by these techniques. It is not an exaggeration to say that chemistry indeed holds the key to future progress in this area.

I acknowledge the contributions from my colleagues of the past several years: in the area of resonant nonlinearity, Dr. A. Suna and Prof. E. Hilinski and his group at Florida State University; in the area of nonresonant nonlinearity, Drs. L.-T. Cheng and N. Herron. I thank W. Farneth for his thorough reading of the manuscript and useful suggestions.

Stereochemistry of Intramolecular Free-Radical Cyclization Reactions†

T. V. (BABU) RAJANBABU

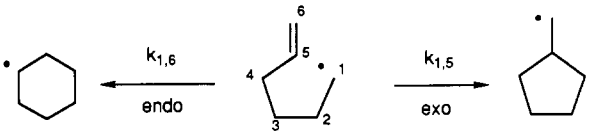
Du Pont Central Research and Development, Experimental Station, P.O. Box 80328, Wilmington, Delaware 19880-0328

Received October 31, 1990 (Revised Manuscript Received February 11, 1991)

Free-radical reactions are ubiquitous in nature. They have been among the most widely used methods for the manufacture of various vinyl polymers for several decades, yet the applications of these reactions for the synthesis of complex organic molecules are of recent origin. Of all the free-radical reactions that have been used for the construction of carbon–carbon bonds,[1] the hex-5-enyl radical cyclization (Scheme I) is the most well-known. The development of this reaction, which was known in the polymer literature since the early 1960s,[2] has followed a traditional course. Following the pioneering synthetic works of Lamb[3] and Julia,[4] several physical organic studies from the laboratories of Walling, Beckwith, and Ingold[5] helped delineate kinetic and thermodynamic parameters for the individual steps of this radical chain process. By the late 1970s synthetic organic chemists realized the power of this method for rapid assembly of architecturally complicated polyfunctional molecules, and a number of elegant syntheses followed.[6-8]

The rapid growth in free-radical synthetic methodology that followed was highlighted by the large number of publications dealing with new methods of generation of the radicals as well as their compatibility with various functional groups and reaction conditions. Application of these developments further enhanced the utility of the hex-5-enyl cyclization. However, the full potential of this reaction was yet to be realized since stereochemistry remained a problem and only limited structural types were accessible by this reaction. The stereochemistry at the newly created centers was predictable in some of these cases, but the origin of the selectivity was not understood. This limitation was rarely addressed in the context of substituted hex-5-enyl radical cyclizations even though Beckwith, in a classic series of papers,[9,10] had laid the foundation for such a study. We undertook a systematic study of these control elements in highly functionalized and synthetically useful systems, and this Account summarizes the significant progress we made in this area. On the basis of our work, we can propose models for transition states which can be used to rationalize the stereochemistry of hex-5-enyl radical cyclizations, including a number of seemingly anomalous results recently reported in the literature. As a corollary, since we can incorporate these

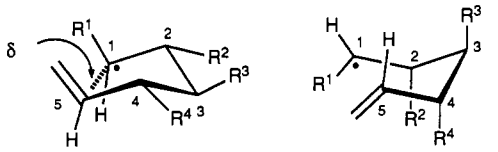
Scheme I
Hex-5-enyl Radical Cyclization[a]



1 2

[a] At 60 °C, $k_{1,5}$ is approximately 10^5–10^6 s^{-1}; $k_{1,5}/k_{1,6} = 50$.

Scheme II
Beckwith's Transition-State Model[a]



3a 3b

[a] For the transition state, $\delta \sim 2.3$ Å. For cyclohexane C_1–C_5, $\delta \sim 2.5$ Å.

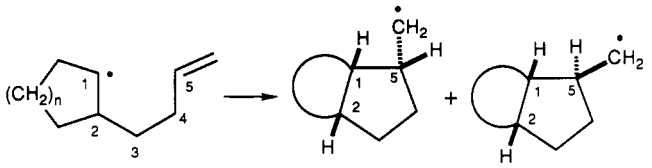
† Dedicated to three outstanding teachers, Professors C. N. Pillai, H. Shechter, and P. C. Varghese.

(1) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: New York, 1986.
(2) Brace, N. O. *J. Am. Chem. Soc.* **1964**, *86*, 523.
(3) Lamb, R. C.; Ayers, P. W.; Toney, M. K. *J. Am. Chem. Soc.* **1963**, *85*, 3483.
(4) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.
(5) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980.
(6) Hart, D. J. *Science* **1984**, *223*, 883.
(7) Curran, D. P. *Synthesis* **1988**, 417, 489.
(8) Stork, G. In *Selectivity-A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Basel, 1984; pp 281.
(9) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
(10) Beckwith, A. L. J.; Easton, J. C.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.

Dr. T. V. RajanBabu did his undergraduate studies at Kerala University and the Indian Institute of Technology, Madras. In 1978, following his graduate studies at the Ohio State University with Professor Harold Shechter, he joined Professor R. B. Woodward's group at Harvard as a research fellow. Since 1980 he has been a member of the research staff at Du Pont Central Research and Development in Wilmington, DE. His principal research interests have been free-radical and organometallic chemistry with an emphasis on their applications in organic synthesis. His work on the nucleophilic catalysis of reactions of enol silanes led to several novel carbon–carbon bond forming reactions with applications in group transfer polymerization and nucleophilic aromatic substitution methods.

