spectroscopy in the presence of an optically active lanthanide shift reagent once again proved effective.

Table IV. Observed and Calculated[a] Mole-Percents for Trans Isomers 2

time, min	(−)-2-c	(−)-2-t	(+)-2-c	(+)-2-t
0	0	0.8	0	1.5
100	11.9 (11.8)	0.6 (0.8)	0.3 (0.2)	6.5 (6.3)
200	20.7 (20.5)	0.8 (1.1)	0.5 (0.5)	10.4 (10.1)
300	26.0 (26.8)	1.8 (1.4)	0.8 (0.9)	13.4 (13.1)
400	31.4 (31.2)	1.7 (1.7)	0.8 (1.2)	13.4 (15.5)
550	34.4 (35.5)	3.3 (2.3)	1.9 (1.9)	17.6 (18.3)
700	37.1 (37.7)	3.5 (2.9)	1.9 (2.5)	20.7 (20.3)
0	0	0	99.6	0
100	0.1 (0.0)	2.5 (2.1)	89.9 (90.7)	0.7 (1.0)
200	0.4 (0.1)	4.1 (4.2)	81.0 (83.1)	2.2 (1.9)
400	0.8 (0.4)	8.2 (8.3)	70.9 (71.3)	3.9 (3.2)
600	1.2 (0.9)	11.2 (11.9)	63.1 (62.6)	4.6 (4.3)

[a] According to the parameters $K_{eq} = 2.94$, $k_1 = 0.95 \times 10^{-5}$ s^{-1}, $k_2 = 2.34 \times 10^{-5}$ s^{-1}, $k_3 = 0.17 \times 10^{-5}$ s^{-1}, $k'_3 = 0.19 \times 10^{-5}$ s^{-1}, $k_{12} = 0.26 \times 10^{-5}$ s^{-1}, $k'_{12} = 0.33 \times 10^{-5}$ s^{-1}, $k_{13} = 0.02 \times 10^{-5}$ s^{-1}, and $k_{23} = 0$. Calculated values are in parentheses.

Upon treatment of the trans isomers with Eu(hfc)$_3$ in benzene-d_6, the two C(3)-H signals (**2-t** and **2-c**) both move downfield in the spectrum. The signal for **2-t** starts farther upfield but shifts more quickly to end up farther downfield. Both signals split into two enantiotopic peaks.

This splitting of both NMR signals represents a redundancy in information, since only one ratio was required, but it allowed for selection of the ratio that could be determined with the greatest precision in each case. Combining these ratios with the previously determined sums of trans isomers allowed the determination of the concentration of each trans isomer for all ten kinetic points.

The same strategy was then applied to the set of four cis isomers, but the necessary separation of enantiotopic C(3)–H NMR signals could not be achieved for either **1-c** or **1-t**. Four optically active lanthanide shift reagents were tried: Eu(hfc)$_3$; tris[3-((trifluoromethyl)hydroxymethylene)-*d*-camphorato]europium(III), Eu(tfc)$_3$; the analogous praseodymium derivative, Pr(tfc)$_3$; and tris[*d*,*d*-dicampholylmethanato]europium(III).[30] The desired splitting of NMR signals could be marginally achieved by using Eu(hfc)$_3$ in benzene-d_6 with added (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)silver(I) to aid complexation,[31] but this result was not reproducible, and the method was therefore abandoned.

When it proved impossible to secure experimental concentration data for all four cis isomers, the one unknown kinetic parameter was deduced through comparisons between observed and calculated concentrations of all four trans isomers for kinetic runs starting from both (−)-**1-c** and (+)-**2-c**.

The best correspondence between observed and calculated concentrations was obtained with $k_1 = 0.95 \times 10^{-5}$ s^{-1}, $k_2 = 2.34 \times 10^{-5}$ s^{-1}, $k_{13} = 0.02 \times 10^{-5}$ s^{-1}, and $k_{23} = 0$. When k_{13} and k_{23} were allowed to rise at the expense of k_1 and k_2 the fit quickly became worse. The experimental and calculated concentrations of the four individual trans isomers are collected in Table IV. The mean and standard deviation for these 40 comparisons is −0.11 ± 0.65%.

Discussion

The rate constants for one-center and two-center thermal epimerizations for the isomers of Chart I found through this kinetic study are summarized in Table V.

The most salient feature of these results is that one-center epimerization at C(1) in these spiro[cyclopropane-1,1′-indenes] is by no means the exclusive stereomutation process; it is not even a predominant process, contributing only 25 and 19% to the total stereomutations in **1** and **2**, respectively. Selective stabilization

(30) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038–1054.
(31) Wenzel, T. J.; Bettes, T. C.; Sadlowski, J. E.; Sievers, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 5903–5904.

Table V. Rate Constants for All One-Center and Two-Center Thermal Epimerizations of 2,3-Dideuterio-2-(methoxymethyl)-spiro[cyclopropane-1,1'-indenes] at 198.9 °C

rate constant[a]	value[b]	%[c]	rate constant[d]	value[b]	%[c]
k_1	0.95	25	k'_1	0.32	19
k_2	2.34	62	k'_2	0.80	48
k_3	0.17	5	k'_3	0.19	12
k_{12}	0.26	7	k'_{12}	0.33	20
k_{13}	0.02	1	k'_{13}	0.007	1
k_{23}	0	0	k'_{23}	0	0

[a] Reactions originating from any of the four isomers **1**. [b] Constant × 10^5 s. [c] Percent of all rate constants. [d] Reactions originating from any of the four isomers **2**.

of the Smith mechanism transition state, which should have been evident if the Smith mechanism were at all important for one-center epimerizations of less particularly substituted cyclopropanes, is not seen. This outcome casts severe experimentally based doubt on the proposition that the Smith mechanism has any role to play in this case or in other less-favored cyclopropane stereomutations.

Benson's judgement that the Smith mechanism would be too energetically demanding to be competitive with alternative paths for one-center thermal epimerizations in cyclopropanes is confirmed after more than 20 years of concern with the issue;[32] recent theoretical work[2] and one incomplete experimental approach[5] to the issue are confirmed as well.

Quantum mechanical[33] and recent thermochemical studies[34] provide no support for trimethylene diradicals as reactive intermediates having substantial lifetimes for cyclopropane stereomutations, yet 0,0 and 0,90 trimethylene diradical forms[1] remain favored models for activated complexes in such reactions.[35]

The kinetic findings of Table V are most readily interpreted in terms of trimethylene diradical species as activated complexes. The fastest of the observed stereomutations may be associated with homolysis of the most substituted bond, C(1)–C(2), while cleavage of C(1)–C(3) may be inferred from the significant magnitudes of k_3 and k'_3.

Even though the isomers of Chart I are interconverted through trimethylene diradical transition states derived from both C(1)–C(2) and C(1)–C(3) bond cleavages, a high degree of stereochemical integrity is maintained. One-centered epimerizations are heavily favored over two-centered processes. The results do not accord with expectations based on freely rotating, relatively long-lived trimethylene diradical intermediates.

