mL). The well-stirred slurry was cooled to 0 °C, and trifluoromethanesulfonic acid (9.0 mL, 0.102 mol) was slowly added over a period of 1 h. The reaction mixture was brought to room temperature and stirred for an additional 1 h, filtered, and concentrated to dryness to afford 25.3 g (98.5%) of an off-white solid. The solid was recrystallized from warm ether–hexane (1:1) and washed well with ice cold ether–hexane (1:1) until colorless. The white crystalline solid was then dried in vacuo to yield 24.6 g (96%). The solid was stored in a dark desiccator. IR (Nujol): 1630 (s), 1250 (s), 1170 (s), 1020 (s) cm^{-1}.

Sodium Trifluoromethanesulfonate. An adaptation of the procedure of De Levie[31] was used. Na_2CO_3 (5.3 g, 0.05 mol) was carefully added in several small portions to a well-stirred solution of trifluoromethanesulfonic acid (8.85 mL, 0.1 mol) in acetone–CH_2Cl_2 (2:1, 120 mL). The red solution was stirred until the evolution of CO_2 ceased. The solution was then diluted with CH_2Cl_2 (100 mL) and cooled to −78 °C. The precipitate formed was filtered and washed with small aliquots of cold CH_2Cl_2 (to decolorize the solid) and dried to yield 17.0 g (100%) of an off white solid. Recrystallization from acetone–CH_2Cl_2 followed by washing with cold CH_2Cl_2 yielded 16.05 g (93%) of a white hygroscopic solid. IR (KBr): 1610 (w), 1385 (w), 1280 (sh), 1260 (s), 1230 (sh), 1195 (sh), 1170 (s), 1040 (s), 635 (s), 515 (w), 420 (m) cm^{-1}.

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Acknowledgment. We are grateful to the National Institute of Health (CA 47348-04) and to Ford Motor Co. for partial support of this work. We are also thankful to the Pittsburg Supercomputing Center for generous amounts of computer time. We also thank Professor Normal Lebel for many helpful discussions.

Stereochemistry of the Reversible Cyclization of ω-Formylalkyl Radicals

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Received April 7, 1992

The reactions of 6-bromo-4-(1′,1′-dimethylethyl)hexanal (4), 5-bromo-3-(1′,1′-dimethylethyl)pentanal (11), and 5-bromo-4-(1′,1′-dimethylethyl)pentanal (17) with tributylstannane have been investigated in detail. The major products are the debrominated aldehydes and cycloalkanols which arise from the cyclization of the intermediate ω-formylalkyl radicals. The stereochemical outcome of the cyclization of these radicals is dependent on the stannane concentration. At high concentrations of stannane the cyclization is essentially irreversible with the cycloalkoxy radicals being trapped before β-scission can occur. Under these conditions the relative amount of cis and trans cycloalkanols formed are equal to the ratio of the rate constants for the two modes of cyclization; both 4 and 17 show a small preference for trans cyclization, but 11 gives equal amounts of the two diastereomers. When the stannane concentration is lowered, the lifetime of the cycloalkoxy radicals increases allowing β-scission to occur. Thus, the cis and trans cycloalkoxy radicals approach a thermodynamic equilibrium which is reflected in the relative yields of the cis and trans cycloalkanols.

The formation of carbon–carbon bonds through intramolecular addition of carbon-centered radicals to alkenes, alkynes, and other unsaturated centers is of considerable mechanistic interest[1] and synthetic utility.[2] Such cyclizations of substituted 5-hexenyl radicals have been studied in detail,[1] and the factors controlling the stereochemical outcome are well understood.

A useful guideline[3] for the ring closure of substituted 5-hexenyl radicals states that 1- or 3-substituted radicals preferentially give cis disubstituted products, while 2- and 4-substituted radicals give mainly trans. The explanation for the behavior of species substituted at C(2), C(3), or C(4) rests on the hypothesis that the transition structure resembles the chair form of cyclohexane, the most favorable conformer of which will contain the substituent in a pseudoequatorial position. A theoretical study,[4] involving an approach based on a combination of molecular orbital and molecular mechanics methods, provided a means for calculating the cis/trans ratio of the cyclization products. Such calculations show very good correlation with experimentally measured data.[4] A later refinement by Spellmeyer and Houk[5] demonstrated that the inclusion into the scheme of a low-energy boatlike transition structure for the formation of the lesser diastereoisomer led to closer correlation between calculated and measured data. This has recently been confirmed by experiment.[5b]

Cyclizations involving intramolecular homolytic addition to the carbonyl group of ketones[6] or aldehydes[7-9] have

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(1) (a) Beckwith, A. L. J. *Rev. Chem. Intermed.* **1986**, *7*, 143. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (c) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; DeMayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 188. (d) Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1980; Vol. 2, p 161. (e) Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553.

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(5) (a) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (b) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.

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(7) (a) Flies, F.; Laland, R.; Maillard, B. *Tetrahedron Lett.* **1976**, 439. (b) Maillard, B.; Gardrat, C.; Bourgeois, M.-J. *J. Organomet. Chem.* **1982**, *236*, 61.

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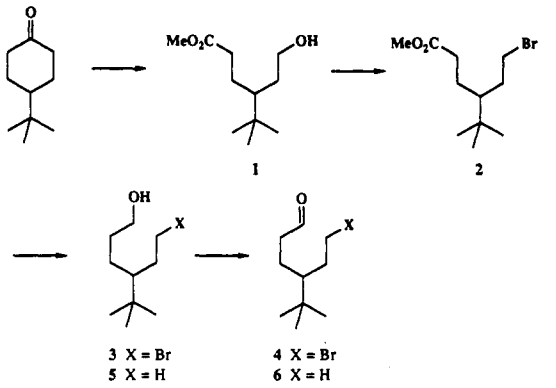
Scheme I



received much less attention, but it is clear that both the formylpentyl and formylbutyl radicals and related species undergo rapid ring closure in the exo mode. An interesting feature of these reactions is that the yields of six-membered cyclic products obtained from radicals containing the formylpentyl system are greater than the yields of five-membered cyclic products obtained from formylbutyl systems when the reactions are conducted under similar conditions.[8,9] This contrasts with the behavior of ω-alkenyl radicals for which 1,6-exo cyclization is less efficient than 1,5-exo cyclization.[1] In part, this difference reflects the reversibility of ω-formylalkyl radical cyclization; the cyclopentyloxyl radical undergoes ring opening by β-fission far more rapidly than does the cyclohexyloxyl radical (k_β = 4.7×10^8 s^{-1} and 1.1×10^7 s^{-1}, respectively, at 80 °C).[9] However, it is also relevant that the forward reactions for cyclization of the formylpentyl radical and the formylbutyl radical have very similar rate constants (8.7×10^5 s^{-1} and 1.0×10^6 s^{-1}, respectively, at 80 °C) whereas the 6-heptenyl radical undergoes exo cyclization much more slowly than does the 5-hexenyl radical ($k_c = 4.3 \times 10^4$ s^{-1} and 1.4×10^6 s^{-1}, respectively, at 80 °C).

The difference in rates and reversibility of cyclization of the formylalkyl radicals and their alkenyl analogs is considered to reflect the differences in thermochemistry and intimate transition structure between the two addition processes. The aim of the present work was to ascertain whether there are similar differences in the stereochemistry of substituted systems.

This paper describes the stereochemical outcome of the cyclization of three *tert*-butyl-substituted ω-formylalkyl radicals (see Schemes III and IV). The *tert*-butyl substituent was chosen for such studies because its steric bulk ensures a strong preference for a pseudoequatorial position in the transition structure. In the case of the 3-*tert*-butyl-5-hexenyl radical this leads to cyclized products with a relatively large cis/trans ratio.[5b] We have measured the selectivities of the actual cyclization steps for 3-*tert*-butyl-5-formylpentyl, 2-*tert*-butyl-4-formylbutyl, and 3-*tert*-butyl-4-formylbutyl radicals and have shown that these reactions may proceed under either kinetic or thermodynamic control depending on the reaction conditions.

Results

(i) The Reaction of 6-Bromo-4-*tert*-butylhexanal with Bu_3SnH. The bromo aldehyde **4** was synthesized as outlined in Scheme I. The lactone formed by Baeyer–Villiger oxidation[10] of 4-*tert*-butylcyclohexanone was ring opened by acid-catalyzed methanolysis to give hydroxy ester **1** which was converted into bromo ester **2** by treatment with CBr_4/PPh_3. The chemoselectivity of reduction of **2** with $LiAlH_4$ depended on the conditions. In ether at room temperature the bromo alcohol **3** was the single product whereas in THF at reflux the reaction gave **5** exclusively. These alcohols were then converted to aldehydes **4** and **6** by oxidation with pyridinium chlorochromate (PCC).

