Stereochemistry of Thermal [1,5] Carbon Shifts in Norcaradienes: Complete Kinetic Analysis of the Degenerate Thermal Isomerization of (+)-2-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene

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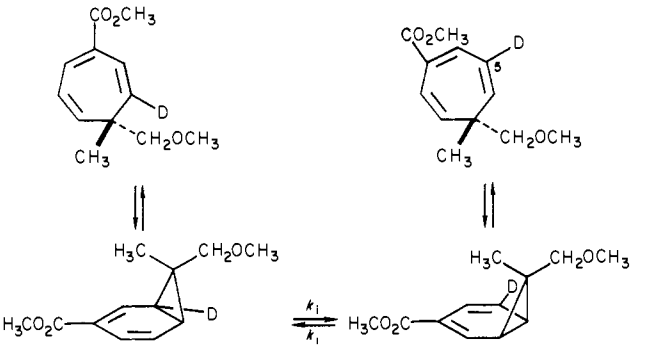
Abstract: (+)-2-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene has been synthesized and its thermal stereomutations have been studied. Pyrolysis at 223.4 °C gave both first-order racemization and first-order equilibration of the deuterium label between C(2) and C(4). The rate of racemization was found to be $(6.13 \pm 0.20) \times 10^{-6}$ s^{-1}; the rate of deuterium scrambling was $(6.07 \pm 0.28) \times 10^{-6}$ s^{-1}. Analysis of the pyrolysis product by NMR at 360 MHz in the presence of an optically active NMR shift reagent permitted determination of concentrations of all four chromatographically inseparable isomers of 2-deuterio- and 4-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene, which led to values for rate constants for three stereochemically distinctive processes: k_i, for [1,5] carbon shift with inversion, $(2.96 \pm 0.09) \times 10^{-6}$ s^{-1}; k_r, for [1,5] carbon shift with retention, $(0.08 \pm 0.17) \times 10^{-6}$ s^{-1}; and k_e, for one-centered epimerization at C(1), $(0.10 \pm 0.13) \times 10^{-6}$ s^{-1}. The [1,5] carbon migration in this norcaradiene–cycloheptatriene system proceeds exclusively with inversion at the migrating carbon, a reaction stereochemistry favored by least motion but forbidden by orbital symmetry theory.

1,3,5-Cycloheptatrienes and bicyclo[4.1.0]hepta-2,4-dienes may interconvert facilely.[1] This valence isomerization is recognized as one of the keys to the chemical behavior of cycloheptatrienes: they may react through the bicycloheptadiene (norcaradiene) form, as in the Diels–Alder reaction with fumaryl chloride at 55 °C,[2] or in the thermal equilibration of 1,7,7-, 2,7,7-, and 3,7,7-trimethylcycloheptatrienes at 300 °C.[3] In the cycloaddition, fumaryl chloride reacts with the norcaradiene form; in the thermal isomerization, [1,5] carbon migrations interconverting the norcaradiene forms are responsible for the observed equilibration of the isomeric cycloheptatrienes.

The stereochemical aspects of these [1,5] carbon migrations have attracted special attention since the reaction was first uncovered. Because predictions of reaction stereochemistry based on the Woodward–Hoffmann rules[4] and the least motion principle[5] are in agreement for [1,3] and [1,7] shifts[6,7] but conflict for [1,5] migrations,[8] [1,5] carbon shifts in cycloheptatrienes provide a particularly valuable testing ground for assessing the limits of applicability of these two theories. Unambiguous experimental determinations of the stereochemical course for this rearrangement, then, have seemed imperative.

Scheme I



Klärner[9] approached the stereochemical question by preparing chiral *n*,7-dimethyl-7-methoxycarbonyl- and *n*,7-dimethyl-7-cyanocycloheptatrienes and following the thermal structural isomerizations and racemizations they exhibited.

The first report on this work[9] relied on an analog computational model for interconversions among the various isomerization products. A subsequent report[10] abandoned the kinetic argument in favor of a stereochemical correlation establishing the relative configurations of two structural isomers. Both studies led to the same conclusions: [1,5] carbon migrations in the norcaradiene forms were found to occur with predominant inversion of stereochemistry at the migrating carbon—a result diametrically conflicting with the theoretical prediction[4] that these suprafacial [1,5] shifts must proceed with retention at the shifting center.

Following Klärner's early report on the stereochemistry of [1,5] carbon shifts in norcaradienes, a theoretical study of this rearrangement by Schoeller[11] found that the walk with inversion was favored over the walk with retention by 1.4 kcal/mol due to subjacent orbital effects.

Another study on the stereochemistry of cycloheptatriene rearrangements was undertaken by Hansen,[12] who found that the rate of racemization of (−)-1-deuterio-3-methoxycarbonyl-7-

(1) Alder, K.; Jacobs, G. *Chem. Ber.* **1953**, *86*, 1528–1539. Doering W. von E.; Laber, G.; Vonderwahl, R.; Chamberlain, N. F.; Williams, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 5448. Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 1–11. Maier, G. *Ibid.* **1967**, *6*, 402–413. Tochtermann, W. *Fortschr. Chem. Forsch.* **1970**, *15*, 378–444. Ciganek, E. *J. Am. Chem. Soc.* **1971**, *93*, 2207–2215. Maier, G. "Valenzisomerisierungen"; Verlag Chemie: Weinheim, 1972. Tsuruta, H.; Mori, S.; Mukai, T. *Chem. Lett.* **1974**, 1127–1130. Klärner, F.-G. *Tetrahedron Lett.* **1974**, 19–22. Klärner, F.-G.; Yaşlak, S.; Wette, M. *Chem. Ber.* **1977**, *110*, 107–123.

(2) Tsuji, T.; Teratake, S.; Tanida, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2033–2037. See also Warner, P. M.; Lu, S.-L. *J. Am. Chem. Soc.* **1980**, *102*, 331–337.

(3) Berson, J. A.; Willcott, M. R., III *J. Am. Chem. Soc.* **1965**, *87*, 2751–2752, 2752–2753; *ibid.* **1966**, 2494–2502; *Rec. Chem. Prog.* **1966**, *27*, 139–149. Berson, J. A. *Acc. Chem. Res.* **1968**, *1*, 152–160.

(4) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Academic Press: New York, 1970.

(5) Hine, J. *J. Org. Chem.* **1966**, *31*, 1236–1244.

(6) The reversible interconversion of 1,5- and 2,5-dimethyl-5-methoxycarbonylbicyclo[2.1.0]pent-2-ene by way of a [1,3] carbon migration occurs with inversion at C(5): Klärner, F.-G.; Adamsky, F. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 674–675.

(7) *cis*-Bicyclo[6.1.0]nona-2,4,6-trienes suffer thermal [1,7] carbon shifts with inversion at C(9): Klärner, F.-G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 832–833.

(8) For stereochemical work on thermal [1,5] carbon migrations, see Boersma, M. A. M.; de Haan, J. W.; Kloosterziel, K.; Van den Ven, L. J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 1168–1169. Danē, L. M.; de Haan, J. W.; Kloosterziel, K. *Tetrahedron Lett.* **1970**, 2755–2758. Grimme, W.; Doering, W. von E. *Chem. Ber.* **1973**, *106*, 1765–1780. Borden, W. T.; Lee, J. G.; Young, S. D. *J. Am. Chem. Soc.* **1980**, *102*, 4841–4843. Kirmse, W.; Kuhr, R.; Murawski, H.-R.; Scheidt, F.; Ullrich, V. *Chem. Ber.* **1980**, *113*, 1272–1279.

(9) Klärner, F.-G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 268–270.

(10) Klärner, F.-G.; Yaşlak, S.; Wette, M. *Chem. Ber.* **1979**, *112*, 1168–1188.

(11) Schoeller, W. W. *J. Am. Chem. Soc.* **1975**, *97*, 1978–1980. For the thermal [1,3] shift in bicyclo[2.1.0]pent-2-enes, retention was the predicted stereochemistry.

(12) Hansen, R. T., Ph.D. Thesis, Yale University, Dec 1976; *Chem. Abstr.* **1977**, *87*, 101708p; *Diss. Abstr. Int. B* **1977**, *37*, 6130.

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methyl-7-methoxymethylcycloheptatriene was 9.3×10^{-5} s^{-1} and its rate of degenerate deuterium scrambling was 6.3×10^{-5} s^{-1}.[13] These kinetic results, that is, the near equality of the two measured rate constants, led to the tentative conclusion that the isomerization takes place by a nonretention pathway. But Hanson recognized and emphasized the limits of his experiment; he stressed that assigning the stereochemistry as a [1,5] shift with inversion of configuration could not be made securely since he had no knowledge of the amount of deuterium at the C(1) and C(5) positions in the new enantiomeric form.[12] A walk with inversion requires that all the deuterium appear at the C(5) position of the new enantiomer (Scheme I).