The proportion of the rate constant k_1 to be attributed to C(1)–C(2) bond cleavage is of course not deducible from the experimental data, and hence the ratio of one-center rate constants k_2/k_1 does not provide a precise measure of rotational propensities as usually defined.[36] But it is clear that one-center epimerization at C(2) is favored over epimerization at C(1) for the trimethylene system derived from C(1)–C(2) bond cleavage: the experimental ratio $k_2/k_1 = 2.46$ sets a lower limit for this comparison, since some of k_1 may be derived from C(1)–C(3) homolysis.

This study constitutes a second instance[7] wherein the observed stereomutations of a cyclopropane cannot be rationalized adequately within the limitations of the most substituted bond assumption. The relative importance of alternative modes of bond cleavage in substituted cyclopropanes is controlled by thermochemical factors, i.e., the relative strengths of the various carbon–carbon bonds. A methoxymethyl or a methyl substituent[7] is not sufficiently better than a hydrogen as a radical-stabilizing substituent to control completely the direction of bond cleavage in **1** or **2** or in 1-cyano-2-methylcyclopropanes.[7] The most substituted bond hypothesis, not surprisingly, is qualitatively correct, but its limits are finite and are now beginning to be defined.

Experimental Section

Routine ^{1}H NMR spectra were obtained on a Varian XL-100-15A instrument operating at 100 MHz. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane, using either tetramethylsilane (δ 0.00), the residual proton in chloroform-*d* (δ 7.24), or the residual proton in benzene-d_6 (δ 7.15) as a reference. Coupling constants are reported in hertz, and unless otherwise stated $CDCl_3$ solutions were employed. All NMR data used in the kinetic analysis were obtained on a Nicolet NT-360 spectrometer, operating at 360 MHz.

Infrared spectra were collected on either a Beckman IR 10 or a Sargent-Welch 3-200 instrument. Absorption positions are reported in cm^{-1} and were calibrated against polystyrene. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Dr. Richard A. Wielesek determined all mass spectra using a CEC-21-110B spectrometer and performed all elemental analyses using a Perkin-Elmer Model 240 CHN Analyzer.

Melting points were determined on a Koefler micro hot stage apparatus with a Riechert Thermopan microscope. All melting points and boiling points are uncorrected. For bulb-to-bulb distillations using a Kugelrohr apparatus the temperature range reported refers to the oven temperature.

All solvents were reagent grade. When necessary, solvents were distilled under a nitrogen atmosphere from an appropriate desiccant: ether was distilled from lithium aluminum hydride, tetrahydrofuran (THF) was distilled from sodium and benzophenone, and dioxane was distilled from molten sodium.[23]

Concentration of solutions following reactions and extractions involved use of a rotary evaporator operating at a reduced pressure of approximately 20 Torr, unless otherwise stated. All reductions using lithium aluminum hydride were worked up by the standard method introduced by Mičovič and Mihailovič.[37]

Vapor-phase chromatography was used to purify analytical samples as well as to analyze for and separate diastereomers. A Varian 1520 A instrument was used, and the following columns were employed: A, 60 cm × 6.2 mm 20% diethylene glycol succinate (DEGS) on 60/80 mesh Chromosorb W NAW; B, 75 cm × 6.2 mm 20% DEGS on 60/80 mesh Chromosorb W AW DMCS HP; C, 1 m × 6.2 mm 20% SE-30 on Chromosorb W AW DMCS HP; D, 3 m × 6.2 mm 20% DEGS on 60/80 mesh Chromosorb W AW DMCS HP with a 30 cm × 6.2 mm 20% SE-30 on 60/80 mesh Chromosorb W AW DMCS HP column on the end to act as a scrubber and catch the DEGS which bled off the main column; E, 7 m × 3.1 mm 10% DEGS on 80/100 mesh Chromosorb W AW DMCS HP.

***trans*- and *cis*-2-(Hydroxymethyl)spiro[cyclopropane-1,1'-indene] (3 and 4).** To a solution of sodium hydride (15.0 g, 625 mmol) in dry THF (600 mL) was added distilled technical grade indene (15.0 g, 116 mmol), and the resulting solution was stirred at room temperature for 10 h under a nitrogen atmosphere. The maroon solution was cooled (0–10 °C) while epichlorohydrin (12 g, 130 mmol) was added dropwise over a 1-h period; the reaction mixture was allowed to warm to room temperature, stirred for another 10 h, and poured carefully into a mixture of water and ice (200 g each). This solution was extracted with ether (5 × 75 mL), and the combined extracts were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated to yield 22.9 g of a brown oil. Kugelrohr distillation (60–110 °C, 4–6 torr) gave 15.5 g of a very viscous yellow oil, estimated by NMR analysis to contain 14.7 g (74%) of product was as a 66:34 mixture of the diastereomers **3** and **4**, characterized individually below.

***trans*- and *cis*-2-Spiro[cyclopropane-1,1'-indene]carboxylic Acids (7 and 8).** A solution of methylene chloride (430 mL) and pyridine (26 mL) was stirred vigorously under a nitrogen atmosphere as chromium trioxide (16.3 g, 163 mmol) was added in small portions.[11] To the red-brown suspension obtained was added all at once a solution of alcohols **3** and **4** (4.52 g, 26.3 mmol) in methylene chloride. The reaction mixture was stirred for 15 min and then filtered through a pad of Florisil. The clear filtrate was washed with 10% aqueous HCl (4 × 75 mL), saturated aqueous $NaHCO_3$ (2 × 75 mL), H_2O, and brine, and then dried ($MgSO_4$), filtered, and concentrated to yield a light orange oil. Analysis by

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NMR indicated the oil contained 3.66 g (82%) of the isomeric aldehydes **5** and **6**: NMR δ 1.94–2.52 (2 H, m), 1.75–2.02 (1 H, m), 6.01 (0.34 H, d, J = 6), 6.42 (0.66 H, d, J = 6), 6.83–7.50 (5 H, m), 9.5–9.62 (1 H, m).

The crude mixture of aldehydes was added to a solution of silver(I) oxide (3.01 g, 13.0 mmol) and sodium hydroxide (5.20 g, 130 mmol) in water (55 mL).[12] The solution was stirred for 30 min and then filtered through a pad of Celite, washed (ether), and acidified (concentrated HCl). The milky solution was extracted with ether (4 × 60 mL), and the combined extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to give 3.49 g of pale yellow solid, a 2:1 mixture of acids **7** and **8** (87%; 71% from the alcohols).

The desired trans isomer **7** was isolated in 97% isomeric purity by crystallization of the solid from 10:1 hexanes/ethyl acetate. Thus 2.11 g of the mixture was crystallized once from 80 mL of 10:1 hexanes/ethyl acetate and gave 1.25 g of **7**, 97% isomeric purity (mp 171.0–173.5°C); NMR δ 1.97 (1 H, d of d, J = 5, 8), 2.34 (1 H, d of d, J = 5, 7), 2.68 (1 H, d of d, J = 7, 8), 6.59 (1 H, d, J = 6), 6.93 (1 H, d, J = 6), 6.95 (1 H, d, J = 7), 7.06–7.48 (3 H, m), 12.04 (1 H, s, b); IR ($CHCl_3$) 3059, 3008, 1704, 1444, 1233; MS, m/z (rel intensity) 186 (M^+, 48), 168 (39), 141 (100), 139 (39), 115 (71).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.38; H, 5.11.