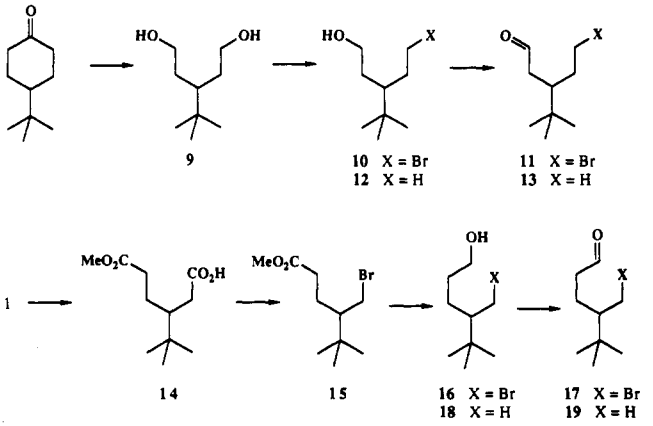
Bromo aldehyde **4** was treated with an excess of Bu_3SnH in benzene at 80 °C, in the presence of 2,2′-azobisisobutyronitrile (AIBN). A number of experiments were carried out with varying concentrations of stannane and **4**; the results obtained when the products were analyzed by GLC are shown in Table I. The products were identified by comparing their retention times with those of authentic samples.[11] The major products were the cyclohexanols **7** and **8** (Scheme III) and the aldehyde **6**. The acyclic alcohol **5** was also detected; this arises from the secondary reduction of **6**.[9b] Table I shows that the relative amounts of **6**, **7**, and **8** formed exhibit a strong dependence on the stannane concentration employed.

Table I. Product Distributions for the Reaction of 4 with Bu_3SnH (Benzene, AIBN, 80 °C, under Nitrogen)

$[Bu_3SnH]_0$[a]	$[4]_0$[a]	[5][b,c]	[6][b,c]	[7][b-d]	[8][b-d]
0.0050	0.000 50	nd	37	42	21
0.0075	0.000 75	nd	36	41	23
0.010	0.0010	nd	32	44	24
0.020	0.0020	nd	31	40	29
0.25	0.025	2.1	22	41	35
0.50	0.050	5.3	24	38	33
0.75	0.075	6.6	24	38	31
1.00	0.100	15	22	34	29
1.50	0.150	21	20	32	27

[a] Initial reactant concentrations in mol/L. [b] All products identified by comparison with authentic samples. [c] Final product concentrations represented as mol %; nd, not detected. [d] See ref 11.

Scheme II



(ii) The Reaction of 5-Bromo-3-*tert*-butylpentanal and 5-Bromo-4-*tert*-butylpentanal with Bu_3SnH. The syntheses of bromo aldehydes **11** and **17** are outlined in Scheme II. The diol **9** obtained from 4-*tert*-butylcyclohexanone by a literature procedure[12] was treated with

(8) (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102. (b) Tsang, R.; Dickson, J. K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. (c) Fraser-Reid, B.; Vite, G. D.; Yeung, B.-W. A.; Tsang, R. *Tetrahedron Lett.* **1988**, *29*, 1645.

(9) (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674.

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(11) Pure samples of *cis*- and *trans*-4-*tert*-butylcyclohexanol were obtained by silica gel chromatography of the commercially available mixture of isomers. The stereochemistry was assigned on the basis of ^1H NMR: **7** δ 3.52 (tt, J = 4.4, 10.8 Hz, C*H*OH); **8** δ 4.04 (quintet, J = 2.7 Hz, C*H*OH).

Table II. Product Distributions for the Reaction of 11 with Bu_3SnH (Benzene, AIBN, 80 °C, under Nitrogen)

$[Bu_3SnH]_0$[a]	$[11]_0$[a]	[12][b,c]	[13][b,c]	[18][b,c]	[19][b,c]	[20][b-d]	[21][b-d]
0.010	0.0010	nd	8.3	nd	18	38	36
0.050	0.0050	1.7	7.7	3.6	13	39	35
0.100	0.0100	3.8	7.4	3.2	7.6	37	41
0.500	0.0500	4.9	16	nd	3.4	37	39
1.00	0.100	5.9	21	nd	nd	38	35
2.00	0.200	8.1	23	nd	nd	34	35
3.00	0.300	13	23	nd	nd	32	32
3.72	0.372	14	25	nd	nd	31	30

[a] Initial reactant concentrations in mol/L. [b] Identified by comparison with an authentic sample. [c] Final product concentrations represented as mol % nd, not detected. [d] See ref 17.

Table III. Product Distributions for the Reaction of 17 with Bu_3SnH (Benzene, AIBN, 80 °C, under Nitrogen)

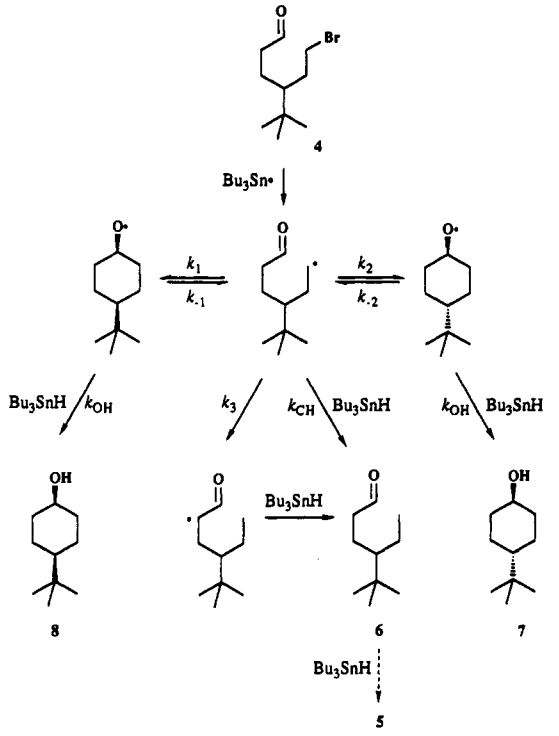
$[Bu_3SnH]_0$[a]	$[17]_0$[a]	[12][b,c]	[13][b,c]	[18][b,c]	[19][b,c]	[20][b-d]	[21][b-d]
0.010	0.0010	nd	8.2	nd	18	35	35
0.100	0.0100	1.3	4.3	2.2	7.6	46	38
0.500	0.0500	nd	2.1	1.0	3.4	56	37
1.00	0.100	nd	1.0	nd	nd	59	37
2.00	0.200	nd	nd	1.9	nd	56	38
3.00	0.300	nd	nd	3.1	nd	55	35
3.72	0.372	nd	nd	3.3	nd	54	35

[a] Initial reactant concentrations in mol/L. [b] Identified by comparison with an authentic sample. [c] Final product concentrations represented as mol %; nd, not detected. [d] See ref 17.

CBr_4/PPh_3 to give a mixture of the diol, bromo alcohol **10**, and the corresponding dibromide. The bromo alcohol **10** was isolated by chromatography in low yield[13] and debrominated with Bu_3SnH to give the alcohol **12**. Oxidation of alcohols **10** and **12** with PCC gave the corresponding aldehydes **11** and **13**. The bromo aldehyde **17** was synthesized from the hydroxy ester **1**. Oxidation of **1** with Jones reagent gave the acid–ester **14** which was converted to bromo ester **15** by methods developed by Barton.[16] The reduction of **15** by $LiAlH_4$ could be controlled to give either **16** or **18** as the exclusive product by controlling the reaction temperature. These alcohols were oxidized to the corresponding aldehydes with PCC.

GC analysis of the mixture obtained when bromo aldehyde **11** was treated with an excess of Bu_3SnH in benzene at 80 °C in the presence of AIBN showed that six products were formed. The cyclopentanols **20** and **21** (Scheme IV) were the major products; aldehydes **13** and **19** and alcohols **12** and **18** were also present. The acyclic alcohols and aldehydes were identified by comparison with synthetic samples, and the cyclopentanols were isolated as a mixture of isomers and characterized by NMR and IR spectroscopy.[17] The formation of products **18** and **19** arises from β-scission of the intermediate cyclopentyloxyl radical along an alternative pathway (Scheme IV). Reaction of bromo aldehyde **17** with Bu_3SnH under the same reaction conditions gave the same six products. The product distributions for reactions of the bromo aldehydes **11** and **17** at various stannane concentrations are shown in Tables II and III, respectively.

Scheme III



Discussion

(i) The Reaction of 6-Bromo-4-*tert*-butylhexanal with Bu_3SnH. Scheme III shows the pathways thought to be involved in the reaction of the bromo aldehyde **4** with Bu_3SnH. Abstraction of the bromine atom from **4** by tributylstannyl radicals gives carbon-centered radicals which then cyclize to afford cycloalkoxy radicals. Both the carbon- and the oxygen-centered radicals abstract hydrogen from the stannane to give products and hence propagate the chain reaction.

Because the experiments listed in Table I were performed with a 10-fold excess of stannane its concentration can be assumed to be constant throughout the reaction.