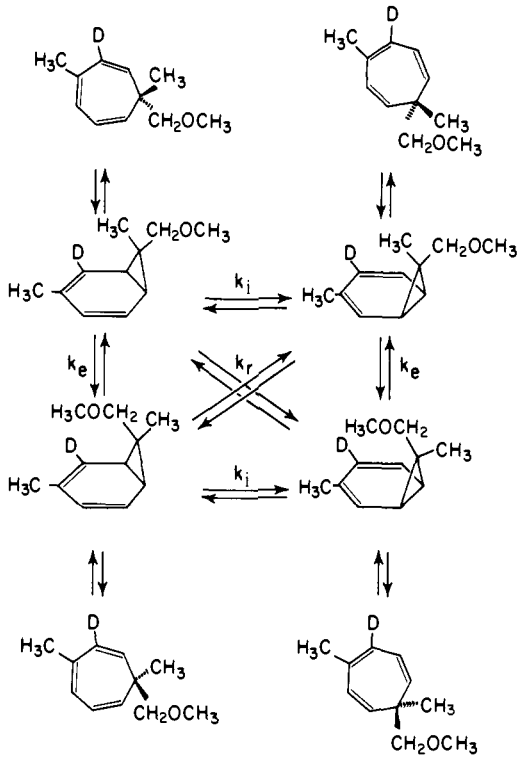
While Klärner's stereochemical model was consistent with his data,[9,10] it was not a uniquely necessary deduction from that data. Four aspects of the work gave us pause: (1) racemization of 3,7-dimethyl-7-methoxycarbonyl- or 3,7-dimethyl-7-cyanocycloheptatrienes through 2-oxabicyclo[3.2.2]nona-3,6,8-triene or 2-azabicyclo[3.2.2]nona-2,3,6,8-tetraene forms[14] might intrude and could be taken as racemization by a [1,5] shift with inversion; (2) the kinetic scheme used to model the isomerizations with an analog computer[9] contained more independent kinetic parameters than observable quantities, and some combinations of assigned rate constants did not honor the requirements of microscopic reversibility; (3) the determination of relative stereochemistry of structural isomers rested in part on the rate constants from the kinetic model; (4) no explicit consideration of possible one-center epimerizations was intrinsic to the experimental design.

Our experimental approach evolved in light of these concerns. We wished to avoid substituents like methoxycarbonyl and cyano that might conceivably introduce additional reaction pathways and to measure explicitly rate constants for a [1,5] shift with inversion (k_i), a [1,5] shift with retention (k_r), and a one-centered epimerization (k_e) at C(7) of the norcaradiene by studying a system labeled sufficiently so that k_e (enantiomerization without [1,5] carbon shift) and k_i (enantiomerization with concomitant [1,5] carbon shift) in a 1,7,7- or 3,7,7-trisubstituted cycloheptatriene could be distinguished.[15]

An optically active 2-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene seemed an ideal substrate for this investigation, for the degenerate isomers that could be formed upon thermal isomerization of this ether (Scheme II) would allow discrimination between k_i and k_e; the ether function introduces a minimal electronic perturbation while offering a weakly basic site for complexation with an optically active NMR shift reagent;[16] no determination of relative configurations of structurally isomeric substrates is required; the kinetic analysis would be exact and simple; and functional groups which might lead to unwanted side reactions are not present.

The experimental determination of the stereochemistry of the [1,5] carbon shift would involve the pyrolysis of substrate at an appropriate temperature followed by reisolation of it and its three degenerate isomers by preparative vapor-phase chromatography. Analysis of the mixture of four isomers by NMR would give the extent of deuterium scrambling; the extent of racemization could be determined either by polarimetry or by NMR in the presence of a chiral shift reagent. The final and most challenging measurement would be determination of the chiral characteristics of both 2-deuterio and 4-deuterio isomers in a pyrolysis mixture. This information could be obtained by NMR in the presence of a chiral shift reagent if the shift reagent would separate the H–C(4) or H–C(2) doublets in the (+) and (−) enantiomers. The above measurements, along with material balance, would allow the determination of the concentration of each of the four degenerate

Scheme II



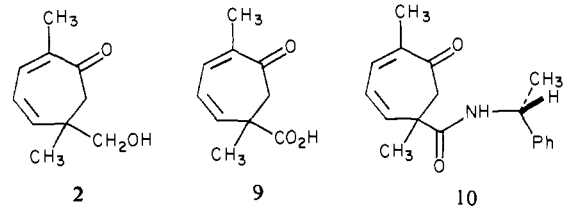
isomers, and with these data the rate constants k_i, k_r, and k_e could be calculated.

Results and Discussion

Synthesis. Scheme III outlines the synthetic route used to prepare 3,7-dimethyl-7-methoxymethylcycloheptatriene and (+)-2-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene.[17]

Selective epoxidation of *l*-carvone ((−)-(5*R*)-2-methyl-5-isopropenyl-2-cyclohexen-1-one) with *m*-chloroperbenzoic acid gave carvone 7,8-oxide (**1**) in 86% yield.[18] Analysis of this keto epoxide with ^{13}C NMR showed it to be a mixture of both anticipated stereoisomers in about a 3:2 ratio. Numerous attempts to separate these diastereomers by thin-layer and gas chromatography were unsuccessful; the mixture was isomerized[19] with lithium diisopropylamide in tetrahydrofuran at 0 °C to give the ring-expanded alcohol **2** in 68% yield.

Our second and third attempts to resolve a precursor of the desired cycloheptatriene fared no better than our initial endeavors to separate the diastereomers of **1**, or to prepare one of the two with high stereoselectivity from *l*-carvone. The alcohol **2** was oxidized with Jones reagent to the corresponding keto acid **9** in 61% yield, but all attempts to resolve **9** through recrystallization of quinine or brucine salts were unsuccessful. The amides **10** were



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then prepared from the keto acid **9** employing (−)-α-methylbenzylamine ((−)-(*R*)-α-methylphenethylamine) and dicyclohexylcarbodiimide. The diastereomeric amides could be separated

(13) Rate constants for racemization and deuterium scrambling were calculated from the data given in Tables 2 and 4 of Hansen's thesis.

(14) Compare 1-aza-1,2,4,6-cycloheptatetraene: Chapman, O. L.; Sheridan, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 3690–3692.

(15) 7,7-Disubstitution is required, else [1,5] hydrogen shifts intrude: ter Borg, A. P.; Kloosterziel, H.; Van Meurs, N. *Proc. Chem. Soc.* **1962**, 359; *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 717–740. ter Borg, A. P.; Kloosterziel, H. *Ibid.* **1963**, *82*, 741–756. Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187–217.

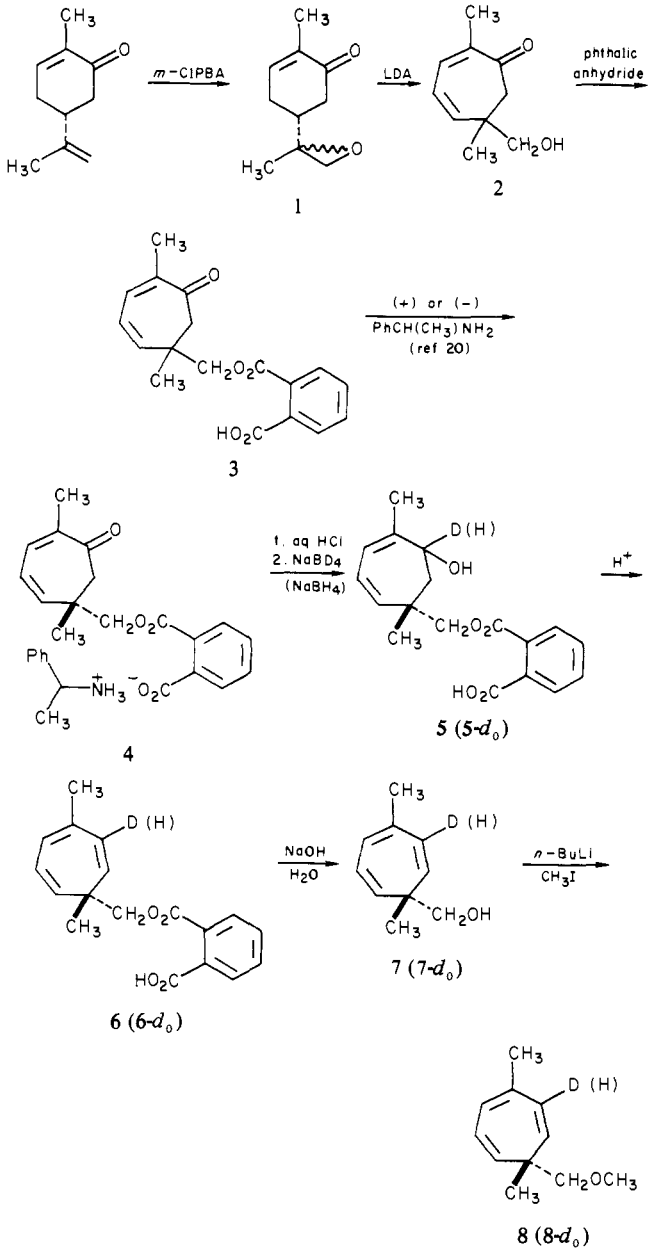
(16) Sullivan, G. R. *Top. Stereochem.* **1978**, *10*, 287–329.

(17) Baldwin, J. E.; Broline, B. M. *J. Am. Chem. Soc.* **1978**, *100*, 4599–4600.

(18) Howe, R.; McQuillin, F. J.; Temple, R. W. *J. Chem. Soc.* **1959**, 363–371.