***trans*-2-(Hydroxymethyl)spiro[cyclopropane-1,1′-indene] (3).** A solution of lithium aluminum hydride (60 mg, 1.58 mmol) in dry ether (5 mL) was stirred under a nitrogen atmosphere while a solution of the trans acid **7** (150 mg, 0.81 mmol) in ether (3 mL) was added dropwise. The reaction solution was heated under reflux for 3 h. The standard workup gave an ethereal solution which was dried (Na_2SO_4), filtered, and concentrated to provide 139 mg (100%) of the hydroxymethyl compound **3** as a clear colorless oil. An analytical sample was purified by VPC (column C, 165 °C): NMR δ 1.25 (1 H, broad s), 1.61 (1 H, d of d, J = 4, 7), 1.91 (1 H, d of d, J = 5, 9), 2.33 (1 H, m), 3.65–4.25 (2 H, m), 6.17 (1 H, d, J = 6), 6.88 (1H, d, J = 6), 7.10–7.56 (4 H, m); IR ($CHCl_3$) 3600, 3070, 3015, 2950, 2890, 1455, 1215, 1040, 1015; MS, m/z (rel intensity) 172 (M^+, 19), 154 (5), 153 (7), 142 (21), 141 (34), 139 (11), 129 (21), 128 (100).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.61; H, 6.93.

***trans*-2-(Methoxymethyl)spiro[cyclopropane-1,1′-indene] (9).** A solution of alcohol **3** (105 mg, 0.61 mmol) in dimethyl sulfoxide (10 mL) was deoxygenated with a stream of nitrogen for 30 min. A crystal of triphenylmethane was added, and then the solution was titrated with n-butyllithium (1.4 M in hexanes) to a pink end point. The anion was immediately quenched with iodomethane (0.6 g, 4.3 mmol), and the solution stirred for 1 h; the reaction mixture was then added to water (50 mL). The hydrolyzed mixture was extracted with ether (4 × 10 mL), and these extracts were combined, washed (H_2O, brine), dried ($MgSO_4$), and concentrated to yield 108 mg (95%) of a light yellow oil. An analytical sample was prepared by VPC (column **C**, 165 °C); NMR δ 1.60–1.88 (2 H, m), 2.88 (1 H, m), 3.34 (3 H, s), (2 H, m), 6.35 (1 H, d, J = 6)8 6.94 (1 H, d, J = 6), 6.90–7.50 (4 H, m); IR ($CHCl_3$) 3060, 3000, 2930, 2875, 1457, 1410, 1350, 1100, 1015, 945; MS, m/z (rel intensity) 186 (M^+, 19), 171 (1), 155 (4), 154 (6), 153 (5), 141 (12), 129 (11), 128 (100), 115 (7), 45 (14).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.87; H, 7.80.

Methyl *trans*-2-Spiro[cyclopropane-1,1′-indene]carboxylate (10). An ether solution of diazomethane (generated from N-methyl-N-nitrosourea in 40% aqueous KOH at 0 °C) was added to an ethereal solution of the trans acid **7** (0 °C) until the yellow color persisted in solution. The solution was allowed to stand for 15 min, and the excess diazomethane was then quenched by the dropwise addition of acetic acid. The resulting solution was washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to give a quantitative yield of **10** as a colorless oil. An analytical sample was purified by VPC (column C, 170°C): NMR δ 1.92 (1 H, d of d, J = 4, 9), 2.43 (1 H, d of d, J = 4, 7), 2.61 (1 H, d of d, J = 7, 9), 3.74 (3 H, s), 6.58 (1 H, d, J = 6), 6.85–7.02 (2 H, m), 7.06–7.46 (3 H, m); IR 3010, 2955, 1728, 1460, 1442, 1389, 1175, 905; MS m/z (rel intensity) 200 (M^+, 41), 185 (2), 169 (13), 168 (35), 158 (19), 141 (100), 139 (43), 115 (77).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.06; H, 6.23.

Optical resolution of (±)-7 was accomplished by recrystallization of the diastereomeric quinine salts. A solution of 1.01 g (5.4 mmol) of **(±)-7** in hot absolute ethanol (10 mL) was added to a hot solution of quinine (1.75 g, 5.4 mmol) in absolute ethanol. The resulting solution was concentrated on a steam bath to about 15 mL, hexanes (3 mL) were added, and the solution was allowed to cool to room temperature. White crystalline salt (1.02 g) was filtered from the solution; this solid was redissolved in a minimum amount of hot ethanol (about 12 mL) and the solution was diluted with hexanes (2 mL). Three such recrystallizations gave 0.50 g of the diastereomerically pure amine salt of **(+)-7**, $[\alpha]_{546}$ 242° ($CHCl_3$), mp 188.5–189.5 °C.

Hydrolysis of the amine salt (0.33 g) was done in 10% aqueous HCl in a separatory funnel. The solution was extracted with ether (4 × 25 mL), and the combined ether extracts were washed (10% aq HCl, H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 113 mg of a white crystalline solid, mp 165.5–167.5°C, $[\alpha]_{546}$ 873° ($CDCl_3$).

The NMR spectrum of **(+)-7** was identical with that of the racemic acid but showed no trace of the diastereomeric impurity **8** (3% of which had been present in the racemic acid mixture). Small samples of salt from the mother liquors of each recrystallization were hydrolyzed, and NMR analysis of the acids thus obtained showed that **8** had been effectively concentrated in the mother liquors after two recrystallizations.

To check the optical purity of **(+)-7** it was esterified as previously described to give the ester **(+)-10** which was then analyzed by NMR in the presence of $Eu(hfc)_3$. Addition of small portions of shift reagent to a benzene-d_6 solution of **(±)-10** causes one of the cyclopropyl ring proton signals to move downfield to δ 3.10, by which point two signals corresponding to enantiotopic protons are evident ($\Delta\nu$ = 0.18 ppm). With the addition of more shift reagent the methyl signal moves downfield to δ 10.60, by which point two enantiotropic methyl signals are observed ($\Delta\nu$ = 0.16 ppm). A sample of **(+)-10** was treated in exactly the same way, showed only one signal in each of these areas, and was thus taken to be optically pure.

Methyl Propiolate. Oxidation of propargyl alcohol (120 g, 2.14 mol) by the method of Wolf[19] using CrO_3 (288 g, 2.88 mol) and concentrated sulfuric acid (460 g) in acetone (1.0 L) yielded 119 g (79.3%) of distilled propionic acid. A solution of this acid (109 g, 1.56 mol) in concentrated sulfuric acid (110 g) and methanol (450 mL) was heated under reflux for 1 h.[19] The mixture was extraced with ether (1 × 400 mL, 8 × 100 mL) after adding H_2O (200 mL) and brine (300 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated on a 1-m vacuum-jacketed distillation column packed with glass helices. The remaining methanol was distilled off as an azeotrope with added methylal before distilling 64.5 g (49.3%) of methyl propiolate, bp 101–102°C; NMR δ 2.91 (1 H, s), 3.81 (3 H, s).

