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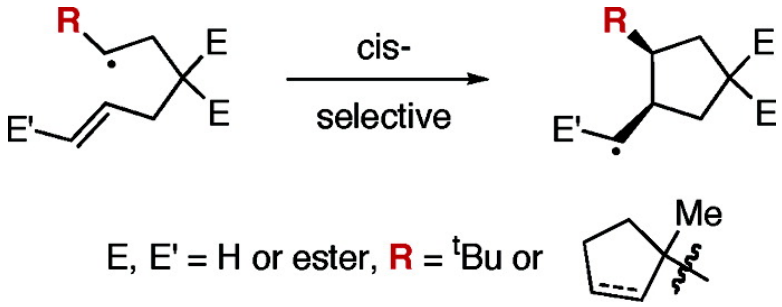
J. Am. Chem. Soc., **2005**, 127 (15), 5518-5527• DOI: 10.1021/ja042595u • Publication Date (Web): 25 March 2005



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Stereochemistry of Hexenyl Radical Cyclizations with *tert*-Butyl and Related Large Groups: Substituent and Temperature Effects

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Abstract: The long held notion that hexenyl radicals bearing large substituents on the radical carbon cyclize to give 1,2-trans-substituted cyclopentanes is experimentally disproved by study of the radical cyclization of an assortment of simple and complex substrates coupled with careful product analysis and rigorous assignment of configurations. X-ray studies and syntheses of authentic samples establish that the published assignments for *cis*- and *trans*-1-*tert*-butyl-2-methylcyclopentane must be reversed. The original assignment based on catalytic hydrogenation of 1-*tert*-butyl-2-methylenecyclopentane was compromised by migration of the double bond prior to hydrogenation. The cyclization of 1-*tert*-butylhexenyl radical is moderately cis selective, and the selectivity is increased by geminal substitution on carbon 3. This selectivity trend is general and extends to relatively complex substrates. It has allowed Ihara to reduce the complexity of an important class of round trip radical cyclizations to make linear triquinanes to the point where two tricyclic products—cis-syn-cis and cis-anti-cis—account for about 80% of the products. However, the further increase in selectivity that was proposed by lowering the temperature is shown to be an artifact of the analysis methods and is not correct. This work solidifies "1,2-cis selectivity" in cyclizations of 1-subsituted hexenyl radicals as one of the most general stereochemical trends in radical cyclizations.

Introduction

Cascade radical cyclizations are powerful reactions for making condensed five-membered carbo- and heterocyclic rings.[1] For reasons of stereocontrol, tricyclic and higher rings are usually constructed by fashioning new rings about at least one preexisting ring.[2] However, strategies for making polycycles from acyclic precursors[3] are especially direct and would be appealing if stereochemical issues could be resolved.[4]

Our model experiments toward the crinipellin class of tetraquinanes[5] summarized in Figure 1[6] are illustrative of both the power and the problems associated with a direct synthesis of polyquinanes from acyclic precursors by a "round trip radical cyclization"[7] strategy. Generation of the radical from **1** can be followed by zero, one, two, or three radical cyclizations, with the third cyclization completing the "round trip". In the experiment, six major products were formed, including four tricyclic products (**2a**,**b**; **3a**,**b**) and two bicyclic ones (**4a**,**b**). Due to the complexity of the mixture, these products could not be isolated individually and were instead characterized by GC-MS and ^{13}C NMR spectroscopy on isotopically labeled samples.[6]

All six of the products of this reaction arise as a consequence of the lack of stereoselectivity in the second cyclization (**6** → **7**). Four stereoisomers of **7** are possible because of face selectivity with respect to the existing stereocenter and simple diastereoselection (cis/trans selectivity). The cis-isomers of **7** close rapidly to form less strained (cis-syn-cis and cis-anti-cis) tricycloundecanes **2a**,**b**, while trans isomers of **7** close more slowly to give more strained trans-fused tricycloundecanes **3a**,**b**. Direct reduction of **7**-*trans* by tin hydride competes with these

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(1) (a) Dhimane, A. L.; Fensterbank, L.; Malacria, M. In *Radicals in Organic Synthesis*; Renard, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 350−382. (b) Aïssa, C.; Delouvrie, B.; Dhimané, A. L.; Fensterbank, L.; Malacria, M. *Pure Appl. Chem.* **2000**, *72*, 1605−1613. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4, pp 715−831.
(2) Curran, D. P. In *Advances in Free Radical Chemisty*; Tanner, D. D., Ed.; JAI: Greewich, CT, 1990; Vol. 1, pp 121−157.
(3) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893−5901.
(4) Review on stereochemistry of radical cyclizations: Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, Germany, 1996; Chapter 2, pp 23−115.
(5) (a) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590−602. (b) Mehta, G.; Rao, K. S.; Reddy, M. S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 693−700. (c) Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272−9284.
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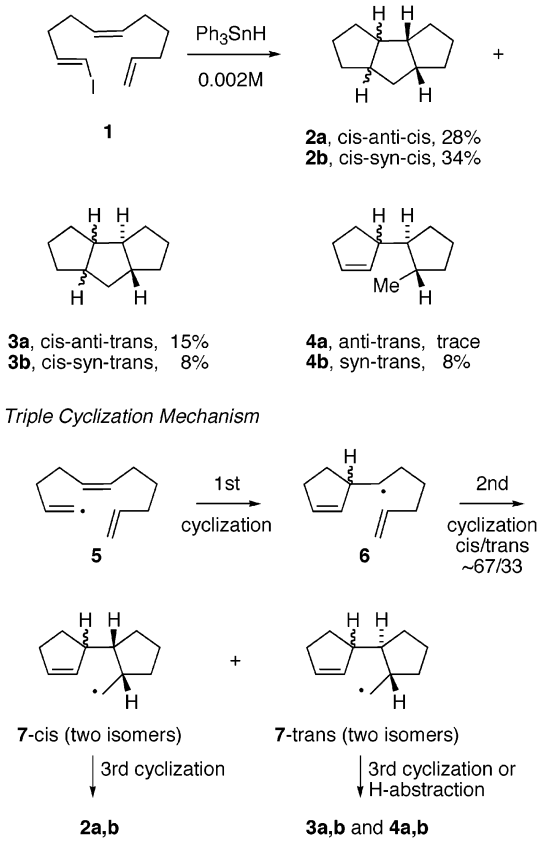


Figure 1. Round trip radical cyclization generating up to three rings but with multiple isomers formed.

cyclizations, so each trans radical gives one tricyclic (**3**) and one bicyclic (**4**) product in a ratio that depends on the tin hydride concentration. About 67% of the radicals partition through cis cyclization pathways (to give **2a**,**b**) and 33% partition through trans cyclization pathways (to give **3a**,**b** and **4a**,**b**). Clearly, methods are needed to control both face selectivity and cis/trans selectivity in these types of reactions.