0001-4842/91/0124-0139$02.50/0

Scheme III
Stereochemistry in Bicyclic Systems

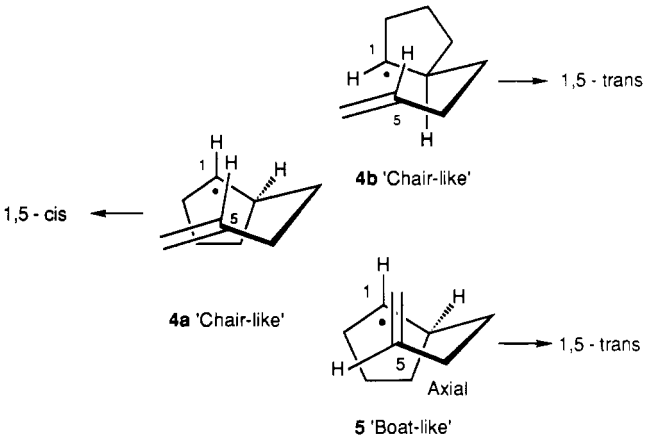


	1,2 - cis; 1,5 - cis	1,2 - cis; 1,5 - trans
n=1 cyclopentyl	8.3	1
n=2 cyclohexyl	3.5	1

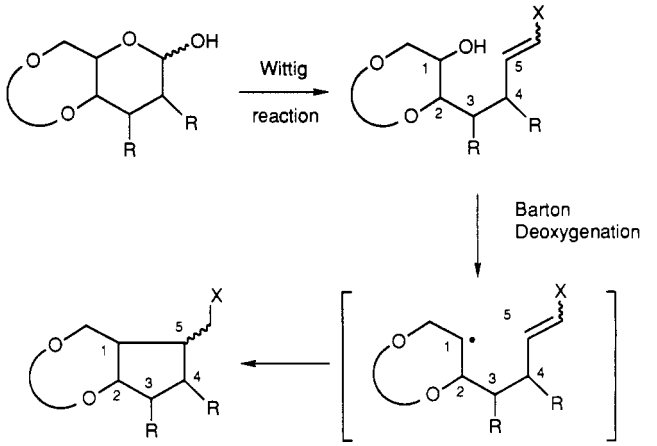
structural elements into appropriate radical precursors, it is now possible to get the desired stereochemistry in the product, thus broadening the scope of this venerable reaction. I shall attempt to include only those studies that are directly relevant to the question of stereochemistry in the hex-5-enyl exo-radical cyclization. Space limitations preclude the coverage of a number of related reactions,[11] even though some of the generalizations drawn from our studies are undoubtedly useful in a broader context.

In his papers, Beckwith proposed general guidelines to predict the stereochemical outcome of the reactions of simple substituted hex-5-enyl radicals.[9,10] The cyclization of 1- and 3-substituted hex-5-enyl radicals leads mostly to cis-disubstituted cyclopentyl products, whereas 2- and 4-substituted radicals give predominantly trans products. The observed stereochemical results were rationalized by invoking a theoretically derived transition state **3** (Scheme II) which has a long incipient bond (ca. 2.3 Å), in accordance with an early transition state predicted for these reactions. This distance is not much different from that between C_1 and C_5 in cyclohexane (ca. 2.5 Å). Beckwith argued that this and other geometric parameters are comparable in the two cases, and therefore conformational features that are well-known in substituted cyclohexanes can be used to rationalize stereochemical results in the hex-5-enyl radical cyclizations. Thus the major products arise via a conformation where the substituents occupy quasi-equatorial positions. Also, in the absence of any special effects, a "chair-like" transition state will be preferred.[12] For example, in the case of a 2-substituted radical,[13] **3a**

Scheme IV
Stereochemistry of 2-But-3-enylcycloalkyl Radicals



Scheme V
A Protocol for the Conversion of Carbohydrates to Carbocycles



will be the preferred transition state, leading to a 2,5-trans-disubstituted cyclopentane.

The ring closure of cyclic 2-but-3-enylcycloalkyl radicals (Scheme III) is similar to that of the open-chain system, except that the constraints of the ring impose an almost exclusive 1,2-cis stereochemistry.[14,15] The critical 1,5-selectivity is still largely cis, and it is this selectivity that had found the most use in the synthesis of polycyclic natural products.[7,16] In the context of the 2-but-3-enylcyclopentyl radical cyclization, it was argued[17] that the 1,5-cis stereochemistry is favored because the "chair-like" transition structure **4a** (Scheme IV) can achieve effective overlap between the SOMO of the radical center and the olefin π orbitals with less strain than the other possible chair **4b**. While this is an adequate rationalization, there is yet another plausible explanation for the origin of the *minor* product: keeping the conformation of the cycloalkyl moiety the same, we propose either a "chair-like" (**4a**) or "boat-like" (**5**) conformation for the cyclization transition state. The former will lead to a 1,5-cis product while the latter

(11) Among them: (a) Begley, M. J.; Bhandal, H.; Hutchinson, J.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1317. (b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003. (c) Chuang, C.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.* **1988**, *53*, 3218. (d) Clive, D. L. J.; Cheshire, D. R.; Set, L. *J. Chem. Soc., Chem. Commun.* **1987**, 353. (e) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (f) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463. (g) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469. (h) Little, R. D.; Fox, D. P.; Hijfte, L. V.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moens, L.; Baizer, M. M. *J. Org. Chem.* **1988**, *53*, 2287. (i) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (j) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (k) Vite, G. D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2271. (l) Watanabe, Y.; Endo, T. *Tetrahedron Lett.* **1988**, *29*, 321. (m) Winkler, J.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708. (n) Yadav, J. S.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1824.