(12) (a) Klein, J.; Stollar, H. *J. Am. Chem. Soc.* **1973**, *95*, 7437. (b) Tichy, M. *Org. Prep. Proced. Int.* **1976**, *8*, 239.

(13) Tetrahydropyran can be converted to 5-bromopentanol by treatment with boron tribromide.[14] Accordingly, a sample of 4-*tert*-butyltetrahydropyran[15] was prepared, but unfortunately reaction with boron tribromide, under a variety of conditions, gave only 1,5-dibromo-3-*tert*-butylpentane as the isolated product.

(14) Kulkarni, S. U.; Patil, V. D. *Heterocycles* **1982**, *18*, 163.

(15) Bailey, W. F.; Bischoff, J. J. *J. Org. Chem.* **1985**, *50*, 3009.

(16) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

(17) (a) An authentic sample of the 3-*tert*-butylcyclopentanols (60% cis, 40% trans) was prepared according to a literature procedure.[17b] The stereochemistry of the radical cyclization was thus assigned by comparison with this authentic sample. (b) Richer, J. C.; Gilardeau, C. *Can. J. Chem.* **1965**, *43*, 3419.

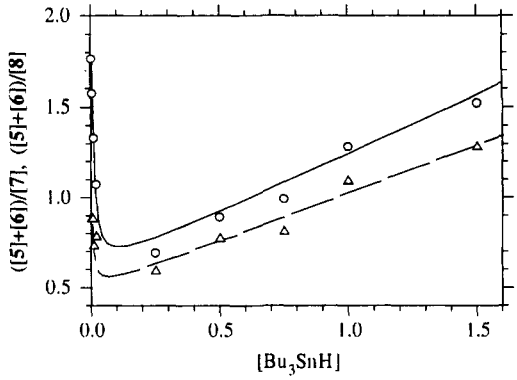


Figure 1. Data from the reaction of **4** with [Bu_3SnH]. Circles show ([5] + [6])/[8] vs [Bu_3SnH]; triangles show ([5] + [6])/[7] vs [Bu_3SnH]. Broken line represents eq 1; solid line represents eq 2.

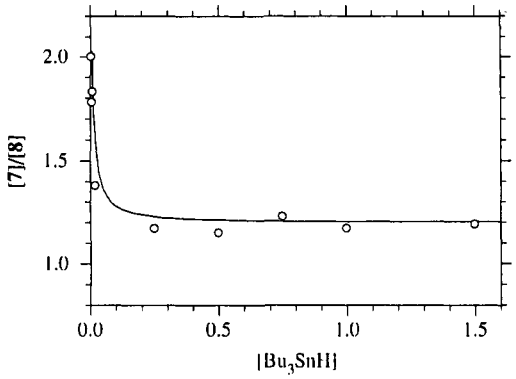


Figure 2. Overall stereochemistry of the cyclization of **4** with [Bu_3SnH]. The solid line represents eq 3.

If it is also assumed that the radicals involved reach steady-state concentrations, then eqs 1–3 can be derived.

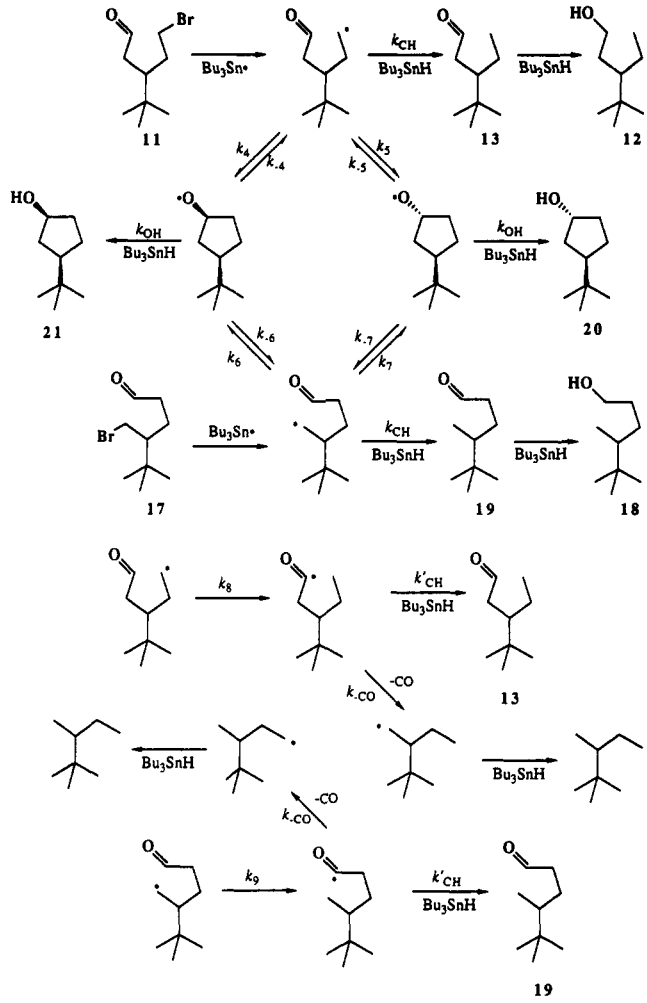
$$\frac{[5]+[6]}{[7]} = \frac{k_{-2}k_3}{k_2k_{OH}}\cdot\frac{1}{[Bu_3SnH]} + \left(\frac{k_{-2}k_{CH}}{k_2k_{OH}} + \frac{k_3}{k_2}\right) + \frac{k_{CH}}{k_2}[Bu_3SnH] \quad (1)$$

$$\frac{[5]+[6]}{[8]} = \frac{k_{-1}k_3}{k_1k_{OH}}\cdot\frac{1}{[Bu_3SnH]} + \left(\frac{k_{-1}k_{CH}}{k_1k_{OH}} + \frac{k_3}{k_1}\right) + \frac{k_{CH}}{k_1}[Bu_3SnH] \quad (2)$$

$$\frac{[7]}{[8]} = \frac{k_2k_{-1} + k_2k_{OH}[Bu_3SnH]}{k_1k_{-2} + k_1k_{OH}[Bu_3SnH]} \quad (3)$$

The rate constants for cyclization (k_1, k_2) and β-scission (k_{-1}, k_{-2}) were estimated by plotting ([5] + [6])/[7]) and ([5] + [6]/[8]) against the stannane concentration and then fitting eqs 1 and 2 to the data (Figure 1). The values for k_{CH} and k_{OH} were taken as 6.4×10^6 M^{-1} s^{-1} and 6.6×10^8 M^{-1} s^{-1}, respectively, at 80 °C. These values correspond to the known rate constants for the abstraction of hydrogen from Bu_3SnH by a primary alkyl radical and the *tert*-butoxy radical, respectively.[18] From these values, k_1 and k_2 were estimated as 1.0×10^7 s^{-1} and 1.2×10^7 s^{-1}, respectively, at 80 °C. The β-scission rate constants, k_{-1} and k_{-2}, were similarly found to be 8.2×10^6 s^{-1} and 3.1×10^6 s^{-1}, respectively, at 80 °C.

Scheme IV



Scheme III includes a 1,5 hydrogen atom transfer in the first-formed ω-formylalkyl radical. Since this process does not produce a unique characteristic product, its occurrence is not experimentally obvious. If this reaction is omitted from Scheme III then kinetic analysis yields the more simple linear relationships between ([5] + [6])/[7], ([5] + [6]/[8], and [Bu_3SnH] shown in eqs 4 and 5. Figure 1

$$\frac{[5]+[6]}{[7]} = \frac{k_{-2}k_{CH}}{k_2k_{OH}} + \frac{k_{CH}}{k_2}[Bu_3SnH] \quad (4)$$

$$\frac{[5]+[6]}{[8]} = \frac{k_{-1}k_{CH}}{k_1k_{OH}} + \frac{k_{CH}}{k_1}[Bu_3SnH] \quad (5)$$

shows quite clearly that plots of ([5] + [6])/[7] and ([5] + [6]/[8] versus [Bu_3SnH] are not linear below a stannane concentration of 0.1 M. Therefore, a kinetic scheme which omits the 1,5 hydrogen migration is quite inadequate. The fitting of the data in Table I to the calculated curves shown in Figures 1 and 2 used a value of 5.9×10^6 s^{-1} for the hydrogen migration rate constant, k_3.

In order to verify that the putative 1,5 migration does in fact occur, an additional experiment was run with Bu_3SnD.[19] The deuterostannane concentration (0.0020 M) was sufficiently low as to be in the range where the anomalous kinetic behavior was observed. The reaction

(18) (a) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (b) Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickrema, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594. (c) Private communication with J. Lusztyk.