In 2001, Takasu, Ihara, and co-workers reported what appeared to be a method to control the cis/trans selectivity in related cyclizations through substituent and temperature effects (eq 1).[8] Cyclization of substrate **8a** under standard conditions with tributyltin hydride at 80 °C was reported to form cis-syn-cis isomer **9a**, cis-anti-cis isomer **10a**, and "other diastereomers" in a ratio of 36/28/36. While the structure of **9a** was fully assigned, the configuration of the ester-bearing center (C7) in **10a** was not assigned, and the structures of the "other diastereomers" were not discussed. By analogy to the cyclization of **1**, we considered the possibility that the other diastereomers were trans-isomers **11a** (if so, then the cis/trans partitioning at 80 °C is 64/36). Alternatively, the other diastereomers could also be stereoisomers of **9a** and **10a** at C7. Intriguingly, conducting the cyclization at room temperature was reported to result in the disappearance of the other diastereomers and provide only **9a** and **10a** in 83% yield in a 57/43 ratio (cis/trans partitioning, 100/0). Similar temperature effects were reported with tris(trimethylsilyl)silane.

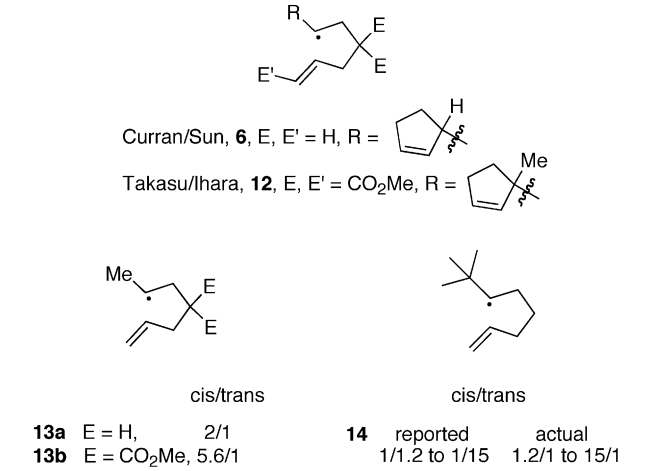
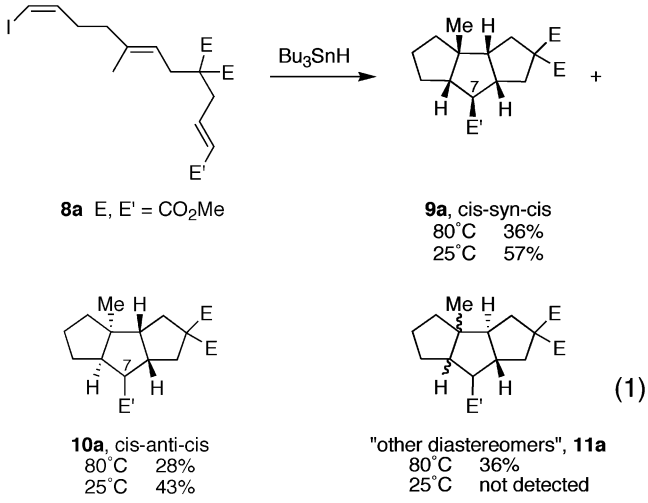


Figure 2. Comparison of radicals in the second cyclization with each other (top) and with literature benchmarks (bottom).



Direct comparison of Ihara's results[8] with ours[6] is complicated because the substrates are materially different in three ways, all of which could affect the key second cyclization. Radical **12** (Figure 2) has a malonate in the connecting chain (E = CO_2Me), a very large (*tert*-butyl-like) substituent on the radical (R = 1-(1-methylcyclopent-2-enyl)), and an ester on the radical acceptor (E′ = CO_2Me). In comparison, E and E′ are H in the parent radical **6** and R is a secondary group and not a tertiary one. While the combined effect of these non-hydrogen substituents is difficult to access, a number of benchmarks in simpler systems are available. There are many examples of radical cyclizations with malonates in the connecting chain,[9] and these are accelerated by the Thorpe−Ingold effect.[10] Typical cyclizations of radicals bearing small or medium groups on the radical carbon have low to moderate cis-selectivity. This selectivity is increased by the presence of a malonate, as shown by examples **13a**,**b** in Figure 2.[11] The presence of an ester (E′) on the radical

(8) Takasu, K.; Maiti, S.; Katsumata, A.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 2157−2160.
(9) (a) De Riggi, I.; Nouguier, R.; Surzur, J. M.; Lesueur, C.; Bertrand, M.; Jaime, C.; Virgili, A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 229−235. (b) Feldman, K. S.; Berven, H. M.; Weinreb, P. H. *J. Am. Chem. Soc.* **1993**, *115*, 11364−11369.
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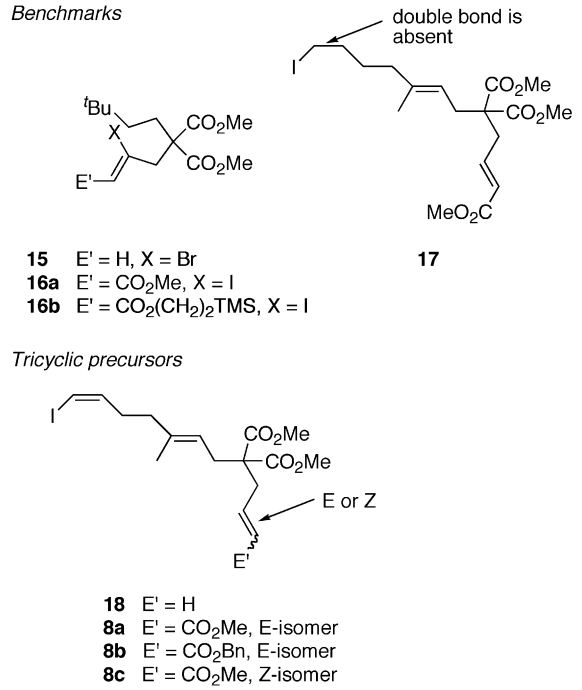

Figure 3. Radical cyclization substrates.

acceptor accelerates the cyclization,[12] but it is not expected to dramatically alter the stereoselectivity.

Beckwith and co-workers reported that the cyclization of the *tert*-butyl-substituted hexenyl radical **14** (Figure 2) is an exception to the broad trend of 1,2-cis selectivity and provides the trans isomer as the major product.[13] Intriguingly, they also reported that there was a significant temperature dependence on the cyclization with cis/trans ratios changing from 47/53 at 90 °C to 7/93 at −33 °C. If one momentarily accepts the assumption that Ihara's "other diastereomers" are trans isomers, then both Ihara's and Beckwith's radicals with related large substituents exhibit powerful temperature dependences but for opposite stereoisomers.

To unravel these puzzling temperature and substituent effects, we have conducted a series of tricyclizations related to Ihara's and extended the study of benchmark systems related to Beckwith's. During this study, we have identified problems with the prior work with respect to configuration assignment and product analysis. We now report that Ihara's radical cyclization is cis selective but does not show a significant temperature effect while the cyclization of the 1-*tert*-butylhexenyl radical **14** is also cis-selective and not trans-selective as reported. These revised results and assignments along with our new results provide a more comprehensive understanding of how very large substituents affect stereoselectivity in radical cyclizations, both alone and in combination with other substituents.

Results

Substrate Selection and Synthesis. Figure 3 shows the substrates used for radical cyclizations in this study. These compounds were all prepared by straightforward malonate alkylations, and details of their syntheses and the associated characterization data are contained in the Supporting Information.

