5-*exo-trig* Versus 6-*endo-trig* Cyclization of Alk-5-enoyl Radicals: The Role of One-Carbon Ring Expansion

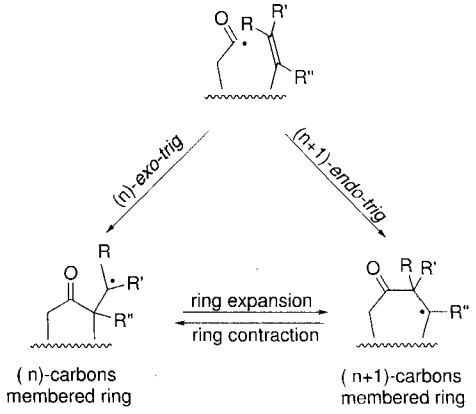
Chryssostomos Chatgilialoglu,* Carla Ferreri, Marco Lucarini, Alessandro Venturini, and Andreas A. Zavitsas

Abstract: Alk-5-enoyl radicals were made to cyclize in *exo* and *endo* modes to give the corresponding cycloketone radicals, which are related through one-carbon ring expansion. Relative kinetic data were determined for the ring closure of the 2-methylhept-5-enoyl radical generated by the reaction of the corresponding phenylseleno ester with Bu_3SnH over the temperature range 233–323 K. The conversion to absolute rates provided Arrhenius expressions for the 5-*exo-trig* and 6-*endo-trig* cyclizations. *Ab initio* and semiempirical (AM1) calculations were performed on the hex-5-enoyl and hept-5-enoyl radicals, respectively, and the outcomes aided in the rationalization of the preexponential factors and activation energies. Both 1,5- and 1,6-ring closure occur via a lower energy "chairlike" transition state. The observed high regioselectivity is due to favorable entropic and enthalpic factors associated with the formation of the smaller ring. The stereoselectivity was higher in the 1,6-ring closure (70:30) than in the 1,5-ring closure (55:45), the *trans* isomer being predominant in both. For the one-carbon ring expansion studies, the radicals of interest were obtained by deoxygenation of suitable alcohols via the *O*-phenyl thiocarbonates with $(TMS)_3SiH$. The one-carbon ring expansion in the cyclopentanone series for the secondary alkyl radicals was studied over the temperature range 343–413 K by means of free-radical clock methodology and yielded the Arrhenius expression. The rate constant was $4.2 \times 10^3\ s^{-1}$ at room temperature and the reverse reaction (ring contraction) was found to be at least 10 times slower. Since the intermediacy of acyl radicals can be excluded, the reaction must occur via 3-membered cyclic intermediate radicals (or transition states).

Keywords
ab initio calculations · cyclizations · cycloketones · radicals · ring expansions

Introduction

In the last two decades, intramolecular C–C bond formation under free-radical conditions has been the workhorse for those who employ radical chemistry in the synthesis of complex molecules.[1] The fields of acyl radical cyclization[2–6] and radical-mediated one-carbon ring expansion in the cycloketone series[7, 8] are extremely active at present, as documented in the recent literature; for example, two related reviews have appeared during the preparation of this manuscript.[4a, b] Scheme 1 shows how these two classes of reactions can be interrelated, that is, acyl radicals containing an olefinic moiety in the appropriate position can cyclize in *exo* and/or *endo* mode to give the corresponding cycloketone radicals, which are connected through one-carbon ring expansion or ring contraction.



Scheme 1. Interrelation between acyl radical cyclizations and one-carbon ring expansion or ring contraction.

Despite the momentous growth of the use of acyl radicals in organic synthesis,[2–6] their absolute reactivity values in solu-

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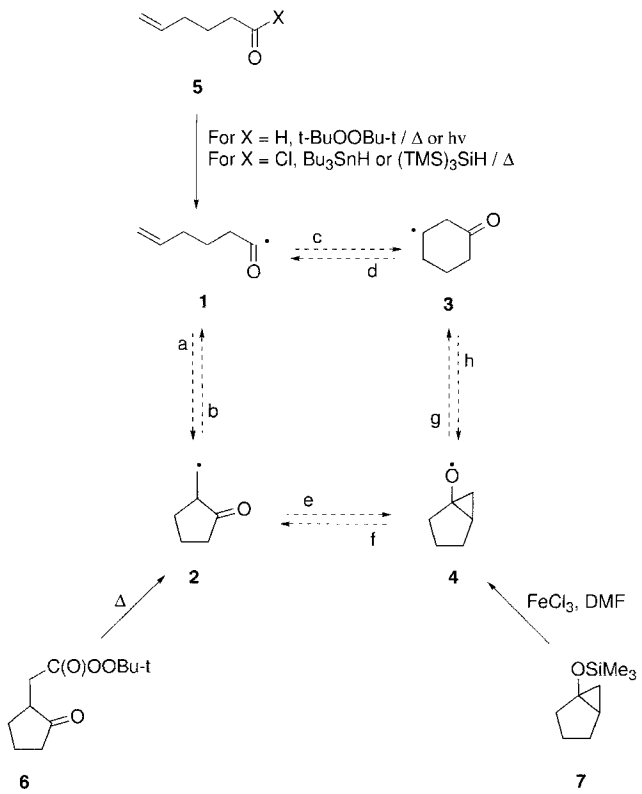
tion are scarce, and as a result mechanistic schemes are abundant, but lack solid foundations. In our laboratory,[9] as well as in others,[10] efforts have been made to fill in this lack of information. Consequently, kinetic data on the formation of acyl radicals[9] and their further reaction with a variety of substrates[9, 10] have recently appeared. Moreover, reliable rate constants and Arrhenius parameters for the decarbonylation reactions are now available,[9a, 11, 12] as they are for addition of primary alkyl radicals to carbon monoxide.[13]

In connection with the cyclization of acyl radicals, the prototype hex-5-enoyl radical (**1**) has received special attention (Scheme 2). Radical **1**, generated by atom abstraction (H, Cl), undergoes a 5-*exo-trig* or 6-*endo-trig* cyclization to give radical **2** or **3**, respectively (steps a and c, Scheme 2). The relative yields



Scheme 2. Proposed mechanistic picture for the prototype hex-5-enoyl radical.

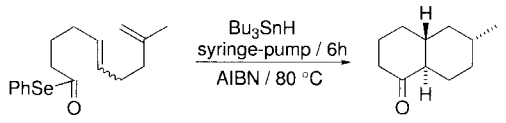
of the two cycloketones derived from the trapping of the two alkyl radicals and their relationship with the experimental conditions are still a subject of debate. The early results[14] were reinterpreted in terms of the reversibility of the 5-*exo-trig* cyclization by Ingold and his coworkers (see step b).[10d] Since the cyclohexanone is the thermodynamically favored product, and the 2-methylcyclopentanone is the kinetically favored product, their ratio mainly depends on the concentration of the radical trap (i.e., the hydrogen donor) and the temperature.

A general method for one-carbon ring expansion in cycloketones (Scheme 1) was introduced in 1987 concurrently by the groups of Beckwith[15] and Dowd.[16] Encouraged by the reports of intramolecular 1,2-acyl migration in acyclic systems,[17] a mechanism involving intramolecular addition to the carbonyl moiety yielding the intermediate cyclopropyloxyl radical, followed by cleavage of the internal C–C bond was indicated as operative in these reactions (cf. steps e and g in Scheme 2).[21, 23] Furthermore, cyclopropyloxyl radical **4** as intermediate has been suggested for the reaction of cyclopropyl silyl ether **7** with ferric chloride to give 2-cyclohexenone (Scheme 2).[24] It is also worth pointing out that in their review Dowd and Zhang[7] proposed the mechanistic picture in Scheme 2 for the corresponding hept-6-enoyl radical, and Beckwith et al.[15b] questioned the intermediate cyclopropyloxyl radical in favor of the three-membered transition state for the one-carbon ring expansion.

Boger and Mathvink examined the cyclization of acyl radicals in a series of papers.[2] They concluded that these reactions are consistent with irreversible, kinetically controlled processes which, in the absence of directing functionality, proceed preferentially in the *exo* mode without subsequent rearrangement of the initial intermediate adduct radicals. In cases where *exo* ring closure is sterically decelerated by the presence of olefin substituents, preferential direct *endo* cyclization can be reliably expected.

In a much more recent report, Ingold, Lusztyk, and coworkers have also reported kinetic data for the cyclization of radical **1**.[10a] In particular, they found by means of time-resolved spectroscopies that the rate constant for the first-order decay of radical **1** is $2.2 \times 10^5\ s^{-1}$ at 296 K, although they were unable to determine the relative extents of the two processes steps a and c. Furthermore, they showed that the prototype radical **2** generated by thermal decomposition of the appropriate *tert*-butylperoxy ester in cyclohexane gave 2-methylcyclopentanone and cyclohexanone in a 3:7 ratio. They interpreted these results in terms of steps b and c (Scheme 2). However, the fact that cyclohexanone was found does not provide any information relevant to making a choice between the two possible paths shown in Scheme 2 for **2** → **3**.