(19) The Bu_3SnD was prepared by the reaction of Bu_3SnCl with $LiAlD_4$ using the procedure of: Kuivila, H. G. *Synthesis* **1970**, 499.

was conducted under conditions identical to those employed in the previous experiments, and the aldehyde fraction was isolated by chromatography on silica gel. ^2H NMR spectroscopy revealed that ca. 75% of the aldehyde **6** was deuterated at the carbon atom α to the carbonyl group, thus confirming the occurrence of intramolecular hydrogen atom transfer.

(ii) The Reaction of 5-Bromo-3-*tert*-butylpentanal and of 5-Bromo-4-*tert*-butylpentanal with Bu_3SnH. Scheme IV shows the steps believed to be involved in the reactions of **11** and **17** with Bu_3SnH. Each of the isomeric ω-formylalkyl radicals gives rise to the same two cycloalkyloxy radicals, which can then undergo β-scission along two possible routes to return to either of the carbon-centered radicals. Hence, treatment of either **11** or **17** with stannane gives the same six products.

The unsubstituted formylbutyl radical has been observed[9b] to undergo a 1,5 hydrogen migration to give an acyl radical. On the reasonable assumption that substituted radicals will behave similarly Scheme IV includes such steps. Due to the complexity of this scheme, a complete kinetic treatment is not practicable. However, the situation can be simplified if consideration is limited to high stannane concentrations. Under such conditions, the β-scission of the substituted cyclopentyloxy radicals will be slow compared with the donation of hydrogen from stannane, i.e., the cyclization of the ω-formylalkyl radicals will be essentially irreversible. For the reduction of **11**, the usual steady-state treatment yields eqs 6 and 7, where

$$\frac{[12]+[13]}{[29]} = \frac{k_{CH}}{k_5}[Bu_3SnH] + \frac{k_8}{k_5}\cdot\frac{1}{(\alpha+1)} \quad (6)$$

$$\frac{[12]+[13]}{[21]} = \frac{k_{CH}}{k_4}[Bu_3SnH] + \frac{k_8}{k_4}\cdot\frac{1}{(\alpha+1)} \quad (7)$$

α is the ratio of the rate for decarbonylation of the acyl radical to the rate for hydrogen abstraction from stannane, i.e., $\alpha = k_{-CO}/(k'_{CH}[Bu_3SnH])$. If the decarbonylation of the acyl radical is slow by comparison with hydrogen abstraction from stannane,[20,22] then eqs 6 and 7 reduce approximately to the linear eqs 6a and 7a.

$$\frac{[12]+[13]}{[20]} = \frac{k_{CH}}{k_5}[Bu_3SnH] + \frac{k_8}{k_5} \quad (6a)$$

$$\frac{[12]+[13]}{[21]} = \frac{k_{CH}}{k_4}[Bu_3SnH] + \frac{k_8}{k_4} \quad (7a)$$

Figure 3 shows the experimentally measured ratios ([12] + [13])/[20] and ([12] + [13])/[21] versus the stannane concentration, for the reaction of **11** with Bu_3SnH. From Table II it is clear that the diastereoselectivity of the cyclization is very close to 1:1; hence, the two ratios plotted in Figure 3 fall on a common line. Furthermore, it can be seen that at high stannane concentrations (>1 M) the curves are linear, indicating that the rate of decarbonylation is slow compared with the rate of hydrogen abstraction from stannane. Standard linear regression of this portion of Figure 3 gave the rate constants for cyclization, namely $k_4 = k_5 = 2.9 \times 10^7\ s^{-1}$ at 80 °C. Treatment of the data in this way also gave an estimate of the rate constant for the 1,5 hydrogen migration; $k_8 = 1.4 \times 10^7\ s^{-1}$ at 80 °C.

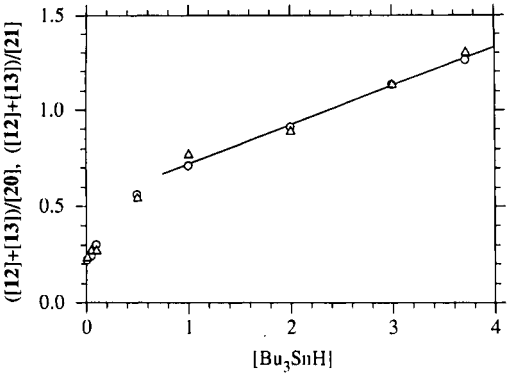


Figure 3. Data from the reaction of **11** with [Bu_3SnH]. Circles show ([12] + [13])/[21] vs [Bu_3SnH]; triangles show ([12] + [13])/[20] vs [Bu_3SnH]. Solid line represents eq 6a.

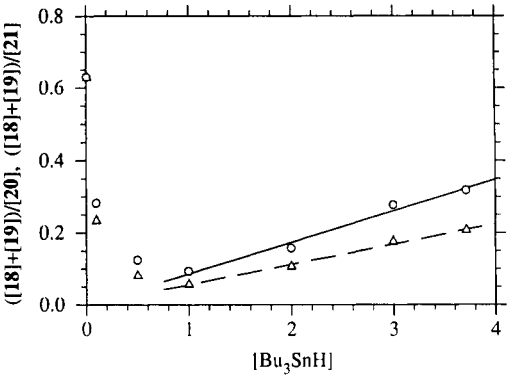


Figure 4. Data from the reaction of **17** with [Bu_3SnH]. Circles show ([18] + [19])/[21] vs [Bu_3SnH]; triangles show ([18] + [19])/[20] vs [Bu_3SnH]. Broken line represents eq 8; solid line represents eq 9.

Figure 4 shows the ratios ([18] + [19])/[20] and ([18] + [19])/[21], plotted as a function of stannane concentration, for the reaction of **17** with [Bu_3SnH]. Again it can be seen that at high concentrations of stannane the curves are linear. Kinetic analysis as before gives the linear eqs 8 and 9. Linear regression analysis of the linear section

$$\frac{[18]+[19]}{[20]} = \frac{k_{CH}}{k_7}[Bu_3SnH] + \frac{k_9}{k_7} \quad (8)$$

$$\frac{[18]+[19]}{[21]} = \frac{k_{CH}}{k_6}[Bu_3SnH] + \frac{k_9}{k_6} \quad (9)$$

of the curves in Figure 4 gives the cyclization rate constants; $k_6 = 7.8 \times 10^7\ s^{-1}$ and $k_7 = 1.2 \times 10^8\ s^{-1}$ at 80 °C. The regression lines of Figure 4 pass through the origin, thus indicating that the 1,5 hydrogen migration rate constant k_9 is small by comparison with the rate constants for cyclization, k_6 and k_7. Within the accuracy of these experiments it is not possible to estimate a value for k_9.

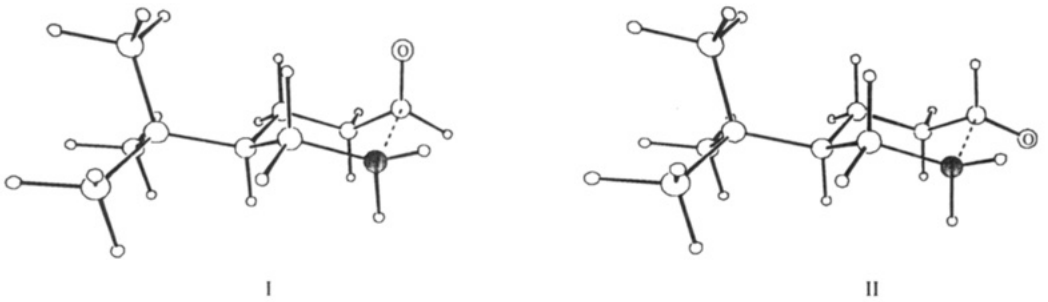
(iii) The Diastereoselectivity of Cyclization. Figure 2 shows the diastereoselectivity of the cyclization of bromo aldehyde **4** as a function of stannane concentration. At stannane concentrations higher than 0.25 M, the trans/cis ratio reaches a constant value of ca. 1.2. Under these conditions, the cyclohexyloxy radicals abstract hydrogen from stannane more rapidly than they undergo β-scission. Consequently, the trans/cis ratio of the isolated cycloalkanols reflects the rate constant ratio k_2/k_1.

