Determination of Association Constants. The determination of the association constants was carried out at four temperatures in the range 240–320 K using nine samples with varying host/guest ratios. The sample-dependent chemical shift of malononitrile was used to iteratively calculate the association constant by the method of de Boer et al.[7]

X-ray Crystallography. X-ray diffraction measurements were performed on a Philips PW1100 or an Enraf-Nonius CAD4 diffractometer, both using graphite-monochromated Mo Kα radiation. Crystal data and data collection parameters are in Table VII. Lattice parameters were determined by least-squares from 20 to 25 centered reflections. Intensities were measured in the $\omega/2\theta$ scan mode and corrected for the decay of three control reflections, measured every hour, and for Lorentz–polarization, but not for absorption.

The structures were solved by direct methods[29] and refined with full-matrix least-squares. Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered to be observed and were included in the refinement (on F). Weights were calculated as $w = 4F_o^2/\sigma^2(F_o^2)$; $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, with $\sigma(I)$ based on counting statistics and p an instability factor obtained from plots of F_o vs weighted error. The malononitrile hydrogens were located on difference Fourier maps and included in the refinement. Due to disorder of methyl groups in some of the structures, not all hemispherand hydrogens could be located. Depending on data quality and data/parameter ratio these hydrogens were included in the refinement or put in calculated positions (C–H distance 0.96 Å) and treated as riding on their parent C atoms ($B_{iso}(H) = 1.2B_{eqv}(C)$). The structure of **1a**·$CH_2(CN)_2$ contains a diethyl ether solvent molecule, which is disordered around a twofold axis; no hydrogens were taken into account. Details concerning the treatment of hydrogens and positional disorder are available as supplementary material.

Parameters refined were the overall scale factor, isotropic extinction parameter g (correction of F_c with $(1 + gI_c)^{-1}$), positional and anisotropic thermal parameters for non-H atoms, positional and isotropic thermal parameters for H atoms (if included), and occupancy factors for positionally disordered atoms. Refinement converged with a shift/error ratio less than unity for all variables, except occasionally for disordered atoms. Final difference Fourier maps showed no significant features. All calculations were done by using SDP.[30]

T_1 Measurements. The T_1 values were determined by inversion–recovery methods. The experimental details were published previously.[17] For the determinations concerning the complexes a fivefold excess of malononitrile was added to make sure that more than 99% of the host was in its complexed form. The concentration of the host varied between 0.05 and 0.1 M.

Molecular Mechanics. Calculations were carried out with Allinger's MMP2 program[31] (based on QCPE programs 395 and 400) as incorporated in the CHEMX suite.[20] All parameters were standard. The error in the relative steric energies is assumed to be less than 1 kcal/mol. For ligand **1a** the calculations were also carried out with the parameters belonging to the AMBER force field.[32] The same order and approximately the same differences for the steric energies of the various conformations were obtained.

Starting conformations for the energy minimizations were obtained by both molecular graphics methods and X-ray coordinates. In order to scan the conformational space the dihedral driver[33] from the MMP2 program was used for the central and flanking methoxy groups of host **1a**.

Acknowledgment. We thank J. M. Visser and J. L. M. Vrielink for performing the T_1 measurements. Use of the services and facilities of the Dutch CAOS/CAMM Center, under Grant No. SON-11-20-700 and STW-NCH-44.0703, is gratefully acknowledged. This investigation was supported by The Netherlands Foundation for Chemical Research (S.O.N.) and The Netherlands Technology Foundation (S.T.W.) with financial aid from The Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

Supplementary Material Available: Tables of coordinates and anisotropic thermal parameters of non-H atoms, coordinates and isotropic thermal parameters of H atoms, bond distances and angles, and selected torsion angles for the five crystal structures (25 pages). Ordering information is given on any current masthead page.

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(32) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230–252.
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Kinetics and Deuterium Kinetic Isotope Effects for the Thermal [1,7] Sigmatropic Rearrangements of *cis,cis*-1,3,5-Octatriene

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Abstract: Thermal isomerizations of *cis,cis*-1,3,5-octatriene at 60–111 °C occur with activation parameters log A = 9.1 and E_a = 21.3 (to *cis,cis,cis*-2,4,6-octatriene) and E_a = 20.2 kcal mol^{-1} (to *cis,cis,trans*-2,4,6-octatriene). Primary deuterium kinetic isotope effects for these [1,7] sigmatropic shifts are found to be 6.4–7.7 and not markedly temperature dependent, indicative of a linear or nearly linear C7–H–C1 geometry in the transition-state structure.

Thermal [1,7] sigmatropic migrations of hydrogen have been well recognized and theoretically codified for more than 20 years.[1] From the pioneering experimental studies on compounds related to calciferol[2] to the recent demonstration of antarafacial stereochemistry across the heptatrienyl unit for the [1,7] hydrogen shifts shown by *cis*-isotachysterol analogues,[3] investigations have typically been concerned with rearrangements shown by comparatively large molecules. Quantitiative kinetic and stereochemical work on

(1) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511–2513. Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic: New York, 1970; pp 114–140. Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187–217.
(2) Havinga, E.; Schlatmann, J. L. M. A. *Tetrahedron* **1961**, *16*, 146–152. Schlatmann, J. L. M. A.; Pot, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1173–1184. Havinga, E. *Experientia* **1973**, *29*, 1181–1193.
(3) Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268–270.