(12) We should note here that a similar and perhaps more realistic transition-state model can be constructed based on the folded envelope-like conformations of methylenecyclopentane. However, we find the cyclohexane model to be more useful, albeit less precise, simply because the conformational preferences are better understood in the cyclohexane system than in methylenecyclopentanes.

(13) Unless otherwise indicated, radical numbering is followed in the text, starting with the radical center as 1.

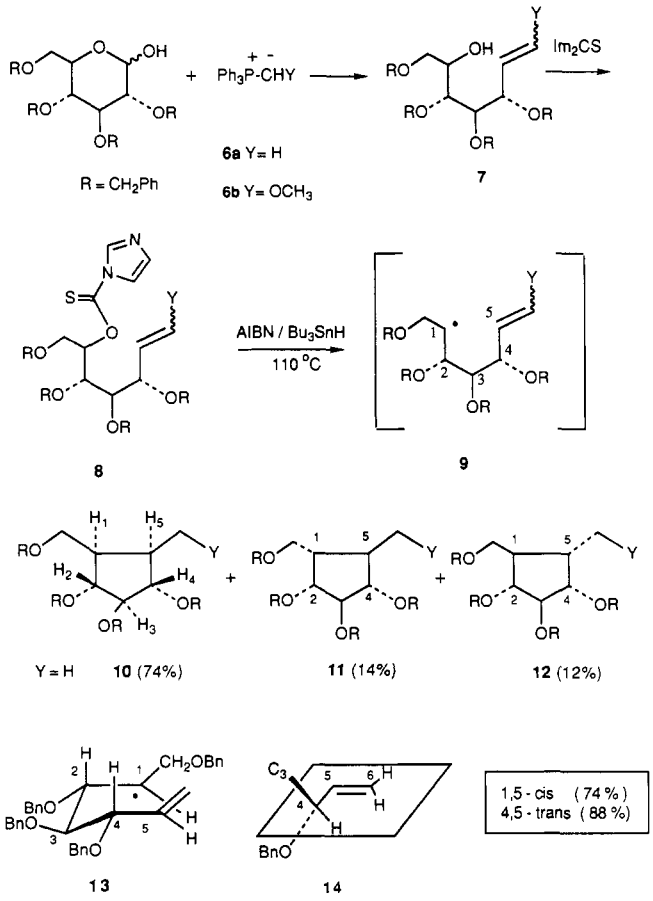
(14) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811.

(15) Wolff, S.; Agosta, W. C. *J. Chem. Res., Synop* **1981**, 78.

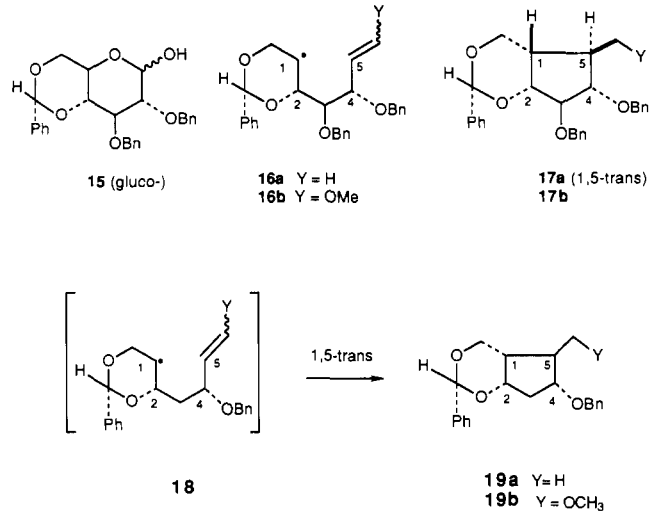
(16) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209.

(17) Curran, D. P.; Rakiewicz, D. M. In *Selectivity and Synthetic Applications of Free Radical Reactions: Tetrahedron Symposia-in-Print*; Giese, B., Ed.; 1985; pp 3943.

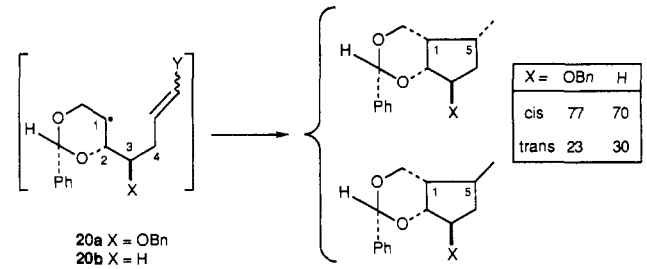
Scheme VI
Latent C_5-Hydroxy as a Radical Precursor in Pyranosides



Scheme VII
Cyclization of Glucose-Derived Radicals



Scheme VIII
Cyclization of 2-Deoxyglucose-Derived Radicals



will give a 1,5-trans product. In this analysis we were encouraged by the theoretical results of Houk and Spellmeyer,[18] who studied the conformations of hex-5-enyl radical transition states. The calculated difference between "chair-like" and "boat-like" transition states is less than 1 kcal/mol! What are the structural features favoring one or the other of these transition states? Could we prepare 1,5-*cis*- and more significantly 1,5-*trans*-dialkylcyclopentanes via hex-5-enyl radical cyclizations starting with precursors that carry appropriate control elements? The latter type of compounds, best exemplified by the carbon framework of prostaglandins or their precursors, have never been prepared by a free-radical cyclization methodology in which the newly formed bond defined the orientation of the α- and β-chains with respect to the ring.[19]

We developed a facile scheme[20] for the preparation of highly substituted radicals from readily available carbohydrates. Aldopyranose sugars readily undergo Wittig reaction to give hex-5-en-1-ols,[21] which can be converted to highly functionalized hex-5-enyl radicals by any one of the variations of the Barton deoxygenation reaction[22] as shown in Scheme V. Because of the ready availability of pyranose sugars of various configurations, such a protocol is also uniquely suited to study the effect of 1-, 2-, 3-, and 4-substituents on the stereochemistry of the cyclization reaction. Furthermore, the well-established protecting-group strategies in carbohydrate chemistry would permit the study of open-chain as well as cyclic radicals with known absolute and relative stereochemistry.