Substrates **15** and **16a** are benchmarks to assess the effect of the malonate on cyclization of a *tert*-butyl-substituted hexenyl radical, while substrate **16b** allows a structural relay between products of the prior two cyclizations for rigorous assignment of configuration. For synthetic convenience, we rely on radical translocation (1,5-hydrogen atom transfer) to generate the radical of interest in this series. Substrate **17** is very closely related to Ihara's—it lacks only a crucial double bond of the vinyl iodide that prevents the round trip from being completed. This greatly simplifies the analysis because no tricyclic products are possible, and there are only two bicyclic products (cis and trans). Substrate **8a** is Ihara's precursor, while **18** is the analogue lacking the ester on the radical acceptor (E′ = H) and benzyl ester **8b** is the structural relay substrate in this series. Finally, *Z*-unsaturated esters have been shown to give higher stereoselectivity in radical cyclizations than *E*-isomers.[4,14] So to assess the effect of alkene geometry, we also prepared **8c**, which is the *Z* α,β-unsaturated ester isomer of **8a**.

Cyclizations of Benchmark Substrates. The cyclizations of the benchmark substrates were all conducted under similar conditions, and the results of these cyclizations are summarized in Table 1. For reactions at 80 °C, a mixture of the cyclization precursor (0.1 mmol), tributyltin hydride (0.12 mmol), and AIBN (0.05 mmol) in benzene (50 mL, 2 mM with respect to the precursor) was heated at reflux for 4 h. After cooling and solvent evaporation, the product mixture was subjected to rapid chromatography to remove most of the tin and provide a crude product mixture. This mixture was subjected to GC and NMR analysis to determine product ratios. The two methods gave very similar ratios, and only the GC results are recorded in the table. Combined isolated yields of cis/trans mixtures of cyclic products were obtained by careful chromatography of the crude mixture. Room-temperature (25 °C) reactions were conducted by a similar procedure with initiation by Et_3B[15] (0.05 mmol) in place of AIBN.

Each of the four benchmark substrates in Table 1 exhibited a moderate level of selectivity in favor of the cis stereoisomer at 80 °C (76/24−80/20, see entries 2, 4, 6, and 8). The directly reduced product (not shown) was not observed in the reductions of **15**, **16a**, or **16b**, but it was observed in small amounts (∼5%) by GC in the reduction of **17**. Reactions conducted at room temperature resulted in detectable but small increases in selectivity (1−5%) for the cis isomer (entries 3, 5, 7). We conclude that the temperature dependence of these cyclizations is not very significant. The level of selectivity (about (3−4)/1) is strikingly similar to that of the methyl-substituted malonyl radical **13b** (5/1; see Figure 2) despite the presence of the large groups on the radical-bearing carbon.

Assignment of Configurations of Benchmark Products. We were not able to preparatively separate the cis and trans isomers of any of the benchmark products in Table 1, and overlapping of resonances in the ^{1}H NMR spectra coupled with concerns about ambiguities in interpretations of NOE experiments led us to pursue a rigorous approach to configuration

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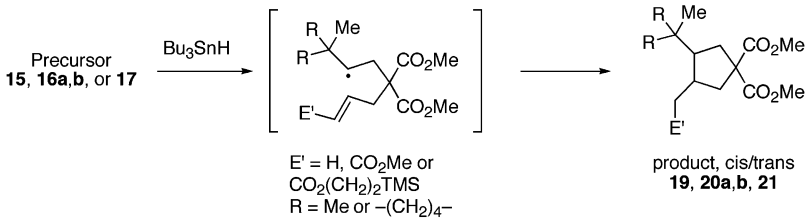
Table 1. Radical Cyclization Products from Benchmark Substrates

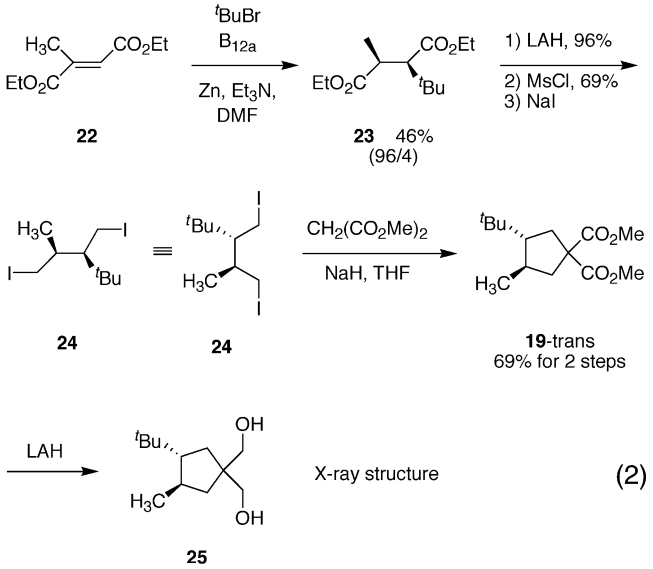


entry	precursor	R	E′	*T* (°C)[a]	prod	cis/trans[b]	% yield[c]
1	**15**	CH_3	H	25	19		
2	**15**	CH_3	H	80	19	76/24	54
3	**16a**	CH_3	CO_2Me	25	20a	83/17	45
4	**16a**	CH_3	CO_2Me	80	20a	78/22	52
5	**16b**	CH_3	$CO_2(CH_2)_2TMS$	25	20b	79/21	35
6	**16b**	CH_3	$CO_2(CH_2)_2TMS$	80	20b	77/23	67
7	**17**	$-(CH_2)_4-$	CO_2Me	25	21	81/19	62
8	**17**	$-(CH_2)_4-$	CO_2Me	80	21	80/20	69

[a] Initiation at 80 °C with AIBN and at 25 °C with Et_3B/O_2. [b] Raw GC ratio. [c] Isolated yield of a cis/trans mixture after flash chromatography.

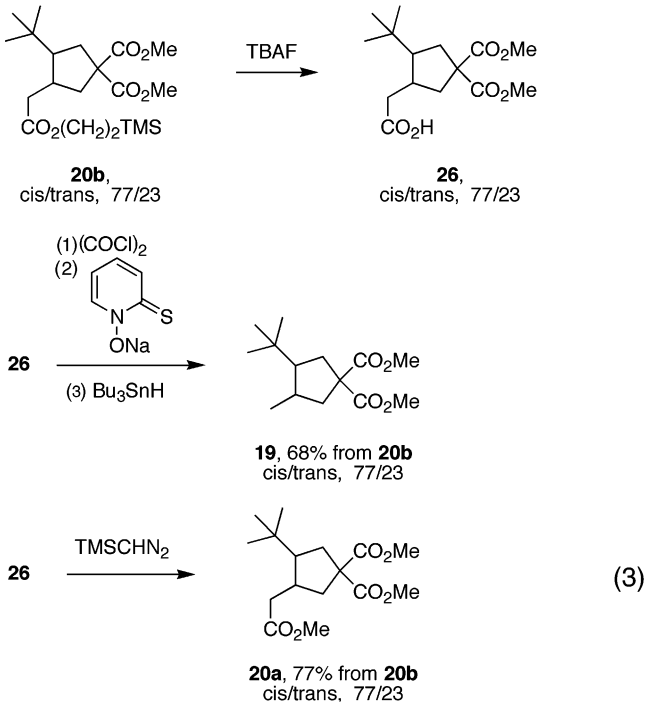
assignment by correlation. Equation 2 shows the synthesis of an authentic sample of **19**-*trans*. Reductive addition of *tert*-butyl bromide to diethyl mesaconate **22** mediated by vitamin B_{12a} and Zn provided known syn-diester **23** (96/4 ratio, syn/anti) in 46% isolated yield.[16] Reduction of the diester to the diol, bis-mesylation, Finkelstein reaction to make the diiodide **24**, and finally double malonate alkylation provided an authentic sample of **19**-*trans*. This was identical by NMR spectroscopy and GC co-injection to the minor product from the cyclization of **15** (Table 1, entry 2). To rigorously confirm the configuration assignment from the radical addition, we reduced diester **19**-*trans* to the diol **25**. This was crystallized by slow vapor-phase diffusion of hexane into an ethyl acetate solution of **25**, and the crystal structure was solved (see Supporting Information).