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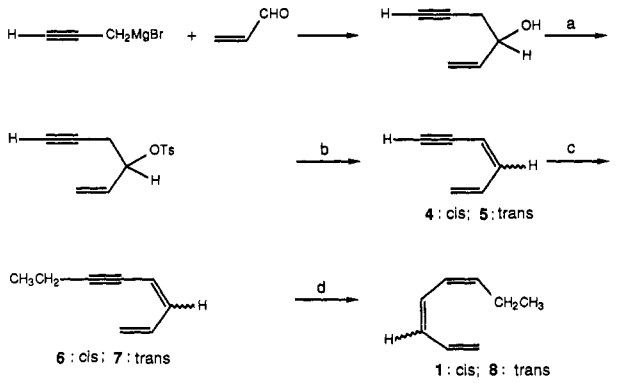
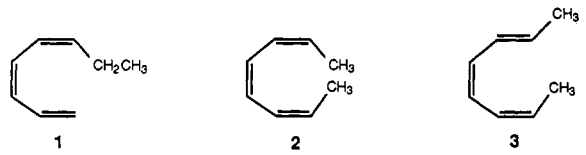
Scheme I[a]



[a] Key: (a) TsCl/KOH, −78 °C, 0.5 h; (b) KOH/H_2O–DMSO (4:1), 100 °C; (c) (i) $NaNH_2$/ether–DMSO, 0 °C, 15 min, (ii) CH_3CH_2Br, 0 °C → room temperature, 1 h; (d) Zn/KCN/MeOH–H_2O, room temperature, 24 h.

simple hydrocarbons, such as suitable heptatrienes and octatrienes, has been conspicuously absent. The parallel computational studies that might be stimulated by such experimental definitions of reactivity parameters for [1,7] hydrogen shifts in simple hydrocarbons have not been undertaken.[4]

We now report an initial effort in response to this lacuna of experimental fact: the thermal isomerizations of *cis,cis*-1,3,5-octatriene (**1**) to the cis,cis,cis and cis,cis,trans isomers of 2,4,6-octatriene (**2** and **3**, respectively) have been followed kinetically. Deuterium-labeled analogues have been made and studied to measure primary and secondary deuterium kinetic isotope effects.



1 2 3

These particular reactions, **1** → **2** and **1** → **3**, were selected for investigation to complement kinetic work on the thermal interconversion of all three isomers, **1**–**3**.[5] The equilibration of **2** and **3**, presumably by way of **1**, is a historically prominent example of kinetically competitive pericyclic reactions:[6,7] **2** ⇄ **3** occurs facilely relative to the electrocyclic isomerizations of **2** and **3** to 5,6-dimethylcyclohexa-1,3-dienes, a circumstance that vitiates all simple attempts to infer stereochemistry of electrocyclic ring closure from cyclohexadiene product mixtures derived from **2** + **3**.[8]

Results

Synthesis. The synthesis of *cis,cis*-1,3,5-octatriene (**1**) was reported by Jaenicke and Seferiadis in 1975 in the course of their demonstration that fucoserratene, the female sex attractant from the ova of the seaweed *Fucus serratus* L., is the trans,cis isomer of 1,3,5-octatriene.[9] Two synthetic routes were demonstrated, and gas chromatography on a packed column at 55 °C provided samples of high isomeric purity for characterization by ultraviolet and infrared spectroscopy. All four isomers of 1,3,5-octatriene gave identical mass spectra and were found to be relatively unstable.[9]

Our route to this triene is shown in Scheme I. The cis and trans isomers of 1,3-hexadien-5-yne are known and relatively

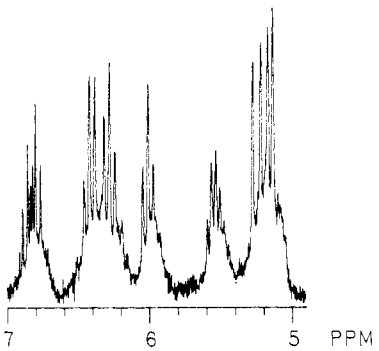


Figure 1. Partial proton NMR spectrum showing the olefinic region of *cis,cis*-1,3,5-octatriene. A sweep width of 3000 Hz and an interpulse delay of 2 s were used, 500 transients were acquired, and an exponential line-broadening function of 0.1 Hz was applied.

Table I. Rate Constants[a] for [1,7] Sigmatropic Rearrangements of *cis,cis*-1,3,5-Octatrienes **1**, **1**-*7-d*, and **1**-*7,7-*d_2

temp, °C	**1**	**1**-*7-d*	**1**-*7,7-*d_2
60	0.084	0.046	0.010
	0.089	0.048	0.011
		0.053	
85	0.72	0.46	0.12
	0.78	0.47	0.13
111	4.93	3.40	0.97
	5.22	3.59	1.01
	5.27		

[a] Times 10^3 s.

accessible intermediates[10] and may be separated, if desired, by preparative gas chromatography without great difficulty. Reaction of dienynes **4** and **5** with sodium amide in ether, followed by dilution with dry dimethyl sulfoxide and the dropwise addition of ethyl bromide or iodide, gave 1,3-octadien-5-ynes **6** and **7** in 80–90% yields.[11] Selective reduction of the triple bond was achieved with zinc dust activated by potassium cyanide in water–methanol;[12] isolation and purification at room temperature, including flash chromatography on silica gel, gave trienes **1** and **8** (fucoserratene). The *all-cis*-triene **1** could be secured free of the 3-trans isomer **8** by reducing dienyne **6** over Lindlar catalyst, followed by HPLC purification. The olefinic portion of the ^1H NMR spectrum of the cis,cis isomer **1**, shown in Figure 1, provides immediate visual confirmation of the isomeric quality and character of the triene secured in this manner.

The synthetic approach of Scheme I was easily adapted to secure the *7-d*- and *7,7-*d_2-labeled analogues of **1**: the mixture of dienyne isomers **4** and **5** was alkylated with either bromoethane-*1-d* or iodoethane-*1,1-*d_2 in place of unlabeled ethyl bromide, and subsequent reactions in the scheme were conducted without modification. 7-Monodeuterio and 7,7-dideuterio analogues of hydrocarbons **1** and **6**–**8** had the expected gas chromatographic, ^1H NMR spectroscopic, and mass spectrometric characteristics, relative to the corresponding unlabeled compounds.

1-7-d **1**-7,7-d_2

While triene **1** did prove thermally unstable, as expected, it could be handled readily as a dilute solution in hydrocarbon solvents or stored without loss for extended periods in a refrigerator. At 60–111 °C, it rearranged in parallel competitive first-order processes to give 2,4,6-octatriene isomers **2** and **3**.