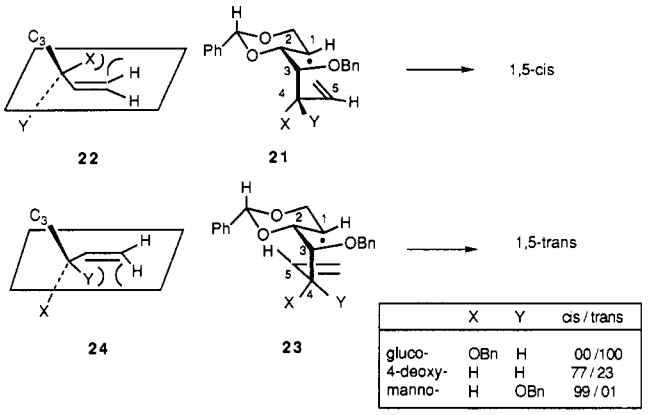
An example of this overall scheme is illustrated in Scheme VI. The radical **9a** cyclizes to give products **10**, **11**, and **12** in a ratio of 74:14:12, in 61% overall yield from **7** (Y = H).[23] Likewise the radical generated from the enol ether **7** (Y = OMe) undergoes facile cyclization to the corresponding products in similar ratios.

In the cyclization of the acyclic radical **9a** (or **9b**), the formation of the 1,5-cis product **10** can be accounted for by a transition state **13**. Note that in this transition state the (phenylmethoxy)methyl substituent at the C_1 position and the C_2, C_3, and C_4 phenylmethoxy groups are all in a quasi-equatorial orientation as suggested by the Beckwith model. Note also that the 4,5-stereochemistry is overwhelmingly trans (combined **10** and **11**: 88%). This can be accounted for by considering the local allylic conformation (C_3–C_6). As pointed out by other workers[24] in the context of both intra- and intermolecular additions, the conformation with the least allylic strain, in this case **14**, is favored, and this leads to the 4,5-trans products.

In sharp contrast to the acyclic radicals, cyclic radicals exhibited much better stereoselectivities. Cyclization of radical **16a** or **16b** prepared from 4,6-*O*-benzylidene-2,3-bis-*O*-(phenylmethyl)-D-glucopyranose

(18) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
(19) In a biogenetically patterned synthesis of prostaglandins, the major radical cyclization product is indeed 1,5-cis. See: Corey, E. J.; Shimoji, K.; Shih, C. *J. Am. Chem. Soc.* **1984**, *106*, 6425.
(20) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609.
(21) For the first example of a related protocol, see: Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546.
(22) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(23) The ratios of products reported here and later in the text and schemes are normalized with respect to the cyclopentane isomers unless otherwise mentioned.
(24) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

Scheme IX
Transition States for the Cyclization of Glucose- and Mannose-Derived Radicals



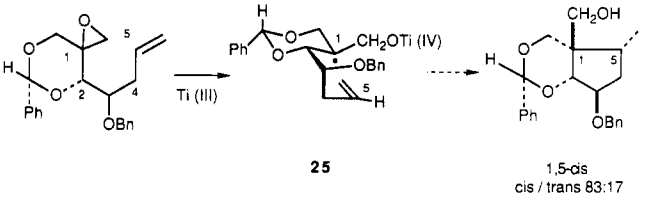
	X	Y	cis/trans
gluco-	OBn	H	00/100
4-deoxy-	H	H	77/23
manno-	H	OBn	99/01

(15) yielded a single 1,5-trans product (**17a** or **17b**) in each case (Scheme VII).[25] Likewise a radical with the 3-benzyloxy substituent removed (**18**) also cyclizes to give almost exclusively the 1,5-trans product **19**.

Does allylic strain at the olefinic center of the hex-5-enyl radical play a role in the formation of **17** and **19**? This can be probed by studying the cyclization of the radicals **20a** and **20b**, which lack these allylic substituents. These cyclic 4-deoxy radicals,[13] generated by routes similar to the ones described above, cyclize with predominantly 1,5-cis (i.e., *endo*-Me) stereochemistry (Scheme VIII). The 3-substituent appears to have very little effect on the course of the reaction.

The preponderant formation of the 1,5-trans products **17** and **19** is totally unexpected, especially since other structurally related radicals (e.g., **20a** or **20b**) and their carbocyclic analogues give a mixture with mostly 1,5-cis products.[7,14,26-29] If one assumes that the dioxane ring maintains the chair conformation and the bulky phenyl and butenyl groups occupy equatorial sites, then the 1,5-trans product can only be rationalized by a boat-like cyclization transition state depicted by structure **23** in Scheme IX, in which the pseudoaxial radical attacks the C=C bond in the pseudoequatorial butenyl side chain. The original preference for a boat-like transition state in the radical **23** was unknown. Some relief of steric compression between the C_2 oxygen (i.e., dioxane O) and the C_4 phenylmethoxy group is expected as the cis decalin-like chair–chair conformation **21** undergoes a change to the chair–boat conformation **23**. However, the conformational studies[30] of various sugar derivatives suggest that this alone would not be sufficient to produce such a dramatic effect. We proposed that the local conformation of the allyl ether portion of the molecule (viz., C_3–C_6) was an important factor in controlling this stereochemistry.[20] The boat-like transition state contains the most favorable allylic conformation[31,32] for the C_3–C_6 portion (**24**) of the molecule, whereas the allylic segment **22** in the chair-like transition state **21** has more