With the configuration of **19** secure, we assigned configurations to **20a**-*cis*/*trans* with the relay products **20b**. Desilylation of a 77/23 mixture of **20b**-*cis*/*trans* to give **26** followed by Barton reductive decarboxylation provided a 77/23 mixture of **19**-*cis*/*trans* (eq 3). Correspondingly, treatment of **26** with (trimethylsilyl)diazomethane ($(TMS)CHN_2$) gave a 77/23 mixture of **20a**-*cis*/*trans*. This proves that the major products in the cyclizations of all three of these substrates are cis. Accordingly, we assigned cis configuration to the major product **21**-*cis* of the interrupted substrate **17** by analogy.



(2)

Comparing the results of Table 1 (cis selective) with those reported for the parent *tert*-butyl-substituted radical **14**[13] (Figure 2, trans selective) suggests that the malonyl group enforces a reversal of stereoselectivity. This conclusion is not evidently inconsistent with literature observations in related malonyl radicals. However, we were discomfited by a comparison of our spectroscopic data with the published data of **28**—the resonances assigned to **28**-*cis* (eq 4) fit the pattern of our trans isomers while those assigned to **28**-*trans* fit the pattern of our cis isomers.[17] This lack of pattern matching suggested that the assignments of **28**-*cis*/*trans* might be incorrect.



(3)

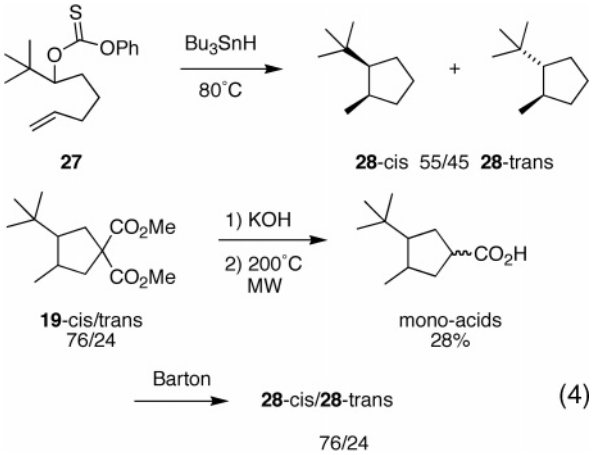
(16) Erdmann, P.; Schäfer, J.; Springer, R.; Zeitz, H.-G.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 638−644.

Table 2. Product Ratios in Cyclizations of Triesters **8a**,**b**

					% composition					
entry	substrate	reducing agent concn (mM)	reducing agent	*T* (°C)	cis-syn-cis **9a**	cis-anti-cis **10a**	cis-anti-trans **29a**	cis-syn-trans **30a**	selectivity (cis/trans)	yield (%)
1	**8a**	syringe pump[a]	Bu_3SnH	25	48	38	8	6	86/14	nd
2	**8a**	syringe pump[a]	Bu_3SnH	80	42	35	9	14	77/23	nd
3	**8a**	2	Bu_3SnH	25	47	39	8	6	86/14	52, 69[b]
4	**8a**	2	Bu_3SnH	80	44	34	9	13	78/22	50, 70[b]
5	**8a**	2	Ph_3SnH	25	44	35	7	14	79/21	48
6	**8a**	2	Ph_3SnH	80	47	37	9	7	77/23	46
7	**8b**	2	Bu_3SnH	25	47	40	6	7	87/13	50
8	**8b**	2	Bu_3SnH	80	42	35	15	8	77/23	35
9	**8c**[c]	2	Bu_3SnH	80	40	51	8	1	91/09	62

[a] A 24 mM solution of reducing agent is added to a 2 mM solution of the iodide over 3 h. [b] Yield determined using octadecane as an internal GC standard. [c] *Z*-unsaturated ester isomer of **8a**. Nd = Not determined.

To revisit the assignment of the products of the radical cyclization of the *tert*-butyl-substituted hexenyl radical **14**, we first prepared thionocarbonate **27** and cyclized it according to the published procedure[13] at 66 °C to provide a 55/45 ratio (GC analysis) of stereoisomers **28** (eq 4). This result matches the 55/45 ratio reported at that temperature, and the matching of spectral data shows that the major products are the same. Next, hydrolysis and microwave-assisted decarboxylation of a 76/24 ratio of **19**-*cis*/*trans* provided a mixture of mono acids in 28% overall yield over two steps. This was not analyzed but was directly subjected to Barton decarboxylation to provide a 76/24 ratio of **28**-*cis*/*trans*. The major products from both of these exercises were identical, as were the minor ones. Accordingly, we conclude that the literature assignments of **28**-*cis* and **28**-*trans* must be reversed. This means that, like most other types of radicals, the cyclization of the parent *tert*-butyl-substituted hexenyl radical **14** is also moderately cis-selective (not trans selective).



Cyclizations of Round Trip Radical Substrates. With a good understanding of both new and existing benchmark cyclizations, we next moved to careful study of the round trip radical cyclization substrates **8a**−**c** and **18**. Our results for cyclizations of Ihara's substrate **8a** under varying conditions are shown in Figure 4 and Table 2. In a repeat of one of Ihara's key experiments, we reduced **8a** with Bu_3SnH at 80 °C (Figures 4 and 5 and Table 2, entry 4). A relatively complex mixture resulted. Flash chromatography was not helpful in separating the mixture, but GC analysis provided a powerful tool.