(4) For the contrasting case of [1,5] hydrogen shifts, see: Jensen, F.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3139–3140 and references therein.
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Table II. Mole Fractions[a] of *cis,cis,trans*-2,4,6-Octatrienes **3**, **3**-*1-d*, **3**-*7-d*, and **3**-*1,7-d*$_2$ in Product Mixtures from **1**, **1**-*7-d*, and **1**-*7,7-d*$_2$

temp, °C	**1**	**1**-*7-d*	**1**-*7,7-d*$_2$
60	0.85	0.83	0.84
85	0.83	0.82	0.81
111	0.82	0.80	0.80

[a] Averages of two or three kinetic runs each; largest standard deviation 0.016.

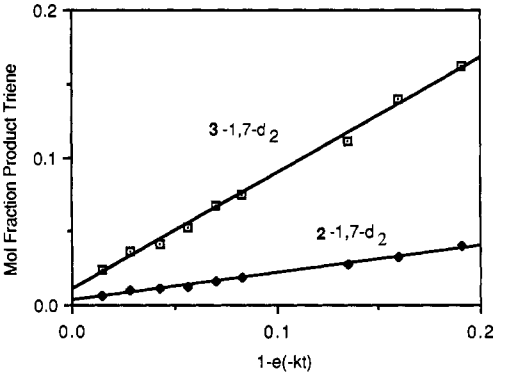


Figure 2. Plot of mole fractions of product trienes **2**-*1,7-d*$_2$ and **3**-*1,7-d*$_2$ versus $1 - \exp(-kt)$ at 85 °C. The slopes of the two lines are 0.186 and 0.788, respectively.

Direct chromatographic, mass spectrometric, and NMR spectroscopic comparisons of these reaction products with authentic, independently synthesized cis,cis,cis and cis,cis,trans isomers **2** and **3** established the structural assignments.[5-7]

Kinetics. Sealed tubes containing triene **1**, or the deuteriated analogue **1**-*7-d* or **1**-*7,7-d*$_2$, as a dilute solution in 2-methylpentane, were heated in a thermostated oil bath at 60, 85, or 111 °C for fixed periods, withdrawn, and cooled rapidly. Analysis by capillary gas chromatography on fused silica capillary columns gave area percent data for starting material **1** and products **2** and **3** as functions of time. Over the relatively short time periods required for a complete kinetic run, the data could be treated satisfactorily as due to two competititve first-order isomerizations,[13] for the thermal reactions of **2** and **3** at these temperatures and time periods were negligible.

Table I gives first-order rate constants for the disappearance through two parallel [1,7] sigmatropic migrations of triene **1** and deuteriated analogues, followed relative to an internal standard. Table II provides data on the fraction of cis,cis,trans to total cis,cis,cis and cis,cis,trans isomers of 2,4,6-octatriene in the product mixtures.

A typical kinetic run, for **1**-*7,7-d*$_2$ at 85 °C, involved analysis by capillary column gas chromatography of reaction mixtures at nine times, ranging from 2 to 29 min. The first-order disappearance of **1**-*7,7-d*$_2$ occurred with first-order rate constant $k = 1.21 \times 10^{-4}$ s^{-1}, while linear plots of mole fractions of products **2**-*1,7-d*$_2$ and **3**-*1,7-d*$_2$ against $1 - \exp(-kt)$ provided, through the ratio of slopes, the partitioning ratio **2**:**3** = 1:4.24, corresponding to 0.81 mol fraction of cis,cis,trans isomer in the rearrangement product mixture (Figure 2).

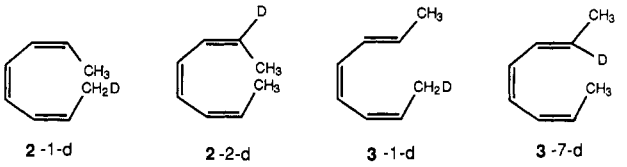
An independent experimental determination of overall deuterium kinetic isotope effects was obtained using gas chromatography/mass spectrometry to follow the relative rates of disappearance of d_i versus d_0 versions of triene **1**. These measurements are recorded in Table III, along with calculated rate ratios derived from the averages of rate constants recorded in Table I. The agreement is within probable error limits for ratios derived by the two distinct methods; for subsequent calculations, the weighted mean[14] values of the ratios obtained by the two methods were employed (Table III).

(13) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; Wiley: New York, 1961; pp 160–162.

(14) Perrin, C. L. *Mathematics for Chemists*; Wiley-Interscience: New York, 1970; p 159.

Calculations and Data Reduction. From the data of Tables I and II one may calculate rate constants for **1** → **2** and **1** → **3** separately, as a function of temperature, and then find the Arrhenius parameters $\log A = 9.1$, $E_a = 21.3$ kcal mol^{-1} for **1** → **2** and $\log A = 9.1$, $E_a = 20.2$ kcal mol^{-1} for **1** → **3**. Alternatively, the temperature dependence of the rate constants may be expressed in terms of the activation parameters (at 85 °C) $\Delta S^{\ddagger} = -19$ eu for both [1,7] shifts and $\Delta H^{\ddagger} = 20.6$ (**1** → **2**) or 19.5 (**1** → **3**) kcal mol^{-1}.

The two possible cis,cis,cis products from **1**-*7-d*, trienes **2**-*1-d* and **2**-*2-d*, were not distinguished by gas chromatography, nor were the two possible cis,cis,trans products **3**-*1-d* and **3**-*7-d*.



2-*1*-d **2**-*2*-d **3**-*1*-d **3**-*7*-d

Reduction of the data in Tables II and III based on 34 kinetic runs to secure primary and secondary deuterium kinetic isotope effects for the two [1,7] hydrogen shift rearrangements being studied at three temperatures may be accomplished even in the absence of an analytical probe for distinguishing the deuterium-label distinct versions of products from starting material **1**-*7-d*.

The d_0 rate constant for a [1,7] shift may be taken as $2k_H$, where k_H is a symmetry-corrected rate constant for the [1,7] shift, unmodified by any isotope effect. The d_1 rate constant is equivalent to $k_H(\alpha + \beta)$, where α is the inverse of the primary deuterium kinetic isotope effect k_H/k_D and β is the inverse of the secondary deuterium kinetic isotope effect. The d_2 rate constant is just $2k_H(\alpha\beta)$, for only one product of a given stereochemistry is formed, and both primary and secondary isotope effects may exert a kinetic influence. Hence, one may readily calculate α and β from the observed rate constant ratios and product partitioning data.