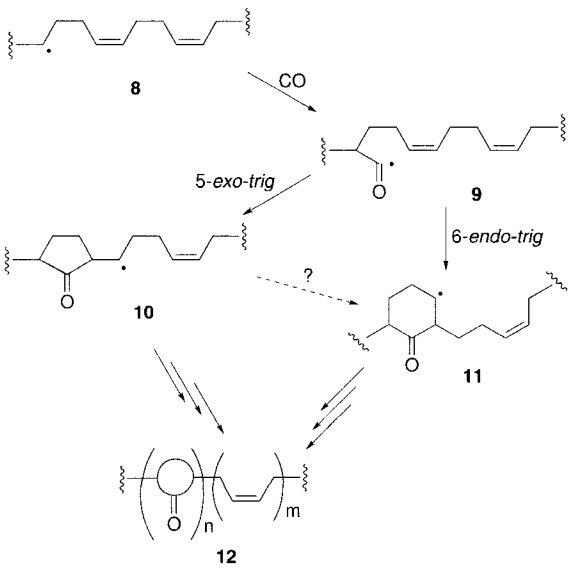
An intriguing variant of this class of reaction was designed by Pattenden and coworkers[5] in which acyl radical-mediated polyene cyclization is directed toward steroid ring synthesis. An example of interest to us is shown in Equation 1, in which the



(1)

phenylseleno ester led to decalone by consecutive 6-*endo-trig* modes of cyclization starting from the corresponding acyl radical.

In recent years our group has been interested in a new class of polymers obtained by the reaction with carbon monoxide of a polydiene containing a structural unit derived from the 1,4-*cis*-polymerization of conjugated dienes in the presence of a free-radical initiator.[25, 26] Scheme 3 shows the elementary steps for the modification of 1,4-*cis*-poly(butadiene). Radical **8**, initially generated by small amounts of the radical initiator, adds to carbon monoxide to form the acyl radical **9** that undergoes either a 5-*exo-trig* or 6-*endo-trig* cyclization to form radicals **10** and **11**, respectively. Radical **11**, in turn, can either add to another CO molecule followed by a 6-*endo-trig* cyclization or

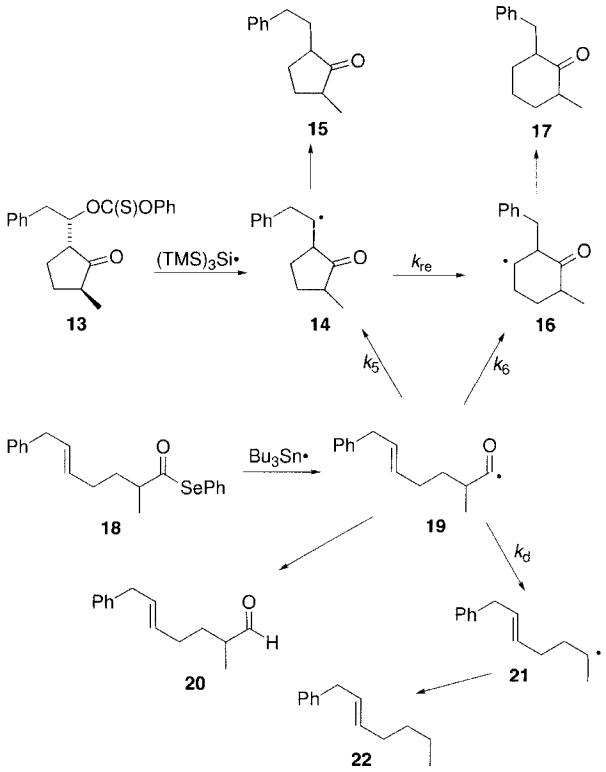


Scheme 3. Mechanism for the modification of 1,4-*cis*-poly(butadiene).

undergo a 5-*exo-trig* cyclization to give carbonyl-containing bicyclic structures. Many repetitions of these elementary steps allow for the formation of polymer **12**, which contains blocks of both cycloketonic groups and 1,4-*cis*-poly(butadiene). An important feature of this polymer modification is that the content of carbonyl units as well as the ratio of cyclopentanone/cyclohexanone depends strongly on the experimental conditions of CO pressure and temperature. Therefore it is necessary to invoke a rearrangement of **10** to **11** in order to explain the ratio recovered in the experiments. It is also worth mentioning that this system and the above-mentioned work of Pattenden et al. [Eq. (1)] are similar but apparently inconsistent. In a preliminary report, we described model studies that showed that in these systems the formation of the six-membered ring is due either to direct cyclization of the acyl radical intermediate or to the ring expansion of the previously formed five-membered ring.[26] In this article we wish to report our detailed work on the cyclization of the alk-5-enoyl radical and the corresponding one-carbon ring expansion.

Results

Reaction mechanism: To a carefully degassed solution of either *erythro-trans* or *threo-trans* thiocarbonate **13** (0.288 g; 0.80 mmol) and α,α′-azoisobutyronitrile (AIBN, 0.013 g; 0.080 mmol) in benzene (5.5 mL), $(TMS)_3SiH$ (2.46 mL; 8.0 mmol) was added.[27] The mixture was then heated at 353 K for ca. 1 h until the starting thiocarbonate disappeared (as monitored by TLC). GC analysis of the crude reaction mixture revealed the formation of cyclopentanone **15** (*trans* isomer) and cyclohexanone **17**[28] in quantitative yield in a 6:1 ratio. The mechanism for this reduction is outlined in Scheme 4. $(TMS)_3Si^{\bullet}$ radicals remove the thiocarbonate moiety to form the secondary alkyl radical **14**.[29] This intermediate either abstracts a hydrogen atom from the silane to give **15** (*trans* isomer) or rearranges to **16** followed by hydrogen transfer to afford **17**. The absence of compounds **20** and **22**[28] excludes the formation of the acyl radical **19** as an intermediate for the following reasons. The 1.0 M concentration of the silane remains essentially constant under our experimental conditions, and since the rate constant for the reaction of secondary alkyl radicals with $(TMS)_3SiH$ is $4.3 \times 10^5\ M^{-1}\ s^{-1}$ at 353 K,[30] we estimate k_{re} (the rate constant for ring expansion) to be nearly $7 \times 10^4\ s^{-1}$ by applying free-radical clock methodology.[31] From kinetic data[9a] the rate constants for reactions **19** → **20** and **19** → **21** were calculated to be $7.2 \times 10^4\ M^{-1}\ s^{-1}$ and $3.7 \times 10^5\ s^{-1}$, respectively, at 353 K. Therefore, if the acyl radical **19** were an intermediate in the ring expansion, the rate constant for reaction **19** → **16** would have to be larger than $10^7\ s^{-1}$ at 353 K, that is, $k_d = 3.7 \times 10^5\ s^{-1}$ multiplied by at least 50 (from the limit of detection of the GC analysis).



Scheme 4. Mechanism for the reductions of thiocarbonate **13** with $(TMS)_3SiH$ and of phenylseleno ester **18** with Bu_3SnH.

In order to measure the rate of the reaction **19** → **16**, we performed the following experiment. To a carefully degassed solution of phenylseleno ester **18** in an (*E*)/(*Z*) isomeric composition of 98/2 (0.200 g; 0.56 mmol) and AIBN (0.009 g; 0.056 mmol) in benzene (1.05 mL), Bu_3SnH (0.75 mL; 2.8 mmol) was added. The mixture was then heated at 353 K for ca. 1 h until the phenylseleno ester disappeared (monitored by TLC). GC analysis of the crude reaction mixture gave cyclopentanone **15** (47%) and cyclohexanone **17** (6%) together with the aldehyde **20** (36%) and the alkene **22** (11%). The sum of these yields is reported normalized to 100%; the actual sum exceeded 90%. The reactions expected to take place upon treatment of phenylseleno ester **18** with Bu_3SnH are also shown in Scheme 4. The acyl radical **19**, generated by the reaction of stannyl radical with phenylseleno ester **18**, could disappear

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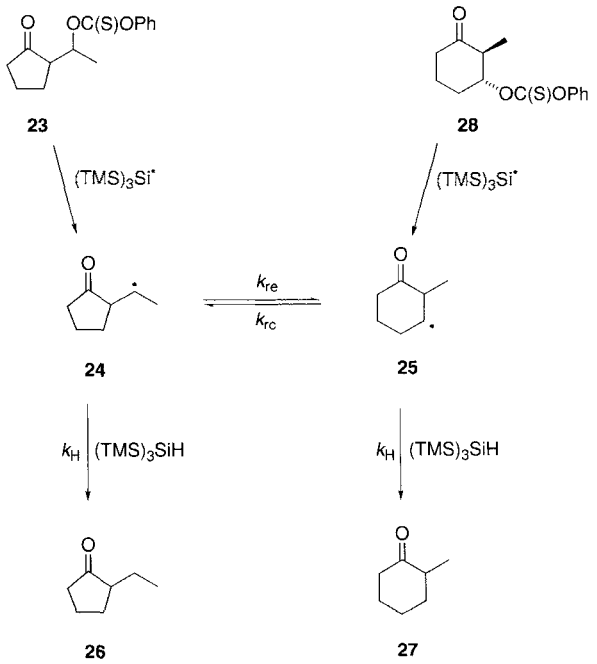
along four independent paths: a) hydrogen abstraction from Bu_3SnH to give **20**; b) decarbonylation to give **21**; c) 5-*exo-trig* cyclization to give **14**, and d) 6-*endo-trig* cyclization to give **16**. At the high concentration of Bu_3SnH used in the experiment above, the rate constant for the path **14** → **15** is at least 50 times faster than k_{rc}.[32] Taking $3.7 \times 10^5\ s^{-1}$ as the rate constant for the decarbonylation (k_d) at 353 K,[9a] we calculated the rate constants for the 5-*exo*- and 6-*endo*-cyclizations (k_5 and k_6) to be 2×10^6 and $2 \times 10^5\ s^{-1}$, respectively.