The trans/cis ratio increases markedly at very low stannane concentrations. Under these conditions hydrogen atom transfer does not compete effectively with ring clo-

(20) There appears to be no rate measurement in the literature for the reaction RCO• + $Bu_3SnH \rightarrow$ RCHO + Bu_3Sn•; however, the decarbonylation rates of acyl radicals are quite low. The decarbonylation rate constants for *t*BuCO• and *i*PrCO• are $5.2 \times 10^4\ s^{-1}$ and $3.9 \times 10^3\ s^{-1}$, respectively, in benzene at 313 K.[21] The rate constants for decarbonylation of MeCO• and *n*PrCO• have been shown to be $\ll 3.9 \times 10^3\ s^{-1}$.[21]

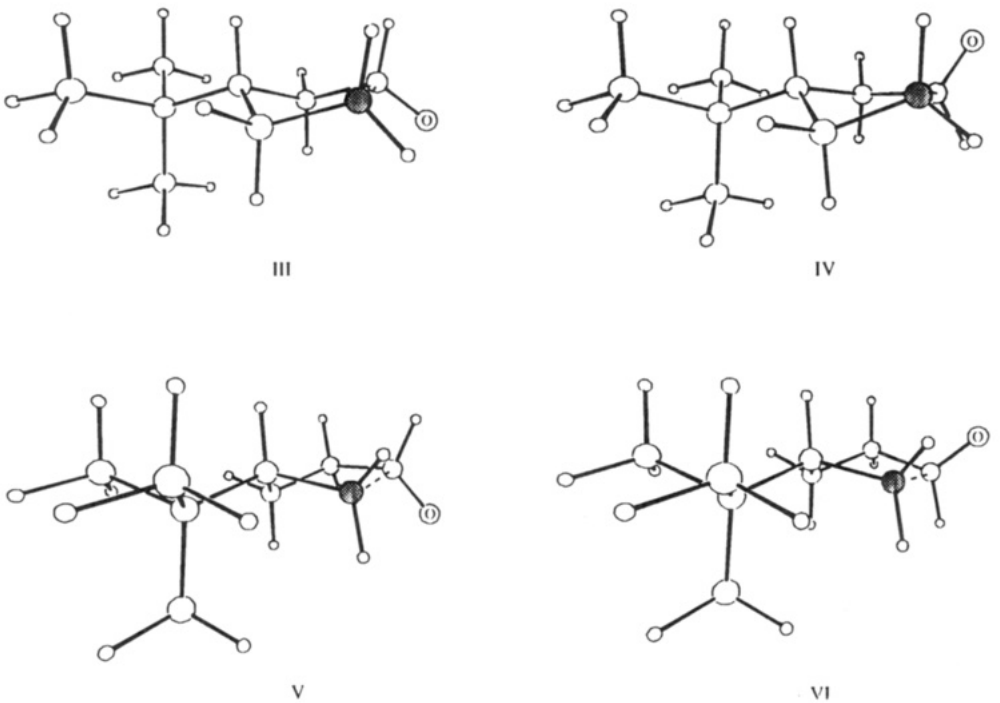
(21) Perkins, M. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1974**, 297.

(22) Product analysis by GC showed no peak that could be attributed to 2,2,3-trimethylpentane, the product of decarbonylation.



I II

Figure 5. Transition structures for the cyclization of the 3-*tert*-butyl-5-formylpentyl radical: I represents the cis transition structure, II represents the trans transition structure. (The radical center is shaded.)



III IV V VI

Figure 6. Transition structures for the cyclization of the *tert*-butyl-substituted 4-formylbutyl radicals: III and IV represent the *cis*- and *trans*-3-*tert*-butyl-4-formylbutyl transition structures, respectively; V and VI represent the *cis*- and *trans*-2-*tert*-butyl-4-formylbutyl transition structures, respectively. (The radical center is shaded.)

sure and ring opening. Consequently, the cyclohexyloxy and ω-formylalkyl radicals approach thermodynamic equilibrium, while the trans/cis ratio of isolated cyclohexanols approaches the value $k_2k_{-1}/(k_1k_{-2})$. The equilibrium constant calculated from the measured rate constants has a value of ca. 3.2. This indicates that the difference between the free energies of *cis*- and *trans*-(3-*tert*-butylcyclohexyl)oxy radicals is ca. 0.8 kcal/mol, in favor of trans. Molecular mechanics calculations indicate the difference between the strain energies of the *cis*- and *trans*-cyclohexyloxy radicals to be ca. 0.7 kcal/mol, in good agreement with the experimentally measured value.

The *tert*-butyl-substituted ω-formylbutyl radicals exhibit similar behavior. At high stannane concentrations (>0.5 M), reaction of **17** with [Bu_3SnH] gives cyclopentanols with a trans/cis ratio of 1.5 corresponding to k_7/k_6. At very low concentrations of stannane, the trans/cis ratio approaches the equilibrium value of 1.0, thus indicating that the *cis*- and *trans*-(2-*tert*-butylcyclopentyl)oxy radicals are of equal free energies. Molecular mechanics calculations indicate that the difference between the strain energies of these diastereoisomeric cyclopentyloxy radicals is <0.05 kcal/mol in agreement with the experimental result.

Cyclization of **11** gives cyclopentanols with a cis/trans ratio of 1.0 regardless of the stannane concentration. At very low concentrations of stannane, the reaction is dominated by thermodynamic control and so the trans/cis ratio is 1.0. As expected under these conditions the product distribution is almost identical with that for the cyclization of **17** (see the entries in Tables II and III corresponding to 0.01 M Bu_3SnH). At high stannane concentrations, the trans/cis ratio is also 1.0 indicating that the two modes of cyclization proceed at the same rate, i.e., $k_4 = k_5$.

Although the thermodynamic ratio of diasteroisomeric products can be predicted by MM2 calculations, it is more difficult to estimate the kinetic ratio. For the analogous alkenyl systems, the differences in strain energies of the transition states calculated by the MNDO–MM2 method afford reliable indicators of the kinetic cis/trans ratio of products.[4,5] We have used the same approach for the cyclization of ω-formylalkyl radicals with mixed results.

In a previous paper[9b] the transition structure for the cyclization of the formylbutyl radical was calculated using the AM1–UHF method. The results gave the distance between the radical center and the carbonyl atom of 1.92 Å. The same distance was assigned to the newly forming bond when the strain energies of the transition structures for ring closure of the 3-*tert*-butyl-5-formylpentyl radical was calculated by the MM2 method. The results for the geometries shown in Figure 5 indicate the difference between the strain energies of the diasteroisomeric transition structures to be 0.45 kcal/mol, in reasonable agreement

Table IV. Relative Energies of the Transition Structures for the Cyclization of Various ω-Formylalkyl Radicals

radical	$(E^{\ddagger}_{trans} - E^{\ddagger}_{cis})_{calc}$[a,b]	$(E^{\ddagger}_{trans} - E^{\ddagger}_{cis})_{exptl}$[b]	(trans/cis)$_{calc}$	(trans/cis)$_{exptl}$
3-*tert*-butyl-5-formylpentyl	−0.45	−0.15	(66:34)	(55:45)
2-*tert*-butyl-4-formylbutyl	−1.25	−0.30	(86:14)	(60:40)
3-*tert*-(butyl-4-formylbutyl	+1.15	0.00	(16:84)	(50:50)

[a] The distance between the radical center and the carbonyl carbon atom was fixed as 1.92 Å. [b] ±0.05 kcal/mol.

with the experimental data (Table IV).

However, an equally satisfactory correspondence between theory and experiment was not observed when similar calculations were performed on substituted formylbutyl radicals. The results given in Table IV show that in these systems the calculations overestimate the diastereoselectivity of cyclization. When the length of the forming bond was fixed at a shorter distance than 1.92 Å, the correlation between experiment and theory was improved. However, close correspondence was only achieved when the new bond distance was fixed at 1.6 Å. Although the more endoergonic cyclizations of substituted formylbutyl radicals would be expected to have later transition states than those of the less endoergonic homologous formylpentyl radicals, the bond distance of 1.6 Å which is only 0.1 Å longer than that of a fully formed carbon–carbon bond, seems unreasonably short.

In general, if a ω-formylalkyl radical cyclizes with a preference for one diastereoisomer then the direction of the preference can be calculated by the AM1–MM2 method. However, the observed stereoselectivity is lower than that predicted. Clearly, more accurate methods must be employed if a better correspondence between theory and experiment is to be achieved.

(iv) The Influence of the *tert*-Butyl Group on the Rates of Cyclization and β-Scission. The rate constant for cyclization of the unsubstituted formylpentyl radical is 1.0×10^6 s^{-1} at 80 °C,[9b] whereas the sum of the rate constants ($k_1 + k_2$) for cyclization of the 3-*tert*-butyl-5-formylpentyl radical is 2.2×10^7 s^{-1} at 80 °C. This indicates that the presence of the *tert*-butyl group gives about a 20-fold acceleration of the cyclization step. Similarly, the rate constant for the cyclization of the unsubstituted formylbutyl radical is 8.7×10^5 s^{-1} at 80 °C while the total cyclization rate constants for the 2-*tert*-butyl-4-formylbutyl ($k_6 + k_7$) and 3-*tert*-butyl-4-formylbutyl radical ($k_4 + k_5$) are 2.0×10^8 s^{-1} and 5.8×10^7 s^{-1}, respectively, at 80 °C. Thus, substitution of a *tert*-butyl group at the 3-position of the formylbutyl radical increases the cyclization rate by a factor of 67 while similar substitution at C-2 increases it by a factor of 230.