The data reduction process may be illustrated with the 60 °C data from Tables II and III. From Table II, at 60 °C the ratios of mole fraction terms for d_1/d_0 and d_2/d_0 substrates are 0.98 and 0.99. From Table III, the ratios of rate constants for d_1/d_0 and d_2/d_0 substrates are 0.53 and 0.13. Then $(0.98)(0.53) = (\alpha + \beta)/2$, and $(0.99)(0.13) = \alpha\beta$. These two equations in two unknowns may be solved to give α and β, and then α^{-1} = primary $k_H/k_D = 7.0$ and β^{-1} = secondary $k_H/k_D = 1.12$. At 85 and 111 °C, the primary isotope effects are found to be 6.9 and 6.4, and the secondary k_H/k_D ratios are derived to be 0.92 and 0.88. Estimated relative errors are on the order of 10% for both isotope effects.

Calculations for **1** → **2**, based on the data of Tables II and III, give 7.7, 6.5, and 6.6 for the primary k_H/k_D effect at 60, 85, and 111 °C and secondary k_H/k_D values of 0.93, 0.86, and 0.76. Here, larger experimental uncertainties in derived isotope effects obtain, for the variations in mole fraction of cis,cis,cis products in product mixtures as a function of deuterium labeling in **1** are less precisely known. Estimated relative errors are on the order of 20% for both isotope effects.

Discussion and Conclusions

The activation parameters found for the [1,7] hydrogen shifts, $\log A = 9.1$ and $E_a = 21.3$ kcal mol^{-1} (**1** → **2**) and $E_a = 20.2$ kcal mol^{-1} (**1** → **3**), are entirely consistent with expectations.[2,15] The observed difference in activation energies for the two isomerizations may be viewed as a small stereochemical sensitivity of the activation energy lowering impact of a methyl substituent at C7 of a parent *cis,cis*-1,3,5-heptatriene system. In the transition-state structures a methyl at C7 is more effective in lowering the transition-state energy when it is stereochemically disposed so as to become trans in the product 2,4,6-triene than when it is oriented so as to become cis. The effect could be a simple manifestation

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Table III. Deuterium Kinetic Isotope Effects on Total Rates of Isomerization of *cis,cis*-1,3,5-Octatrienes **1**, **1**-7-d_2, and **1**-7,7-d_2

temp, °C	k(**1**-7-d)/k(**1**)			k(**1**-7,7-d_2)/k(**1**)		
	MS[a]	GC[b]	WM[c]	MS[a]	GC[b]	WM[c]
60	0.52 ± 0.03	0.56 ± 0.05	0.53 ± 0.03	0.12 ± 0.01	0.13 ± 0.01	0.13 ± 0.01
85	0.62 ± 0.03	0.63 ± 0.04	0.62 ± 0.02	0.16 ± 0.01[d]	0.16 ± 0.01	0.16 ± 0.01
111	0.66 ± 0.01	0.68 ± 0.04	0.66 ± 0.01	0.17 ± 0.01	0.19 ± 0.01	0.18 ± 0.01

[a] Except as noted, average of two runs. [b] Calculated from average rate constants for each temperature and starting triene in Table I. [c] Weighted mean[14] of MS- and GC-determined ratios of rate constants. [d] Average of four runs, 0.156 ± 0.003.

of relative product stability influencing relative transition-state energies.

In spite of a large primary isotope effect, the mole fractions of cis,cis,cis and cis,cis,trans products from **1**-7-*d* are nearly identical with the ratios observed for d_0 substrate (Table II). At first glance this might seem surprising, or somehow related to the circumstance that **1**-7-*d* was employed as a racemic compound. But deliberate analysis makes clear that the same result would be seen with chiral **1**-7-*d*: hydrogen or deuterium [1,7] shifts could take place antarafacially to either face of the triene at C1, so that either antipode could give four achiral products. The competitive situation never restricts **1**-7-*d* to a choice between only two reactions giving one geometrical isomer of product with hydrogen transfer and the other with deuterium transfer.

For all six instances of [1,7] sigmatropic rearrangement studied kinetically in this work, the primary k_H/k_D ratios were found to range from 6.4 to 7.7, values that may be considered perfectly unexceptional for a hydrogen transfer.[16]

An earlier report[17] of $k_H/k_D \sim 45$ for hydrogen versus deuterium [1,7] transfer in the vitamin D_3–previtamin D_3 thermal equilibrium remains anomalous and may, in light of the present work, merit some reinvestigation.

The apparent temperature dependence noted for the primary k_H/k_D effects is at best very minor, and thus one may conclude that the transition-state structures for hydrogen migration is C7–H–C1 linear, or very nearly linear.[18] The probable errors in the primary k_H/k_D values do not permit a more categorical assertion.

These probable errors seem all but inevitable for a system in which primary and secondary deuterium isotope effects are simultaneously of influence and of substantially different magnitudes. Greater precision may be attained through experiments designed to measure only one effect at a time, rather than various combinations of both effects acting simultaneously.

Experiments to look for a possible temperature dependence larger than probable uncertainties in primary k_H/k_D values for [1,7] shifts in a simple linear hydrocarbon triene, and for possible stereochemically specific secondary k_H/k_D values in such trienes, are now in progress.

Experimental Section

Diethyl ether was distilled from sodium benzophenone ketyl immediately before use. Dimethyl sulfoxide, pentane, bis(2-ethoxyethyl) ether (diethyl carbitol, diethylene glycol diethyl ether), and methylene chloride were distilled from CaH_2. 1,1-Dideuterioethyl iodide (>98 atom %) was obtained from MSD Isotopes. 2-Methylpentane, used as solvent for the kinetic studies, was >99% pure (Aldrich). All reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Proton NMR spectra were recorded for $CDCl_3$ solutions on a Mohawk 250, an in-house-designed 5.87-T FT spectrometer based on Cryomagnet Systems rf equipment and a Nicolet 1280 computer, or on a GE QE 300 spectrometer. Chemical shifts (δ) are expressed relative to internal Me_4Si, and coupling constants (J values) are given in hertz. Chemical shift assignments were confirmed by proton homonuclear decoupling experiments.