To summarize the above results, the 5-*exo-trig* cyclization of acyl radical **19** is ca. 10 times faster than the 6-*endo-trig* cyclization, and the one-carbon ring expansion occurs without the intermediacy of the acyl radical. With this information in our hands, we redesigned our initial substrates (see below) for detailed kinetic studies.

Kinetics for the ring expansion and ring contraction: By means of free-radical clock methodology[31] a rate constant for the ring expansion can be obtained, provided that conditions can be found in which the intermediate radical **24** is partitioned between the two reaction channels (Scheme 5), that is, reaction



Scheme 5. Mechanism for the reductions of thiocarbonates **23** and **28** with $(TMS)_3SiH$.

with the silicon hydride and ring expansion. In order to determine the kinetics of the rearrangement of **24** into **25** under pseudo-first-order conditions, a series of experiments was conducted in which the thiocarbonate **23** (mixture of *erythro* and *threo* isomers)[29] was treated with a large excess of tris(trimethylsilyl)silane ($[(TMS)_3SiH]_0 \approx 20 \times [\mathbf{23}]_0$) in known concentrations at various temperatures. Compounds **26** and **27** were the reduction products, the relative concentrations of which varied in the expected manner at each temperature as the concentration of $(TMS)_3SiH$ was changed. Since the silane concentration during the reaction remained essentially constant under our experimental conditions, and assuming that the secondary alkyl radicals **24** and **25** abstract H atom from the silane with an identical rate constant, the relation (2) is obeyed,[31a] where $[\mathbf{26}]_f$ and $[\mathbf{27}]_f$ represent the final concentrations

$$[\mathbf{26}]_f/[\mathbf{27}]_f = k_{rc}/k_{re} + k_H/k_{re}[(TMS)_3SiH]_0 \quad (2)$$

of the two products. The plots in Figure 1 provide values of k_H/k_{re} at several temperatures and the data are summarized in Table 1. Linear regression analysis of a $\log(k_H/k_{re})$ vs. $1/T$ plot

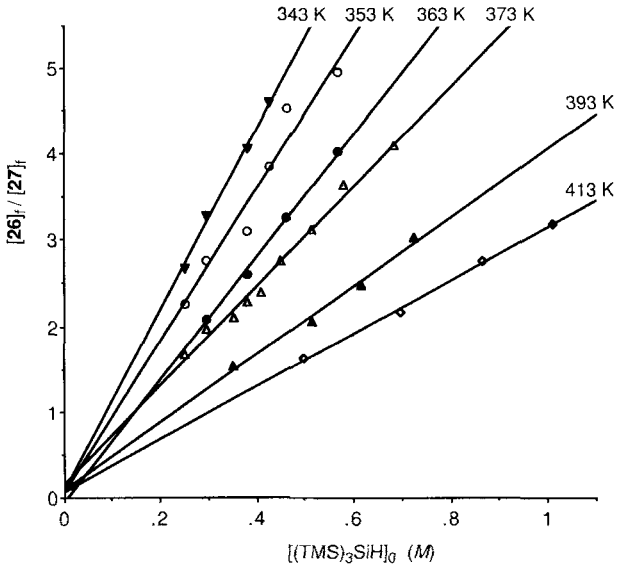


Figure 1. Plots of $[\mathbf{26}]_f/[\mathbf{27}]_f$ vs. $[(TMS)_3SiH]_0$ for the reaction of **23** with ≈20 mol.equiv of $(TMS)_3SiH$. The slopes (k_H/k_{re}) and intercepts (k_{rc}/k_{re}) are reported in Table 1.

Table 1. Kinetic data for the reaction of thiocarbonate **23** with $(TMS)_3SiH$ in toluene at various temperatures.

T, K	$[(TMS)_3SiH]$, M [a]	k_H/k_{re}, M^{-1} [b]	Intercept
343	0.251–0.425	10.551±0.628	0.086±0.20
353	0.251–0.567	8.860±1.018	0.061±0.42
363	0.294–0.567	7.144±0.267	−0.053±0.12
373	0.250–0.682	5.789±0.262	0.156±0.12
393	0.350–0.725	3.969±0.269	0.094±0.15
413	0.498–1.010	3.080±0.083	0.079±0.06

[a] Range of concentration employed. [b] Errors correspond to one standard deviation.

yields the relative Arrhenius parameters given by Equation (3), in which $\theta = 2.3RT\ kcal\,mol^{-1}$ and the errors correspond to one standard deviation.

$$\log k_{re}/k_H\ (M) = (2.22 \pm 0.08) - (5.10 \pm 0.13)/\theta \quad (3)$$

Combination of the Arrhenius expression for k_{re}/k_H [Eq. (3)] with the known Arrhenius parameters for k_H [Eq. (4)][30] yields Equation (5), which gives the temperature dependence of k_{re} (the rate constant for ring expansion). The value of k_{re} can be calculated as $4.2 \times 10^3\ s^{-1}$ at 298 K.

$$\log k_H\ (M^{-1}\,s^{-1}) = (8.29 \pm 0.37) - (4.29 + 0.46)/\theta \quad (4)$$

$$\log k_{re}\ (s^{-1}) = (10.51 \pm 0.45) - (9.39 \pm 0.59)/\theta \quad (5)$$

Information on the reverse rate constant k_{rc} (ring contraction) can be obtained from the intercepts of Equation (2) $k_{rc}/k_{rc} = 1/K$. The values of the intercepts obtained from the plots in Figure 1 are also reported in Table 1. However, the values of the intercepts are small, near zero, and are obtained by extrapolation of the kinetic data. As a result, accurate estimates of k_{re}/k_{rc} cannot be obtained, even though the plots of Figure 1 are adequately linear. Since the ring expansion is irreversible in the limiting case of $k_{rc}/k_{rc} = 0$, we can say that in Scheme 5 the ring contraction is an order of magnitude slower than ring expansion. The average value of the intercepts listed in Table 1 leads to $k_{re}/k_{rc} = 14$, while the minimum value is 6.4 from the kinetic measurements at 373 K.

An attempt was also made to estimate the rate constant for ring contraction by treating the thiocarbonate **28** with $(TMS)_3SiH$ (Scheme 5). GC analysis revealed only the presence of compound **27** and no evidence for **26**. However, under the conditions employed it was possible to obtain an upper limit value of $5 \times 10^3\ s^{-1}$ for the ring contraction at 353 K, based on the limits of detection of the GC analysis. The agreement of the two independent approaches is gratifying and indicates that the equilibrium **24**⇌**25** lies in favor of **24** with an equilibrium constant of at least 10.

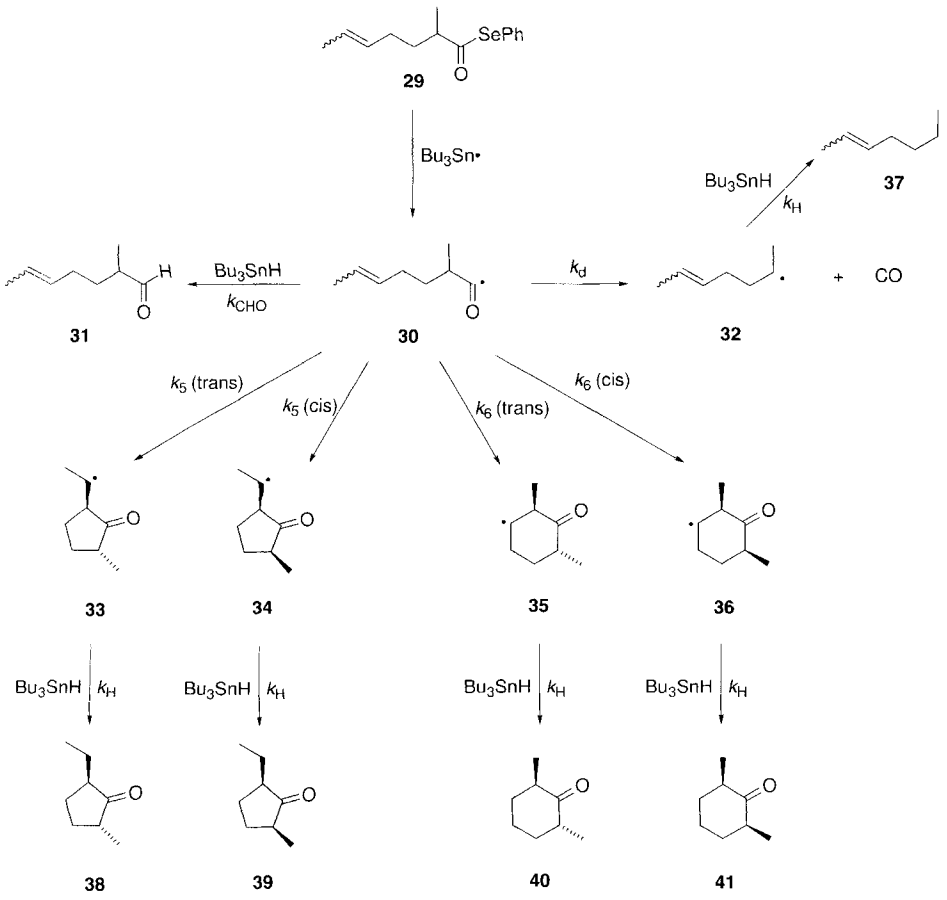
Kinetics studies of the cyclization of acyl radicals: The reactions expected to take place upon treatment of phenylseleno ester **29** with a large excess of Bu_3SnH in order to avoid ring expansion are shown in Scheme 6.[33, 34] The quantities of (*E*)- and (*Z*)-aldehyde **31**,[35] (*E*)- and (*Z*)-alkene **37**,[35] cyclopentanones **38** and **39**, and cyclohexanones **40** and **41** were obtained by GC analysis following the thermally or photolytically initiated radical chain reaction, and with an internal standard. In order to determine the kinetics of the 5-*exo-trig* and 6-*endo-trig* cyclizations, a series of experiments was conducted. Since the Arrhenius equations for k_{CHO} (**30** → **31**) and k_d (**30** → **32**) are known,[37, 38] the rate constants of the 5-*exo-trig* and 6-*endo-trig* cyclizations can be obtained, in principle, either by competition with the unimolecular decarbonylation process (method A) or by competition with the bimolecular reaction of acyl radicals with Bu_3SnH (method B).[31]