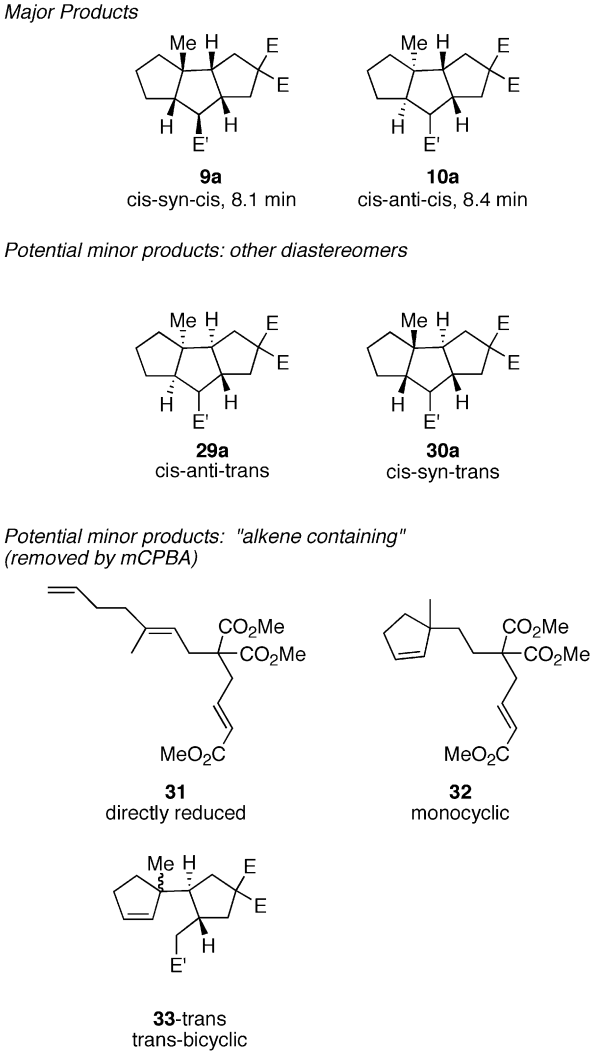


Figure 4. Structure assignments for cyclization products from Ihara's precursor **8a** (E, E′ = CO_2Me).

After exposure of the crude reaction mixture to a standard DBU workup[18] to remove most of the tin, GC analysis of the crude product provided the chromatogram shown in Figure 5 (top). In addition to the two major peaks at 8.1 and 8.4 min (45% and 35%, respectively), there were at least six minor peaks in the chromatogram, one of which (7.6 min, 3%) was readily

(17) After structural correction, the relative chemical shifts of the methyl and *tert*-butyl resonances exhibit the same trends for **19** and **28**: **28**-*cis*, 0.93 (s, 9 H), 0.85 (d, 3 H, J = 7.1 Hz); **28**-*trans* 0.97 (d, 3 H, J = 6.8 Hz), 0.84 (s, 9 H); **19**-*cis*, 0.96 (s, 9 H), 0.91 (d, 3 H); **19**-*trans*, 1.00 (d, 3 H, J = 7 Hz), 0.88 (s, 9 H). In the cis isomer, the methyl doublet resonates upfield from the *tert*-butyl singlet, while in the trans isomer the positions of these resonances are reversed.

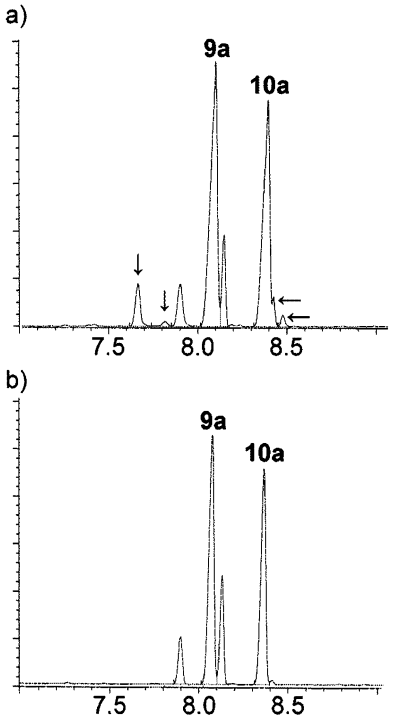


Figure 5. GC chromatograms of cyclization products from **8a** (E, E′ = CO_2Me) before (a) and after (b) mCPBA treatment.

identified as the directly reduced product **31** (Figure 4). We tentatively assigned the two major products as cis-syn-cis **9a** and cis-anti-cis **10a** on the basis of Ihara's work. We later confirmed that assignment (see below) and showed that the peak with the shorter retention time corresponded to the cis-syn-cis isomer **9a**. Proton NMR spectra of this crude product showed small resonances in the alkene region in addition to those belonging to the directly reduced product **31**. We tentatively attribute these resonances to monocyclized product **32** and doubly cyclized products **33**-*trans* in which the second and third stages of the round trip journey were interrupted by tin hydride reduction.

To remove the doubly cyclized and other alkene-containing products from the tricyclic products (non-alkene-containing), we exposed the crude product mixture to *meta*-chloroperoxybenzoic acid (mCPBA) with the expectation that alkene-containing products would be epoxidized and thereby rendered more polar. Flash chromatography of the resulting mixture then provided a nonpolar fraction (52% isolated yield) whose NMR spectrum exhibited no epoxide or alkene resonances and whose GC chromatogram is shown in Figure 5 (bottom). Several of the minor peaks are gone, and the remaining four peaks (two major and two minor) all exhibited virtually identical mass spectra in a GCMS experiment, suggesting that they are all tricyclic.

Ihara reported that the major product **9a** from this cyclization was partially separable from the others, and he kindly provided spectra of this product. We were not able to preparatively separate **9a** by column chromatography; however, in a complementary experiment conducted in association with Prof. M. Newcomb and R. E. P. Chandrasena, we were able to isolate by preparative GC a fraction enriched to the level of 93% in cis-syn-cis isomer **9a** and confirm Ihara's structural proposal by a combination of 2D NMR experiments to assign resonances followed by NOE experiments. At the same time, we were able to confirm that the peak at 8.4 min corresponds to the cis-anti-cis isomer **10a** by recording NMR spectra of the other prep GC fraction enriched in that isomer.

The assignments of the two minor isomers as cis-anti-trans **29a** and cis-syn-trans **30a** are tentative because neither was isolated in pure enough form for detailed characterization. We considered the possibility that one or both of these compounds could have no trans ring fusion and instead be stereoisomers of **9a** and **10a** at the ester-bearing C7; however, the relay experiments with substrate **8b** lacking that ester suggest that this is not the case (see below).

With a good analytical method in hand, we then conducted a series of cyclizations with Bu_3SnH and Ph_3SnH at 80 and 25 °C to determine the temperature dependence on the stereoselectivity in cyclizations of methyl ester **8a** (Table 2, entries 1−6) and benzyl ester **8b** (entries 7, 8). Each crude product was treated with mCPBA, chromatographed to remove alkene-derived (epoxide) products, and then subjected to GC analysis. Eight reactions were conducted under diverse conditions varying concentration (syringe pump addition or fixed 0.0024 M in tin hydride), reagent (Bu_3SnH, Ph_3SnH), and temperature (80 °C, AIBN initiation; 25 °C, Et_3B initiation). The ratios of the four products formed in these experiments hardly varied at all as shown in Table 2. Also shown are the cis/trans ratios of the second cyclization calculated by dividing the sum of the two major cis/cis products (structures firmly assigned) by the sum of the two minor cis/trans products (structures tentatively assigned). Consistent with the results in Table 1, but inconsistent with the results of Ihara, there is a very small temperature dependence on these ratios with the average cis/trans ratio being 78/22 at 80 °C and 86/14 at 25 °C. As a caveat, these ratios may be slightly overstated since the minor products removed in the mCPBA step are likely to result predominately or even exclusively from trans cyclization. Because the total of these products is relatively small (<10%) and because the cis/trans selectivities are quite similar to the benchmark cases and are not very concentration dependent, we conclude that this error is small.