Mass spectral data were secured with Hewlett-Packard (HP) 5890, 5970B, and 9836 instruments and computer. Analytical gas chromatographic analyses were done with a 0.2-mm i.d. 25-m cross-linked 5% phenyl methyl silicone fused silica capillary column and a 0.2-mm i.d. 25-m methyl silicone capillary column, a HP 5780 instrument with fid detectors, and HP 3390A and 3392A reporting integrators. Preparative gas chromatographic analyses were accomplished with a Varian A-90-P3 instrument using column A, Carbowax 20M on Chromosorb G 60/80 (0.6 cm × 9.7 m); B, SE-30 on Chromosorb W 60/80 (0.6 cm × 11 m); or C, DMCS on Chromosorb P 60/80 (0.6 cm × 7.4 m).

1-Hexen-5-yn-3-ol, from the reaction of propargyl magnesium bromide with acrolein:[19] bp 105 °C (200 mm); ^{1}H NMR (300 MHz) δ 2.07 (t, 1 H, J = 2.7 Hz, C6 H), 2.44–2.54 (m, 3 H, C4 H_2, OH), 4.29 (apparent q, 1 H, J = 5.9 Hz, >CHO), 5.18–5.36 (AB of ABX, 2 H, $\Delta\delta$ = 0.16, 2 H, C1-cis-H, C1-trans-H, J_{AX} = 5.9 Hz, J_{BX} = 14.2 Hz), 5.88–5.99 (m, 1 H, m, C2 H).

3-[(*p*-Tolylsulfonyl)oxy]-1-hexen-5-yne. 1-Hexen-5-yn-3-ol (10.0 g, 0.1 mol) in 200 mL of ether was treated with *p*-toluenesulfonyl chloride (25.7 g, 0.13 mol) in the presence of potassium hydroxide[10] (46 g, 0.8 mol) at −78 °C for 30 min. The reaction mixture was allowed to warm to room temperature and diluted with 200 mL of water. The aqueous mixture was extracted with ether (2 × 100 mL), and the extracts were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford 25 g of the crude pale yellow tosylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3 H, CH_3), 2.59 (m, 3 H, C6 H, C4 H_2), 4.97 (dt, 1 H, C3 H), 5.21 (d, 1 H, J = 10.7 Hz, C1-cis-H), 5.26 (d, 1 H, J = 18.7 Hz, C1-trans-H), 5.79 (m, 1 H, C2 H), 7.32 (d, 2 H, J = 8 Hz, aromatic), 7.79 (d, 2 H, J = 8.3 Hz, aromatic).

1,3-Hexadien-5-ynes 4 and 5. Following Brandsma,[10] the crude tosylate prepared immediately above was added dropwise to a solution of KOH (36 g) in 50 mL of 4:1 water–dimethyl sulfoxide maintained at about 100 °C. The hexadienyne isomers[11] distilled from the reaction mixture into a receiver cooled in a dry ice–acetone bath. After the addition, the reaction flask was heated at 160–170 °C for 10 min, until only water started to distill. The clear top layer of products (7.7 g, 77% overall from 1-hexen-5-yn-3-ol) was removed from the receiving flask with a Pasteur pipette, leaving behind the frozen water and dimethyl sulfoxide. A capillary GC analysis showed the mixture to consist of 3-cis and 3-trans isomers in a relative ratio of 55:45. The isomers were separated on preparative GC with column C. The retention times were ca. 3 and 4 min for the cis and the trans isomers, respectively, at a column temperature of 70 °C. There was no significant peak overlapping for 10-μL injection volumes.

1,3-*cis*-Hexadien-5-yne (4): ^{1}H NMR (250 mHz) δ 3.23 (d, 1 H, J = 2.21 Hz, C6 H), 5.32 (d, 1 H, J = 10.3 Hz, C1-cis-H), 5.40 (d, 1 H, J = 16.91 Hz, C1-trans-H), 5.46 (d, 1 H, J = 9.56 Hz, C4 H), 6.47 (apparent t, J = 10.5 Hz, C3 H), 6.92 (m, 1 H, C2 H).

1,3-*trans*-Hexadien-5-yne (5): ^{1}H NMR (250 MHz) δ 3.03 (d, 1 H, J = 2.21 Hz, C6 H), 5.22 (d, 1 H, J = 10.3 Hz, C1-cis-H), 5.33 (d, 1 H, J = 16.91 Hz, C1-trans-H), 5.6 (d, 1 H, J = 16.18 Hz, C4 H), 6.36 (m, 1 H, C2 H), 6.68 (dd, 1 H, J = 10.3, 15.7 Hz, C3 H).

Ethanol-*1*-*d*. A three-necked round-bottomed flask equipped with a serum cap, magnetic stirring bar, and short-path distillation head was flame dried under nitrogen and allowed to cool. Solvent bis(2-ethoxyethyl) ether (8 mL) was placed in the flask, lithium aluminum deuteride (0.5 g, 11.9 mmol, Aldrich, 98 atom % *d*) was dispersed in the solvent at 0 °C, and acetaldehyde (2.1 g, 2.7 mL, 48 mmol) was added dropwise to the reaction mixture through the serum cap with a syringe equipped with a "mininert" syringe valve (Supelco, Catalog No. 2-2285). After being stirred for a further 30 min at 0 °C, the reaction mixture was quenched with 1-phenylethanol (5 mL), and after a further 15 min, the product ethanol-*1*-*d* was distilled from the reaction mixture. The distillate was redistilled with a 35-cm Vigreux column to obtain the pure ethanol-*1*-*d*: bp 78 °C; 1.6 g, 71% yield; ^{1}H NMR (300 MHz) δ 1.23 (d, 3 H, J = 6 Hz, CH_3), 3.71 (br q, 1 H, CHD).