Method A was expected to be straightforward since the pertinent measurements are independent of the Bu_3SnH concentration. However, this approach proved to be unsatisfactory for detailed studies in the temperature range 293–353 K. In order to suppress the ring expansions of **33** and **34** into **35** and **36**, a high concentration of the reducing agent was needed. This caused a loss in the efficiency of decarbonylation. In particular, the reproducibility of the amount of (*Z*)-**37** in the GC analysis was poor due to the limits of its detectability. At the best conditions found, 80 °C and with 1 M Bu_3SnH, the following values were obtained: $k_5(trans)/k_d = 2.0$, $k_5(cis)/k_d = 1.7$, $k_6(trans)/k_d = 0.2$, and $k_6(cis)/k_d = 0.1$.

Method B was found to be the better choice in the temperature range 233–323 K. Furthermore, the kinetic treatment was further simplified by the fact that a large excess of Bu_3SnH was employed; thus the second-order trapping of radicals by Bu_3SnH could be treated as pseudo-first-order. From measurements of the relative yields of both aldehyde **31** and the appropriate cyclokctone and by applying the following equation, it is possible to calculate the rate constant ratio k_c/k_{CHO}, where k_c denotes the rate constant for each cyclization (k_5 and k_6 in Scheme 6).

$$k_c/k_{CHO} = [Bu_3SnH][\text{cycloketone}]/[\text{aldehyde}] \quad (6)$$

The [aldehyde]/[cycloketone] ratio varied in the expected manner with the change in the hydride concentration. Only data obtained at low conversion levels were used, in order to avoid the accumulation of byproducts and to maintain the validity of Equation (6), which was used to obtain mean values of k_c/k_{CHO} from four different tin hydride concentrations. Analysis of these data (Figure 2) provided the Arrhenius expressions for k_c/k_{CHO} listed in Table 2. It should be pointed out that the accuracy of the measurements for 5-*exo-trig* cyclizations is much higher than that for 6-*endo-trig* cyclizations, due to errors associated



Scheme 6. Mechanism for the reduction of phenylseleno ester **29** with Bu_3SnH.

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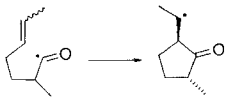
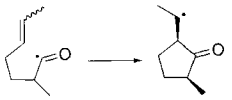
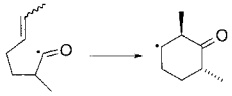
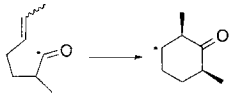
Table 2. Arrhenius parameters for acyl radical cyclizations.

Reaction	$\log(A_c/A_{CHO}/M)$ [a]	$E_c - E_{CHO}$, kcal mol^{-1} [a]	$\log(A_c/s^{-1})$	E_c, kcal mol^{-1}	$k^{298\,K}$, s^{-1}
	1.43±0.15	2.53±0.19	9.6	6.0	1.6×10^5
	1.42±0.16	2.60±0.20	9.6	6.1	1.3×10^5
	0.77±0.15	2.92±0.19	9.0	6.4	2.0×10^4
	0.54±0.08	3.26±0.10	8.7	6.8	5.2×10^3

[a] Errors correspond to one standard deviation.

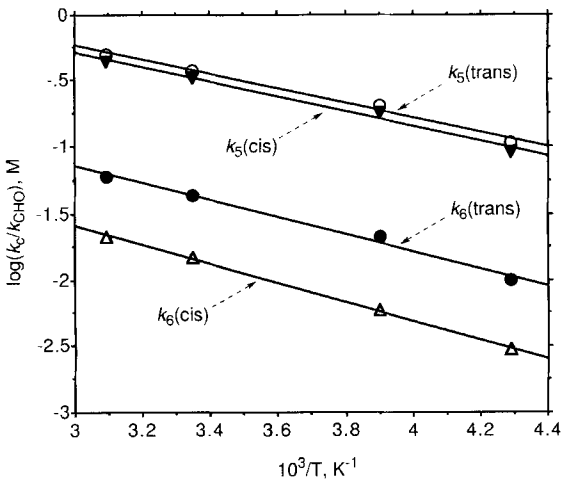


Figure 2. Arrhenius plots for the k_c/k_{CHO} ratios obtained at various temperatures for the cyclization of acyl radical **30**.

with experiments performed at higher Bu_3SnH concentrations and lower temperatures. Relative Arrhenius parameters calculated from the product yields can be converted to absolute Arrhenius parameters for the four cyclizations by means of the absolute kinetic data for H-atom abstraction from Bu_3SnH by an acyl radical.[38] These data, together with the absolute rate constants at 298 K, are also summarized in Table 2.

Theoretical studies: In order to obtain a better understanding of the regioselectivities in the cyclization of alk-5-enoyl radicals, we undertook a theoretical study of the ring closure of the prototype hex-5-enoyl radical by means of high-level ab initio calculations and of the hept-5-enoyl radical by means of AM1 semiempirical calculations.

High-level ab initio calculations were carried out using the GAUSSIAN 92 series of programs[39] for the reactant, products, and transition structures of hex-5-enoyl radical cyclizations (cf. Scheme 2). For each 5-*exo-trig* and 6-*endo-trig* cyclization, two distinct pathways were found with lower energy "chairlike" and higher energy "boatlike" transition states. Herein we limit our discussion to the two lowest energy "chairlike" pathways. Geometries were fully optimized at the CASSCF/6-31G* level. Calculated total energies are presented in Table 3. It is worth emphasizing that the ab initio results are in excellent agreement with the enthalpy of reactions **1** → **2** and **1** → **3** (steps a and c, respectively, in Scheme 2) obtained by using the NIST database and Benson's group additivity method.[40]

The active space used in all computations (5 electrons and 5 orbitals) included the two π and π* orbitals/electrons which describe the C=C double bond, the uncoupled σ orbital/electron of the acyl carbon and the two π and π* orbitals/electrons that describe the C=O double bond. However, each critical point was fully characterized by diagonalization of the corresponding Hessian matrix, which was computed analytically in all cases at the SCF level. In order to include the effects of additional electron correlation to calculate a correct energy barrier, CASPT2N calculations were performed using the MOLCAS package.[43] CASPT2N employs second-order perturbation theory to obtain the correlation energy for all the electrons in a molecule starting from a MCSCF reference wave function. Calculated total energies obtained with this approach are also listed in Table 3. Some of the more important structural features of the transition states for the 5-*exo-trig* and 6-*endo-trig* cyclizations are shown in Figure 3. This figure also shows schematically the energy barriers obtained with CASPT2N.

We constructed a potential energy surface covering the isomerizations shown in Scheme 7 by the AM1 semiempirical MO

Table 3. CASSCF and CASPT2N/6-31G* energies (E, Hartree) and energy barriers (ΔE, kcal mol^{-1}) for the chairlike 5-*exo-trig* and 6-*endo-trig* cyclizations of the hex-5-enoyl radical.

	E (CASSCF)	ΔE	E (CASPT2N)	ΔE
reactant	−307.29701	0.0	−308.20481	0.0
TS5 chair	−307.27354	14.7	−308.19166	8.3
TS6 chair	−307.26924	17.4	−308.18885	10.0
Cy5 chair	−307.31465	−12.2	−308.22492	−12.6
Cy6 chair	−307.32201	−15.7	−308.23198	−17.0

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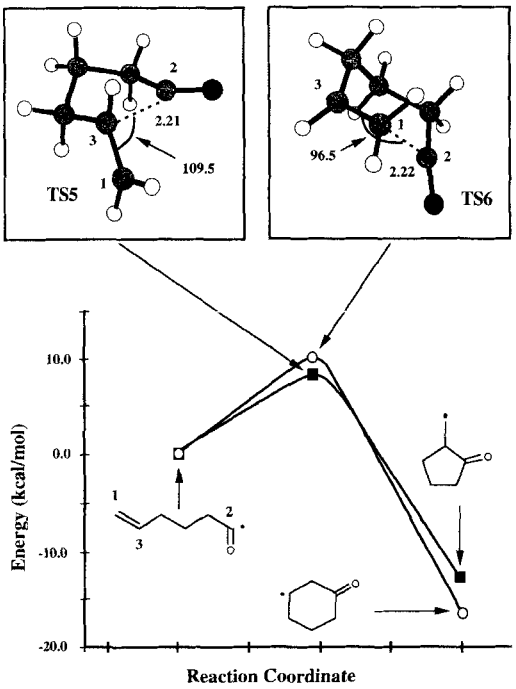
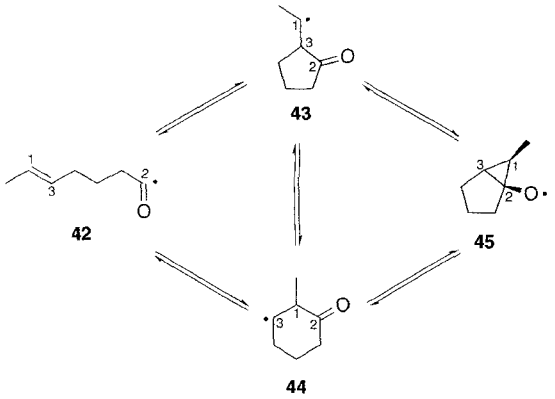


Figure 3. Schematic diagram showing the energy barriers for the 5-*exo* and 6-*endo*-cyclizations obtained by CASPT 2N. The energies of the reactant and products refer to the linear and chair arrangements, respectively. The inserts show some important features of the optimized transition structures.



