Chapter 19
Compounds With Carbon–Carbon Multiple Bonds II: Cyclization Reactions

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I. Introduction

The structural requirements for a molecule destined to undergo radical cyclization are that it contain a substituent from which a radical (almost always a carbon-centered one) can be generated and that it have a properly positioned multiple bond. Carbohydrates that meet these requirements include unsaturated iodides, bromides, thionocarbonates, cyclic thionocarbonates, xanthates, and phenyl selenides. Ring formation in the reactions of these compounds usually is regiospecific and often highly stereoselective.

II. Ease of Reaction between a Carbon-Centered Radical and a Multiple Bond

Once structural requirements have been met, successful radical cyclization depends on reaction rates. The basic question is “Will ring formation occur before competing reactions inter-
vene?” The answer to this question depends upon the nature of the radical center and multiple bond and on the separation between these two. The ability of a radical to add to a multiple bond to form a new ring will be addressed first; then, the effect of the separation between the radical center and the multiple bond will be considered.

\[
\begin{align*}
\text{CH}_2\text{OAc} & + \text{CH}_2\text{=CHCN} \Rightarrow \text{CH}_2\text{CH}_2\text{CN} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CN} \\
\text{CN} & \quad \text{COCH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{V-70} = \text{CH}_3\text{OCCH}_2\text{CN-CNCH}_2\text{COCH}_3 \\
\end{align*}
\]

A beginning point for discussing reactivity between a radical center and a multiple bond during internal addition is to recall some of the findings in Chapter 18 about addition reactions that are not internal. Such reactions take place rapidly when a radical is nucleophilic (as are most carbon-centered radicals) and a multiple bond is electron-deficient. This description fits the reaction shown in eq 1.\(^1,2\) If a multiple bond is not electron-deficient, radical addition normally is too slow to compete with hydrogen-atom abstraction; however, minimizing or eliminating effective hydrogen-atom donors from a reaction mixture can enable addition to occur even when the multiple bond is not electron-deficient. An example of this type of reaction is shown in eq 2, where \(\text{Bu}_3\text{SnH}\) is not present in the reaction mixture even though \(\text{Bu}_3\text{Sn}\) is there and acts as the chain-carrying radical.\(^3,4\)

Addition of a radical to a multiple bond is potentially much faster when the reaction is intramolecular. If a radical center and a multiple bond in a molecule are positioned so that they frequently come within bonding distance, the rate of internal addition increases to the point that even for a multiple bond that is not electron-deficient, cyclization competes effectively with hydrogen-atom abstraction. In the reaction shown in eq 3, internal addition to a double bond that is not electron-deficient takes place even in the presence of \(\text{Bu}_3\text{SnH}\).\(^5\)
III. Reaction Selectivity

Chemoselectivity, regioselectivity, and stereoselectivity are defining characteristics of radical reactions. Nowhere are they more important (particularly the latter two) than when a new ring is being formed. Understandably then when regioselectivity and stereoselectivity were broached in Chapters 10 and 11 of Volume I, discussion often turned to cyclization reactions. Some of the ideas and topics from these chapters are revisited here but now with an exclusive focus on their importance to new ring formation.

A. Chemoselectivity

Chemoselectivity enters into consideration at two places in radical cyclization reactions. The first is during radical formation, where it determines which atom or group in a molecule will react
to form the radical that adds to a multiple bond. Chemoselectivity next is of consequence when a newly formed radical has the possibility of adding to more than one multiple bond. In the reaction shown in eq 4, for example, halogen-atom abstraction from the bromide 1 produces a radical that can add to either of two double bonds. Addition to one produces a five-membered ring while reaction with the other forms a six-membered ring. Although these two bonds are comparable in reactivity, the product with the five-membered ring forms more rapidly. (The reasons for usually forming a product with a five-membered ring are discussed in the next section.) If, however, the double bond for which reaction produces a six-membered ring, is decidedly more reactive (i.e., substantially more electron-deficient), as is the case in compound 2 (eq 5), the chemoselectivity of the cyclization process changes, and only the product with the larger ring forms.