Bromoethane-*1*-*d*. Ethanol-*1*-*d* (1.6 g, 34 mmol) was dissolved in 5 mL of bis(2-ethoxyethyl) ether in a 50-mL three-necked round-bottomed flask equipped with a magnetic stirrer, a serum cap, and a 35-cm Vigreux column attached to a short-path distillation head. The flask contents were cooled to 0 °C, and phosphorus tribromide (5.7 g, 2 mL, 21 mmol)

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was added dropwise in 5–10 min through the serum cap by a syringe equipped with a mininert syringe valve. The reaction mixture was warmed to room temperature, and the compound was distilled from the reaction mixture with a heat gun. Redistillation of the distillate using a 35-cm Vigreux column yielded 2.2 g (59.5%) of the bromoethane-*1-d*: bp 38–40 °C; ^{1}H NMR (300 MHz) δ 1.66 (d, 3 H, J = 6 Hz, CH_3), 3.42 (br q, 1 H, CHD).

1,3-Octadien-5-ynes 6 and 7. A mixture of cis and trans isomers of 1,3-hexadien-5-yne (1.9 g, 13.9 mmol) was dissolved in 5 mL of anhydrous ether and was placed in a flame-dried three-necked round-bottomed flask equipped with a serum cap, a reflux condenser with a nitrogen inlet, and magnetic stirrer. The flask was cooled to 0 °C, and sodium amide (0.59 g, 15 mmol, Aldrich) was added in small portions during 2–3 min. An exothermic reaction commenced, and instantaneous ammonia evolution was observed. After 15 min, 5 mL of dry DMSO was added and was followed by the dropwise addition of ethyl bromide (1.63 g, 1.1 mL, 15 mmol) through a syringe equipped with a mininert syringe valve. The reaction was mildly exothermic. After being stirred for a further 1 h at room temperature, the reaction mixture was diluted with ice-cold water (10 mL). The contents were poured into a separatory funnel containing 100 mL of water and were extracted with ether (3 × 50 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentraton of the filtrate by distillation under reduced pressure provided the octadienynes contaminated with only traces of ether: bp 72–73 °C (70 mm); 1.32 g (12.4 mmol, 90% yield). Other preparations of these dienynes gave 80–90% yields. The isomers were separated by GC on column A at a column temperature of 110 °C, the retention times being 4 and 5 min for the cis and the trans isomers, respectively, with a base-line separation. Typical injection volumes were 30–40 μL.

1,3-*cis*-Octadien-5-yne (6): ^{1}H NMR (300 MHz) δ 1.19 (t, 3 H, J = 7.5 Hz, CH_3), 2.39 (dq, 2 H, J = 7.41, 2.1 Hz, CH_2), 5.23 (d, 1 H, J = 10.2 Hz, C1-cis-H), 5.33 (d, 1 H, J = 17.4 Hz, C1-trans-H), 5.45 (d, 1 H, J = 10.45 Hz, C4 H), 6.31 (t, 1 H, J = 10.7 Hz, C3 H), 6.8–6.93 (m, 1 H, C2 H); MS, m/z 106 ($M^{\bullet+}$).

3-*trans*-1,3-Octadien-5-yne (7): ^{1}H NMR (300 MHz) δ 1.16 (t, 3 H, J = 7.4 Hz, CH_3), 2.34 (dq, 2 H, J = 7.5, 2.2 Hz, CH_2), 5.12 (d, 1 H, J = 9.9 Hz, C1-cis-H), 5.24 (d, 1 H, J = 17.1 Hz, C1-trans-H), 5.61 (d, 1 H, J = 15.5 Hz, C4 H), 6.31–6.4 (m, 1 H, C2 H), 6.46–6.55 (m, 1 H, C3 H); MS, m/z 106 $M^{\bullet+}$).

1,3-*cis*-Octadien-5-yne-7,7-d_2: ^{1}H NMR (300 MHz) δ 1.19 (s, 3 H, CH_3), 5.24 (d, 1 H, J = 10.1 Hz, C1-cis-H), 5.35 (d, 1 H, J = 16.9 Hz, C1-trans-H), 5.47 (d, 1 H, J = 10.5 Hz, C4 H), 6.33 (t, 1 H, J = 10.7 Hz, C3 H), 6.89 (m, 1 H, C2 H); MS, m/z 108 ($M^{\bullet+}$).

1,3-*trans*-Octadien-5-yne-7,7-d_2: ^{1}H NMR (300 MHz) δ 1.17 (s, CH_3), 5.14 (d, 1 H, J = 9.85 Hz, C1-cis-H), 5.26 (d, 1 H, J = 16.3 Hz, C1-trans-H), 5.63 (d, 1 H, J = 15.4 Hz, C4 H), 6.36 (m, 1 H, C2 H), 6.53 (m, 1 H, C3 H); MS, m/z 108 ($M^{\bullet+}$).

1,3-*cis*-Octadien-5-yne-7-*d*: ^{1}H NMR (300 MHz) δ 1.18 (d, J = 6.3 Hz, 3 H, CH_3), 2.38 (br dq, 1 H, CHD), 5.22 (d, 1 H, J = 10.18 Hz, C1-cis-H), 5.33 (d, 1 H, J = 17 Hz, C1-trans-H), 5.45 (d, 1 H, J = 10.7 Hz, C4 H), 6.33 (t, 1 H, J = 10.72 Hz, 10.7 Hz, C3 H), 6.87 (m, 1 H, C2 H); MS, m/z 107 ($M^{\bullet+}$).

1,3-*trans*-Octadien-5-yne-7-*d*: ^{1}H NMR (300 MHz) δ 1.15 (d, J = 6 Hz, 3 H, CH_3), 2.33 (br q, 1 H, CHD), 5.12 (d, 1 H, J = 9.92 Hz, C1-cis-H), 5.24 (d, 1 H, J = 16.6 Hz, C1-trans-H), 5.61 (d, 1 H, J = 15.36 Hz, C4 H), 6.34 (m, 1 H, C2 H), 6.51 (m, 1 H, C3 H); MS, m/z 107 ($M^{\bullet+}$).