(19) Compare the conversion of carvone to eucarvone: Baeyer, A. *Ber.* **1894**, *27*, 810–816. Corey, E. J.; Burke, H. J. *J. Am. Chem. Soc.* **1956**, *78*, 174–180.

Scheme III



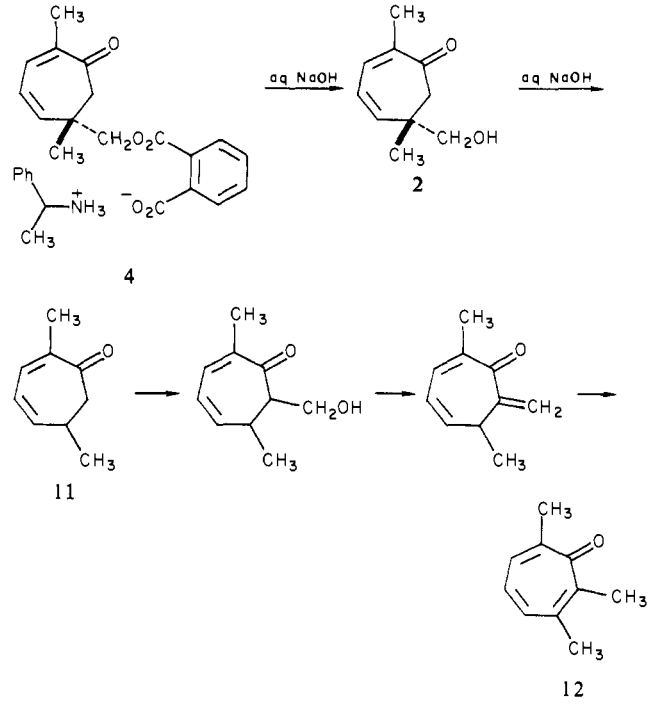
readily by column chromatography on silica gel employing 15% ethyl acetate in benzene as the eluent, but this method of resolution was frustrated by two factors; the highest yield obtained for the preparation of the amide **10** was 12% and all attempts to hydrolyze the amide resulted only in decomposition.

A successful method for the resolution was found based on the hemiphthalate **3**, prepared by treatment of the alcohol **2** with phthalic anhydride in pyridine. The hemiphthalate **3** was converted to its (−)-α-methylbenzylamine salt **4**[20] in an 89% yield from the alcohol **2**. The salt could be efficiently resolved by successive recrystallizations from ether–chloroform; five recrystallizations of 54 g of the amine salt **4** gave 14.5 g of material that was greater than 90% diastereomerically pure and had $[\alpha]_D$ +60.2° ($CHCl_3$). The amine salt was converted to chiral hemiphthalate **3** in nearly quantitative yield upon treatment with aqueous hydrochloric acid.

An attempt to convert the amine salt **4** to chiral 2,6-dimethyl-6-hydroxymethylcyclohepta-2,4-dien-1-one (**2**) with

(20) The absolute stereochemistry of chiral α-methylbenzylamine in structure 4 is not specified; the *R*-(−) amine was used and led to (+)-**8**, and the *S*-(+) amine would have provided (−)-**8**. Scheme III portrays one of these possibilities, since the absolute stereochemistry of (+)-**8** and its precursors is not known at present.

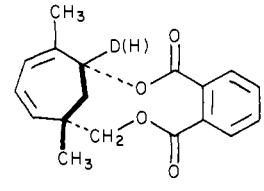
Scheme IV



aqueous methanolic sodium hydroxide gave 2,3,7-trimethyltropone (**12**:[21] 47% crude yield, 29% yield after purification) as the only identifiable product. Formation of this product was rationalized (Scheme IV) as involving initial hydrolysis to alcohol **2** followed by a retro aldol condensation giving dienone **11**. Addition of formaldehyde to dienone **11** at C(7), followed by dehydration and isomerization of an exocyclic double bond into the ring, would lead to the observed trimethyltropone. Treatment of alcohol **2** with aqueous methanolic sodium hydroxide also gave 2,3,7-trimethyltropone (**12**).

Hydrolysis of the hemiphthalate **3** under a variety of acidic conditions gave unacceptably low yields of keto alcohol **2**, and we adopted an alternative approach based on selective reduction of the cycloheptadienone function. Treatment of the hemiphthalate **3** with sodium borohydride in isopropyl alcohol gave alcohol **5**-d_0; the deuterated compound **5** was prepared under identical conditions employing sodium borodeuteride. The alcohol proved to be a viscous oil; when all attempts to induce crystallization were unsuccessful, it was converted to the triene **6** without purification.

Dehydration of intermediate **5** with *p*-toluenesulfonic acid in benzene at reflux gave the desired triene, but it suffered partial decomposition under the reaction conditions. This problem was overcome by using dichloromethane as the solvent with removal of the dichloromethane–water azeotrope. The triene **6** was obtained in 64% yield along with about 30% of a side product having an NMR spectrum suggestive of the bislactone structure **13**.



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(21) The structural assignment for 2,3,7-trimethyltropone rests primarily on spectral data and literature precedent; see: Wilson, J. M.; Ohashi, M.; Budzikiewicz, H.; Djerassi, C.; Itō, S.; Nozoe, T. *Tetrahedron* **1963**, *19*, 2247–2253. Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **1961**, *83*, 599–602. Mayor, C.; Jones, W. M. *J. Org. Chem.* **1978**, *43*, 4498–4502. Brady, W. T.; Hieble, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 4278–4284. Noyori, R.; Makino, S.; Takaya, H. *Ibid.* **1971**, *93*, 1272–1273.

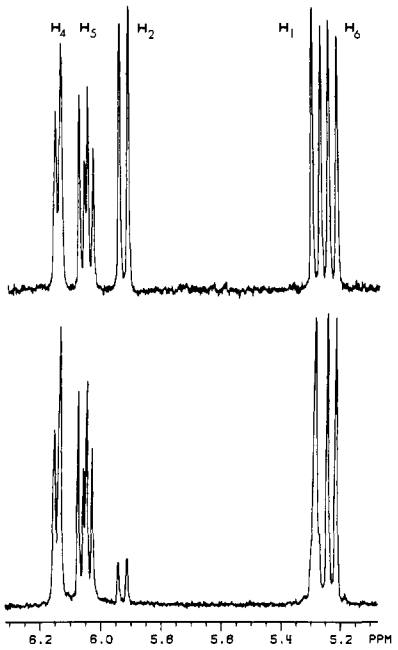

Figure 1. 360-MHz NMR spectra in benzene-d_6 of the vinyl proton region of 2-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene (**8**) and its unlabeled analogue **8**-d_0.

The triene **6** was hydrolyzed with aqueous sodium hydroxide at 70 °C to give the alcohol **7** in 75% yield. This alcohol was methylated with *n*-butyllithium and iodomethane in dimethyl sulfoxide to give a 92% yield of ether **8**. This material had $[\alpha]_{365}$ 65.0° ($CHCl_3$), contained 86.4% of one deuterium at C(2), and was 90.7% optically pure as determined by NMR analysis in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).[22,23]

Kinetics. The (+)-2-deuterio-3,7-dimethyl-1-methoxymethylcycloheptatriene ((+)-**8**) used in kinetic runs was purified by vapor-phase chromatography on a FFAP column; after purification 41-mg samples were each diluted to 0.5 mL with toluene containing 0.5% triethylamine. The solution of (+)-**8** was placed in a base-washed ampule, degassed, and sealed under high vacuum. The ampules were heated at 223.4 °C in a eutectic salt bath for the appropriate time, then cooled; the thermolysis products were purified by gas chromatography.

Numerous stationary phases were investigated to find one fully adequate for the separation of the enantiomers of **8** and of 4-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene (**14**) from structural isomers, such as the 1-deuterio-2,7-dimethyl-7-methoxymethylcycloheptatrienes (**15**). The only suitable stationary phase found was di-*n*-butyl tetrachlorophthalate (DBTCP). At the column temperature employed (120 °C), the material isolated from the vapor-phase chromatography column was contaminated with traces of the stationary phase;[24] this problem was overcome by the use of a short SE-30 column attached to the end of the DBTCP column. With a 6.4 mm × 2.5 m 10% DBTCP on 60/80 Chromosorb W NAW column coupled with a 6.4 mm × 0.3 m SE-30 on 60/80 Chromosorb W NAW column at 120 °C and a flow rate of 60 mL/min, **8** and its degenerate isomers **14** had a retention time of 50 min while the 1-deuterio-2,7-dimethyl-7-methoxymethylcycloheptatrienes (**15**) exhibited a retention time of 41 min.