Diazoindene. Indene (107 g) and p-toluenesulfonyl azide[17] (164.5 g) were combined as described by Rewicki and Tuchscherer;[18] the reaction mixture was diluted with water (500 mL) and petroleum ether (bp 35–60 °C; 500 mL). After separation of the layers the aqueous phase was extracted with petroleum ether (7 × 75 mL), and the combined extracts were washed extensively with water (8 × 100 mL). At several points during the washing and extraction procedures a yellow byproduct precipitated and was removed by filtration. The organic solution was dried (Na_2SO_4), concentrated to about 250 mL, and cooled to −4°C in the freezer to precipitate the remaining byproduct. Filtration and Kugelrohr distillation (40–90 °C, 0.01 torr) gave a red oil from which most of the unreacted indene was then distilled (32 °C, 1 torr). The oil which remained after three separate reactions starting with a total of 344 g (2.67 mol) of indene and 529 g (2.67 mol) of tosyl azide amounted to 85.4 g of material containing 60.9 g (16.1%) of diazoindene (NMR δ 6.36 (1 H, d, J = 5), 6.99 (1 H, d, J = 5), 7.10–7.64 (4 H, m)); the major contaminants were unreacted indene and N,N-diethyl-p-toluenesulfonamide.

Methyl 5′-Spiro[indene-1,3-(3*H*-pyrazole)]carboxylate (11) and Methyl 4′-Spiro[indene-1,3′-(3*H*-pyrazole)]carboxylate (12). Methyl propiolate (13.0 g, 155 mmol) was added dropwise to a solution of diazoindene (20 g, 141 mmol) in ether (50 mL) at room temperature. The reaction solution was stirred in the dark for 42 h and then concentrated at reduced pressure to give 38.6 g of dark red semisolid material. This was divided in half and each portion was chromatographed on 200 g of silica gel (hexanes, then 5% ethyl acetate/hexanes). The red chromatographic fractions were cooled to −4 °C; a total of 6.3 g of one of the regioisomers, **11** or **12**, was obtained as red needles, mp 78–81°C dec; NMR δ 3.88 (3 H, s), 6.63 (1 H, d, J = 5.5), 6.78 (1 H, s), 6.92 (1 H, d of d, J = 1, 5.5), 7.10–7.35 (3 H, m), 7.50–7.65 (1 H, m). Concentration of filtrates led to 16.0 g of a red oil, estimated by NMR to contain 14.8 g of product (**11** and **12**). Analytical data was collected on the mixture (7:3) of regioisomers: NMR δ 3.87 (3 H, s), 6.40–7.35 (6 H, m), 7.50–7.65 (1 H, m); IR ($CHCl_3$) 2078, 1710, 1615, 1436, 1305, 1250; MS m/z (rel intensity) 226 (M^+, 40), 198 (25), 155 (16), 153 (21), 139 (100), 127 (14), 113 (24); exact mass calcd for $C_{13}H_{10}N_2O_2$, 226.074; found, 226.075.

This reaction was run three times: a total of 55.7 g (392 mmol) of diazoindene was reacted with 37.8 g (450 mmol) of methyl propiolate to afford 65.1 g of the two regioisomers (97% average purity after chromatography: 63.1 g, 71% yield), which was used without further purification to make deuterium-labeled spiro[cyclopropane-1,1′-indenes].

A similar, small-scale preparation led to 3.43 g of the pyrazoles **11** and **12** which was used to synthesize the unlabeled methyl ether **17**.

Photolysis Filter Solution. The filter solution described by Arnold, Humphreys, and Leigh[21] was prepared by dissolving 1.70 g of bismuth chloride hydrate ($BiCl_3 \cdot H_2O$) in 1.20 L of 10% aqueous hydrochloric acid; ultraviolet absorbance (1-cm pathlength): 0.1 (362 nm), 1.0 (354 nm), 2.0 (350 nm), and 3.0 (346 nm).

***cis*-2-Spiro[cyclopropane-1,1′-indene]carboxylic Acid (8).** Photolysis of a solution of spiropyrazoles **11** and **12** (3.42 g, 15.1 mmol) in benzene (50 mL) at 15 °C using a medium-pressure Hanovia 450-W mercury lamp and a Pyrex glass filter as well as an aqueous $BiCl_3$ filter solution[21] led to loss of the red color after 7 h. Analysis by NMR indicated a quantitative conversion to the spirocyclopropene **13**. The photolysis solution was concentrated to give a light yellow oil: NMR δ 3.72 (3 H, s), 6.18 (1 H, d, J = 5.5), 6.95 (1 H, d, J = 5.5), 7.00–7.45 (4 H, m), 8.25 (1 H, s); IR ($CHCl_3$) 3145, 1780, 1713, 1438, 1225; UV (cyclohexane) λ_{max} 224 nm (ϵ 2.69 × 10^4); MS, m/z (rel intensity) 198 (M^+, 25), 155 (19), 153 (13), 139 (100), 127 (13), 113 (8). Exact mass: calcd for $C_{13}H_{10}O_2$: 198.068. Found: 198.068. (In syntheses of deuterium labeled molecules, the concentration step was omitted and some loss of the intermediate spirocyclopropene through polymerization was thus avoided.)

The oil was dissolved in dioxane (180 mL), and to this was added 5.80 g (30 mmol) of potassium azodicarboxylate, followed by the dropwise addition of acetic acid (3.60 g, 60 mmol) as a solution in dioxane (20 mL) over 1 h.[22] After the solution was stirred for another 30 min, water (100 mL) was added and the mixture was extracted with ether (4 × 50 mL). The extracts were combined, washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to give 4.2 g of brown oil.

This oil was treated with 10% aqueous sodium hydroxide (30 mL) and stirred at 90 °C for 13 h. The mixture was cooled, washed (ether), and acidified to pH 1–2 (concentrated HCl). The milky solution was extracted with ether (5 × 50 mL), and the combined extracts were washed (H_2O, brine), treated with decolorizing charcoal, dried ($MgSO_4$), filtered, and concentrated to yield 1.27 g of a pale yellow solid (45% from the pyrazoles), a 96:4 ratio of acids **8** and **7**, respectively.

An analytical sample prepared by recrystallization (hexanes/ethyl acetate) had mp 151.5–153 °C; NMR δ 2.05 (1 H, d of d, J = 5, 8), 2.24 (1 H, d of d, J = 5, 7), 2.75 (1 H, d of d, J = 7, 8), 6.03 (1 H, d, J = 6), 6.91 (1 H, d, J = 6), 7.00–7.55 (4 H, m), 11.59 (1 H, s); IR ($CHCl_3$) 3060, 3002, 1703, 1450, 1425, 1230; MS, m/z (rel intensity) 186 (M^+, 95), 168 (57), 141 (100), 115 (48).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.08; H, 5.28.