Lindlar Reduction of 1,3-*cis*-Octadien-5-yne. A sample of *cis*-dienyne **6** (0.1 g, 0.94 mmol) obtained by preparative gas chromatographic separation of the mixture of cis and trans isomers was dissolved in 2 mL of methanol in a 5-mL flask fit with a serum cap. Lindlar catalyst (50 mg, Aldrich) and two drops of freshly distilled quinoline were added, the flask was evacuated with a water aspirator, and hydrogen gas was introduced through a three-way stopcock (Pharmaseal Inc., K75) connected to a hydrogen-filled balloon. The progress of the reaction was monitored by occasionally withdrawing samples through a syringe, filtering through a small pad of silica gel, and analyzing by capillary GC. As the reaction progressed, considerable amounts of over-reduced products were observed. The reaction was stopped when about two-thirds of the starting material had been consumed, and an attempted isolation and purification by preparative GC on column A at 80 °C, and a detector temperature of 170 °C resulted only in the isomerization of 1,3-*cis*,5-*cis*-octatriene into isomeric hydrocarbons, according to analytical GC as well as the NMR examination of the collected material.

However, when the reaction was stopped at ca. 50% completion, worked up in the usual manner, and followed by HPLC separation, an analytically pure sample of the triene was obtained (cf. Figure 1, and below).

Table IV. Retention Times of Octatriene Isomers on Fused Silica Capillary Columns at 80 °C

column	isomer				
	8	**1**	*t,c,t*-2,4,6	**3**	**2**
phenyl methyl silicone	4.09	4.28	5.09	5.41	5.78
dimethyl silicone	3.68	3.83	4.52	4.78	5.05

1,3-*cis*,5-*cis*-Octatriene (1). A gas chromatographically purified sample of 1,3-*cis*-octadien-5-yne (50 mg, 0.47 mmol) was reacted with Zn dust (5 g, 76 mmol) and potassium cyanide (260 mg, 4 mmol)[12] in a solution of water and methanol (1:1, 14 mL). After completion of the reaction (24 h), as monitored by capillary GC, the reaction mixture was poured into 100 mL of water and was extracted with three 30-mL portions of pentane. The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated by rotary evaporation until most of the solvent had been removed. The residue contained some impurities, mainly the rearranged 3-trans isomer, and to a minor extent, over-reduced products. Purification by flash chromatography on a small column of silica gel by elution with 2-methylpentane removed most of the impurities. However, most of the trans isomer was not separated. Since this isomer (**8**) proved to be thermally stable at 60–111 °C for periods of time empoyed in the kinetic studies of the thermal isomerizations of **1**, 2-methylpentane solutions of the two isomers were used for pyrolyses. Besides the solvent, the 1,3-*trans*,5-*cis*-octatriene amounted to 26% and the 1,3-*cis*,5-*cis*-octatriene was 64% of the mixture.

1,3-*cis*,5-*cis*-Octatriene (1): ^{1}H NMR (300 MHz) δ 1.01 (t, 3 H, J = 7.5 Hz, CH_3) 2.21 (quin, 2 H, J = 7.4 Hz, CH_2), 5.14 (d, 1 H, J = 10.3 Hz, C1-cis-H), 5.24 (d, 1 H, J = 16.7 Hz, C1-trans-H), 5.54 (m, 1 H, C6 H), 6.01 (t, 1 H, J = 11 Hz, C3 H), 6.27 (t, 1 H, J = 11 Hz, C4 H), 6.41 (t, 1 H, J = 11.2 Hz, C5 H), 6.76–6.88 (m, 1 H, C2 H); MS, m/z 108 ($M^{\bullet+}$).

1,3-*cis*,5-*cis*-Octatriene-7,7-d_2: ^{1}H NMR (300 MHz) δ 0.99 (s, 3 H, CH_3), 5.15 (d, 1 H, J = 10.2 Hz, C1-cis-H), 5.24 (d, 1 H, J = 16.7 Hz, C1-trans-H), 5.54 (d, 1 H, J = 10.7 Hz, C6 H), 6.01 (t, 1 H, C3 H), 6.27 (t, 1 H, J = 11.1 Hz, C4 H), 6.41 (t, 1 H, J = 11.1 Hz, C5 H), 6.76–6.88 (m, 1 H, C2 H); MS, m/z 110 ($M^{\bullet+}$).

1,3-*cis*,5-*cis*-Octatriene-7-*d*: MS, m/z 109 (M^+). A 10-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirrer was charged with zinc (0.12 g, 1.8 mmol), cuprous chloride (0.03 g, 0.32 mmol), and 2 mL of 95% ethanol. The contents were then refluxed for 15 min to form the zinc/copper couple. Then 1,3-*trans*-octadien-5-yne (0.1 g, 0.9 mmol) dissolved in 1 mL of ethanol was added to the flask contents in one portion. The reaction mixture was refluxed overnight; in the morning it was monitored by GC, and the reaction appeared over. It was filtered into 100 mL of water; the aqueous filtrate was extracted with dichloromethane (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), and filtered. After concentration of the filtrate by rotary evaporation, the residue was purified by preparative GC with column A to afford triene **8**:[9,20] ^{1}H NMR (300 MHz) δ 1.0 (t, 3 H, J = 7.6 Hz, CH_3), 2.21 (dq, J = 7.44 , 7.48 Hz), 5.08 (d, J = 10 Hz, C1-cis-H), 5.21 (d, J = 16.7 Hz, C1-trans-H), 5.48 (m, 1 H, C6 H), 5.98 (t, 1 H, J = 11 Hz, C5 H), 6.2 (dd, 1 H, J = 10.7, 14.79 Hz, C3 H), 6.34–6.55 (m, 2 H, C2 H, C4 H); MS, m/z 108 ($M^{\bullet+}$).

Aliquots of a dilute solution of triene **8** (10 mg in 1 mL) in decane were sealed in capillary tubes and heated at 111 °C for up to 1 h without change, relative to an internal standard of comparable signal intensity.

Table IV shows the relative retention times observed for the octatriene isomers on the capillary GC columns, at a column temperature of 80 °C.