Scheme X
Cyclization of a Ti(III)/Epoxy-Derived Radical

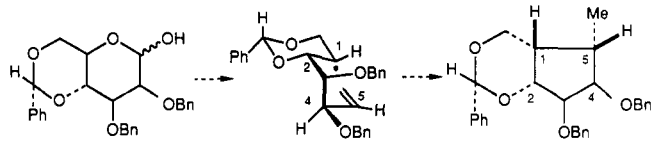


strain because a bulky group (X = OBn) eclipses one of the vinylic hydrogen atoms. The relief of the allylic strain more than compensates for the formation of the normally unfavorable boat-like transition state. Another hitherto unrecognized stereoelectronic component may be influencing the course of this unusual stereochemical outcome. Additions of alkyl radicals to olefins appear to be nucleophilic in nature;[1] and if so, an activation of the olefin π^* orbital by the allylic β-CO-σ^* may play an important role in the acceleration of the reaction rates. In some conformations (for example, the "boat-like" **23**) the alignment of the β-CO-σ^* with respect to the π system is more favorable than in others, and reactions proceeding through these transition states would be expected to be faster. Since the various conformations of the starting material are in rapid equilibrium, these reactions are probably under the Curtin–Hammett regime and these kinetic effects might play an important role in deciding the course of the reaction. Studies on substrates with differing allylic β-CX-σ^* bond energies might throw some light on this aspect of the reaction. Notably, a slightly lower selectivity is observed in a system that has an allylic CC bond in an analogous steric situation.[33] Presumably a σ^*-CC is much higher in energy than a σ^*-CO and cannot interact with the π system as favorably as the latter.

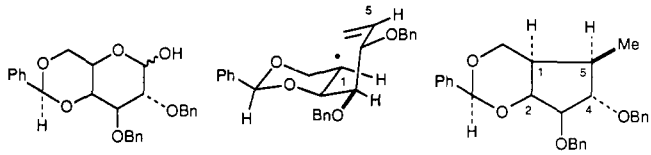
In the absence of an allylic alkoxy group, the allylic strain (and the possible stereoelectronic effect) is not present and the reaction proceeds through a low-energy "chair-like" transition state such as **21** to give predominantly the 1,5-cis products. This is the case with the 4-deoxy radicals **20a** and **20b** giving cis/trans ratios of 77:23 and 70:30, respectively (Scheme VIII). The minor 1,5-trans products in these systems could arise via a "boat-like" transition state **23** (X = Y = H). The same rationale applies to the stereochemistry of cyclization of the radical **25** (Scheme X), which is generated by treating the starting epoxide with Cp_2TiCl.[25,34]

Further confirmation that the C_4 oxygen is the control element comes from the cyclization of the mannose (**26**) derived radical **21** (X = H; Y = OBn). In this case the configuration of the key C_4 center is inverted as compared to that of the glucose-derived radical **16**, and in accord with the prediction, predominant formation of the 1,5-cis product (cis/trans, 99:1) is observed. As shown in Scheme IX, the "chair-like" conformation of the transition state **21** incorporates the low-energy conformation of the allylic (C_3–C_6) segment (i.e., **22**, X = H; Y = OBn). The advantages of using readily available sugars as precursors for substituted radicals is further highlighted by the ease with which one can

(25) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.
(26) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.
(27) Pradhan, S. K.; Kolhe, J. N.; Mistry, J. S. *Tetrahedron Lett.* **1982**, *23*, 4481.
(28) RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296.
(29) Clive, D. L. J.; Beaulieu, P. L. *J. Chem. Soc., Chem. Commun.* **1983**, 307.
(30) Auge, J.; David, S. *Tetrahedron* **1984**, *40*, 2101.
(31) Karabatsos, G. J.; Fenglio, D. J. *Top. Stereochem.* **1970**, *5*, 167.
(32) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
(33) Choi, J.; Ha, D.; Hart, D. J.; Lee, C.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.
(34) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. soc.* **1988**, *110*, 8561.



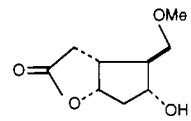
26 (manno-) **21** (X = H; Y = OBn) (1,5-cis)



27 (galacto-) **28** **29** (1,5-cis)

generate a radical with a totally different structure to test the predictive power of these models. Thus the radical **28**, which was readily prepared from galactose, cyclizes via a chair–chair transition state to give only the 1,5-cis product (**29**). It is interesting to note that the galactose-derived radical **28** has an enantiomeric relationship with the mannose-derived radical **21**, except for the C_3 configuration. Both these radicals produce almost exclusively the 1,5-cis products, again confirming the relative lack of influence of the C_3 oxygen substituent on the stereochemistry, when a C_4 substituent is also present.