Methyl *cis*-2-Spiro[cyclopropane-1,1′-indene]carboxylate (16). An ether solution of the cis acid **8** (50 mg, 0.27 mmol) was treated with diazomethane as previously described in the synthesis of **10** to give **16** in quantitative yield as a clear colorless oil. An analytical sample was purified by VPC (column C, 170 °C): NMR δ 2.01 (1 H, d of d, J = 5, 8), 2.29 (1 H, d of d, J = 5, 8), 2.78 (1 H, t, J = 8), 3.65 (3 H, s), 6.04 (1 H, d, J = 6), 6.90 (1 H, d, J = 6), 7.04–7.60 (4H, m); IR ($CHCl_3$) 3010, 2955, 1730, 1460, 1440, 1396, 1177, 910; MS, m/z (rel intensity) 200 (M^+, 63), 185 (2), 169 (21), 168 (53), 158 (27), 141 (100), 115 (59).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.82; H, 6.35.

Ethyl alcohol-*d*, prepared from tetraethyl orthosilicate and deuterium oxide,[24] was distilled from magnesium under a nitrogen atmosphere before use. Analysis of the material by NMR spectroscopy indicated that it had greater than 99% deuterium incorporation.

Potassium Azodicarboxylate. The 197 g of potassium azodicarboxylate[22] used to generate dideuteriodiimide was slurried successively with absolute ethanol (2 × 500 mL) and absolute methanol (3 × 500 mL) followed each time by suction filtration. It was then placed under vacuum to remove residual solvent and stored over P_2O_5 under reduced pressure (0.01 torr) for several weeks. Preliminary experiments using this washed and thoroughly dried salt as a precursor to dideuteriodiimide indicated that it contained proton sources. Portions of the salt were therefore ground gently to a powder in a dry nitrogen atmosphere and treated with an equal weight of ethyl alcohol-*d*.[24] The slurry was left standing for 12 h, the ethanol was removed at reduced pressure, and then the residue was placed under vacuum at 0.01 torr and stored over P_2O_5 as before.

***cis*-2-(Hydroxymethyl)spiro[cyclopropane-1,1′-indene] (4).** A solution of cis acid **8** (120 mg, 0.65 mmol) in ether (3 mL) was added dropwise to a solution of lithium aluminum hydride (40 mg, 1.05 mm) in ether (5 mL). The mixture was heated under reflux for 3.5 h under a nitrogen atmosphere and then quenched. Standard workup gave 102 mg (92%) of **4** as a clear, colorless oil. An analytical sample was purified by VPC (column A, 165 °C): NMR δ 1.25 (1 H, broad s), 161 (1 H, d of d, J = 5, 7), 1.91 (1 H, d of d, J = 5, 9), 2.33 (1 H, m), 3.65–4.25 (2 H, m), 6.17 (1 H, d, J = 6), 6.88 (1 H, d, J = 6), 7.10–7.56 (4 H, m); IR ($CHCl_3$) 3600, 3070, 3015, 2950, 2890, 1455, 1215, 1040, 1015; MS, m/z (rel intensity) 172 (M^+, 19), 154 (5), 153 (7), 142 (21), 141 (34), 139 (11), 129 (21), 128 (100), 115 (34).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.61; H, 6.93.

***cis*-2-(Methoxymethyl)spiro[cyclopropane-1,1′-indene] (17).** A solution of alcohol **4** (60 mg, 0.35 mmol) in dimethyl sulfoxide (10 mL) was deoxygenated with a nitrogen bubbler for 30 min. A crystal of triphenylmethane was added, and the solution was titrated with *n*-butyllithium (1.2 *M* in hexanes) to the red end point. The anion was immediately quenched with iodomethane (0.5 g, 3.5 mmol), and the solution was stirred for 2 h. After adding water (40 mL) the solution was extracted with ether (4 × 25 mL). The ether extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to give 64.1 mg (99%) of methyl ether **17** as a light yellow oil, which was contaminated with 3–4% of the trans methyl ether **9**.

An analytical sample was purified by VPC (column A, 165 °C): NMR δ 1.60 (1 H, d of d, J = 5, 7), 1.90 (1 H, d of d, J = 5, 9), 2.22 (1 H, m), 3.24 (3 H, s), 4.73 (2 H, ABX, $\Delta\nu$ = 0.14 ppm, J = 7, 11), 6.15 (1 H, d, J = 5.5), 6.84 (1 H, d, J = 5.5), 7.04–7.50 (4H, m); IR ($CHCl_3$) 3070, 3010, 2930, 2825, 1457, 1345, 1102, 942, 915; MS, m/z (rel intensity) 186 (M^+, 16), 171 (1), 155 (4), 154 (5), 153 (5), 141 (13), 129 (15), 128 (100), 115 (8).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.49; H, 7.84.

Methyl *trans,trans*-2,3-Dideuterio-*cis*-2-spiro[cyclopropane-1,1′-indene]carboxylate (20). A solution of pyrazoles **11** and **12** (20.14 g, 89.1 mmol) in benzene (2.5 L) was irradiated at 15 °C with a 450-W Hanovia medium-pressure mercury lamp for 4.5 h. The light was filtered by both Pyrex glass and a filter solution of aqueous bismuth chloride.[21] The resulting light yellow solution of cyclopropene **13** was concentrated on a rotary evaporator at room temperature to a volume of 200 mL and dried[23] (4-A molecular sieves) in the dark under a nitrogen atmosphere for 4 h.

A 1-L three-necked oven-dried flask was fitted with a magnetic stir bar and nitrogen inlet and was charged with 35.0 g (180 mmol) of potassium azodicarboxylate. Dry dioxane was distilled from sodium into the flask, followed by the addition of the benzene solution of **13**. The solution was stirred at room temperature while acetic acid-*d* (24.8 g, 406 mmol, 99% deuterium content; Norell) was added; 12 mL was added over the 1st h and 14 mL over the next 12 h. Stirring was continued for 21 h after the addition was complete, then H_2O (500 mL) and ether (150 mL) were added. Separation of the layers followed by extraction of the aqueous phase with ether (4 × 70 mL) gave, after combining the extracts, an organic phase which was washed (saturated aqueous $NaHCO_3$, H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 21.60 g of dark brown oil. Repeating this procedure twice, using a total of 63.16 g (279 mmol) of pyrazoles, gave 60.56 g of crude oily product. This material was divided in two, and each half was chromatographed on 200 g of silica gel (5% ethyl acetate/hexanes). Concentration of the appropriate fractions gave 26.34 g of a light yellow oil. Analysis by MS and NMR indicated that the oil contained the cyclopropyl ester product, side product **18** (from reduction of the indenyl double bond), and a small amount of an impurity containing a tosyl group, carried through from a previous synthetic reaction.

Purification of **20** was accomplished by using low-pressure HPLC partition chromatography. A 40 cm × 1.2 cm column was packed with silica gel (Biorad, HA minus 325 mesh) that had been coated (20% by weight) with diethylene glycol succinate. Elution with 3% ethyl acetate/hexanes separated the two esters (**20** and **18**). Though these two compounds were not completely resolved by this chromatography column, by recycling overlap material 19.10 g of a clear pale yellow oil was obtained which contained less than 0.3% of the overreduced material **18** (analysis by VPC, column A). This oil was (89% by weight) a mixture of cis (**20**) and trans cyclopropyl esters (17.00 g, 30% from pyrazoles **11** and **12**), in a 96:4 ratio favoring the desired cis isomer **20**; NMR δ 2.27 (1 H, s), 3.64 (3 H, s), 6.04 (1 H, d, J = 6), 6.84 (1 H, d, J = 6), 7.05–7.55 (4 H, m).