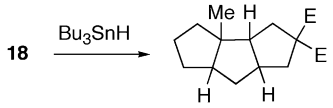
Results for cyclization of the benzyl ester relay substrate at 25 and 80 °C are shown in Table 2, entries 7 and 8, and are very similar to each other and to those of the methyl ester; the products were assigned by relay (see below). Figures S1 and S2 in the Supporting Information show GC chromatograms for these products before and after mCPBA treatment. Finally, cyclization of the *Z*-isomer **8c** at 80 °C gave the same four tricyclic products as *E*-isomer **8a** but in an improved cis/trans ratio of 91/9.

In short, we have confirmed the formation of Ihara's two major products and located two candidates for the "other diastereomers". But at the same time we have shown that there is no large temperature dependence on stereoselectivity for this reaction. These results call into question Ihara's identification of other diastereomers.

To study the effect of ester on the radical acceptor, we conducted radical cyclizations of **18** in a manner similar to that for **8a**,**b**. As before, several minor peaks (<10% total) were eliminated by treatment of the crude product with mCPBA (see

(18) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157.

Table 3. Product Ratios in Cyclizations of Diesters 18



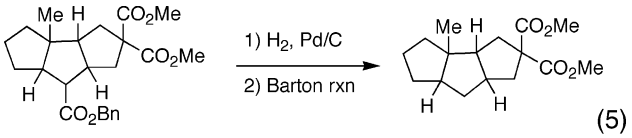
34, cis-syn-cis
35, cis-anti-cis
36, cis-anti-trans
37, cis-syn-trans

				% composition					
entry	reducing agent concn (mM)	reducing agent	*T* (°C)	cis-syn-cis **34**	cis-anti-cis **35**	cis-anti-trans **36**	cis-syn-trans **37**	selectivity (cis/trans)	yield (%)
1	syringe pump[a−c]	Ph_3SnH	25	43	39	15	3	82/18	nd
2	syringe pump[a,b]	Ph_3SnH	80	40	36	19	5	76/24	nd
3	syringe pump[a]	Bu_3SnH	25	44	39	11	6	83/17	51
4	syringe pump[a]	Bu_3SnH	80	42	38	14	6	80/20	52
5	2[c]	Bu_3SnH	25	40	42	13	5	82/18	nd
6	2	Bu_3SnH	80	40	37	19	4	77/23	nd
7	2	$(TMS)_3SiH$	25	43	38	12	7	81/19	nd
8	2	$(TMS)_3SiH$	80	41	41	11	7	82/18	nd
9	2	Ph_3SnH	25	47	36	13	6	83/17	nd
10	2	Ph_3SnH	80	45	38	14	3	83/17	nd

[a] A 24 mM solution of reducing agent is added to a 2 mM solution of the iodide over 3 h. [b] Ihara's protocol. [c] Required the addition of 1 equiv of PPh_3 to avoid exclusive formation of a directly reduced product.

GC chromatograms in Supporting Information, Figures S3 and S4), leaving two major peaks and two minor peaks, whose ratios are shown in Table 3. Again, extensive variation of concentration, reducing reagent (now including TTMSH), and temperature had little effect on the product ratio.

The products from these two series of experiments were correlated through the benzyl ester relay substrate **8b** (eq 5). Hydrogenation of a mixture of **9b**/**10b**/**29b**/**30b** provided an acid mixture, which was converted to the methyl ester by $TMSCHN_2$ (not shown). GC injection of this sample with the product from the radical cyclization of **8a** showed the same four products in about the same ratios. Barton decarboxylation of this acid mixture (eq 5) provides a mixture of four products **34**−**37**; the three major products were identical by GC with those produced from the cyclization of **18**.[19]



(5)

mixture of four isomers
9b, **10b**, **29b**, **30b**

mixture of four isomers
34, **35**, **36**, **37**

Revisiting Prior Work To Identify Problems. We have shown that a key structure assignment by Beckwith and coworkers is incorrect[13] and that a large temperature dependence on a radical cyclization proposed by Takasu and Ihara[8] does not exist. As stated in the Introduction, it was easily possible at the outset to accommodate the incorrect assignment and nonexistent temperature effect together within the framework of existing results to make a plausible picture; indeed, this accommodation was a premise of our work. Ironically, separate accommodation of one error without the other seemed less plausible (though certainly not impossible).

Beckwith used the cis/trans assignments of **28** to support two sets of force field calculations (Houk/Spellmeyer[20] and Beckwith/Schiesser), both of which predicted a trans-selective cyclization of radical **14**. This calculated trans selectivity was supported by hydrogenation and NOE experiments. In the hydrogenation approach to configuration assignment, alkene **38** was reduced to give a 95/5 mixture of products (Figure 6). The major product was assigned as cis by adopting the hypothesis that hydrogenation occurs trans to the *tert*-butyl group. Molander and Winterfeld have also posited cis-selectivities in related systems.[21]

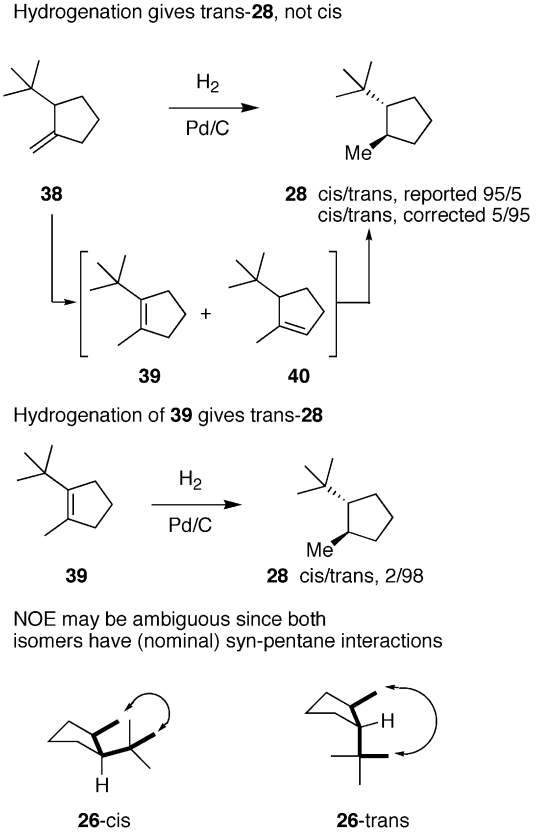


Figure 6. Revisiting the stereochemical assignment of **28**.

To shed light on the hydrogenation stereoselectivity issue, we prepared **38** and repeated its hydrogenation with palladium

(19) One minor product peak from this experiment did not match the GC peak for the very minor product **37** formed in the reduction of **18**. This suggests either that the structure of **37** might be wrong or that **10a** and **11a** might be isomers at the ester bearing carbon rather than the ring fusion. Since the structures of all these minor product are tentative and since **37** was only formed in trace amounts, we decided not to pursue this issue further.

(20) (a) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−974. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941.