Scheme 7. Isomerizations for which a potential energy surface constructed by the AM1 semiempirical MO method is shown in Figure 4.

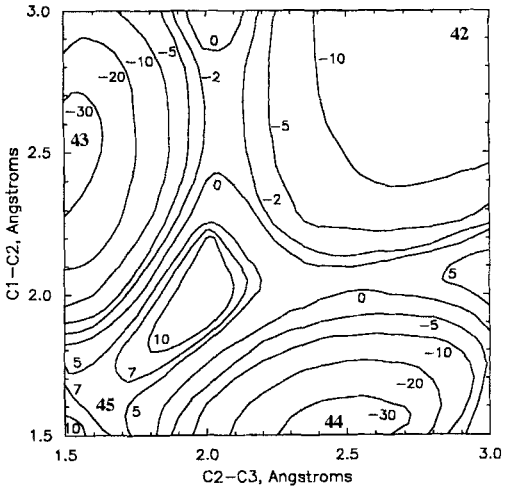


Figure 4. Potential energy surface linking structures **42**, **43**, **44**, and **45** of Scheme 7, as obtained by AM1 with the C. I. = 2 option. The lines of equal energy are calculated ΔH_f° in kcal mol^{-1} for the specified C1–C2 and C2–C3 distances with full optimization of all other geometric parameters. Scheme 7 gives the numbering designations for C1, C2, and C3.

method.[44] The C. I. = 2 option (Dewar's half-electron correction) was used, since it appears to be better suited to calculations involving radicals.[45] The surface is shown in Figure 4 and is the result of over 500 individual energy–geometry optimizations at various "fixed" bond-length combinations of C1–C2 and C2–C3; the surface was constructed by starting from the geometry of the stable cyclopropanol analogous to **45**[46] and stretching the O–H bond in small increments up to 6.00 Å, where the O–H bond is essentially broken, and then removing the hydroxylic hydrogen while "fixing" the C1–C2 and C2–C3 distances. The output geometry of one calculation was used as input for adjacent points. It is known that the AM1 method usually overestimates the stabilities of radicals and is dependable only in terms of relative stabilities of related structures. This is demonstrated by comparing the estimated ΔH_f° values[40] with the heats of formation calculated by AM1 (C. I. = 2) for **42**, **43**, and **44**: AM1 predicts that **42** is more stable by 18.2 kcal mol^{-1},[47] **43** more stable by 22.4, and **44** more stable by 20.1. Therefore, the potential energy surface of Figure 4 is lowered, when compared to thermodynamic estimates, by unequal amounts in the upper right corner (the region of **42**), the upper left corner (the region of **43**), and the lower right corner (the region of **44**). Since ΔH_f° (**45**) cannot be estimated from thermodynamic measurements,[40] the region in the lower left corner cannot be calibrated, and thus the energy in this region could be displaced up or down relative to the other three corners.

Sections through the potential surface of Figure 4 show that the "pass" that leads directly from **42** to **44** is narrower than that from **42** to **43**; at C2–C3 = 2.05 Å, a greater range of C1–C2 distances have the correct geometry for **42** → **43**, compared to suitable C2–C3 distances at C1–C2 = 2.05 for **42** → **44**. This is shown graphically in Figure 5, and the prediction can be made that the preexponential term for **42** → **43** will be greater than that for **42** → **44**.[48]

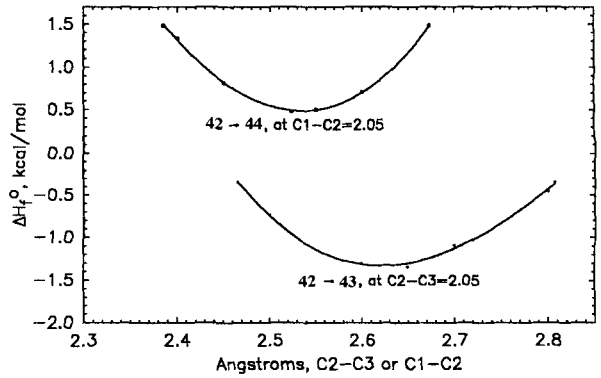


Figure 5. Sections through the potential energy surface of Figure 4 for TS(**42** → **43**) and TS(**42** → **44**). The sections extend to 1.0 kcal mol^{-1} above the minimum in each "pass".

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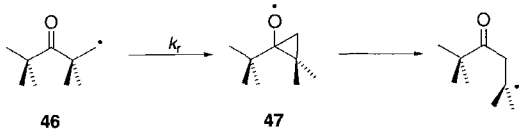
Discussion

The Arrhenius parameters obtained for the ring expansion [Eq. (5)] can be compared with those reported for 1,2-acyl migration in the acyclic system [Eqs. (7) and (8)].[19] The two *A* factors are within the experimental errors and are in the expected range for a three-membered transition state. However, the small difference may be significant, since in the transition state of the acyclic rearrangement [Eq. (7)] two C–C bond rotations



(7)

46 **47**

must be "frozen", whereas in the transition state of the ring expansion (Scheme 5) one C–C bond rotation and the entire ring must be "frozen". Moreover, an *A* factor closer to $10^{13}\ s^{-1}$ would have been expected if the elimination–reclosure mechanism had been operative and the rate-controlling process for ring expansion had been the β-elimination.[42]

$$\log k_r\ (s^{-1}) = (10.94 \pm 0.49) - (7.77 \pm 0.75)/\theta \qquad (8)$$

The higher barrier for the ring expansion (E_a = 9.4 kcal mol^{-1}) compared to 1,2-acyl migration (E_a = 7.8 kcal mol^{-1}) may reflect a) the nature of the attacking alkyl radical, that is, secondary versus primary, b) the greater difficulty for **24** with respect to **46** in achieving the transition state, and c) the "*gem*-dimethyl accelerating factor" or the Thorpe–Ingold effect.[49]

The agreement between the $k_5 = 1.6 \times 10^5\ s^{-1}$ at 298 K (Table 2) and the rate constant for the cyclization of the prototype hex-5-enoyl radicals obtained recently by time-resolved infrared spectroscopy,[10a] $2.2 \times 10^5\ s^{-1}$, is gratifying. The predominant formation of five-membered rings is consistent with the Baldwin–Beckwith rules for radical cyclizations.[50]

The preexponential factors for the 5-*exo-trig* cyclizations are both $10^{9.6}\ s^{-1}$ and are consistent with the freezing-out of four hindered rotations in the transition state. Furthermore, these values are $10^{0.6}$ and $10^{0.9}\ s^{-1}$ larger than those for the 6-*endo-trig* cyclizations and, in accordance with the entropy change accompanying the loss of rotational freedom, cyclization becomes less favorable as the size of the ring formed increases. These conclusions are consistent with Figure 5, which shows sections through the potential energy surface in Figure 4: the "pass" for TS(**42** → **43**) is clearly wider than that for TS(**42** → **44**).

The observed regioselectivity in the alk-5-enoyl radical cyclization is also a result of the favorable enthalpy of activation associated with the formation of the 5-membered ring. In the analogous alk-5-enyl radical cyclization the discussion was based on the stereoelectronic factors.[51, 52] Similar conclusions can be reached from our theoretical approaches. The ab initio calculations predict a difference of 1.7 kcal mol^{-1} in the activation barrier between the 5-*exo-trig* and 6-*endo-trig* cyclizations, the latter being 4.4 kcal mol^{-1} more exothermic. Figure 3 shows the transition states for the two chairlike pathways. The forming bond lengths ($C_1 \cdots C_2$) are the same (2.21 and 2.22 Å), providing evidence for the early transition state predicted for these reactions, whereas the preferred angle of attack is substantially different. In fact, the C_1-C_2-C_3 bond angle in **TS5** is 109.5° while in **TS6** it is 96.5° (see inserts in Figure 3).