The radical cyclization products derived from sugars are useful for the synthesis of cyclopentanoid natural products. For example, the unprecedented 1,5-trans stereochemistry seen in the case of 4,6-*O*-benzylideneglucose-derived radicals can be used to prepare optically active prostaglandin intermediates such as Corey lactone **30**.[35]



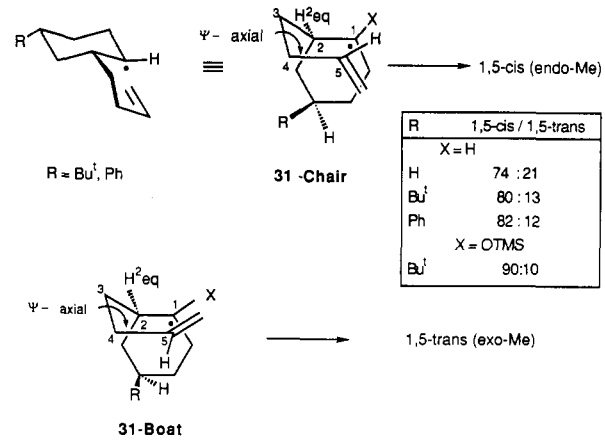
30

In every case of conformationally locked systems reported in the literature[26,27] and in the ones we have so far discussed (**21**, **23**, **25**, and **28**), the but-3-enyl group is in an equatorial orientation. In the absence of any special effects, such as the allylic strain, all these systems yield 1,5-cis selectivity. These results cast some doubt on the original contention[14] that efficient ring closure can occur only through an effective overlap of the SOMO of the radical with the p orbitals of an axially disposed but-3-enyl group. On the contrary, a careful examination of the cis decalin-like transition state reveals that if the but-3-enyl group were in an axial orientation, a "chair-like" transition state should yield predominantly 1,5-trans product (vide infra, Scheme XII). In an effort to delineate these effects, we studied the ratio of 1,5-cis to 1,5-trans products in fused bicyclo[4.3.0]nonanes prepared by the radical cyclization of axially and equatorially disposed 2-but-3-enylcyclohexyl radicals which are conformationally locked.[28] These results are shown in Schemes XI and XII.

As expected, radicals with an equatorial butenyl group (Scheme XI) give mostly 1,5-cis products, the selectivity being highest in the conformationally rigid

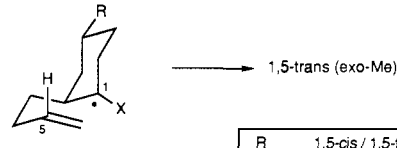
(35) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522.

Scheme XI
Cyclization of Equatorial 2-But-3-enylcyclohexyl Radical



R	1,5-cis / 1,5-trans
X = H	
H	74 : 21
Bu^t	80 : 13
Ph	82 : 12
X = OTMS	
Bu^t	90:10

Scheme XII
Cyclization of Axial 2-But-3-enylcyclohexyl Radical



R	1,5-cis / 1,5-trans
X = H	
Bu^t	22 : 62
Ph	31 : 61
X = OTMS	
Bu^t	25:75

(4-Ph and 4-Bu^t) systems. For the unsubstituted parent system,[14] this ratio is 74:21, and for the corresponding 4-phenyl dioxa system (Scheme VIII), it is 70:30. This is consistent with the fact that the 1,5-cis products arise from "chair-like" transition states, depicted by **31**-chair, in which the substituents are all in the most favorable equatorial positions of the cyclohexane ring. The minor ring-closure products may result from "boat-like" transition states (for example, **31**-boat). As suggested earlier, the energy difference between the chair-like and boat-like transition states could be small relative to the energy of activation for cyclization.[18]

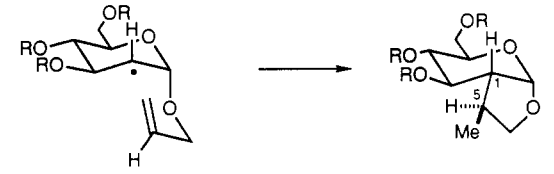
In contrast, radicals with an axially disposed 2-but-3-enyl group give a higher proportion of the 1,5-trans product. This 1,5-trans preference in the cyclization of radicals with an axial but-3-enyl group may be most reasonably rationalized by the "chair-like" transition state depicted by structure **32**-chair, which retains the butenyl group in the axial position. However, since the conformational equilibrium may not be as one-sided as in the case of diequatorial intermediates such as **31**-chair, even when an anchoring group is present, 1,5-trans selectivity is lower than the cis selectivity observed in the case of equatorially disposed butenyl compounds. This is further reflected in the decrease of the cis/trans ratio from 1:2 to 1:3 when going from phenyl (*A* value, conformational free energy difference: 3.1 kcal) to Bu^t (*A* value 5.0 kcal).

Cyclization of 2-but-3-enylcyclohexanones mediated by zinc in the presence of trimethylsilyl chloride may also be influenced by the same controlling factors. Corey[26] reported that *cis*-2-but-3-enyl-4-*tert*-butylcyclohexanone gave mostly an *endo*-methyl-*cis*-hydrindanol. The 1,5-cis/trans ratio was reported to be 66:7. We carried out the same reaction with the cor-

responding trans isomer having an axial but-3-enyl group under slightly modified conditions[28] and found that 1,5-trans ring closure is prefered over cis, but only by a ratio of 75:25. These results closely parallel those with the other cyclohexyl radicals discussed above and are readily understood within the framework of the transition states **31** (X = O^- or OTMS) and **32** (X = O^- or OTMS).

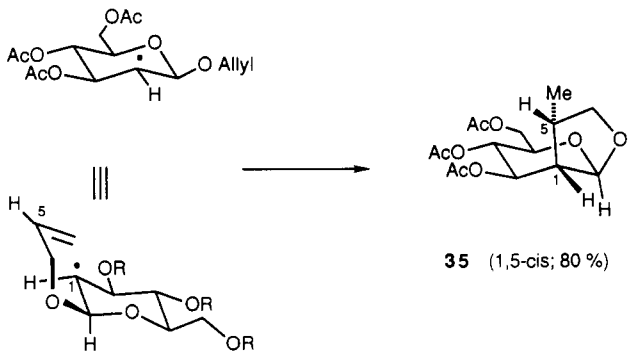
Extensions of the models we have discussed can be used to rationalize the stereochemical outcomes of complex hex-5-enyl radical cyclization reactions reported in the literature, including seemingly anomalous results that defy the classical 1,5-cis (i.e., *endo*-methyl) selectivity rule.