***trans,trans*-2,3-Dideuterio-*cis*-2-spiro[cyclopropane-1,1′-indene]carboxylic Acid (19).** A solution of 16.11 g (79.8 mmol) of the mixture of ester **20** and its trans isomer (96:4) in 10% aqueous sodium hydroxide was heated to 82 °C for 14 h. After cooling, the solution was washed (ether), acidified to pH 1–2 (concentrated HCl), and extracted with ether (6 × 100 mL). The combined ether extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to furnish 14.62 g (96.5%) of a pale yellow solid, which proved to be a 96:4 mixture of cis and trans dideuterio acids. The tosyl impurity contributed less than 1% to the mixture. In an earlier reaction, 1.01 g (5.0 mmol) of esters had been

treated in a like manner to give 0.81 g of the acid mixture. Analysis by NMR indicated 96% deuterium incorporation; NMR δ 2.02 (0.04 H, d, J = 5), 2.23 (1 H, s), 2.73 (0.04 H, d, J = 7), 6.00 (1 H, d, J = 6), 6.90 (1 H, d, J = 6), 7.00–7.52 (4 H, m), 11.59 (1 H, br s).

Optical Resolution of Cis Acid 19. To a solution of (±)-**19** (7.80 g, 41.5 mmol) in hot absolute ethanol (750 mL) quinine monohydrate (13.44 g, 41.5 mmol) was added. The clear solution was allowed to cool to room temperature and to stand for 5 h. Filtration of the solution provided 12.9 g of salt, which was recrystallized from a minimum amount of hot ethanol (approximately 500 mL). Filtration provided 7.51 g of a white solid ($[\alpha]_D$ +48° ($CHCl_3$)), which was recrystallized again from a minimum amount of hot ethanol (approximately 400 mL) to give 5.70 g of a fluffy white solid ($[\alpha]_D$ +54.8° $CHCl_3$)). Similar treatment of the remaining cis acid (7.70 g) gave after three recrystallizations 4.80 g of salt ($[\alpha]_D$ +54.1° ($CHCl_3$)). Both of these samples were hydrolyzed in 10% aqueous hydrochloric acid (300 mL), and the carboxylic acid was isolated by extraction with ether (5 × 60 mL). The combined extracts were washed (10% aqueous HCl, H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to give a combined yield of 3.88 g (100%) of an extremely viscous light yellow oil, (+)-**19**.

The mother liquors from the above recrystallizations were concentrated to yield second crops of crystalline material. These precipitates were filtered from the solutions and recrystallized twice from the minimum amount of absolute methanol to yield two samples of salt: 3.90 g ($[\alpha]_D$ −139.9° ($CHCl_3$)) and 6.57 g ($[\alpha]_D$ −144.6° ($CHCl_3$)). These samples were combined and then recrystallized again from hot methanol (400 mL) to give 8.40 g of salt having $[\alpha]_D$ −150.3° ($CHCl_3$).

This sample of salt was hydrolyzed in 400 mL of 10% aqueous hydrochloric acid as previously described to give 3.163 g (100%) of (−)-**19** as a clear, colorless, and extremely viscous oil.

Accurate specific rotations for these two antipodes were not obtained because they were never entirely freed of solvent; even subjecting these acids to a vacuum of 0.01 torr for several hours while the samples were maintained at 60 °C did not prove adequate. The observed specific rotations after purification on a low-pressure chromatography column (15–40-μm silica gel, acetic acid/ethyl acetate/hexanes) were $[\alpha]_{546}$ +221.9° ($CHCl_3$) and $[\alpha]_{546}$ −236.5° ($CHCl_3$) for cis acids (+)-**19** and (−)-**19**.

The NMR spectra of the two antipodes were identical with each other and with that of the racemic cis acid except for absorptions reflecting differing amounts of a diastereomeric impurity, the anti acid. The cis and trans isomers are easily distinguishable by examination of the olefinic region, and in the spectrum of (+)-**19** no trace of trans isomer could be seen. The spectrum of (−)-**19** did indicate the presence of approximately 2% of anti isomer.

To determine the optical purity of the two acids (+)-**19** and (−)-**19** small samples of each were esterified with diazomethane. The esters obtained, (+)-**20** and (−)-**20**, respectively, after purification by low-pressure chromatography on silica gel and concentration to clear oils, had specific rotations $[\alpha]_{546}$ +126.6° and −125.5° ($CHCl_3$). These esters, as well as a sample ($[\alpha]_{546}$ −51.8°) prepared by combining unequal amounts of these two antipodes, were dissolved in benzene-d_6 and treated with small portions of Eu(hfc)$_3$. The methyl signal in all three samples moved downfield in the spectra, and in the case of the artificial mixture of antipodes it had split into two well-resolved enantiotopic singlets ($\Delta\nu$ = 0.07 ppm) around 4.8 ppm, with the minus isomer farther downfield. Continued addition of Eu(hfc)$_3$ moved these signals down to 9.5 ppm, at which point the enantiotopic signals were again well separated, but with the plus isomer farther downfield. The signal for the cyclopropyl ring proton also moved downfield and split into two enantiotopic signals, which when centered around 4.3 ppm were separated by an unusually large chemical shift difference of 0.53 ppm. Methyl esters (+)-**19** and (−)-**19** in the presence of Eu(hfc)$_3$ each only showed one methyl peak and one C(3)–H signal.

(−)-(1*S*,2*S*,3*S*)-*trans*,*trans*-2,3-Dideuterio-*cis*-2-(hydroxymethyl)-spiro[cyclopropane-1,1′-indene] (21). A solution of carboxylic acid (−)-**19** (1.24 g, 6.57 mmol) in ether (15 mL) was added slowly to a cooled solution of lithium aluminum hydride (318 mg, 8.37 mmol) in 50 mL of ether. The solution was heated under reflux for 3 h under a nitrogen atmosphere; workup in a standard manner led to an ethereal solution, which was dried (Na_2SO_4), filtered, and concentrated to give **21** (1.119 g, 98%) as a colorless oil. An analytical sample (26.2 mg) was purified by VPC (column C, 165 °C); NMR δ 1.27 (1 H, broad s), 1.50 (1 H, s), 3.59 (2 H, AB, $\Delta\nu$ = 0.24 ppm, J = 12), 6.14 (1 H, d, J = 5.5)8 6.83 (1 H, d, J = 5.5), 7.06–7.50 (4 H, m).