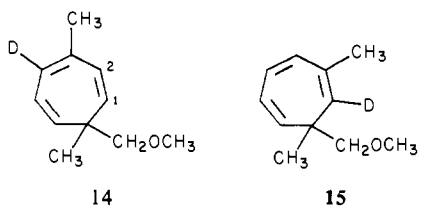

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Table I. Thermal Equilibration of 2-Deuterio- and 4-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene at 223.4 °C

time (min)	% D at C(2)	label purity	−ln [label purity]
0	100	1.00	0
400	94.7	0.894	0.112
600	91.1	0.822	0.196
800	88.5	0.770	0.261
1000	84.8	0.696	0.362
1200	82.7	0.654	0.424

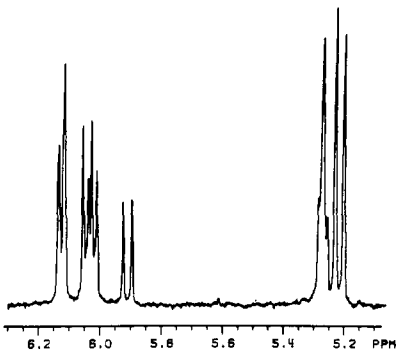

Figure 2. 360-MHz ^1H NMR spectrum of the 1200-min kinetic point from the thermolysis of **8** at 223.4 °C.

The chromatographically isolated set of the four isomeric 2- and 4-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatrienes was assayed by NMR to determine the rate of deuterium scrambling. In the vinyl region of the 100-MHz ^1H NMR spectrum of 3,7-dimethyl-7-methoxymethylcycloheptatriene (**8**-d_0) in $CDCl_3$, the C(1) and C(6) protons appear as doublets at δ 5.22 and 5.15, respectively, while the C(2) and C(4) protons show overlapping doublets at δ 6.04 and the C(5) proton exhibits a pseudo-triplet at 6.24 ppm. In the 2-deuterio version of this triene, H–C(1) is no longer split into a doublet; the overlapping doublets at δ 6.04 are of reduced intensity, but they still show such complexity that a good quantitative estimation of the relative proportions of 2-deuterio and 4-deuterio isomers may not be obtained from 100-MHz ^1H NMR spectra.

At 360 MHz, however, this limitation was overcome. Figure 1 shows the 360-MHz ^1H NMR spectra of **8** and undeuterated triene **8**-d_0 in benzene-d_6. All protons are cleanly resolved, thus allowing determination of the required data; they were collected in the Fourier transform mode employing quadrature phase detection using an 8.5-μs acquisition time and a 10-s pulse delay. Sixteen transients were collected; the data handling was done using a Nicolet NTCFT-1180 computer system. To ensure that saturation was not a factor, a spectrum of **8**-d_0 was acquired with a 60-s pulse delay and compared to the spectrum obtained with a 10-s pulse delay; the relative integrations of the vinyl protons were, within estimated experimental error, identical.

The percent deuterium at C(2) was determined by comparing the area of the H–C(2) doublet to the area of the H–C(5) multiplet; the percent deuterium for each kinetic point was then normalized to account for the residual proton in the C(2) position in the starting material. The rate of deuterium scrambling was obtained from the slope of a linear plot of −ln (label purity) vs. time, where label purity was defined as the difference between the fractional amount of deuterium at C(2) and C(4). The data used for determination of the rate of deuterium scrambling are summarized in Table I; the rate constant for approach to deuterium scrambling equilibrium was found to be (6.07 ± 0.28) × 10^{-6} s^{-1}.[25]

(22) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913–5914.
(23) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S.; Latimer, J. *J. Am. Chem. Soc.* **1974**, *96*, 1493–1501.
(24) While the maximum recommended temperature for this stationary phase is 150 °C (McNair, H. M.; Bonelli, E. J. "Basic Gas Chromatography"; Varian Aerograph: Walnut Creek, CA, 1969; p 72), we observed column bleeding at temperatures as low as 110 °C.

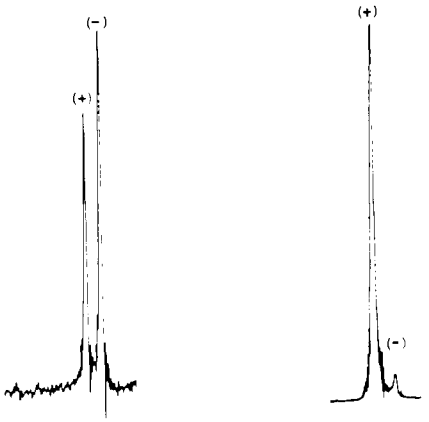

Figure 3. Resolution of the enantiotopic C(7) methyl resonances of (−)-**8**-d_0 (at left; 17.6% optically pure) and of (+)-**8** (at right; 90.7% optically pure) in the presence of the chiral NMR shift reagent Eu(hfbc)$_3$.

Table II. Racemization of (+)-2-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene at 223.4 °C

time (min)	opt. purity	normalized opt. purity	−ln [normalized opt. purity]
0	0.907	1.00	0
400	0.803	0.885	0.122
600	0.724	0.798	0.226
800	0.680	0.750	0.288
1000	0.635	0.700	0.357
1200	0.586	0.646	0.437

Figure 2 shows the 360-MHz spectra of the vinyl region of the 1200-min kinetic point. The migration of protium to the C(2) position can be clearly seen from the increase in intensity of the doublet at δ 5.93.

The rate of racemization might have been determined by polarimetry, but consideration of the error involved in weighing small samples and the possibility of trace contamination of the sample with material of unknown rotation caused us to select NMR spectroscopy at 100 MHz in the presence of an optically active shift reagent as our analytical tool. Preliminary studies showed that chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfbc)$_3$[26] in benzene-d_6 cleanly resolved the enantiotopic C(7) methyl groups of **8**-d_0 into two singlets. Figure 3 shows the C(7) methyl resonances of **8**-d_0 that is 17.6% optically pure (enriched in the (−) enantiomer) and of **8** that is 90.7% optically pure (enriched in the (+) enantiomer).

The racemization data were obtained by adding sufficient Eu(hfbc)$_3$ to a benzene-d_6 solution of the chromatographically purified product to split the enantiomeric C(7) methyl resonances. The resolution of the NMR spectrum could be improved, if needed, by filtration of the sample followed by deoxygenation of the solution with a fine stream of dry nitrogen. The spectra were run with a 500-Hz sweep width and reduced rf power settings to avoid saturation. Twelve integrations per kinetic point were run allowing 20–30 s between scans. These data could also be obtained by peak-height measurements; the values obtained by the two methods were in good agreement. The racemization data are summarized in Table II and the rate constant for racemization was determined from the slope of a linear plot of −ln (optical purity) vs. time to be (6.13 ± 0.20) × 10^{-6} s^{-1}.

The final distinction required to determine the concentrations of the four degenerate isomers was an evaluation of the amount of deuterium at C(2) and C(4) in one of the enantiomeric pairs.

(25) The error limits reported are standard deviations.
(26) The abbreviation Eu(hfbc)$_3$ is derived from an alternative name of this shift reagent: tris(3-heptafluorobutyryl-*d*-camphorato)europium(III).

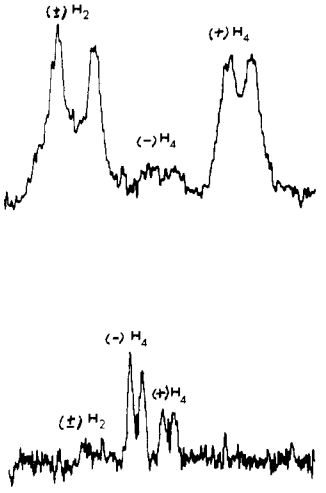

Figure 4. 100-MHz NMR spectra of (+)-**8**-d_0 (top: 500-Hz sweep width; $[\alpha]_{365}$ +42° ($CHCl_3$)) and of (−)-**8** (bottom: 1000-Hz sweep width; $[\alpha]_{365}$ −25° ($CHCl_3$)) in the presence of Eu(hfbc)$_3$, illustrating the resolution of enantiotopic protons at C(4).

Once again, we turned to NMR spectroscopy in the presence of an optically active shift reagent.

A variety of conditions were examined for the shift reagent studies. Experiments using tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III)[23] as the shift reagent in solvents such as $CDCl_3$, CCl_4, and C_6D_6 were not successful. Trials using Eu(hfbc)$_3$ in CCl_4 and $CDCl_3$ were also unsuccessful, and the initial results using Eu(hfbc)$_3$ in C_6D_6, while somewhat encouraging, did not resolve the required protons readily. Tris(*d*,*d*-dicampholylmethano)europium(III), Eu(dcm)$_3$, was prepared from *d*-camphor by the method of Whitesides and co-workers,[27] but it also proved ineffective.

At this point we reinvestigated the use of Eu(hfbc)$_3$ in benzene-d_6. The addition of 0.5 mL of a saturated solution of Eu(hfbc)$_3$ in dry benzene-d_6 to approximately 8 mg of the substrate followed by filtration and deoxygenation with dry nitrogen gave an NMR sample which showed the enantiotopic protons at C(4) as clearly resolved resonances, even at 100 MHz. Figure 4 exhibits a portion of the vinyl region of the 100-MHz spectra of **8**-d_0 (top: $[\alpha]_{365}$ +42° ($CHCl_3$), recorded with a 500-Hz sweep width) and **8** (bottom: $[\alpha]_{365}$ −25° ($CHCl_3$), recorded with a 1000-Hz sweep width). These spectra show that the C(4) proton is resolved into two doublets for the (+) and (−) enantiomers. It can also be seen that the most downfield doublet is the proton at C(2).