Kinetic Measurements. Kinetics of thermolyses were measured with sealed 0.5-mm capillary tubes and an oil bath fit with a mechanical stirrer, heating elements controlled by a Bayley precision temperature controller, Model 253, and a Hewlett-Packard 2802A digital thermometer. While temperature at a fixed position in the bath was kept constant to ±0.1 °C, temperature variations across the entire bath was constant to only ±1 °C. Typically, 8 μL of the thermolysis solution was placed in each capillary tube, cooled with a dry ice–acetone bath, and sealed either directly or after establishing an argon atmosphere: samples sealed either way were kinetically indistinguishable. Thermolyses of the unlabeled and d_1- and d_2-labeled substrates were monitored by a capillary GC at a column temperature of 80 °C, and the mixtures of labeled and unlabeled substrates ($d_1 + d_0$ and $d_2 + d_0$) were monitored by MS/GC. The sample tubes were withdrawn at appropriate time intervals, quenched in liquid nitrogen, and directly injected into the GC or GC/MS instrument. The ratio of the peak areas was measured with HP 3392A and HP 3390A integrator plotters attached to the capillary GC. Kinetic

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studies employing mass spectrometry were done in selected ion monitoring (SIM) mode, observing the molecular ion peaks 108, 109, and 110. The abundances of the M − 1, M, M + 1, and M + 2 peaks for the authentic samples were obtained before the kinetic runs, and appropriate corrections were made to the observed intensities in the kinetic analyses using the following general equation

$$[\mathbf{1}]/[\mathbf{1}-d_i] = \left[1-\left(\frac{108+i}{108}\right)\left(\frac{108}{108+i}\right)_D\right]\Big/\left[\left(\frac{108+i}{108}\right)-\left(\frac{108+i}{108}\right)_H\right]$$

where 108 and (108 + i) refer to mass spectral ion intensities at m/e 108, 109, or 110; subscripts H and D refer to unlabeled **1** or **1** − d_i, respectively; and (108 + i)/108 gives the observed ion intensity ratio for a mixture of **1** and **1** − d_i.

The kinetic results are summarized in Tables I–III above.

Acknowledgment. We are indebted to the National Science Foundation for support of our work on hydrocarbon rearrangements.

Carbon–Carbon Bond-Forming Reactions of Zinc Homoenolate of Esters. A Novel Three-Carbon Nucleophile with General Synthetic Utility

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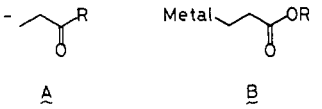
Abstract: In the presence of suitable catalysts and additives, the zinc homoenolate of alkyl propionate and its congeners undergo a variety of carbon–carbon bond-forming reactions, e.g., addition onto carbonyl compounds, allylation, arylation, vinylation, and acylation, to produce diverse kinds of alkanoates and cyclopropane derivatives. The moderately reactive zinc homoenolate exhibited a very high degree of chemoselectivity in these reactions. Me_3SiCl has been found to greatly accelerate 1,2- or 1,4-addition and the allylation reaction of the zinc reagent.

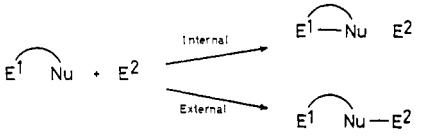
Homoenolate anion (A) represents an archetypal synthon in the concept of Umpolung (inversion of polarity)[1] and is important probably next to the ubiquitous acyl anion synthon.[2] The virtue



A B

of the homoenolate is derived from its function as an inverse-polarity Michael acceptor. Despite such conceptual importance, homoenolate anion has gained very limited success in actual application.[3] In the present work, we describe the versatile reactivities of zinc homoenolate of propionate (B) and its congeners to demonstrate for the first time the great potential of homoenolate chemistry in organic synthesis[4] (cf. Scheme I).

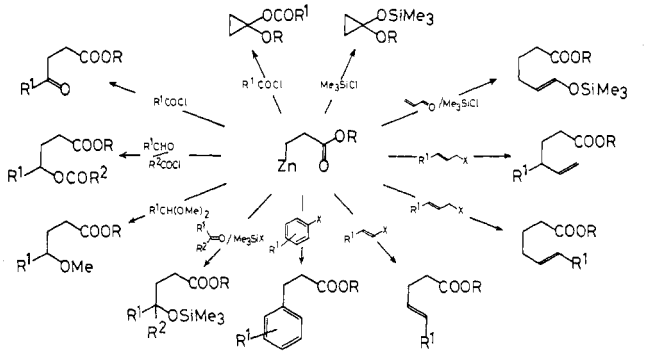
The inherent difficulty in using homoenolates for nucleophilic reactions is associated with the problem of competition between internal and external electrophilic sites (eq 1), in which an entropy



(1)

factor represents a major obstacle. The anionic site of the homoenolate A therefore cannot be too reactive, and the metal homoenolates so far reported undergo only limited types of reactions.[5] Any attempts to challenge such a difficult internal/external problem must achieve very fine control over the nucleophilicity of the anionic center, and research along these lines would also realize a high level of chemoselectivity among external electrophiles, which has been a constant recent concern of synthetic organic chemists.

Scheme I



The reaction of siloxycyclopropane **1** and $ZnCl_2$ in ether produces in over 80% yield zinc homoenolate **2**,[6] which exists as

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(2) Groebel, B. T.; Seebach, D. *Synthesis* **1977**, 357.
(3) (a) For the cause and the solution to the problem, see: Werctiuk, N. H. *Tetrahedron* **1983**, *39*, 205. Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (b) Review on metal homoenolate: Ryu, I.; Sonoda, N. *Yuki Gosei Kagaku Kyokaishi* (*J. Org. Synth. Chem. Jpn.*) **1985**, *43*, 112. See also references in ref 5a.
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(5) (a) Carbonyl addition: Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745. (b) Conjugate addition: Giese, B.; Horler, H.; Zwick, W. *Tetrahedron Lett.* **1982**, *23*, 931. (c) Carbonylation: Ryu, I.; Matsumoto, K.; Ando, M.; Murai, S.; Sonoda, N. *Synth. Commun.* **1984**, *14*, 1175. (d) Dimerization: Ryu, I.; Ando, M.; Ogawa, A.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* **1983**, *105*, 7192.
(6) (a) Nakamura, E.; Shimada, J.; Kuwajima, I. *Organometallics* **1985**, *4*, 641. (b) For experiments to isolate pure solvent-free zinc homoenolate **4**, use of excess $ZnCl_2$ should be avoided. Otherwise homoenolate **2** forms a complex with $ZnCl_2$, which either does not dissolve in a nonpolar solvent or tends to carry zinc-complexed ether into the extract. (c) Standardization of the homoenolate solution by iodine described previously[3d] tends to give much lower concentration than actual and should be avoided.

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