An unexpectedly high proportion of 1,5-trans products was obtained in the cyclization of the α-allyl (axial) glycoside radicals **33a** and **33b**.[36,37] As our model would



33a R = Ac
33b R = H
(α-glycoside)

R = Ac 1,5-trans 50 %
R = H 1,5-trans 75 %



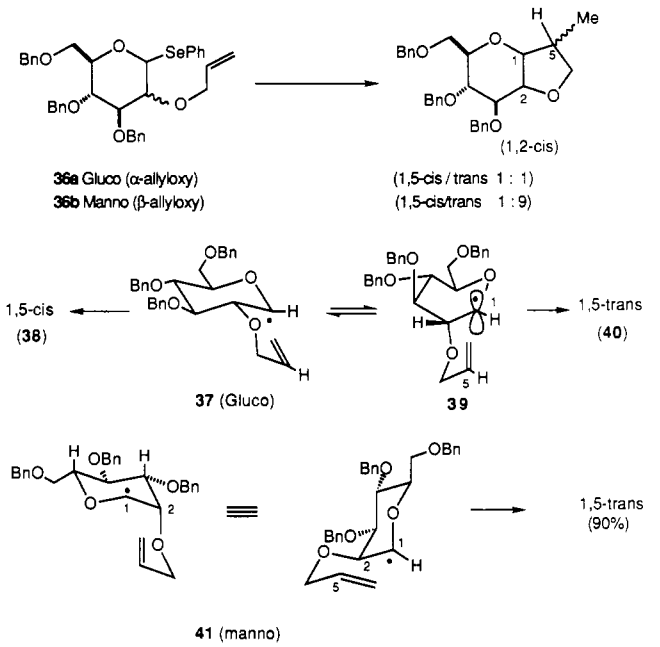
34 (β-glycoside)

35 (1,5-cis; 80 %)

have predicted, a significant portion of the reaction must proceed through the chair–chair conformation leading to this product. Since the triacetoxy sugar is conformationally flexible,[38] especially at the temperatures at which the cyclization is carried out, it is not surprising that the 1,5-cis product is also observed, albeit in low yield. The proportion of the 1,5-trans product is even greater in the case of the unprotected (R = H) sugar derivative. The stereochemistry of the products from the corresponding equatorial β-allyloxy derivative has not been determined.[36] We predict that the major (75%) product would be the endo isomer **35** arising through a chair–chair transition state **34**. The special stabilization via β-CO-σ* interaction (see below) is not applicable in this case, since radicals without an α-oxy substituent do not interact with neighboring CO bonds.

(36) Audin, C.; Lancelin, J.; Beau, J. *Tetrahedron Lett.* **1988**, *30*, 3691.
(37) De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57.
(38) Hydroxy and acetoxy groups are small (*A* value 0.7 kcal), and it is likely that nonchair conformations are populated at temperatures at which the radicals are generated; see refs 30 and 42.

Scheme XIII
Stereochemistry of Intramolecular Radical C-Glycosidations



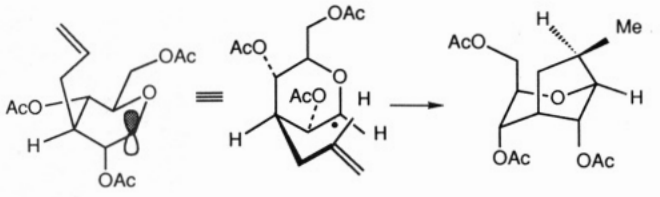
36a Gluco (α-allyloxy)
36b Manno (β-allyloxy)

(1,2-cis)
(1,5-cis / trans 1 : 1)
(1,5-cis/trans 1 : 9)

1,5-cis (**38**)
37 (Gluco)
39
1,5-trans (**40**)
41 (manno)
1,5-trans (90%)

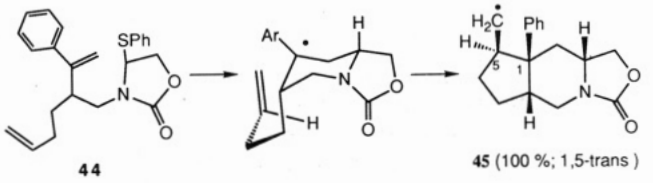
In addition to the axial vs equatorial nature of the but-3-enyl group, special stabilization of an intermediate radical can also play an important role in the stereochemical outcome of hex-5-enyl radical cyclizations. The surprising results of De Mesmaeker[39] on the stereochemistry of intramolecular C-glycosidation reactions (Scheme XIII) can be satisfactorily rationalized if one also takes into account this important stabilization effect in considering our models. For example, the anomeric radical from **36a** would be expected to cyclize via chair-like transition state **37** leading to **38** as the major product, but up to 53% of the exo isomer (**40**) is also formed in the reaction. In the light of epr studies, carried out on related systems by Giese and Sustmann,[40] one may assume that an α-oxy radical (glycosyl radical) such as **37** undergoes a conformational change into the boat form **39**. In this form the electronic stabilization from the β-CO-σ*–SOMO interaction can more than compensate for the apparent strain invlved in the high-energy conformation. A chair transition state for the cyclization now leads to the 1,5-trans product. A more compelling case for this scenario is provided by the cyclization of the mannose (from **36b**) derived radical **41**, where this conformational change of the sugar is not needed for the radical stabilization. The stable chair conformation of the sugar radical is helped by the axial nature of the β-CO bond. As expected, very high selectivity (90:10 = exo:endo) for the 1,5-trans product is observed. Such an unusual anomeric radical stabilization is also involved in the formation of **43** as the major product via the transition state **42**.[41] Parenthetically it should be added that this stabilization does not exist in the case of radicals that lack an α-electron-withdrawing group (e.g., **33** or **34**).[42]