(−)-(1*S*,2*S*,3*S*)-*trans*,*trans*-2,3-Dideuterio-*cis*-2-(methoxymethyl)-spiro[cyclopropane-1,1′-indene] ((−)-1-c). A solution of alcohol **21** (1.093 g, 6.26 mmol) in dimethyl sulfoxide (65 mL) was deoxygenated by bubbling a stream of nitrogen through the solution for 30 min. Triphenylmethane (2–3 mg) was added to the solution which was then titrated to a pink end point using 1.2M *n*-butyllithium in hexanes (about 5.6 mL). The anion was quenched immediately with excess iodomethane (4.56 g, 32 mmol) and stirred for 5 h. The reaction mixture was added to a mixture of water (300 mL) and brine (100 mL) before extracting with ether (5 × 50 mL). The combined ethereal extracts were washed with water (5 × 50 mL) and brine (2 × 50 mL) before they were dried ($MgSO_4$), filtered, and concentrated to yield 1.21 g of an orange oil. This material was distilled by using a Kugelrohr apparatus (50–70°C, 0.05 torr) to give 1.11 g of a light yellow oil. An analytical sample purified by VPC (column D, 165 °C) had $[\alpha]_{546}$ −171.7° ($CHCl_3$): NMR δ 1.58 (1 H, s), 3.23 (3 H, s), 3.71 (2 H, AB, $\Delta\nu$ = 0.18 ppm, J = 11), 6.13 (1 H, d, J = 5), 6.82 (1 H, d, J = 5), 7.04–7.48 (4H, m); IR ($CHCl_3$) 3070, 2985, 2920, 2885, 2815, 1415, 1352, 1192, 1130, 1085, 937; MS, m/z (rel intensity) 188 (M^+, 17), 157 (4), 156 (4), 155 (4), 154 (4), 143 (10), 130 (12), 129 (100), 116 (6).

The specific rotation of −171.7° was measured on a sample of this methyl ether that had been purified by VPC using a column of sufficient length (column D) to separate it from a small amount of the trans isomer. The samples used in the kinetic work were purified by VPC on a shorter column (column C, 165 °C), which did not separate this diastereomeric impurity. Careful analysis by NMR integration of the signals for C-(2′)–H, C(3)–H, and the methyl group showed that the sample of (−)-**1-c** used in kinetic runs contained 2.3% of isomer **2**-t derived from the trans acid which came through the resolution step. This information combined with the observed specific rotation of the starting material for thermolysis (−165.9°, $CHCl_3$) and that of optically pure trans isomer (+)-**2-c** indicated that this 2.3% was a mixture of the two enantiomers (+)-**2**-t and (−)-**2**-t in a 65:35 ratio.

Methyl (+)-(1*R*,2*R*,3*R*)-*trans*,*trans*-2,3-Dideuterio-*cis*-2-spiro[cyclopropane-1,1′-indene]carboxylate ((+)-20). An ethereal solution of carboxylic acid (+)-**19** (3.42 g, 18.2 mmol) was esterified at 0 °C by the addition of excess diazomethane (generated from 10 g of Diazald[38]) until a yellow color persisted in the solution. Excess diazomethane was quenched with acetic acid before the solution was washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 3.51 g (95.5%) of cis ester (+)-**20** as a colorless oil. The NMR spectrum of this material was identical with that of the racemic material previously described.

tert*-Butyl alcohol-*d was prepared by the method of Young and Guthrie[26] from *tert*-butyl orthoborate[39] and deuterium oxide. The alcohol was distilled from sodium *tert*-butoxide under a dry nitrogen atmosphere just prior to use. Analysis by NMR spectroscopy indicated greater than 98% deuterium incorporation.

Epimerization of Cis Ester (+)-20. A dry benzene solution of (+)-**20** (1.07 g, 5.31 mmol) in 20 mL of dry benzene was concentrated by distillation under a dry nitrogen atmosphere to a volume of about 4 mL. This concentrate was then added to a solution of freshly sublimed potassium *tert*-butoxide[25] (250 mg, 2.2 mmol) in approximately 15 mL of *tert*-butyl alcohol-*d*;[26] the reaction solution was heated to 70 °C for 3 h under a nitrogen atmosphere, cooled to room temperature, and diluted with deuterium oxide (2 mL). After the quenched reaction mixture had been stirred for 5 min, water (75 mL) was added and the resulting solution was neutralized (18% aqueous HCl) and extracted with ether (5 × 30 mL). The combined ether extracts were extracted with aqueous sodium bicarbonate (4 × 20 mL), washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 700 mg of a mixture of *tert*-butyl and methyl esters as a clear, colorless oil; 86% of this mixture of esters had the trans configuration.

The aqueous sodium bicarbonate extracts were acidified to pH 1–2 and extracted with ether (4 × 20 mL). The ether extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 287 mg (29%) of a 4:1 mixture of cis acid (+)-**19**:trans acid (+)-**22**.

This reaction was repeated by using 1.20 g (5.94 mmol) of cis ester (+)-**20** and gave comparable yields of the neutral and acidic products.

The esters isolated from the epimerization reactions were combined (1.565 g, approximately 60% yield) and hydrolyzed in a mixture of dimethoxyethane (50 mL) and 10% aqueous hydrochloric acid (50 mL) heated to 60 °C for 2 days. The reaction mixture was poured into water (250 mL) and the resulting solution was then extracted with ether (5 × 50 mL). The ether extracts were combined and extracted with saturated aqueous sodium bicarbonate (5 × 50 mL). These aqueous extracts were then acidified (concentrated HCl) to pH 1–2 and extracted with ether (5 × 50 mL). The ether extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 1.106 g (52% from the cis methyl ester (+)-**20**) of a light yellow solid. Analysis by NMR indicated it to be an 86:14 mixture of trans acid (+)-**22** and cis acid (+)-**19**, respectively. It also showed that there had been a slight loss of deuterium content at the epimerized center, from 96 down to 93%.

(38) Fieser, L. F.; Fieser, M. *op. cit.* p 191.
(39) Lippencott, S. B. U.S. Patent; *Chem. Abs.* **1954**, *48*, 4581h.

Isolation of (+)-(1*R*,2*S*,3*R*)-*cis*,*trans*-2,3-Dideuterio-*trans*-2-spiro[cyclopropane-1,1'-indene]carboxylic Acid ((+)-22). The trans acid (+)-**22** was separated from the mixture of (+)-**22** and (+)-**19** by fractional crystallization of the respective quinine salts. The 86:14 mixture of acids (+)-**22** and (+)-**19** (1.10 g, 5.85 mmol) was dissolved in a hot mixture of absolute ethanol (6 mL) and hexanes (6 mL). This solution was added to a hot solution of quinine (1.85 g, 5.74 mmol) in ethanol (12 mL). The following day, filtration gave 2.22 g of white crystalline quinine salt. This salt was dissolved in a minimum volume of hot absolute ethanol (about 20 mL), and hexanes (5 mL) were then added before the solution was allowed to cool. Filtration of the solution furnished 1.71 g of crystalline salt. After two more recrystallizations there remained 1.22 g of salt having $[\alpha]_{546}$ +257.2° (ethanol). The mother liquors were combined and fractionally crystallized in a similar manner to yield only 0.22 g of material of comparable isomeric purity (assessed by NMR after hydrolysis of a small sample). The remainder of the salt, when forced to yield crystalline material, gave a eutectic mixture of the two quinine salts in a 3:2 ratio favoring the salt of the trans isomer, (+)-**22**.