Despite the limitations of the AM1 method, the general shape of the potential energy surface is still informative in that relative energy errors should be small within limited regions of space in Figure 4. When going from **42** directly to **44**, the transition structure (at C1–C2 = 2.05 and C2–C3 = 2.53 Å, AM1 calculated heat of formation $\Delta H_f^\circ = 0.5$ kcal mol^{-1}) is 1.8 kcal mol^{-1} higher than the TS for **42** converting directly to **43** (at C1–C2 = 2.65 and C2–C3 = 2.05 Å, AM1 calculated heat of formation $\Delta H_f^\circ = -1.3$ kcal mol^{-1}). This is consistent with the observed preference for 5-*exo-trig* cyclization of **42**. As noted in the previous section, calibration of the AM1 values with thermodynamic estimates[40] shows that AM1 overestimates the stability of **43** by 2.3 kcal mol^{-1} relative to that of **44**; a reasonable approximation is that one half this overestimate is reflected in the $\Delta(\Delta H_f^\circ)$ of the two transition structures described above. Thus, the calibration allows the correction: ΔH_f°(**42** → **44**) − ΔH_f°(**42** → **43**) − 2.3/2 = 0.65 kcal mol^{-1}, which is in excellent agreement with the experimentally determined value of $\Delta E_c = 0.4$–0.7 kcal mol^{-1}, favoring 5-*exo-trig* cyclization (Table 2).

Figure 4 also shows that the transition structures for **43** → **42** and for **44** → **42** are not separated by any substantial energy "hill". When going from the TS of **43** → **42** to the TS of **44** → **42**, the acyl radical interacts with either one or the other of the p orbitals of the incipient double bond with no significant change in stability; the potential energy surface is quite flat. For example, at the symmetrical arrangement between **43** and **44** where C1–C2 = 2.22 and C2–C3 = 2.22 Å, C1–C3 is equal to 1.35 (nearly a double bond) and the structure can be described as being similar to a cyclopropenone with very elongated C–C single bonds. This provides a direct channel for **43** → **44**, without the ring opening to **42** being necessary. The potential energy surface also shows a channel for **43** rearranging directly to **44** through a cyclopropane-like structure through the pass at the lower left-hand region of Figure 4. AM1 indicates that this path has an energy of activation about 5.9 kcal mol^{-1} higher than direct **43** → **44** or ring opening but, since this area of the AM1 potential energy diagram could not be calibrated with experimental heats of formation, no definitive conclusion can be drawn from this calculation about the importance of this channel for **43** → **44**.

For both 1,5- and 1,6-ring closure of radical **30** we observed preferential formation of the *trans* product. These results can be rationalized in the same way that Beckwith and others[51, 53] interpreted the cyclizations of substituted hex-5-enyl radicals. Thus, in the "chairlike" transition state of 1,5-ring closure of **30**, the 2-methyl substituent occupies either axial or equatorial positions. The preferential formation of the *trans* product occurs because the appropriate transition complex is equatorially substituted, whereas the one leading to the *cis* product is axially substituted.

Conclusions

The cyclization of alk-5-enoyl radicals occurs in 5-*exo* and 6-*endo* mode to give the corresponding cyclopentanone and cyclo-

hexanone radicals, which are related by a one-carbon ring expansion. Thus, the formation of the six-membered ring is due either to direct cyclization of the 2-methylhept-5-enoyl radical ($k_6 = 2.0 \times 10^4\ s^{-1}$ at room temperature) or to the expansion ($k_{re} = 4.2 \times 10^3\ s^{-1}$) of the previously formed five-membered ring ($k_5 = 1.6 \times 10^5\ s^{-1}$). Therefore, the reaction of alk-5-enoyl radicals in the presence of a fast hydrogen donor like Bu_3SnH in relatively high concentration will give primarily cyclopentanones whereas under high dilution (syringe-pump addition of the hydrogen donor) will give cyclohexanones. For the first time, our kinetic data provide both a background for the reinterpretation of the numerous mechanistic conclusions which appeared in the last few years and useful information for synthetic planning. Although we are conscious that the reaction mechanism could be influenced by the size of the ring and the nature of substituents directly involved, we believe that our data can be extrapolated to related systems.

Experimental Section

General methods: NMR spectra were recorded on a Varian VXM200 spectrometer. All chemical shifts are reported against tetramethylsilane as an internal standard and with deuterated chloroform as solvent. GC analyses were performed on an HP 5890 Series II using undecane as internal standard. GC/MS spectra were recorded on an HP 5890 Series II spectrometer interfaced with a mass-selective detector HP 5972, using splitless injection on a 30 m × 0.25 mm cross-linked 5% phenylsilicone capillary column (HP5). High-resolution mass spectra (HRMS) were recorded on a VG 7070. IR spectra were recorded from $CHCl_3$ solutions on a Nicolet FT-IR 205 spectrometer. Elemental analyses were performed on a Perkin Elmer 2400 CHN. TLC was carried out using Merck PF254 silica gel plates; flash chromatography was carried out on 230–400 mesh silica gel 60 (Merck).

Materials: Dry THF and diethyl ether were freshly distilled over $LiAlH_4$ under nitrogen atmosphere. Dry benzene was distilled from sodium. Dry methylene chloride was obtained by passage through an Al_2O_3 column and distillation over P_2O_5. *cis*- and *trans*-2-heptene (**37**), 2-ethylcyclopentanone (**26**), 2-methylcyclohexanone (**27**), and *cis*- and *trans*-2,6-dimethylcyclohexanone (**41**, **40**) were commercially available. 1-(Trimethylsilyloxy)-5-methylcyclopentene was prepared as described by House et al.[54] (*E*)-1-Phenyl-2-heptene (**22**)[55] and *cis*- and *trans*-2-methyl-6-benzylcyclohexanone (**17**)[56] were prepared according to literature procedures.

2-Methyl-5-(2′-phenylethan-1′-ol)cyclopentanone (precursor of **13**): A solution of 1-(trimethylsilyloxy)-5-methylcyclopentene (2.55 g; 0.015 mol) in anhydrous methylene chloride (15 mL) was added dropwise to a mixture of phenylacetaldehyde (2.04 g; 0.017 mol) and $TiCl_4$ (3.2 g; 0.017 mol) in the same solvent (130 mL) under argon atmosphere at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, hydrolyzed at that temperature and extracted with diethyl ether; the organic layer was washed with water and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the crude mixture was flash-chromatographed on silica gel (eluent: chloroform). Two fractions were obtained, corresponding to a 7:3 mixture of *erythro-trans* and *erythro-cis* (1.4 g; 0.0064 mol; 43% yield) and a 9:1 mixture of *threo-trans* and *threo-cis* isomers (0.35 g; 0.0016 mol; 11% yield) respectively.[57, 58]

***erythro* isomers**: ^{1}H NMR: $\delta = 1.08$ (d, 30% of 3H, $J = 6.8$ Hz, ang. CH_3 in *cis* isomer), 1.11 (d, 70% of 3H, $J = 6.5$ Hz, ang. CH_3 in *trans* isomer), 1.52 (m, 2H), 2.20 (m, 4H), 2.72 (dd, 1H, $J = 13.8$, 7.7 Hz, benzylic CH), 2.92 (dd, 1H, $J = 13.9$, 4.03 Hz, benzylic CH), 3.85 (dd, 30% of 1H, $J = 9.3$, 3.8 Hz, CHO in the *cis* isomer), 3.96 (dt, 70% of 1H, $J = 8.2$, 4.0 Hz, CHO in the *trans* isomer), 7.28 (m, 5H); ^{13}C NMR, *erythro-trans*: $\delta = 14.2$, 24.8, 29.6, 41.2, 44.9, 52.6, 53.43, 71.8, 126.4, 128.3, 128.4, 128.6, 129.2, 129.6, 138.0, 212.3; δ = *erythro-cis*: 15.0, 24.1, 28.7, 41.2, 44.2, 52.1, 73.3, 126.4, 128.3, 128.6, 129.2, 129.6, 138.0, 213.1; GC/MS: $m/z = 200$ [$M^+ - 18$], 185, 130, 105, 91, 77, 55; Anal. calcd for $C_{14}H_{18}O_2$: C 77.03, H, 8.31; found C 76.93, H, 8.30.

***threo* isomers**: ^{1}H NMR: $\delta = 1.05$ (d, 10% of 3H, $J = 7.1$ Hz, ang. CH_3 in *cis* isomer), 1.09 (d, 90% of 3H, $J = 6.8$ Hz, ang. CH_3 in *trans* isomer), 1.38 (m, 2H), 2.18 (m, 4H), 2.78 (d, 100% of 2H, $J = 7.1$ Hz, benzylic CH_2 in both isomers), 3.92 (d, 10% of 1H, $J = 8.2$ Hz, CHO in the *cis* isomer), 4.35 (dt, 90% of 1H, $J = 4.0$, 8.1 Hz, CHO in the *trans* isomer), 7.28 (m, 5H); ^{13}C NMR *threo-trans*: $\delta = 13.9$, 20.8, 29.6, 41.6, 45.2, 53.4, 71.1, 126.5, 126.6, 128.6, 129.2, 129.4, 138.0, 221.8; *threo-cis*: $\delta = 14.5$, 20.5, 29.2, 41.6, 43.1, 52.6, 71.3, 126.5, 126.6, 128.8, 129.2, 129.4, 138.0, 222.7; GC/MS: $m/z = 200$ [$M^+ - 18$], 185, 130, 105, 91, 77, 55; Anal. calcd for $C_{14}H_{18}O_2$: C 77.03, H 8.31; found C, 76.75, H 8.32.