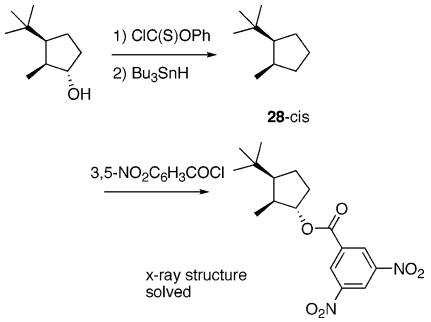
(21) Molander, G.; Winterfeld, J. *J. Organomet. Chem.* **1996**, *524*, 275−279.

on carbon. Indeed, we ultimately observed a 95/5 ratio of **28**-*trans*/**28**-*cis*. So the literature ratio for this hydrogenation is correct, but the assumption of cis selectivity is not. Further insight was gained by following the time course of the hydrogenation by GC. Alkene **38** disappeared quickly, and alongside the isomers of **28** were formed two new major products, which we tentatively assigned as isomerized structures **39** and **40**. Isomerizations of hindered double bonds during palladium-catalyzed hydrogenations are well-known.[22] After several hours, the peaks assigned to **39** and **40** disappeared and the 95/5 ratio of **28**-*trans*/*cis* resulted.

Tetrasubstituted alkene **39** is a known compound that was independently synthesized[23,24] and shown to have the same retention time by co-injection with one of the intermediates in the hydrogenation of **38**. Independent hydrogenation of **39** provided a 98/2 ratio of **28**-*trans*/**28**-*cis*. Direct hydrogenation of **39** cannot possibly give **28**-*trans* because such hydrogenations are well-known to be stereospecific for the cis isomer.[25] So **39** must also isomerize prior to hydrogenation. Taken together, these results suggest that **38** (exclusively), **39** (to a large extent), and possibly also **40** isomerize prior to hydrogenation and that this isomerization process determines the trans/cis selectivity. We speculate that disubstituted cyclopentenes (not shown) resulting from further isomerizations of **38**−**40** are the species undergoing hydrogenation and that the trans selectivity is the result of a thermodynamically controlled isomerization. Whatever the case, **38** is not directly hydrogenated, so assumptions about its cis hydrogenation selectivity are probably correct but are certainly not relevant.

NOE experiments showed a 10% enhancement of the *tert*-butyl singlet of the major product of the hydrogenation of **38** when the methyl doublet was irradiated.[13] This was taken as evidence for formation of the cis isomer, yet we now know that **28**-*trans* was used in the experiment. NOE studies on the actual cis isomer (**28**-*cis*) were not reported, presumably because it was not available in pure form. How does the trans isomer exhibit such a large NOE? Figure 6 shows that both cis and trans isomers of this compound have approximate *syn*-pentane interactions. Such interactions should result in healthy NOEs,

(22) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497−3505.
(23) Hupe, E.; Denisenko, D.; Knochel, P. *Tetrahedron* **2003**, *59*, 9187−9198.
(24) The alcohol shown below is formed by hydroboration of **40**, and the stereoselectivity of the hydroboration (addition trans to the *tert*-butyl group) suggests that the Beckwith assumption of (kinetic) addition of hydrogen trans to the *tert*-butyl group is reasonable. To confirm the configuration of this alcohol, we converted it to the thionocarbonate followed by Barton−McCombie deoxygentation. This gave **28**-*cis* as the only product. Further, the crystal structure of the derived 3,5-dinitrobezoate ester was also solved. See the Supporting Information for details.



(25) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 8, pp 417−442.

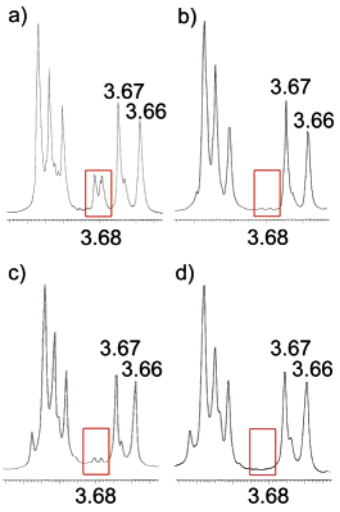


Figure 7. Comparison of methyl group resonances in ^{1}H NMR spectra ($CDCl_3$) of reaction products of cyclization of **8a**: (a) Ihara's spectrum, Bu_3SnH, 80 °C; (b) Ihara's spectrum, Bu_3SnH, 25 °C; (c) this work, Bu_3SnH, 80 °C, prior to mCPBA treatment; (d) this work, Bu_3SnH, 80 °C, after mCPBA treatment. Spectra similar to (c) and (d) were obtained when conducting reactions at 25 °C. Boxes highlight the key resonances at 3.68 ppm that are assigned to methyl esters of alkene-containing products.

and therefore, NOE experiments might not be a reliable method to differentiate these isomers.

It is difficult to see how Beckwith and co-workers could have assigned structures correctly without substantial additional experimentation—even in hindsight, a view of their calculations and the experiments seems to suggest that reasonable conclusions were drawn on the basis of the available information.

The problem with Ihara's work, in contrast, turns on analysis: how were the amounts of "other diastereomers" quantitated? Prof. Ihara kindly responded to this question with helpful data that were not in the original paper. The top of Figure 7 shows expansions of the methyl ester regions of two ^{1}H NMR spectra that Ihara provided to us. The left spectrum (a) corresponds to a tin hydride cyclization conducted at 80 °C while the right one (b) corresponds to a similar cyclization at 25 °C. Ihara assigned the signals at 3.67 and 3.66 ppm to one of the three methyl esters of the cis-syn-cis **9a** and cis-anti-cis **10a** products, respectively, and we confirmed this assignment with the enriched samples isolated from the preparative GC separation. Ihara further assigned the signals at about 3.68 ppm to single methyl esters of the "other diastereomers". Product ratios then follow from integration.

New experiments show that this assignment is not correct. The lower part of Figure 7 shows expanded regions of two of our spectra that are qualitatively similar to Ihara's. In our hands, the spectra like that on the left were reliably produced by simply working up the reaction and removing the tin, as Ihara did. These spectra (c) have small amounts of the key resonances that Ihara assigned to "other diastereomers". In contrast, spectra (d) like that on the right are reliably produced by treating the crude reaction products with mCPBA followed by flash chromatography to remove polar products. Accordingly, we conclude the resonances around 3.68 ppm do not belong to "other diastereomers" but instead to constitutional isomers that result from incomplete round trip cyclization—these are the resonances that correspond to the small peaks in the GC that are removed on mCPBA oxidation.

While these experiments add a few more pieces, the puzzle here is not quite complete. We could reliably observe the absence of presence of the small extra methyl ester resonances and GC peaks on the basis of whether the crude product was treated with mCPBA, and these effects did not exhibit a significant temperature dependence. In contrast, Ihara did not treat any crude reactions products with mCPBA and reports that the peaks appear or not as a function of temperature. Thus, we cannot explain this experimental discrepancy between our work and Ihara's.

Nonetheless, the correlation of the minor NMR peaks with the minor GC peaks and the disappearance of all these peaks on mCPBA treatment support our conclusion that these arise from constitutional isomers and not other diastereomers. Further, we have identified and tentatively assigned other diastereomers **29a** and **30a** by GC, and NMR experiments show that they do not have any methyl ester resonances in the region integrated by Ihara. We conclude that NMR integration is simply not up to the task of determining product ratios because there are two major products and at least five minor products, each of which has three nonequivalent methyl esters. Even though the GC analysis is incomplete because we cannot rigorously assign structures to all the minor peaks, it is still much more informative than NMR integration because the GC peaks can be individually classified as tricyclic or not and can be individually integrated.