The efficacy of the shift reagent proved to be extremely susceptible to the presence of trace impurities in the shift reagent as well as small amounts of water. The shift reagent used in this study was dried at 100 °C and 0.01 mm for 16 h prior to use, and the saturated shift reagent solutions were stored over activated 4-Å molecular sieves. Even with these precautions, some batches of the commercially available shift reagent[28] contained impurities which reduced efficiency to such a point that the H–C(4) resonances were not well resolved, and in some cases the impurities showed NMR signals in the region of interest.

The chiral shift reagent NMR method was substantially improved at 360 MHz. Figure 5 shows the 360-MHz proton spectrum of a portion of the vinyl region of **8** (bottom: 90.7% optically pure, enriched in the (+) enantiomer) and nondeuterated **8** (top: 17.6% optically pure, enriched in the (−) enantiomer). These spectra again show the separation of the enantiotopic C(4) protons.[29]

(27) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038–1054.
(28) The shift reagents used in this study were purchased from the Aldrich Chemical Co., Milwaukee, WI.
(29) The spectra of Figures 4 and 5 should allay any doubts that the H–C(4) enantiotopic protons of the *R* and *S* enantiomers of **8** may indeed be resolved with the aid of Eu(hfbc)$_3$.

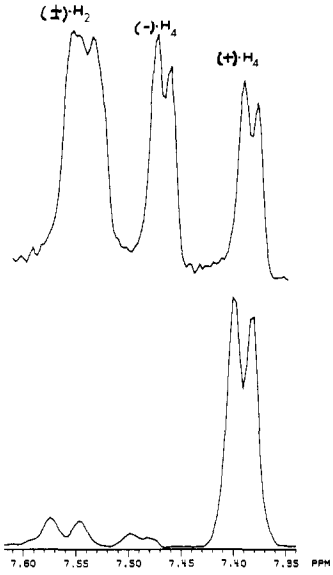

Figure 5. 360-NHz NMR spectra of (+)-**8** (90.7% optically pure; bottom) and (−)-**8**-d_0 (17.6% optically pure; top), illustrating the resolution of the enantiotopic protons at C(4). The top and bottom spectra were recorded at slightly different sweep widths.

Table III. Observed Integrals from 360-MHz ^{1}H NMR Chiral Shift Reagent Kinetic Study of the Degenerate Rearrangement of (+)-2-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene at 223.4 °C

	normalized integrals		
time (min)	(±)H–C(2)	(−)H–C(4)	(+)H–C(4)
0	10.9	3.45	85.6
400	17.4	3.64	78.9
600	17.7	5.95	76.3
800	18.7	5.58	75.7
1000	21.6	5.47	73.0
1200	23.7	6.12	70.2

The saturated shift reagent data were collected as described for the deuterium scrambling data with a pulse delay of 5 s and an acquisition time of 8 μs; 96 transients were collected. As a check on the consistency of the data, the optical purity and deuterium incorporation in the starting material were calculated from the saturated shift reagent data and were found to be in good agreement with the values previously obtained. Table III summarizes the normalized integration data obtained from the 360-MHz NMR shift reagent study.

Table III presents observed NMR relative integral intensities; these had to be corrected for contributions from undeuterated 3,7-dimethyl-7-methoxymethylcycloheptatriene before the concentrations of the four monodeuterio isomers could be deduced. The area of the (±)H–C(2) resonance was corrected for d_0 material by subtracting 10.9, the zero time integral, from the normalized areas determined for each kinetic point. The contribution of d_0 material to the observed (−)-H–C(4) and (+)-H–C(4) resonances was determined by partitioning the d_0 material (10.91%) between the (+) and (−) forms in accord with the initial optical purity (90.7%) and the rate of racemization determined for the mixture of (+)-2-deuterio- and unlabeled 3,7-dimethyl-7-methoxymethylcycloheptatriene. The contribution of d_0 material to the (−)-H–C(4) resonance at the six times in Table III was calculated to be 0.51, 1.19, 1.48, 1.77, 2.03, and 2.27%; the contribution of d_0 material to the (+)-H–C(4) resonance at each time was 10.91 − [(−)-H–C(4) contribution]. Subtracting these values from the normalized integrals of Table III and renormalizing so that 100% would represent d_1 isomers only provided the values presented in Table IV.

The saturated shift reagent study provided the final experimental data required for the calculation of the concentrations of the four isomers (+)-**8**, (−)-**8**, (+)-**14**, and (−)-**14**. Since the data

Table IV. Normalized Integrals of the Enantiomers of 2-Deuterio- and 4-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene at 223.4 °C

	normalized integrals		
time (min)	(±)-H–C(2) [(±)-D–C(4)]	(−)-H–C(4) [(−)-D–C(2)]	(+)-H–C(4) [(+)-D–C(2)]
0	0	3.76	96.2
400	8.35	3.14	88.5
600	8.72	5.72	85.6
800	9.99	4.87	85.1
1000	13.64	4.40	82.0
1200	16.31	4.91	78.8

Table V. Mole Percent Concentrations of the 2- and 4-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatrienes at 223.4 °C

time (min)	(+)-8	(−)-8	(+)-14	(−)-14
0	96.2	3.8	0	0
400	88.5	3.1	1.7	6.7
600[a]	85.6	5.7	0.6	8.1
800	85.1	4.9	0	10.0
1000	82.0	4.4	0	13.6
1200	78.8	4.9	0.5	15.8

[a] Data omitted from subsequent plot according to eq 5.

in Table IV are corrected for d_0 material, the area of the (+)-H–C(4) resonance is equal to the concentration of (+)-**8**, and the area of the (−)-H–C(4) resonance gives the concentration of (−)-**8** in each kinetic point. The area of the (±)H(2) resonance gives the sum of (+)-**14** and (−)-**14**; the concentrations of (+)-**14** and (−)-**14** can be calculated using material balance (eq 1) and the definition of optical purity (eq 2).

$$[(+)\text{-}\mathbf{8}] + [(-)\text{-}\mathbf{8}] + [(+)\text{-}\mathbf{14}] + [(-)\text{-}\mathbf{14}] = 100\% \quad (1)$$

$$[(+)\text{-}\mathbf{8}] - [(-)\text{-}\mathbf{8}] + [(+)\text{-}\mathbf{14}] - [(-)\text{-}\mathbf{14}] = \%\ \text{optical purity} \quad (2)$$

Equations 1 and 2 were solved for the concentrations of (+)-**14** and (−)-**14** by substituting the known concentrations of (+)-**8** and (−)-**8** and using the experimentally determined optical purity of each kinetic point as shown in Table II. The observed mole percent concentrations of the four isomers are shown in Table V.[30]

The concentrations shown in Table V allow the calculation of the three rate constants k_i, k_r, and k_e. Appropriate linear combinations of the differential equations that describe the time dependence of the concentrations of the four isomers may be integrated to give eq 3–6.

$$-\ln([(+)\text{-}\mathbf{8}] - [(-)\text{-}\mathbf{8}] + [(+)\text{-}\mathbf{14}] - [(-)\text{-}\mathbf{14}]) = 2(k_i + k_e)t \quad (3)$$

$$-\ln([(+)\text{-}\mathbf{8}] + [(-)\text{-}\mathbf{8}] - [(+)\text{-}\mathbf{14}] - [(-)\text{-}\mathbf{14}]) = 2(k_i + k_r)t \quad (4)$$

$$-\ln([(+)\text{-}\mathbf{8}] - [(-)\text{-}\mathbf{8}] - [(+)\text{-}\mathbf{14}] + [(-)\text{-}\mathbf{14}]) = 2(k_r + k_e)t \quad (5)$$

Inspection of these equations shows that each describes first-order kinetic behavior. The ln term of eq 3 is the optical purity of each kinetic point while the ln term of eq 4 is the label purity; thus the values of $2(k_i + k_e)$ and $2(k_i + k_r)$ are known from the previously discussed data on the rates of racemization and deuterium scrambling of (+)-**8**. The final sum of rate constants is available from eq 5; a five-point linear plot of $-\ln([(+)\text{-}\mathbf{8}] - [(-)\text{-}\mathbf{8}] - [(+)\text{-}\mathbf{14}] + [(-)\text{-}\mathbf{14}])$ vs. time revealed that $2(k_r + k_e) = (0.35 \pm 0.16) \times 10^{-6}$ s^{-1}. Thus eq 6 7, and 8 obtain.

$$k_i + k_e = (3.06 \pm 0.10) \times 10^{-6}\ \text{s}^{-1} \quad (6)$$

(30) The concentrations of (+)-**14** for the 800- and 1000-min points were calculated to be −0.6 and −1.1% and were assigned a value of 0.0.

$$k_i + k_r = (3.04 \pm 0.14) \times 10^{-6}\ s^{-1} \quad (7)$$

$$k_r + k_e = (0.18 \pm 0.08) \times 10^{-6}\ s^{-1} \quad (8)$$

Solving eq 6, 7, and 8 for the rate constants for the three stereochemically distinct processes reveals that $k_i = (2.96 \pm 0.09) \times 10^{-6}\ s^{-1}$, $k_r = (0.08 \pm 0.17) \times 10^{-6}\ s^{-1}$, and $k_e = (0.10 \pm 0.13) \times 10^{-6}\ s^{-1}$. Thus within defined experimental uncertainties, the [1,5] sigmatropic carbon shift occurs exclusively with inversion of configuration at the migrating carbon. Neither a [1,5] shift with retention nor a one-centered epimerization contributes significantly to the thermal chemistry of the system of four degenerate isomers (+)-**8**, (−)-**8**, (+)-**14**, and (−)-**14**.