***O*-Phenyl thiocarbonate of 2-methyl-5-(2′-phenylethan-1′ol)cyclopentanone (13)**: To a stirred solution of the *erythro* (or *threo*) alcohol (used as mixture of *cis* and *trans* isomers, 0.9 g; 0.004 mol) dissolved in anhydrous methylene chloride (30 mL), dry pyridine (1.2 mL; 0.015 mol) and *O*-phenyl chlorothiocarbonate (1.0 mL; 0.055 mol) were consecutively added.[59] After 48 h the solvent was evaporated and the residue was partitioned between ethyl acetate and water, followed by successive washings of the organic phase with cold 1 N HCl/H_2O, sat. $NaHCO_3/H_2O$ and sat. $NaCl/H_2O$, and then drying (Na_2SO_4). The crude mixture was flash-chromatographed on silica gel (eluent: *n*-hexane/ethyl acetate 95:5) to afford the *erythro-trans* (or *threo-trans*) thiocarbonate isomer as pure material. A second fraction consisting of a ca. 1:1 mixture of *cis* and *trans* isomers was also obtained.

erythro-trans: 0.3 g; 0.008 mol; 20% yield; ^{1}H NMR: $\delta = 1.10$ (d, 3H, $J = 7$ Hz, ang. CH_3), 1.34 (m, 1H), 1.75 (m, 1H), 2.05 (m, 2H), 2.18 (m, 1H), 2.53 (dt, 1H, $J = 7.7$, 3.5 Hz), 3.30 (dd, 2H, $J = 6.9$, 2.2 Hz), 5.70 (dt, 1H, $J = 7.4$, 3.5 Hz, CHO), 7.03 (d, 2H, $J = 7.1$ Hz), 7.36 (m, 8H); ^{13}C NMR: $\delta = 13.7$, 24.0, 29.4, 36.5, 45.4, 46.1, 85.5, 121.8, 121.9, 126.5, 126.8, 128.6, 129.5, 129.9, 136.2, 153.2, 193.7, 218.6; IR: $\tilde{\nu}$ (cm^{-1}) = 1737 (C=O), 1226 (carbonate O–C–O), 1200 (C=S).

threo-trans: 0.4 g; 0.011 mol; 27% yield; ^{1}H NMR: $\delta = 1.10$ (d, 3H, $J = 6.8$ Hz, ang. CH_3), 1.35 (m, 1H), 2.15 (m, 2H), 2.30 (m, 4H), 2.91 (dd, 1H, $J = 13.1$, 9.6 Hz, benzylic CH), 3.48 (dd, 1H, $J = 13.1$, 5.1 Hz, benzylic CH), 5.90 (m, 1H, CHO), 7.02 (d, 2H, $J = 8.2$ Hz), 7.35 (m, 3H); ^{13}C NMR: $\delta = 14.0$, 22.3, 29.5, 37.3, 44.8, 50.3, 83.7, 121.9, 126.5, 127.1, 128.7, 128.5, 129.4, 129.6, 136.0, 153.3, 193.8, 218.5; IR: $\tilde{\nu}$ (cm^{-1}) = 1738 (C=O), 1222 (carbonate O–C–O), 1200 (C=S).

(*E*)-2-Methyl-7-phenylhept-5-enoic acid (precursor of **18**): To a magnetically stirred solution of diisopropylamine (0.02 mol; 3 mL) in anhydrous THF (15 mL), kept under argon at −78 °C, *n*BuLi (0.022 mol; 13 mL of a 1.6 M solution in *n*-hexane) was added dropwise. After 30 min, propanoic acid (0.009 mol; 0.7 mL) dissolved in anhydrous THF (5 mL) was added, and the reaction was allowed to reach 0 °C. The formation of a milky suspension was observed; HMPA (0.010 mol; 1.8 mL) was then added and the reaction mixture again became homogeneous.[60, 61] Stirring was continued for 30 min at ambient temperature; the mixture was then cooled at 0 °C, and (*E*)-5-bromo-1-phenylpent-2-ene[62] (2.13 g; 0.009 mol) was added rapidly. After 1.5 h at RT, the reaction was quenched by adding cold 10% aq. HCl, and extracted with diethyl ether. The ethereal phases were washed with brine, dried over sodium sulfate and evaporated. The crude mixture was flash-chromatographed on silica gel (eluent: *n*-hexane/diethyl ether 95:5) to give (*E*)-2-methyl-7-phenylhept-5-enoic acid (1.52 g; 0.007 mol; 73% yield) as low melting point crystals. ^{1}H NMR: $\delta = 1.21$ (d, 3H, $J = 7$ Hz), 1.58 (m, 1H), 1.82 (m, 1H), 2.12 (q, 1H, $J = 7.5$ Hz), 2.37 (q, 1H, $J = 7.5$ Hz), 2.45 (sextet, 1H, $J = 7$ Hz), 3.36 (d, 2H, $J = 6$ Hz), 5.56 (m, 2H), 7.19 (m, 5H), 10.35 (brs, 1H); ^{13}C NMR: $\delta = 16.8$, 27.3, 30.3, 38.9, 39.0, 125.9, 128.3, 128.4, 128.5, 129.8, 130.3, 182.3; Anal. calcd for $C_{14}H_{18}O_2$: C 77.03, H 8.31; found C 77.22, H 8.35.

(*E*)-2-Methyl-7-phenylhept-5-enoyl phenylseleno ester (18): To a magnetically stirred solution of *N*-phenylselenophthalimide (2.4 g; 0.008 mol) in anhydrous THF (20 mL), tributylphosphine (2 mL; 0.008 mol) was added;[63] a mildly exothermic reaction took place, and then the acid (0.87 g; 0.004 mol), dissolved in the same solvent (5 mL), was added in one portion. The reaction was stirred at RT for 3.5 h. After this period, the reaction was worked up; the solvent was evaporated under reduced pressure and the crude mixture was flash-chromatographed on silica gel (eluent: *n*-hexane/diethyl ether 100:1). The expected seleno ester was isolated as an oil (0.75 g; 0.0021 mol; 52% yield). ^{1}H NMR: $\delta = 1.25$ (d, 3H, $J = 7$ Hz), 1.54 (m, 1H), 1.87 (m, 1H), 2.13 (m, 2H), 2.68 (m, 1H), 3.35 (d, 2H, $J = 6.2$ Hz), 5.56 (m, 2H), 7.28 (m,

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5H), 7.48 (m, 3H), 7.62 (m, 2H); ^{13}C NMR: δ = 17.2, 29.9, 33.4, 39.0, 51.2, 125.9, 127.7, 128.3, 128.4, 128.5, 128.7, 128.9, 129.2, 130.0, 135.6, 183.4.

***cis*- and *trans*-2-Methyl-5-(2′-phenylethane)cyclopentanone (15)**: To a degassed, magnetically stirred solution of thiocarbonate **13** (used as a mixture of diastereoisomers) (1.18 g; 0.003 mol) in dry benzene (11.5 mL), kept under argon, $(TMS)_3SiH$ (4.1 g; 0.017 mol) and AIBN (0.054 g; 0.0003 mol) were added consecutively. The reaction was left under reflux for 1 h; after this time TLC (eluent: *n*-hexane/diethyl ether 9:1) and GC indicated the complete consumption of the starting material. The solvent was carefully evaporated under vacuum, and the crude mixture was flash-chromatographed on silica gel (eluent: *n*-hexane), affording two fractions. The first fraction corresponded to a mixture of *cis* and *trans* isomers of 2-methyl-6-benzylcyclohexanone (**17**, 0.075 g; 0.0004 mol; 11% yield) recognized by comparison with an authentic sample obtained by other routes.[56] The second fraction contained 2-methyl-5-(2′-phenylethane)cyclopentanone (**15**, 0.43 g; 0.002 mol; 64% yield) as a 1:1 mixture of *cis* and *trans* isomers.

trans: ^{1}H NMR: δ = 1.10 (d, 3H, J = 6.9 Hz), 1.37 (m, 2H), 1.62 (m, 2H), 2.24 (m, 4H), 2.65 (m, 2H), 7.21 (m, 5H); ^{13}C NMR: δ = 14.4, 27.8, 29.9, 32.0, 33.5, 44.3, 48.1, 125.9, 128.3, 128.4, 222.3; GC/MS: m/z = 202 [M^+], 104, 98, 91, 56, 44, 41; HRMS: m/z for $C_{14}H_{18}O$ calcd 202.1358, found 202.1363.

cis: ^{1}H NMR: δ = 1.03 (d, 3H, J = 6.7 Hz), 1.35 (m, 2H), 1.62 (m, 2H), 2.25 (m, 4H), 2.67 (m, 2H), 7.21 (m, 5H); ^{13}C NMR: δ = 15.2, 26.6, 30.0, 31.4, 33.5, 43.2, 47.2, 125.9, 128.3, 128.4, 222.7; GC/MS: m/z = 202 [M^+], 104, 98, 91, 70, 55, 41; HRMS: m/z for $C_{14}H_{18}O$ calcd 202.1358, found 202.1360.

(*E*)-2-Methyl-7-phenylhept-5-en-1-al (20): From the above reported (*E*)-2-methyl-7-phenylhept-5-enoic acid, the corresponding aldehyde was prepared in 75% overall yield by LAH reduction and PCC oxidation.[64] ^{1}H NMR: δ = 1.09 (d, 3H, J = 7.0 Hz), 1.22 (m, 1H), 1.43 (m, 2H), 1.80 (m, 1H), 2.07 (m, 1H), 2.35 (m, 1H), 3.32 (d, 2H, J = 6.3 Hz), 5.52 (m, 2H), 7.27 (m, 5H), 9.62 (s, 1H, CHO); ^{13}C NMR: δ = 13.2, 29.7, 37.9, 38.4, 45.6, 125.9, 128.3, 128.4, 130.1, 130.5, 204.9; GC/MS: m/e = 202 [M^+], 159, 143, 129, 117, 104, 91, 77, 65, 51.