The *tert*-butyl group also increases the rate of 1,5-hydrogen migration. The rate constant for this process in the unsubstituted formylbutyl radical has been measured as 1.5×10^5 s^{-1} at 80 °C,[9b] whereas the value measured for the 3-*tert*-butyl-4-formylbutyl radical was estimated to be 1.4×10^7 s^{-1} at 80 °C. 1,5-Hydrogen atom transfer in the 3-*tert*-butyl-5-formylpentyl radical was also found to be fast; $k_3 = 5.9 \times 10^6$ s^{-1} at 80 °C.

The rates of β-scission of the cyclohexyloxy radicals are retarded by substitution. The unsubstituted radical undergoes β-scission with a rate constant of 2.0×10^7 at 80 °C whereas in the *cis*- and *trans*-(4-*tert*-butylcyclohexyl)oxy radicals β-scission occurs with rate constants of 8.2×10^6 and 3.1×10^6 s^{-1}, respectively, at 80 °C. The faster rate of β-scission for the cis isomer reflects the steric strain associated with the oxygen atom occupying an axial position. Although values for the β-scission rates of the *cis*- and *trans*-(3-*tert*-butylcyclopentyl)oxy radicals cannot be obtained, we can deduce that these rates are also retarded by substitution. Since β-scission occurs to a negligible extent (<5%) at stannane concentrations above 1 M, an upper limit of 3.5×10^7 s^{-1} for the β-scission of the (3-*tert*-butylcyclopentyl)oxy radicals at 80 °C can be set if $k_{CH} = 6.6 \times 10^8$ s^{-1} at 80 °C. This is much lower than the known value of 8.5×10^8 s^{-1} for the unsubstituted cyclopentyloxy radical at that temperature.[9b]

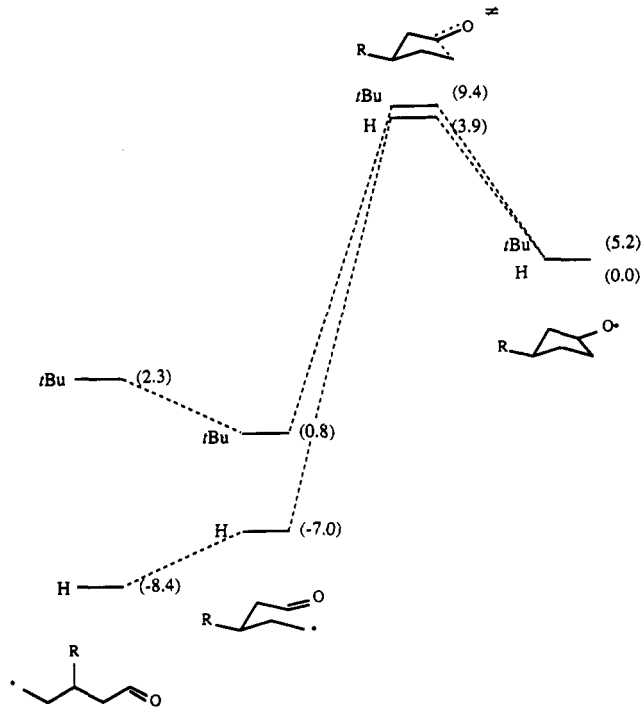


Figure 7. Relative MM2 energies of various conformations and transition structures of 4-formylbutyl and 3-*tert*-butyl-4-formylbutyl radicals. The values in parentheses are the calculated energies (kcal/mol) relative to the cyclopentyloxy radical. The energy levels of the *tert*-butyl-substituted radicals have been offset by 5.2 kcal/mol so that the energy levels of the substituted cyclopentyloxy radicals are superimposed.

The influence of the *tert*-butyl group on the rates of cyclization of β-scission is consistent with Allinger's[23] interpretation of the Thorpe–Ingold effect according to which substitution of an acyclic system creates more new gauche interactions than the same substitution in the cyclic form. Such substitution therefore lowers the enthalpy difference between linear and cyclic alkanes.

The effect of *tert*-butyl substitution on the 4-formylbutyl radical is shown in Figure 7. The energy difference between the substituted and unsubstituted cyclopentyloxy radicals is 5.2 kcal/mol, whereas the energy difference between the 4-formylbutyl and the substituted formylbutyl radical is 10.7 kcal/mol. Hence, substitution decreases the energy difference between the open-chain carbon-centered radical and the cycloalkoxy radical. Figure 7 also shows that substitution destabilizes the chair conformation of the carbon-centered radical to a lesser extent than it destabilizes the open-chain conformation. Thus, the substituted radical prefers the chair over the open-chain conformation; this is the reverse of the situation for the unsubstituted formylbutyl radical.

The MM2 calculations (Figure 7) also show that substitution destabilizes the chair conformation of the for-

(23) Allinger, N. C.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.

mylbutyl radical more than it destabilizes the chair transition structure. Therefore, the activation energy for the cyclization should decrease upon substitution of the radical. This is consistent with experimental observation, viz. the 3-*tert*-butyl-4-formylbutyl radical undergoes cyclization at a much faster rate than the unsubstituted 4-formylbutyl radical. Similarly, Figure 7 shows that the calculated activation energy for the β-scission of the substituted cyclopentyloxy radical is slightly higher than that of the unsubstituted cyclopentyloxy radical. Experimental observation also suggests that the rate of β-scission of the cyclopentyloxy radical is retarded by substitution.

Summary

The stereochemical outcome of the cyclizations of *tert*-butyl-substituted ω-formylbutyl and ω-formylpentyl radicals is dependent on the stannane concentrations employed. At high concentrations, the cis/trans ratio of cyclized products is kinetically controlled. At low concentrations, the radicals start to approach an equilibrium and thus the cis/trans ratio is controlled by the thermodynamic stability of the cycloalkyloxy radicals. MM2 calculations can predict the relative energies of the cycloalkyloxy radicals and hence the thermodynamic ratio of the cyclized products can be estimated. MM2 calculations of the energies of the transition structures can also predict the stereochemical preference of the reaction; however, such calculations overestimate the trans/cis ratio of the cyclized products.

Experimental Section

Nuclear magnetic resonance spectra were recorded on either a Varian XL-200 or a Gemini 300 spectrometer. All spectra were measured in $CDCl_3$ solvent and chemical shifts are quoted as ppm relative to TMS. ^{13}C multiplicities were determined by either DEPT or APT pulse sequences. Analysis by gas chromatography was performed on a Varian 3400 with a 25-m, 0.25-mm i.d. phenyl methyl silicone capillary column; the response of the flame ionization detector was calibrated with authentic samples. 4-*tert*-Butylcyclohexanone, 4-*tert*-butylcyclohexanol, and Bu_3SnH were purchased from Aldrich. The purity of the Bu_3SnH and Bu_3SnD[19] was in each case >95% as determined by hydrogen evolution from dichloroacetic acid. The purity (>98%) of all new compounds was established by gas chromatography.

Reactions of 4, 11, and 17 with Bu_3SnH. In a typical experiment, a vial fitted with a Teflon-surfaced rubber septum was charged with 1.00 mL of a benzene solution of Bu_3SnH. It was then sealed, the contents were frozen in liquid nitrogen, and the vial was evacuated and filled with nitrogen via a needle through the septum. The sample was then immersed in a thermostated bath (±1 °C). After 15 min, the desired amount of benzene solution containing **4**, **11**, or **17** and 0.05 molar equiv (with respect to Bu_3SnH) of AIBN was injected to start the reaction. After 30–40 min the vials were cooled and the contents were analyzed by gas chromatography.

Synthesis of Bromo Aldehydes and Reaction Products. Methyl 4-(1′,1′-Dimethylethyl)-6-hydroxyhexanoate (1). 5-(1′,1′-Dimethylethyl)-2-oxepanone[10] (2.00 g, 12 mmol) was refluxed in methanol (100 mL) containing *p*-toluenesulfonic acid (50 mg) for 60 min. The solution was then poured onto ice and extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with saturated $NaHCO_3$ (2 × 50 mL), dried, and evaporated to give the hydroxy ester **1** (2.28 g, 96%) as a colorless oil: bp 150 °C (1 mmHg); ^1H NMR (300 MHz) δ 3.69 (3 H, s), 3.65 (2 H, t, J = 7 Hz), 2.38 (2 H, m), 1.96 (1 H, br s), 1.82 (2 H, m), 1.39 (1 H, m), 1.29 (1 H, m), 1.02 (1 H, m), 0.88 (9 H, s); ^{13}C NMR (75.5 MHz) δ 175.06 (s), 62.49 (t), 51.41 (q), 43.94 (d), 33.92 (t), 33.65 (t), 27.27 (3 × q), 26.13 (t); IR (film) 3400, 1730 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.53; H, 10.92.