The kinetic results now reported agree perfectly with the stereochemical conclusions of Klärner[9,10] and co-workers; they provide an alternative and quantitative validation of the stereochemical character of the cycloheptatriene–norcaradiene ring-walk isomerization he first advanced in 1974.[9]

The present results do *not* accord with our preliminary communication on this work,[17] for at that time an undetected experimental shortcoming still adulterated the kinetic study. Uncovering the deficiencies in the initial work required a protracted effort; sufficient stimulus for that effort was afforded by Klärner and Brassel's 1980 report[31,32] that chiral **15**-d_0 isomerizes thermally to chiral **8**-d_0 with predominant inversion of configuration and by our subsequent confirmation of this stereochemical deduction by way of an independent assignment of the relative configurations of **8** and **14**.[33]

The hidden problem which vitiated our 1978 stereochemical conclusions was finally traced to an inadequacy in the vapor-phase chromatographic purification of the 3,7-dimethyl-7-methoxymethylcycloheptatrienes following a pyrolysis. On the FFAP column originally used, the perfectly symmetrical peak for the 2- and 4-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatrienes contained as well as small amounts of the 2,7-dimethyl isomers. At low relative concentrations, this contamination was not detected by NMR spectroscopic scrutiny, yet it led to substantial errors in the derived rate constants.[34]

Thermal interconversion of the 2,7- and 3,7-dimethyl-7-methoxymethylcycloheptatrienes takes place with a change in the sign of rotation, and the relative absolute magnitude of specific rotation for the 2,7-dimethyl isomer is about 1.4 times larger than for the 3,7 isomer of identical optical purity.[31-33] The undetected[17] first-order conversion of (+)-2-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene ((+)-**8**) to (−)-1-deuterio-2,7-dimethyl-7-methoxymethylcycloheptatriene ((−)-**15**) led to a high polarimetric estimate of $k_{rac} = 2(k_i + k_e)$. The initial shift reagent study gave exaggerated estimates of (−)H–C(4) integral intensities, for a proton in the 2-methyl contaminant (−)-**15** absorbed just where the (−)H–C(4) resonance was expected (Figure 6). In consequence, the value of $(k_r + k_e)$ derived was much too large, some four times larger than the value secured with properly purified degenerate 3,7-dimethyl isomers. In retrospect, it is obvious that the error in chromatography should have been detected at once, and the subsequent errors in polarimetric kinetic measurements and in NMR spectral interpretation (cf. Figures 4, 5, and 6) might have been avoided. But they were not, at the time, and they remained elusive until an authentic sample of 2,7-dimethyl-7-methoxymethylcycloheptadiene was synthesized[33] and analyzed chromatographically and spectroscopically.

Summary

This work demonstrates quantitatively that the degenerate thermal isomerization of (+)-2-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene by way of norcaradiene forms involves a [1,5] carbon shift with inversion of configuration. Both a [1,5] carbon shift with retention and thermal epimerization at C(7) without a carbon shift are found to be kinetically insignificant. These findings are in complete accord with and extend only slightly the stereochemical conclusions reached earlier by Klärner;[9,10,31] the [1,5] carbon shift takes place not only predominantly, but exclusively, with inversion of stereochemistry.

Since the degenerate deuterium-labeled isomers used in this study and the corresponding structural isomers utilized by Klärner and Brassel[31] involve only modest electronic and steric perturbations, it is likely that a [1,5] shift with inversion is the general pathway for [1,5] carbon sigmatropic shifts in norcaradienes.

The [1,5] carbon shift with inversion may be favored by subjacent orbital effects, or it may involve a diradical intermediate in which rotation at the tertiary radical site is much slower than closure to form the inversion product. Whether this interpretive distinction may be gained through experimental or theoretical efforts remains to be seen.

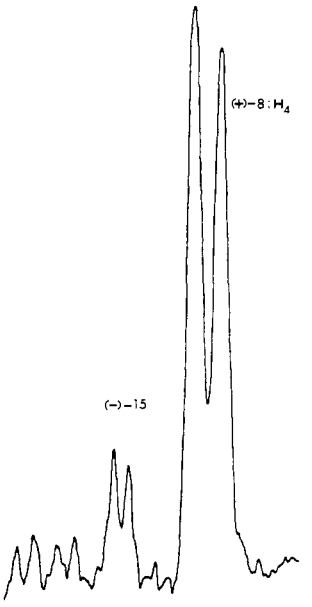

Figure 6. 100-MHz NMR spectrum of (+)-**8** after 679 min at 223.4 °C and preparative VPC on an FFAP column in the presence of Eu(hfbc)$_3$; compare Figures 4 and 5.

Experimental Section

Elemental analyses and electron impact mass spectra were determined by Dr. Richard A. Wielesek using CEC-21-110B or Hewlett-Packard 5930A instruments.

Routine proton NMR spectra were obtained on a Varian-XL-100-15A instrument operating at 100 MHz employing deuteriochloroform as the solvent unless otherwise stated. Chemical shifts are given in parts per million (ppm) and are referenced either to tetramethylsilane ($\delta = 0.00$ ppm) or the residual proton signal in the deuteriochloroform ($\delta = 7.27$ ppm); coupling constants are given in hertz. Carbon-13 NMR spectra were determined on the same instrument operating at 25.2 MHz and are also referenced to internal tetramethylsilane. Preparative and analytical vapor phase chromatography (VPC) was carried out on a Varian 1520 instrument employing a thermal conductivity detector. Infrared spectra were determined on a Beckmann IR-7 instrument. Melting points were determined on a Koefler hot stage apparatus and are uncorrected. Boiling points given for Kugelrohr distillations are the air oven temperature ranges over which the compounds were collected and do not represent true boiling points. The reaction temperatures specified are the temperatures of the heating or cooling baths and do not necessarily represent the temperatures of reaction mixtures. Unless otherwise states, "concentrated" implies concentration using a rotary evaporator at a pressure of approximately 25 mm.

Reagent grade or distilled solvents were employed. Solvents were dried by distillation under a dry nitrogen atmosphere as follows: ether was distilled from lithium aluminum hydride, tetrahydrofuran (THF) was distilled from a deep purple solution of the sodium benzophenone ketyl, and amines were distilled from potassium hydroxide.

Carvone 7,8-Oxide (1). A solution of *l*-carvone (50.0 g, 0.333 mol) in methylene chloride (1 L) was cooled (0 °C) under a nitrogen atmo-

(31) Klärner, F.-G.; Brassel, B. *J. Am. Chem. Soc.* **1980**, *102*, 2469–2470.
(32) Brassel, B. Diplomarbeit, Bochum, 1979.
(33) Baldwin, J. E.; Broline, B. M. *J. Org. Chem.*, in press.
(34) We now read Professor Benson's declaration that "Errors due to small amounts of secondary reactions are the most frequent type of systematic error encountered in kinetic studies" (Benson, S. W. "The Foundations of Chemical Kinetics"; McGraw-Hill: New York, 1960; p 86) with deepened appreciation.

sphere and 85% *m*-chloroperbenzoic acid (75.0 g, 0.369 mol) was added portionwise over a 20-min period. The reaction mixture was stirred at 0 °C for 13 h, and then 100 mL of 10% aqueous sodium sulfite was added; the solids were removed by filtration and washed well with methylene chloride. The combined filtrate and washes were washed (satd. $NaHCO_3$, H_2O, brine), dried (K_2CO_3), filtered, and concentrated to yield the crude epoxide as a yellow liquid. This liquid was Kugelrohr distilled (58–61 °C (0.05 mm)) to give 47.8 g (86.5%) of the epoxide as a clear colorless liquid: ^1H NMR 1.32 (3 H, s), 1.78 (3 H, s), 2.0–2.8 (7 H, m), 6.78 (1 H, m); ^1H decoupled ^{13}C NMR (acetone-d_6) 15.9, 18.7, 28.4, 40.5, 41.9, 52.4, 58.1 (assigned as C(8); two nearly coincident absorptions of relatively intensity 3:2), 135.7, 144.4, 198.0; IR (neat) 2970, 2915, 1675, 1450, 1430, 1380, 1360, 1110, 950 cm^{-1}.

A small portion of the epoxide was converted to the semicarbazone and recrystallized from methanol: mp 153–155 °C (lit.[18] mp 155 °C).