The two samples of 1.22 g and 0.22 g were combined and hydrolyzed in 10% aqueous hydrochloric acid. The solution was extracted with ether (5 × 25 mL), and the combined extracts were washed (10% aq HCl, H_2O, brine), dried ($MgSO_4$), filtered and concentrated to yield 548.5 mg of white crystalline material, mp 164–166°C; NMR δ 1.97 (1 H, s), 6.59 (1 H, d, J = 6), 6.93 (1 H, d, J = 6), 7.02–7.44 (4 H, m), 11.58 (1 H, broad s).

(1*R*,2*S*,3*R*)-*cis*,*trans*-2,3-Dideuterio-*trans*-2-(hydroxymethyl)spiro[cyclopropane-1,1'-indene] (17). Reduction of carboxylic acid (+)-**22** (548 mg, 2.91 mmol) was accomplished by using lithium aluminum hydride in an ether solution as described previously. This procedure yielded 484 mg (97%) of alcohol as a clear colorless oil; NMR δ 1.56 (1 H, broad s), 1.76 (1 H, s), 3.81 (2 H, AB, $\Delta\nu$ = 0.37, J = 12), 6.36 (1 H, d, J = 6), 6.98 (1 H, d, J = 6), 6.85–7.50 (4 H, m).

(+)-(1*R*,2*S*,3*R*)-*cis*,*trans*-2,3-Dideuterio-*trans*-2-(methoxymethyl)-spiro[cyclopropane-1,1'-indene] ((+)-2-c). Alkylation of the alcohol prepared immediately above (484 mg, 2.79 mmol) using the procedure previously described for alkylation of the unlabeled alcohol gave 544 mg of an orange oil. An analytical sample was purified by VPC (column C, 165 °C); $[\alpha]_{546}$ 269.0° ($CHCl_3$); NMR δ 1.74 (1 H, s), 3.34 (1 H, s), 3.61 (2 H, AB, $\Delta\nu$ = 0.10 ppm, J = 9), 6.35 (1 H, d, J = 6), 6.93 (1 H, d, J = 6), 7.02–7.48 (4 H, m); IR ($CHCl_3$) 3050, 3000, 2930, 2890, 2825, 1457, 1378, 1168, 1103, 994, 947, 896, 820; MS, m/z (rel intensity) 188 (M^+, s), 154 (6), 153 (5), 142 (9), 130 (5), 129 (100), 116 (15).

This material was purified by VPC (column C, 165°C) before thermolysis. Careful analysis of the purified material by NMR showed that it contained approximately 0.4% of cis isomer **1-c**. This was apparently derived from incomplete separation of the trans and cis acids (+)-**22** and (+)-**19**, and was therefore assigned the (+)-**1-c** configuration in order to account for its presence explicitly in kinetic analyses.

Methyl (−)-1,1,2-Cyclopropanetricarboxylate ((−)-24). To a solution of partially resolved trans acid (−)-**7** (168 mg, 0.89 mmol, $[\alpha]_{546}$ −238.4° ($CHCl_3$)) in a mixture of acetonitrile (4 mL), carbon tetrachloride (4 mL), and water (8 mL) was added 3.8 g (17.8 mmol) of sodium periodate (sodium metaperiodate) and a catalytic amount (~5 mg) of $RuCl_3(H_2O)_{1-3}$.[27]

The solution was stirred vigorously for 72 h at room temperature before acetone (50 mL) was added, and the resulting solution was filtered and concentrated to dryness. The 325 mg of white solid obtained was then dissolved in 15 mL of methanol and treated with an ethereal solution of diazomethane until a yellow color persisted in solution. During this addition some material precipitated from solution and was removed by filtration after the excess diazomethane had been quenched through dropwise addition of acetic acid. The solution was concentrated to a volume of 3 mL by distillation of solvent through a 10-cm Vigreux column. The product was purified by VPC (column C, 135 °C) to give 40 mg of (−)-**24**, $[\alpha]_{546}$ −37.9° ($CHCl_3$). The spectral features of this material were identical with those previously reported.[28]

Sealed Tube Kinetics. The pyrolysis ampules were prepared from 7-mm borosilicate glass tubing. The tubes were soaked in an ammonium hydroxide/EDTA solution at 60 °C for at least 24 h and then rinsed well with distilled water and dried in an oven at 130 °C for 24 h.

Methyl ethers (−)-**1-c** and (+)-**2-c** were purified by VPC (column C, 165 °C), and samples of 40–100 mg were diluted with toluene to a volume of about 0.75 mL and sealed under vacuum (10^{-5} torr) in the pyrolysis ampules. The sealed ampules were typically 8 cm long.

The ampules were attached to a wire cage and submerged in a molten salt bath heated to 198.9 °C, as determined with a Hewlett-Packard 2802 A platinum resistance thermometer. The temperature of the bath decreased to 198.6 °C upon immersion of a tube, but recovered to a temperature of 198.9 °C within 2 min. Following a period in the kinetic bath, a pyrolysis tube was immediately cooled with tap water. The ratio of the four degenerate cis isomers to the set of four degenerate trans isomers was determined by VPC using column E with an oven temperature of 168 °C. These conditions produced retention times of approximately 140 and 160 min for the cis and trans isomers, respectively. The two isomer sets were then preparatively separated by using VPC (column D, 165 °C; retention times of 108 and 129 min, respectively). The set of four cis isomers (**1**) was first analyzed by polarimetry. Optical rotations were measured at a wavelength of 546 nm on samples of 11–20 mg dissolved in 4 mL of chloroform. The solvent was then removed, and the samples were redissolved in chloroform-*d* for analysis by NMR at 360 MHz.

The vapor-phase chromatographically homogeneous set of four degenerate trans isomers was first dissolved in chloroform-*d* for preliminary analysis by NMR (360 MHz). This solvent was then removed and replaced by benzene-d_6 before further analysis by NMR in the presence of an optically active shift reagent ($Eu(hfc)_3$).

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Supplementary Material Available: Ten NMR and $Eu(hfc)_3$ NMR spectra for representative substrates and thermolysis product mixtures (5 pages). Ordering information is given on any current masthead page.

Carbonyl Oxide Chemistry. The NIH Shift

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Abstract: Benzophenone oxide has been shown to oxidize 1-chloronaphthalene and *p*-xylene with accompanying NIH shift of chlorine and methyl, respectively. Similar oxidation of toluene leads to a mixture of *o*-, *p*-, and *m*-cresols while *N*-acetyl-L-phenylalanine ethyl ester is oxidized to the corresponding tyrosine derivative. The results are discussed in terms of their relationship to the "activation" of polycyclic aromatic hydrocarbons in polluted atmospheres and the possible production of mutagens/carcinogens.

Criegee was the first to suggest that carbonyl oxides are important intermediates in the ozonolysis reaction.[1] The experimental evidence[2] is overwhelmingly supportive of this suggestion. Interestingly enough there has been only one report[3] of the physical characterization of a carbonyl oxide. In addition, there are a few reports[4-6] describing the characterization by physical methods of

† Taken in part from a dissertation submitted by Shailendra Kumar to the faculty of the University of Missouri-St. Louis in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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