Methyl 6-Bromo-4-(1′,1′-dimethylethyl)hexanoate (2). The hydroxy ester **1** (2.00 g, 9.9 mmol) and carbon tetrabromide (7.0 g, 21 mmol) were dissolved in ether (50 mL). Triphenylphosphine (5.5 g, 21 mmol) was added to the stirred solution, and stirring was continued for 3 h. The suspension was then filtered and evaporated, and the residue was chromatographed on silica gel to give the bromo ester **2** (1.83 g, 70%) as a colorless oil: bp 150 °C (0.3 mmHg); ^1H NMR (300 MHz) δ 3.69 (3 H, s), 3.42 (2 H, m), 2.38 (2 H, m), 2.04 (1 H, m), 1.87 (1 H, m), 1.62 (1 H, m), 1.36 (1 H, m), 1.07 (1 H, m), 0.90 (9 H, s); ^{13}C NMR (50.1 MHz) δ 173.77 (s), 51.42 (q), 46.90 (d), 34.84 (t), 33.87 (t), 33.35 (t), 27.45 (3 × q), 21.11 (t); IR (film) 1740 cm^{-1}. Anal. Calcd for $C_{11}H_{21}BrO_2$: C, 49.82; H, 7.98. Found: C, 50.14; H, 8.21.

6-Bromo-4-(1′,1′-dimethylethyl)hexanol (3). The bromo ester **2** (0.90 g, 3.4 mmol) in dry ether (10 mL) was added to a stirred solution of lithium aluminium hydride (120 mg, 3.2 mmol) in dry ether (20 mL) at 10 °C; stirring was continued at this temperature for 20 min. Water (3 mL) was then added, and the suspension was stirred at room temperature for a further 10 min. The suspension was extracted with dichloromethane (2 × 30 mL), and the organic phase was dried and evaporated to give the bromo alcohol **3** (0.67 g, 82%) as a colorless oil: bp 145 °C (0.5 mmHg); ^1H NMR (300 MHz) δ 3.65 (2 H, t, J = 6 Hz), 3.44 (2 H, m), 2.05 (1 H, m), 1.80 (1 H, br s), 1.62 (4 H, m), 1.09 (2 H, m), 0.89 (9 H, s); ^{13}C NMR (50.1 MHz) δ 62.43 (t), 47.31 (d), 35.07 (t), 33.61 (t), 32.47 (t), 27.39 (3 × q), 26.81 (t); IR (film) 3350 cm^{-1}. Anal. Calcd for $C_{10}H_{21}BrO$: C, 50.64; H, 8.92. Found: C, 50.70; H, 9.22.

4-(1′,1′-Dimethylethyl)hexanol (5). The bromo ester **2** (0.90 g, 3.4 mmol) in dry tetrahydrofuran (10 mL) was added to a stirred solution of lithium aluminium hydride (180 mg, 4.8 mmol) in dry tetrahydrofuran (20 mL), and the solution was refluxed for 45 min. Water was then added, and the solution was stirred for a further 10 min. Workup as above gave the alcohol **5** (0.42 g, 78%) as a colorless oil: bp 125 °C (0.6 mmHg); ^1H NMR (300 MHz) δ 3.60 (2 H, t, J = 7 Hz), 2.69 (1 H, br s), 1.64 (1 H, m), 1.52 (3 H, m), 1.08 (3 H, m), 0.92 (3 H, t, J = 7 Hz), 0.88 (9 H, s); ^{13}C NMR (50.1 MHz) δ 63.13 (t), 50.40 (d), 33.87 (s), 33.14 (t), 27.71 (3 × q), 26.78 (t), 23.71 (t), 14.31 (q); IR (film) 3340 cm^{-1}. Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.85; H, 14.01.

6-Bromo-4-(1′,1′-dimethylethyl)hexanal (4). The bromo alcohol **3** (0.60 g, 2.5 mmol) was stirred with PCC (0.60 g, 2.8 mmol) in dichloromethane (25 mL) for 2 h. The suspension was then diluted with ether (25 mL) and passed through a column of Florisil. The eluate was dried and evaporated to give the bromo aldehyde **4** (0.51 g, 87%) as a colorless oil: bp 120 °C (0.3 mmHg); ^1H NMR (200 MHz) δ 9.76 (1 H, t, J = 2 Hz), 3.51 (2 H, m), 2.51 (2 H, m), 2.03 (1 H, m), 1.81 (1 H, m), 1.65 (1 H, m), 1.32 (1 H, m), 1.10 (1 H, m), 0.88 (9 H, s); ^{13}C NMR (50.1 MHz) δ 201.80 (d), 46.61 (d), 43.57 (t), 34.49 (t), 33.70 (s), 33.44 (t), 27.33 (3 × q), 22.66 (t); IR (film) 2820, 2720, 1725 cm^{-1}. Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.08; H, 8.14. Found: C, 50.72; H, 8.36.

4-(1′,1′-Dimethylethyl)hexanal (6). The alcohol **5** (0.35 g, 2.2 mmol) was stirred with PCC (0.52 g, 2.4 mmol) in dichloromethane (20 mL) for 2 h. Workup as described above gave the aldehyde **6** (0.31 g, 91%) as a colorless oil: bp 80 °C (2 mmHg); ^1H NMR (300 MHz) δ 9.78 (1 H, t, J = 2 Hz), 2.52 (1 H, m), 2.42 (1 H, m), 1.83 (1 H, m), 1.55 (1 H, m), 1.38 (1 H, m), 1.09 (1 H, m), 0.92 (3 H, t, J = 7 Hz), 0.88 (9 H, s), 0.85 (m, 1 H); ^{13}C NMR (75.5 MHz) δ 203.37 (d), 49.84 (d), 44.11 (t), 33.88 (s), 27.57 (3 × q), 23.19 (t), 22.61 (t), 14.12 (q); IR (film) 2810, 2710, 1725 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.59; H, 12.89.

5-Bromo-3-(1′,1′-dimethylethyl)pentanol (10). The diol[12] **9** (6.00 g, 38 mmol) and carbon tetrabromide (13.0 g, 39 mmol) were dissolved in ether (150 mL). Triphenylphosphine (10.0 g, 38 mmol) was added to the stirred solution, and stirring was continued for 3 h. The suspension was then filtered and evaporated, and the residue was chromatographed on silica gel. Elution with dichloromethane/pentane (25:75) gave 1,5-dibromo-3-(1′,1′-dimethylethyl)pentane[12a] (3.1 g, 29%). Further elution with dichloromethane gave the bromo alcohol **10** (1.61 g, 19%) as a colorless oil: bp 150 °C (0.9 mmHg); ^1H NMR (200 MHz) δ 3.65 (2 H, m), 3.46 (2 H, m), 2.50 (1 H, br s), 2.12 (1 H, m), 1.81 (1 H, m), 1.63 (1 H, m), 1.36 (1 H, m), 1.22 (1 H, m), 0.88 (9 H, s); ^{13}C NMR (75.5 MHz) δ 62.37 (t), 43.63 (d), 35.07 (t), 34.02 (t), 33.80 (t), 33.55 (s), 27.42 (3 × q); IR (film) 3350 cm^{-1}. Anal. Calcd for $C_9H_{19}BrO$: C, 48.44; H, 8.58. Found: C, 48.12; H, 8.66.

3-(1′,1′-Dimethylethyl)pentanol (12). The bromo alcohol **10** (0.50 g, 2.2 mmol) was refluxed with Bu_3SnH (0.6 mL, 2.2

mmol) in benzene (20 mL), under nitrogen and in the presence of AIBN (10 mg), for 30 min. The solution was then cooled, the solvent evaporated, and the residue chromatographed on silica gel to give the alcohol **12** (214 mg, 68%) as a colorless oil: bp 110 °C (0.5 mmHg); ^{1}H NMR (200 MHz) δ 3.65 (2 H, m), 2.63 (1 H, br s), 1.7 (2 H, m), 1.3 (2 H, m), 1.1 (1 H, m), 0.92 (3 H, t, J = 7 Hz), 0.88 (9 H, s); ^{13}C NMR (50.1 MHz) δ 63.16 (t), 46.75 (d), 34.75 (t), 33.64 (s), 27.57 (3 × q), 23.89 (t), 13.99 (q); IR (film) 3350 cm^{-1}. Anal. Calcd for $C_9H_{20}O$: C, 74.94; H, 13.97. Found: C, 74.96; H, 13.68.

5-Bromo-3-(1′,1′-dimethylethyl)pentanal (11). The bromo alcohol **10** (1.00 g, 4.5 mmol) was stirred with PCC (1.10 g, 5.1 mmol) in dichloromethane (40 mL) for 2 h. Workup, as described for the preparation of **4**, gave the bromo aldehyde **11** (0.81 g, 82%) as a colorless oil: bp 85 °C (0.3 mmHg); ^{1}H NMR (200 MHz) δ 9.82 (1 H, t, J = 1 Hz), 3.41 (2 H, m), 2.60 (1 H, ddd, J = 2, 7, 18 Hz), 2.19 (1 H, ddd, J = 2, 6, 18 Hz), 1.9 (1 H, m), 1.6 (1 H, m), 1.2 (1 H, m), 0.90 (9 H, s); ^{13}C NMR (50.1 MHz) δ 202.35 (d), 45.61 (t), 41.20 (d), 34.72 (t), 33.32 (s), 32.32 (t), 27.39 (3 × q); IR (film) 2710, 1730 cm^{-1}. Anal. Calcd for $C_9H_{17}BrO$: C, 48.88; H, 7.75. Found: C, 49.24; H, 8.04.