2-(Ethan-1′-ol)cyclopentanone (precursor of **23**): Reaction of acetaldehyde with 1-(trimethylsilyloxy)cyclopentene following the procedure reported above for the precursor of **13**. Flash-chromatography of the crude mixture (eluent: *n*-hexane/diethyl ether 8:2) afforded the *erythro* and *threo* isomers in the ratio of 1:2.

erythro: ^{1}H NMR: δ = 1.13 (d, 3H, J = 6.4 Hz), 1.42 (m, 1H), 1.75 (m, 1H), 2.05 (m, 4H), 2.25 (m, 1H), 4.17 (m, 1H); ^{13}C NMR: δ = 20.8, 23.4, 26.7, 39.1, 55.5, 66.0, 68.7, 213.3.

threo: ^{1}H NMR: δ = 1.09 (d, 3H, J = 6.4 Hz), 1.43 (m, 1H), 1.71 (m, 1H), 2.05 (m, 4H), 2.27 (m, 1H), 3.73 (m, 1H); ^{13}C NMR: δ = 21.2, 23.4, 26.7, 38.4, 39.1, 55.2, 65.9, 66.7, 222.3.

***O*-Phenyl thiocarbonate of 2-(ethan-1′-ol)cyclopentanone (23)**: Following the preparation of thiocarbonate **13**, the desired product was isolated by flash chromatography (eluent: chloroform) as *erythro* and *threo* isomers.

erythro: ^{1}H NMR: δ = 1.48 (d, 3H, J = 6.5 Hz), 1.83 (m, 2H), 2.15 (m, 2H), 2.31 (m, 2H), 2.71 (m, 1H), 5.67 (m, 1H), 7.06 (d, 2H, J = 7.1 Hz), 7.27 (m, 1H), 7.39 (m, 2H); ^{13}C NMR: δ = 17.4, 20.5, 24.6, 38.7, 53.6, 79.5, 120.3, 121.9, 126.4, 129.5, 194.1, 217.8; Anal. calcd for $C_{14}H_{16}O_2S$: C 67.71, H 6.49; found C 67.50, H 6.51.

threo: ^{1}H NMR: δ = 1.41 (d, 3H, J = 6.5 Hz), 1.85 (m, 2H), 2.12 (m, 2H), 2.33 (m, 2H), 2.74 (m, 1H), 5.67 (m, 1H), 7.08 (d, 2H, J = 8.2 Hz), 7.28 (m, 1H), 7.38 (m, 2H); ^{13}C NMR: δ = 15.9, 20.5, 25.2, 38.8, 51.9, 80.7, 120.3, 121.2, 126.5, 129.6, 194.2, 217.8; IR: $\tilde{\nu}$ (cm^{-1}) = 1700, 1225, 1215; Anal. calcd for $C_{14}H_{16}O_2S$: C 67.71, H 6.49; found C 67.62, H 6.50.

***O*-Phenyl thiocarbonate of *trans*-3-hydroxy-2-methylcyclohexanone (28)**: Following the preparation of **13**, *trans*-2-methyl-3-hydroxy cyclohexanone[65] was transformed into the corresponding thiocarbonate, which was isolated by flash chromatography (eluent: chloroform/methanol 95:5); ^{1}H NMR: δ = 1.23 (d, 3H, J = 6.9 Hz), 1.70 (m, 1H), 2.02 (m, 2H), 2.35 (m, 1H), 2.47 (m, 2H), 2.82 (m, 1H), 5.26 (m, 1H), 7.12 (d, 2H, J = 8.0 Hz), 7.35 (m, 3H); ^{13}C NMR: δ = 11.5, 20.1, 28.3, 39.6, 50.3, 86.5, 120.8, 121.7, 126.7, 129.4, 194.1, 209.3; IR: $\tilde{\nu}$ (cm^{-1}) = 1715, 1257, 1200.

2-Methylhept-5-enoyl phenylseleno ester (29): Following the preparation of **18**, 2-methylhept-5-enoic acid[61] (used as a 9:1 mixture of (*E*) and (*Z*) isomers) was transformed into the corresponding seleno ester, an oil isolated by flash chromatography on silica gel (eluent: *n*-hexane/diethyl ether 95:5); ^{1}H NMR: 1.21 (d, 3H, J = 7 Hz), 1.51 (m, 1H), 1.66 (d, 3H, J = 5.2 Hz), 1.87 (m, 1H), 2.05 (m, 2H), 2.81 (m, 1H), 5.41 (m, 2H), 7.38 (m, 3H), 7.48 (m, 2H); ^{13}C NMR: δ = 17.2, 17.9, 30.0, 33.5, 51.2, 126.1, 126.4, 128.7, 128.9, 129.2, 130.0, 135.9, 182.2.

***cis*- and *trans*-2-methyl-5-ethylcyclopentanone (39,38)**: To a magnetically stirred solution of 1-(trimethylsilyloxy)-5-methylcyclopentene (3.1 g; 0.018 mol) and ethyl iodide (8.5 g; 0.05 mol) in anhydrous THF (30 mL), kept under argon at 0 °C, tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F)[66] (4.9 g; 0.018 mol) was added in one portion; the reaction mixture was kept at 0 °C for 1 h and was then allowed to warm to RT. After 12 h the reaction was worked up by addition of *n*-hexane (50 mL). The organic phase was washed with water and dried over sodium sulfate; the solvent was carefully evaporated, affording a crude mixture, which was distilled. The product was isolated as a 40:60 mixture of *cis*- and *trans*-2-methyl-5-ethylcyclopentanone (1.26 g; 0.01 mol; 55.5% yield); b.p. 58–60 °C/15 mmHg; ^{1}H NMR: δ = 0.81 (t, 3H, J = 7.6 Hz, *trans* isomer), 0.93 (t, 3H, J = 7.4 Hz, *cis* isomer), 1.06 (d, 3H, J = 7.3 Hz, *trans*), 1.11 (d, 3H, J = 7.1 Hz, *cis*), 1.43 (m, 3H), 1.72 (m, 1H), 1.82 (m, 2H), 2.25 (m, 2H); ^{13}C NMR: δ = 11.7 (*trans*), 11.9 (*cis*), 14.9 (*trans*), 15.2 (*cis*), 25.9 (*trans*), 27.0 (*cis*), 29.0, 29.1, 29.6, 29.8, 42.78, 44.27, 222.3 (*trans*), 222.7 (*cis*); GC/MS: m/e = 126 [M^+], 111, 97, 44.

2-Methylhept-5-en-1-al (31): From the previously described 2-methylhept-5-enoic acid, LAH reduction followed by PCC oxidation[64] afforded the corresponding aldehyde (87% overall yield). ^{1}H NMR: δ = 1.08 (d, 3H, J = 7.0 Hz), 1.42 (m, 1H), 1.64 (d, 3H, J = 4.7 Hz), 1.80 (m, 1H), 2.02 (m, 2H, allyl CH_2), 2.17 (m, 1H), 5.40 (m, 2H), 9.61 (s, 1H, CHO); ^{13}C NMR: δ = 13.2, 17.7, 29.7, 30.4, 45.5, 125.1, 125.9, 129.3, 130.1, 204.8; GC/MS: m/e = 126 [M^+], 108, 98, 79, 68, 55, 41.

Kinetic experiments: Toluene containing a small amount of undecane as an internal GC standard was used as solvent. $(TMS)_3SiH$ and thiocarbonate **23** or Bu_3SnH and phenylseleno ester **29** were added in a ratio of ca. 20:1. Samples of these reaction mixtures were degassed and sealed under argon in Pyrex ampoules. Reactions of thiocarbonate were initiated either photolytically (343, 353, 363, 373, and 393 K) or thermally (di-*tert*-butyl peroxide/413 K). Reactions of phenylseleno ester were initiated photolytically (233, 266, 299, and 323 K). The products of interest were identified by comparison of their retention times with authentic materials.

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[35] Both $(TMS)_3Si^\bullet$ and $Bu_3Sn^\bullet$ radicals are able to isomerize acyclic olefins by an addition–elimination sequence. However, the equilibration of the two geometrical isomers is dependent on several parameters such as attacking radical and its concentration, reaction temperature, and time [36]. The isomeric composition of the olefinic moiety, (*E*)/(*Z*) = 90/10, in the starting phenylseleno ester **29** was different from those of aldehyde and alkene. For example, in the series of experiments where the concentration of Bu_3SnH was 0.75 M, (*E*)/(*Z*) ratios of 89/11, 88/12, 86/14, and 85/13 were obtained at 233, 256, 298, and 323 K respectively.

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[48] For **45**, even though no local minimum appears in Figure 4 for such a structure, AM1 indicates the possibility of a metastable intermediate with a small barrier for decomposition, since the O–H bond in the corresponding alcohol can be stretched up to 6.00 Å without beta scission. It is only when the hydroxylic hydrogen is completely removed, or is removed in one step from the alcohol, that AM1 optimizes radical **45** to **44**.
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