(39) De Mesmaeker, A.; Hoffmann, P.; Ernst, B.; Hug, P.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 6307.
(40) Korth, H.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453.
(41) Groninger, K. S.; Jager, K. F.; Giese, B. *Liebigs Ann. Chem.* **1987**, 731.
(42) Korth, H.; Sustmann, R.; Groninger, K. S.; Witzel, T.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1461.



There are a number of other instances[43–45] where the heuristic models presented above can be used to rationalize unusual stereochemical outcomes in hexenyl radical cyclizations including an interesting case of a tandem cyclization (Scheme XIV).[46]

Scheme XIV
Stereochemistry of a Tandem Cyclization



Conclusions

In this study of cyclizations of conformationally rigid 2-but-3-enylcyclohexyl radicals, we have conclusively shown that the stereochemical outcome of the reaction is critically influenced by the orientation of the butenyl side chain; an equatorial butenyl group leads predominantly to 1,5-cis cyclization products, whereas an axial butenyl group preferentially gives rise to 1,5-trans products.[47] These stereochemical consequences can be satisfactorily accounted for by the cyclohexane "chair-like" transition states originally proposed by Beckwith and co-workers for *acyclic* hex-5-enyl radical cyclizations. In related but conformationally less rigid systems, the transition states having an equatorial and an axial butenyl side chain may compete. Minor ring-closure products also may arise from less favorable "boat-like" transition states. As shown in several of the sugar-derived radicals, the formation of these boat-like transition states may sometimes be helped by the configuration at the C_4 center. In the presence of a C_4 substituent, the local allylic conformation dictates the choice between the "chair-like" and "boat-like" transition states, and the one with the lowest 1,3-strain controls the course of the reaction. This results in an unprecedented control of the 1,5-stereoselectivity of the hex-5-enyl radical cyclization. In systems with C_3 and C_4 substituents, the C_4 substituent is the control element and the C_3 substituent exerts only a marginal influence on the 1,5-stereoselection. Special effects, such as the stabilization a β-CO-σ^* provides for an α-oxy radical, should be taken into account before considering these models.

Finally the predictive value of these conformational models is illustrated with several examples from the literature. We believe that these heuristic models and the carbohydrate to carbocycle conversion protocols developed during the course of these investigations will become valuable tools in planning the synthesis of highly functionalized cyclopentanoid natural products.

I acknowledge valuable discussions with Dr. T. Fukunaga. I am deeply indebted to Drs. W. A. Nugent and A. Casalnuovo for critical review of the manuscript. Dr. G. W. Parshall has been a constant source of encouragement and support, and his leadership role is gratefully appreciated. Technical assistance was provided by Mr. T. H. Kline, Jr., and Mrs. M. S. Beattie.

(43) Hashimoto, H.; Furuichi, K.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1002.
(44) De Mesmaeker, A.; Hoffmann, P.; Winkler, T.; Waldner, A. *Synlett* **1990**, *1*, 201.
(45) Nouguier, R.; Lesueur, C.; Riggi, E. D.; Bertrand, M. P. *Tetrahedron Lett.* **1990**, 3541.
(46) Kano, S.; Yuasa, Y.; Yokamatsu, T.; Asami, K.; Shiroshi, S. *J. Chem. Soc., Chem. Commun.* **1986**, 1717.
(47) Since alkylation of cyclohexanones can be carried out to produce axial (kinetic) or equatorial (thermodynamic) 2-but-3-enyl ketones, this control element can be parlayed into annulation stereochemistry by the appropriate choice of radical cyclization methodology.

Developing Artificial Hydrolytic Metalloenzymes by a Unified Mechanistic Approach

JIK CHIN

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

Received October 5, 1990 (Revised Manuscript Received March 12, 1991)

Nature has developed many hydrolytic metalloenzymes. They have evolved to hydrolyze some of the most important molecules of life including proteins, phospholipids, and DNA. Over the years numerous hydrolytic metalloenzyme models have been designed and studied. Much has been learned through elegant designs and careful analyses of simple enzyme models. However, a major difference between enzymes and their models is their reactivity. In most enzyme model studies, either the substrates are highly activated or they are permanently anchored to various catalytic groups preventing any catalytic turnover. The principal focus of this account is on true catalysts that hydrolyze unactivated substrates with catalytic turnover. A mechanisitically unified approach to developing metal complexes that hydrolyze esters,[1–3] amides,[4] nitriles,[5]

Jik Chin did his undergraduate and graduate studies at the University of Toronto, receiving his B.Sc. in 1977, M.Sc. in 1978, and Ph.D. in 1981. After postdoctoral studies at Columbia University, he joined the faculty at McGill University in 1983. His current research interest is biocatalyst design.

(1) Chin, J.; Zou, X. *J. Am. Chem. Soc.* **1984**, *106*, 3687.
(2) Chin, J.; Jubian, V. *J. Chem. Soc., Chem. Commun.* **1989**, 839.

0001-4842/91/0124-0145$02.50/0