3-(1′,1′-Dimethylethyl)pentanal (13). The alcohol **12** (150 mg, 1.0 mmol) was stirred with PCC (250 mg, 1.2 mmol) in dichloromethane (10 mL) for 2 h. Workup, as described for the preparation of **4**, gave the aldehyde **13** (127 mg, 86%) as a colorless oil: bp 115 °C (20 mmHg); ^{1}H NMR (300 MHz) δ 9.81 (1 H, t, J = 2 Hz), 2.51 (1 H, ddd, J = 2, 5, 17 Hz), 2.21 (1 H, ddd, J = 2, 6, 17 Hz), 1.64 (1 H, m), 1.34 (1 H, m), 1.08 (1 H, m), 0.92 (3 H, t, J = 7 Hz), 0.88 (9 H, s); ^{13}C NMR (75.5 MHz) δ 204.26 (d), 46.61 (d), 45.45 (t), 33.46 (s), 27.42 (3 × q), 23.47 (t), 13.37 (q); IR (film) 2720, 1725 cm^{-1}. Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 75.86; H, 12.69.

5-(Methoxycarbonyl)-3-(1′,1′-dimethylethyl)hexanecarboxylic Acid (14). The hydroxy ester **1** (2.00 g, 9.9 mmol) was dissolved in acetone (50 mL). Jones reagent was added dropwise until the orange color persisted. The solution was then diluted with water (50 mL) and extracted with ether (3 × 50 mL). The organic extracts were washed with water (2 × 50 mL), dried, and evaporated to give the acid–ester **14** (1.97 g, 92%) as a colorless oil: bp 200 °C (0.5 mmHg); ^{1}H NMR (300 MHz) δ 3.67 (3 H, s), 2.51 (1 H, dd, J = 6, 21 Hz), 2.35 (2 H, m), 2.10 (1 H, dd, J = 8, 21 Hz), 1.95 (1 H, m), 1.69 (1 H, m), 1.36 (1 H, m), 0.92 (9 H, s); ^{13}C NMR (75.5 MHz) δ 180.16 (s), 173.94 (s), 51.42 (q), 44.07 (d), 35.45 (t), 33.52 (s), 33.06 (t), 27.16 (3 × q), 26.28 (t); IR (film) 3500–2500, 1735, 1705 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.15; H, 9.53.

Methyl 5-Bromo-4-(1′,1′-dimethylethyl)pentanoate (15). The ester–acid **14** (2.00 g, 9.3 mmol) was stirred in oxalyl chloride (10 mL) for 30 min at room temperature. The volatile products were then removed in vacuo to give the acid chloride: IR (film) 1800, 1740 cm^{-1}. The acid chloride, dissolved in carbon tetrachloride (10 mL), was added to a stirred solution of *N*-hydroxypyridine-2-thione sodium salt (1.65 g, 11.1 mmol) and DMAP (100 mg, 0.8 mmol) in a mixture of carbon tetrachloride (20 mL) and bromotrichloromethane (30 mL) at reflux. After 15 min, the reaction mixture was allowed to cool and was washed with water (2 × 50 mL). The organic phase was dried, evaporated, and then chromatographed on silica gel to give **15** (1.70 g, 73%) as a colorless oil: bp 120 °C (0.5 mmHg); ^{1}H NMR δ 3.69 (3 H, s), 3.56 (1 H, dd, J = 4, 11 Hz), 3.38 (1 H, dd, J = 7, 11 Hz), 2.56 (1 H, ddd, J = 5, 11, 16 Hz), 2.35 (1 H, ddd, J = 6, 10, 16 Hz), 2.05 (1 H, m), 1.70 (1 H, m), 1.51 (1 H, m), 0.97 (9 H, s); ^{13}C NMR (75.5 MHz) δ 174.07 (s), 51.37 (q), 49.23 (d), 35.35 (t), 34.23 (s), 33.35 (t), 27.62 (3 × q), 24.56 (t); IR (film) 1740 cm^{-1}. Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C, 48.05; H, 7.33.

5-Bromo-4-(1′,1′-dimethylethyl)pentanol (16). The bromo ester **15** (1.00 g, 4.0 mmol) was reduced to the bromo alcohol **16** (0.84 g, 94%) with lithium aluminium hydride, under the same conditions as those used into convert **2** into **3**: bp 140 °C (0.9 mmHg); ^{1}H NMR (300 MHz) δ 3.67 (2 H, t, J = 6 Hz), 3.63 (1 H, dd, J = 4, 10 Hz), 3.38 (1 H, dd, J = 6, 10 Hz), 2.14 (1 H, br s), 1.76 (1 H, m), 1.61 (2 H, m), 1.49 (1 H, m), 1.42 (1 H, m), 0.95 (9 H, s); ^{13}C NMR (75.5 MHz) δ 62.78 (t), 49.91 (d), 36.38 (t), 34.25 (s), 32.18 (t), 27.76 (3 × q), 25.35 (t); IR (film) 3350 cm^{-1}. Anal. Calcd for $C_9H_{19}BrO$: C, 48.44; H, 8.58. Found: C, 48.28; H, 8.91.

4-(1′,1′-Dimethylethyl)pentanol (18). The bromo ester **15** (0.50 g, 2.0 mmol) was reduced to the alcohol **18** (0.21 g, 73%) with lithium aluminium hydride, under the same conditions as those used to convert **2** into **5**: bp 105 °C (0.6 mmHg); ^{1}H NMR δ 3.61 (2 H, t, J = 7 Hz), 2.68 (1 H, br s), 1.67 (1 H, m), 1.55 (1 H, m), 1.42 (1 H, m), 1.11 (1 H, m), 0.95 (1 H, m), 0.87 (9 H, s), 0.83 (3 H, d, J = 7 Hz); ^{13}C NMR (75.5 MHz) δ 63.09 (t), 42.79 (d), 32.83 (s), 31.68 (t), 27.45 (t), 27.06 (3 × q), 13.92 (q); IR (film) ν_{max} 3340 cm^{-1}. Anal. Calcd for $C_9H_{20}O$: C, 74.94; H, 13.97. Found: C, 75.13; H, 13.76.

5-Bromo-4-(1′,1′-dimethylethyl)pentanal (17). The bromo alcohol **16** (0.75 g, 3.4 mmol) was stirred with PCC (0.88 g, 4.1 mmol) in dichloromethane (25 mL) for 2 h. Workup as described for the preparation of **4** gave the bromo aldehyde **17** (0.66 g, 89%) as a colorless oil: bp 90 °C (0.2 mmHg); ^{1}H NMR (300 MHz) δ 9.81 (1 H, t, J = 1 Hz), 3.62 (1 H, dd, J = 3, 11 Hz), 3.36 (1 H, dd, J = 7, 11 Hz), 2.68 (1 H, m), 2.52 (1 H, m), 1.95 (1 H, m), 1.68 (1 H, m), 1.51 (1 H, m), 0.97 (9 H, s); ^{13}C NMR (75.5 MHz) δ 202.54 (d), 49.40 (d), 43.42 (t), 35.56 (t), 34.40 (s), 27.64 (3 × q), 21.54 (t); IR (film) 2820, 2720, 1730 cm^{-1}. Anal. Calcd for $C_9H_{17}BrO$: C, 48.88; H, 7.75. Found: C, 49.17; H, 8.04.

4-(1′,1′-Dimethylethyl)pentanal (19). The alcohol **18** (150 mg, 1.0 mmol) was stirred with PCC (260 mg, 1.2 mmol) in dichloromethane (10 mL) for 2 h. Workup, as described for the preparation of **4**, gave the aldehyde **19** (117 mg, 79%) as a colorless oil: bp 110 °C (20 mmHg); ^{1}H NMR (300 MHz) δ 9.79 (1 H, t, J = 1 Hz), 2.48 (1 H, m), 2.35 (1 H, m), 1.92 (1 H, m), 1.14 (2 H, m), 0.88 (9 H, s), 0.82 (3 H, d, J = 6 Hz); ^{13}C NMR (75.5 MHz) δ 203.53 (d), 43.01 (t), 42.50 (d), 32.96 (s), 26.99 (3 × q), 23.71 (t), 13.66 (q); IR (film) 2820, 2720, 1755 cm^{-1}. Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 75.83; H, 12.67.

Acknowledgment. One of us (K.D.R.) gratefully acknowledges the receipt of a Postdoctoral Fellowship from the Australian Research Council.