2,6-Dimethyl-6-hydroxymethylcyclohepta-2,4-dien-1-one (2). A solution of dry diisopropylamine (27.3 g, 0.270 mol) in dry THF (500 mL) was cooled (0 °C) under a nitrogen atmosphere and a 2.4 M hexane solution of *n*-butyllithium (92 mL, 0.22 mol) was added dropwise over a 1-h period. The resulting solution was stirred at 0 °C for 1 h; then a solution of carvone 7,8-oxide (18.0 g, 0.108 mol) in dry THF (70 mL) was added over a 2-h period. The reaction mixture was stirred at 0 °C for 5 h and water (200 mL) was added. The aqueous phase was separated and extracted with ether (3 × 100 mL). The ether extracts and the THF solution were combined and washed (5% HCl, satd. $NaHCO_3$, H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to leave a thick yellow liquid. This material was Kugelrohr distilled (70–80 °C (0.025 mm)) to give 12.3 g (68.3%) of 2,6-dimethyl-6-hydroxymethylcyclohepta-2,4-dien-1-one as a light yellow liquid. The analytical sample was purified by VPC on a 6.4 mm × 3.0 m 20% SE-30 on 60/80 Chromosorb W column at 190 °C: NMR 1.05 (3 H, s), 1.95 (4 H, s, CH_3 + OH), 2.73 (2 H, AB, $\Delta\nu \sim 24$, $J = 14$), 3.47 (2 H, AB, $\Delta\nu \sim 12$, $J = 10$), 5.80–6.10 (2 H, m), 6.40–6.59 (1 H, m); IR (neat) 3440, 2960, 2920, 1650, 1450, 1380, 1060, 1040, 740 cm^{-1}; mass spectrum *m/z* (rel intensity) 166 (m^+, 1), 136 (100), 121 (65), 107 (54), 91 (75).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.17; H, 8.39.

2,6-Dimethyl-1-ketocyclohepta-2,4-diene-6-methyl Hydrogen Phthalate (3). A solution of 2,6-dimethyl-6-hydroxymethylcyclohepta-2,4-dien-1-one (9.35 g, 0.056 mol) and phthalic anhydride (12.5 g, 0.084 mol) in dry pyridine (125 mL) was stirred under a nitrogen atmosphere at 60 °C for 60 h. The reaction mixutre was cooled to room temperature, acidified (pH 1), and extracted with ether (4 × 100 mL). The combined ether extracts were washed (10% HCl, H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 17.4 g (98.3%) of the hemiphthalate **3** as a thick yellow oil which was used without further purification: NMR 1.08 (3 H, s), 1.87 (3 H, s), 2.81 (2 H, AB, $\Delta\nu \sim 28$, $J = 14$), 4.17 (2 H, AB, $\Delta\nu \sim 14$, $J = 11$), 5.77–6.15 (2 H, m), 6.40–6.57 (1 H, m), 7.44–7.95 (4 H, m), 10.5 (1 H, s); IR (neat) 2980, 1720, 1650, 1360, 740 cm^{-1}; mass spectrum *m/z* 314 (m^+, 91), 149 (100), 136 (53), 121 (22), 91 (27). Exact mass: calcd for $C_{18}H_{18}O_5$, 314.114; found, 314.114.

Preparation and Resolution of the (−)-α-Methylbenzylamine Salt of 2,6-Dimethyl-1-ketocyclohepta-2,4-diene-6-methyl Hydrogen Phthalate (4). A solution of the hemiphthalate **3** (17.4 g, 0.055 mol) in ether (200 mL) was treated with (−)-α-methylbenzylamine (7.3 g, 0.061 mol, Aldrich) and the resulting mixture was stirred at room temperature for 30 min. The solid formed was filtered, washed well with ether, and dried to give 22.0 g (91.3%) of the amine salt **4** as a white solid.

The amine salt 4 was resolved by successive recrystallizations from a ether–chloroform solution. At the early stages of the resolution, 20% ether/$CHCl_3$ (v/v) was employed. The amine salt was dissolved in the hot solvent system (5.5 mL/g of amine salt) and the solution was allowed to stand at room temperature overnight. The solid formed was filtered and the mother liquors were cooled (0 °C) to obtain a second crop of crystals. Five recrystallizations gave amine salt with $[\alpha]_D$ +60.2° ($CHCl_3$) and mp 132–133 °C. Approximately 54 g of racemic amine salt gave 14.5 g of amine salt of high diastereomeric purity (≥90%): NMR 1.00 (3 H, s), 1.53 (3 H, d, $J = 7$), 1.90 (3 H, s), 2.76 (2 H, AB, $\Delta\nu \sim 28$, $J = 14$), 3.99 (2 H, AB, $\Delta\nu \sim 14$, $J = 12$), 4.29 (1 H, q, $J = 6$), 5.74–6.08 (2 H, m), 6.40–6.54 (1 H, m), 7.10–7.72 (9 H, m), 7.90 (3 H, s); IR (KBr) 2960, 1725, 1650, 1550, 1400, 1380, 1080 cm^{-1}.

Anal. Calcd for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.57; H, 6.42; N, 3.07.

Hydrolysis of Amine Salt 4. A mixture of amine salt 4 (3.0 g, 6.9 mmol) in ether (50 mL) and 10% hydrochloric acid (100 mL) was stirred vigorously at room temperature for 2 h. The ether layer was separated and the aqueous layer was extracted with ether (3 × 25 mL). The combined ether layers were washed (10% HCl, H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 2.2 g (100%) of the optically active hemiphthalate **3** as a thick oil.

2,3,7-Trimethyltropone (12). A solution of the amine salt 4 (1.0 g, 2.3 mmol) in methanol (100 mL) was treated with 3 N sodium hydroxide (30 mL) and the resulting solution was heated at reflux for 4 h. The reaction mixture was diluted with water (100 mL) and extracted with ether (3 × 50 mL), and the combined ether extracts were washed (10% HCl, H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 0.16 g of an orange solid. This material was sublimed (30 °C, 19 mm) to give 0.10 g (29% of 2,3,7-trimethylcyclohepta-2,4,6-trien-1-one (2,3,7-trimethyltropone)[21] as a white volatile solid: IR ($CHCl_3$) 1560 cm^{-1}; UV (cyclohexane) λ_{max} 237 nm (log ε 4.35), 313 (3.73); NMR 2.28 (6 H, s), 2.33 (3 H, s), 6.58–6.96 (2 H, m), 7.18 (1 H, broad d, $J = 8$); IR (C_6H_{12}) 1585, 1370, 780; mass spectrum *m/z* (rel intensity) 148 (m^+, 14), 120 (17), 105 (100), 91 (17), 77 (19).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.81; H, 8.24.

2,6-Dimethyl-1-hydroxycyclohepta-2,4-diene-6-methyl Hydrogen Phthalate (5-d_0). A solution of the hemiphthalate **3** (2.2 g, 7.0 mmol) in 2-propanol (100 mL) was cooled to 0 °C under a nitrogen atmosphere and sodium borohydride (0.38 g, 10 mmol) was carefully added. The resulting mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for an additional 1.5 h; then the reaction mixture was carefully acidified (10% HCl) to pH 1. The resulting mixture was diluted with water (200 mL) and extracted with ether (4 × 100 mL); the combined ether extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 2.2 g (100%) of the alcohol **5-d_0** as a viscous white oil which was used without further purification: NMR 1.13 and 1.19 (3 H, two singlets for diastereomeric C(6) methyl groups), 1.88–2.36 (5 H, m), 3.90–4.69 (3 H, m), 5.20–5.66 (3 H, m), 7.13 (2 H, s), 7.50–7.96 (4 H, m); IR ($CHCl_3$) 3500–3100, 2970, 1720, 1290, 1260, 1125, 790 cm^{-1}; mass spectrum *m/z* (rel intensity) 316 (m^+, 1), 298 (2), 168 (50), 149 (100). Exact mass: calcd for $C_{18}H_{20}O_5$, 316.131; found, 316.130.

3,7-Dimethylcyclohepta-1,3,5-triene-7-methyl Hydrogen Phthalate (6-d_0). A solution of the alcohol **5-d_0** (3.0 g, 9.5 mmol) in dry methylene chloride (150 mL) was placed in a flask fitted with an addition funnel and distillation head and the solution was heated to boiling; a catalytic amount of *p*-toluenesulfonic acid monohydrate was added and the methylene chloride–water azeotrope was slowly distilled. During the distillation additional dry methylene chloride was added with the addition funnel at a rate equal to the rate of distillation. The reaction was complete after 4 h; approximately 500 mL of distillate had been collected. The reaction mixture was concentrated, dissolved in ether (150 mL), and extracted with saturated $NaHCO_3$ (4 × 75 mL). The combined sodium bicarbonate extracts were acidified to pH 1 with concentrated HCl and extracted with ether (4 × 50 mL). The combined ether extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to give 1.8 g (64%) of the triene as a thick yellow oil which was used without further purification: NMR 1.14 (3 H, s), 2.03 (3 H, s), 4.14 (2 H, s), 5.10 (1 H, d, $J = 6$), 5.21 (1 H, d, $J = 6$), 5.96–6.38 (3 H, m), 7.48–8.00 (4 H, m), 10.94 (1 H, s); IR (neat) 3500–3100, 3010, 2970, 2930, 1720, 1600, 1580, 1450, 1380, 1290, 1120, 1075, 740 cm^{-1}; mass spectrum *m/z* (rel intensity) 298 (m^+, <0.01), 149 (31), 132 (100), 119 (65), 117 (72), 91 (35). Exact mass: calcd for $C_{18}H_{18}O_4$, 298.120; found, 298.121.