Calculations. Clearly then, the computational methods employed in the earlier study of Beckwith and Schiesser predict the incorrect stereochemical outcome for the cyclization of **14** and would presumably also fail for other hexenyl radicals bearing bulky substituents at position 1. What is special about these 1-substituted systems such that simple steric arguments fail to compute the correct reaction outcome? To explore this question further, it is necessary to employ computational methods that are designed to provide a more holistic approach to this chemistry. Accordingly, we sought recourse to ab initio and density functional quantum techniques.

Previous work has shown that, without going to very high levels of theory (e.g. G3-RAD),[26] the BH and HLYP (BHLYP, density functional) method provides a very cost-effective computational technique for studying free-radical reactions,[27] while B3LYP often provides poor data for radicals and MP2 calculations are often highly spin contaminated;[25,28] indeed, the MP2/6-311G** calculated transition states for **14** provided $\langle s \rangle$ values approaching unity, while the analogous BHLYP data were typically below 0.82.

Searching for the $C_{10}H_{19}$ potential energy surface at all levels of theory[29] employed in this study, we located four transition states for the cyclization of **14**: *cis-chair* (**41**), *trans-chair* (**42**), *cis-boat* (**43**), and *trans-boat* (**44**), in keeping with the earlier publication by Beckwith and Schiesser.[13] The BHLYP/6-311G** optimized structures (**41**−**44**) are displayed in Figure 8, while the calculated differences in activation energy are listed in Table 4. Full details (Gaussian Archive Entries) are available as Supporting Information.

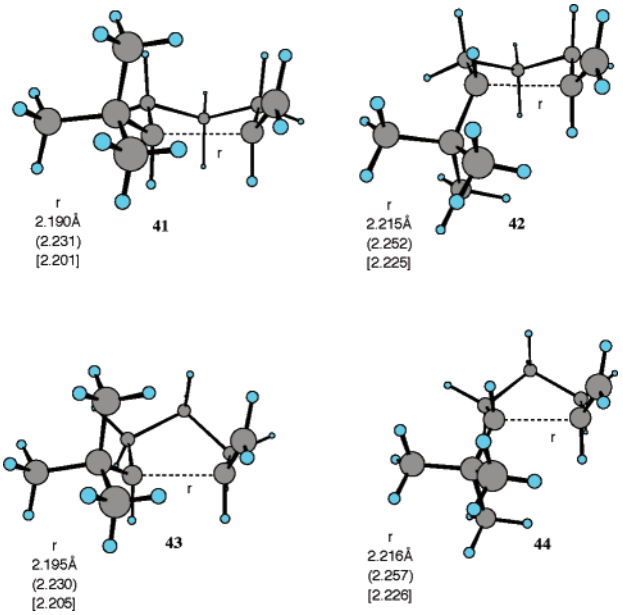


Figure 8. BHLYP/6-311G** optimized transition structures **41**−**44** for cyclization of radical **14**. MP2/6-311G** data are in parentheses, and BHLYP/cc-pVDZ data are in brackets.

Table 4. Calculated Differences in Activation Energy (kJ mol^{-1}) for the Different Modes of Ring-Closure of Radical **14**

entry	method	cis-chair **41**	trans-chair **42**	cis-boat **43**	trans-boat **44**
1	MP2/6-311G**	0	1.1	9.0	4.6
2	BHLYP/6-311G**	0	2.2	12.5	4.5
3	BHLYP/6-311G**+ZPE	0	2.5	12.8	3.8
4	BHLYP/cc-pVDZ	0	2.7	13.4	5.0
5	BHLYP/cc-pVDZ+ZPE	0	3.0	13.5	4.3
6	BHLYP/aug-cc-pVDZ	0	1.5	12.6	4.2

Inspection of Figure 8 reveals the length of the forming C−C bond in each transition state to lie in a narrow range around 2.2 Å, with BHLYP calculations predicting a slightly later transition state in each case, as has been observed previously for other systems. Inspection of Table 4 clearly indicates that higher level quantum calculations do indeed predict the correct stereochemical outcome for the ring-closure of **14**; the *cis-chair* structure **41** is calculated to be the lowest energy transition state at all levels of theory. The magnitude of the preference for the cis mode of cyclization is somewhat underestimated, the largest energy difference of 3.0 kJ mol^{-1} calculated at the BHLYP/cc-pVDZ + ZPE level of theory being some 10 kJ mol^{-1} less than that determined for the ring-closure of **14** in hexane. The cyclization of **14** displays a pronounced solvent dependence, while the calculated data reflect gas-phase chemistry more closely. Alternatively, very accurate data may only be achievable

(26) Gómez-Balderas, R.; Coote, M. L.; Henry, D. J.; Radom, L. *J. Phys. Chem. A* **2004**, *108*, 2874−2883.
(27) Mohr, M.; Zipse, H.; Marx, D.; Parrinello, M. *Phys. Chem. A* **1997**, *101*, 8942−8948.
(28) For examples, see: Morihovitis, T.; Schiesser, C. H.; Skidmore, M. A. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2041−2047.
(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.05; Gaussian, Inc.: Pittsburgh, PA, 2003.

using higher level methods such as G3-RAD. In any case, it would appear that the stereochemical preferences exhibited by hexenyl radicals bearing bulky substituents at position 1 are dictated by electronic as well as steric phenomena because quantum computational techniques are able to correctly predict the outcome of cyclization, while the molecular mechanics techniques used previously are unable to predict the outcome.

Conclusions

This work helps to solidify our understanding of both stereoselectivity and temperature effects in the cyclizations of hexenyl radicals bearing very large substituents on the radical carbon. The long held notion that such cyclizations are trans selective is shown to be incorrect; the cyclization of the 1-*tert*-butylhexenyl radical is moderately cis selective, and the selectivity is increased by geminal substitution on carbon 3. Modern ab initio calculations reproduce this selectivity satisfactorily. This selectivity trend is very general and extends to relatively complex substrates such as **8a**−**c**, **17**, and **18**. It has allowed Ihara to reduce the complexity of round trip radical cyclizations to the point where two tricyclic products—cis-syn-cis and cis-anti-cis—account for about 80% of the products. We further increased this to about 90% by using the corresponding *Z*-α,β-unsaturated ester. However, the increase in selectivity that was proposed by lowering the temperature has been shown to be an artifact of the analysis methods and is not correct.

There have been very few exceptions to the generalization that hexenyl radicals bearing 1-substituents cyclize with cis selectivity. Now there is one fewer.

Acknowledgment. We thank the National Science Foundation for funding this work, and we thank Dr. Steven J. Geib for solving the crystal structures. We thank Prof. M. Ihara for providing copies of key NMR spectra, and we thank Professor M. Newcomb and R. E. P. Chandrasena for the preparative GC purification. Support of the Victorian Institute for Chemical Sciences High Performance Computing Facility is gratefully acknowledged. We dedicate this paper to Professor Keith U. Ingold in honor of his 75th birthday and in celebration of his 50 years at the National Research Council of Canada.

Supporting Information Available: Complete experimental procedures, compound characterization data, and Gaussian Archive entries for all optimized structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA042595U