3,7-Dimethyl-7-hydroxymethylcycloheptatriene. A solution of the hemiphthalate **6-d_0** (1.9 g, 6.4 mmol) in 3 N sodium hydroxide (100 mL) was heated at 70 °C for 20 h. The reaction mixture was extracted with ether (3 × 50 mL) and the combined ether extracts were washed (satd. $NaHCO_3$, H_2O, brine), dried (K_2CO_3), filtered, and concentrated to yield 0.72 g (75%) of the alcohol **7-d_0** as a light yellow liquid: NMR 1.13 (3 H, s), 2.02 (3 H, s), 3.30 (2 H, s), 5.06 (1 H, d, $J = 8$), 5.17 (1 H, d, $J = 8$), 5.97–6.35 (3 H, m); IR (neat) 3360, 3000, 2960, 2920, 1445, 1440, 1040 cm^{-1}; mass spectrum *m/z* (rel intensity) 150 (m^+, 4), 132 (26), 119 (100), 91 (36).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.98; H, 9.24.

3,7-Dimethyl-7-methoxymethylcycloheptatriene (8-d_0). A solution of the alcohol **7-d_0** (0.22 g, 1.5 mmol) in dimethyl sulfoxide (20 mL) was deoxygenated with a stream of nitrogen for 30 min, a crystal of triphenylmethane was added, and the resulting mixture was titrated to the pink triphenylmethane end point with a 1.6 N hexane solution of *n*-butyllithium. The reaction mixture was stirred at room temperature for 10 min, iodomethane (0.9 g, 6.4 mmol) was added, and the solution was stirred at room temperature for 1.5 h. The reaction mixture was poured into water (100 mL) and extracted with ether (4 × 20 mL). The combined ether extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered, and concentrated to yield 0.22 g (92%) of the ether **8-d_0** as a light yellow liquid. The analytical sample was purified by VPC on a 6.4 mm × 2.4 m 10% FFAP on 60/80 Chromosorb G NAW DMCS column at 155 °C: NMR 0.97 (3 H, s), 2.02 (3 H, s), 3.21 (2 H, s), 3.34 (3 H, s), 5.12 (1 H, d, $J = 6$), 5.23 (1 H, d, $J = 6$), 5.92–6.32 (3 H, m); IR (neat) 2980,

Table VI. Observed Integrals for Determination of the Rate of Deuterium Scrambling

time, min	area H–C(5)	area H–C(2)	% D at H(2)
0	47.4	6.4	86.4
400	58.2	10.6	81.8
600	45.7	9.7	78.7
800	36.6	8.6	76.5
1000	91.0	24.4	73.2
1200	79.5	22.7	71.4

2930, 2800, 1460, 1270, 1110; mass spectrum m/z (rel intensity) 164 (m^+, 5), 132 (11), 119 (100), 91 (16).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.14; H, 9.96.

(+)-2-Deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene (8) was prepared exactly as described above for the undeuterated triene. Reduction of the resolved 2,6-dimethyl-1-ketocyclohepta-2,4-diene-6-methylene hydrogen phthalate with sodium borodeuteride gave 1-deuterio-1-hydroxy-2,6-dimethylcyclohepta-2,4-diene-6-methylene hydrogen phthalate (**5**) in quantitative yield. Acid-catalyzed dehydration of 3.6 g of alcohol **5** afforded the 2-deuterio triene **6** in 71% yield. Saponification of the hemiphthalate and methylation of the hydroxymethyl intermediate **7** gave **8**. According to NMR analysis, this triene contained 86.4% deuterium at C(2) (Figure 1); it had $[\alpha]_{365}$ +65.0, $[\alpha]_{436}$ +31.9° ($CHCl_3$), and NMR in the presence of Eu(hfbc)$_3$ employing benzene-d_6 as the solvent showed this material to be 90.7 ± 0.9% optically pure.

Sealed-Tube Kinetics. Pyrolysis tubes were constructed from 7-mm borosilicate tubing; they were soaked in a concentrated ammonium hydroxide–EDTA solution at 40 °C for 16 h, rinsed well with distilled water, and dried at 130 °C for 24 h.

The substrate was purified by VPC on the FFAP column. In a typical kinetic run, 41 mg of purified **8** was diluted to 0.5 mL with freshly distilled toluene containing 0.5% triethylamine, and the resulting solution was placed in a pyrolysis tube. The tube was placed on a high-vacuum line and degassed by two freeze–pump–thaw cycles; it was sealed under high vacuum (10^{-5} mm) to give a tube approximately 10 cm in length.

A tube was placed in a wire cage and immersed in a eutectic salt bath heated to 223.4 °C. On immersion of the tube, the temperature of the bath decreased to 223.2 °C and required 2 min to recover. The salt bath consisted of a well-insulated stainless steel beaker approximately 20-cm in diameter and 20-cm in height filled with an equimolar mixture of $NaNO_2$ and KNO_3.[35] The bath was fitted with two stainless steel immersion heaters powered through variacs and a third heater powered by a Bailey Instrument Co. Model 253 precision temperature controller. The molten salt was stirred with a "Lightnin" stirrer and the temperature was measured with a frequently calibrated Hewlett-Packard 2802 A platinum resistance thermometer.

The tube was heated for the appropriate time, removed, cooled with tap water, and opened. The contents of the tube were purified on a 6.4 mm × 2.5 m 10% DBTCP on 60/80 Chromosorb W NAW column coupled with a 6.4 mm × 0.3 m 10% SE 30 on 60/80 Chromosorb W NAW column at 120 °C with a helium flow rate of 60 mL/min. The substrate **8** and degenerate isomers **14** showed a retention time of 50 min under these conditions; the 2-methyl structural isomer **15** exhibited a 41-min retention time.

The VPC purified material was then analyzed by 360-MHz NMR in benzene-d_6 to determine the extent of deuterium scrambling. The percent deuterium at C(2) was determined by integrating the area of the H–C(2) doublet and comparing this with the area of the H–C(5) multiplet. Table VI summarizes the primary data for deuterium scrambling; these data were used to calculate the data shown in Table I.

The optical purity of each kinetic point was determined by NMR; the sample used for determination of percent deuterium was treated with sufficient Eu(hfbc)$_3$ to split the enantiomeric C(7) methyl resonances. The optical purity was determined by integration, and the data obtained are shown in Table II.

The final measurement required for the determination of the concentrations of the four degenerate isomers was obtained by saturating the NMR samples used for determination of the optical purity with Eu(hfbc)$_3$. The NMR samples were allowed to stand with excess Eu(hfbc)$_3$ for at least 2 h; then the samples were filtered through a disposable pipet plugged with clean glass wool and deoxygenated with a slow stream of dry nitrogen for 15 min. During the course of an analysis it was sometimes necessary to subject a sample to additional deoxygenations to improve the spectrum resolution.

(35) Cason, J.; Rapoport, H. "Laboratory Text in Organic Chemistry"; Prentice-Hall: Englewood Cliffs, NJ, 1970, p 302.

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Registry No. (*S*)-**1**, 81205-75-6; (*R*)-**1**, 81205-76-7; (±)-**2**, 69268-52-6; (±)-**3**, 69268-53-7; (+)-**3**, 69268-56-0; (±)-**4**, 81205-77-8; (+)-**4**, 81205-78-9; **5**-d_0, 81205-79-0; **5**, 81205-80-3; (+)-**6**-d_0, 81205-81-4; (+)-**6**, 81218-90-8; (+)-**7**-d_0, 81205-82-5; (+) **7**, 81205-83-6; (+)-**8**-d_0, 81244-87-3; (+)-**8**, 69268-48-0; (−)-**8**, 69268-49-1; (−)-**8**-d_0, 80721-88-6; **12**, 81205-84-7; (+)-**14**, 69268-50-4; (−)-**14**, 69268-51-5; *l*-carvone, 6485-40-1; (*R*)-(−)-α-methylbenzylamine, 3886-69-9.

Interconversion of Dipoles by the Flash Vacuum Pyrolysis of Oxadiazolinones

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Abstract: The flash vacuum pyrolysis of a series of 2-phenyl-*N*-allyl-substituted 1,3,4-oxadiazolin-5-ones was investigated. The reactions can best be rationalized in terms of an initial loss of carbon dioxide to generate an *N*-allyl-substituted nitrilimine. This species undergoes a subsequent 3,3-sigmatropic shift to give a rearranged diazoalkene. The products obtained are most simply explained by invoking loss of nitrogen to generate a carbene intermediate followed by either hydrogen or vinyl migration. The formation of the 1,2-dihydronaphthalene ring can be rationalized in terms of a thermally allowed disrotatory electrocyclic reaction followed by a 1,5-sigmatropic hydrogen shift. The initially generated carbene also undergoes insertion into a neighboring methyl group to give a transient vinylcyclopropane, which is converted into a phenylcyclopentene derivative under the thermal conditions employed. The pyrolysis of *N*-benzyl-2-phenyl-1,3,4-oxadiazolinone generates a nitrilimine which rearranges to a diazoalkene via a 1,3-sigmatropic benzyl shift. Loss of nitrogen followed by a 1,2-phenyl or hydrogen migration nicely accounts for the products observed.

During the past several years, we have been engaged in a systematic study of the chemistry of nitrilium betaines, a class of 1,3-dipoles containing a central nitrogen atom and a π-bond orthogonal to the 4π-allyl system.[2a] 1,3-Dipolar cycloaddition

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