B. Regioselectivity

Radical cyclization is nearly always a kinetically controlled process. Kinetic control often leads to regiospecific formation of the less stable cyclic radical. In the reaction shown in Scheme 1, for example, even though cyclization to give a six-membered ring is possible and would generate a more stable radical, the only reaction pathway followed leads to the smaller ring and the less stable radical. The reaction shown in Scheme 2, where the primary radical 3 forms in preference to the tertiary radical 4, provides a particularly striking example of a kinetically controlled, radical cyclization.

There are cyclization reactions that take place under thermodynamic control when the proper conditions are met. In the reaction shown in eq 6 the major product contains a six-membered ring,
Compounds With Carbon–Carbon Multiple Bonds II: Cyclization Reactions

Scheme 2

when reaction is conducted in dilute Bu$_3$SnH solution,$^{11}$ but at high Bu$_3$SnH concentration reaction regioselectivity changes to give a product with a five-membered ring.$^{11,12}$ This concentration dependence can be explained by the more rapidly formed, but less stable, radical 5 having sufficient time and energy, when the concentration of Bu$_3$SnH is low, to be converted into the more stable radical 6, either by a rearrangement that involves a cyclic transition state or by a fragmentation-addition sequence (Scheme 3).$^{13}$ At high Bu$_3$SnH concentration hydrogen-atom abstraction occurs before ring expansion can take place.
1. Five-Membered Versus Six-Membered Ring Formation
   a. Five-Membered Rings

   If a radical center and a multiple bond in a molecule are situated so that either a five- or six-membered ring is possible, the smaller ring generally will form.¹⁴,¹⁵ The reason for producing the smaller ring is that the strain engendered in reaching the transition state leading to a six-membered ring is greater than that necessary for forming a ring with five members (Scheme 4).¹⁶–¹⁸ Both chair-like¹⁴,¹⁶ and boat-like¹⁶,¹⁹ transition-states are possible during five-membered-ring formation (Scheme 5). For the unsubstituted 5-hexenyl radical the chair-like transition state is calculated to be lower in energy than its boat-like counterpart, but only slightly so.¹⁶ (The “flagpole” and eclipsing interactions that contribute to making the boat conformation of cyclohexane much less stable than the chair conformation are not as severe in the boat-like transition state for radical cyclization.) Both transition states (boat-like and chair-like) leading to a
five-membered ring (Scheme 5) are calculated to be lower in energy than any transition states leading to a six-membered ring. These calculations match well the experimental observation that cyclization of the 5-hexenyl radical gives a five-membered ring in a highly regioselective fashion (eq 7, \( R = H \)).\textsuperscript{14,20} They also are consistent with the reactions shown in Schemes 1 and 2, where five-membered rings form in preference to six-membered ones.

The greater ease of formation of five-membered rings when compared to six-membered ones is illustrated in a quantitative fashion by the approximately fifty-fold difference in rate constants for cyclization of the 5-hexenyl (eq 8) and 6-heptenyl (eq 9) radicals.\textsuperscript{20} A qualitative example of this type of difference in reactivity involving a pair of carbohydrates is found in the reactions shown in equations 10 and 11, where formation of a five-membered ring occurs in the normal manner, but cyclization to give a six-membered ring does not take place rapidly enough to compete with simple reduction.\textsuperscript{21}
Scheme 5

chair-like transition state

boat-like transition state

\[ \text{Scheme 5} \]

\[ \begin{align*}
\text{ vinyl} & \xrightarrow{k_1} \text{ cyclopentane} + \text{ cyclohexane} \quad (8) \\
\text{ vinyl} & \xrightarrow{k_2} \text{ cyclohexane} + \text{ cyclohexane} \quad (9)
\end{align*} \]

\[ \frac{k_1}{k_2} \approx 50 \]

\[ \begin{align*}
\text{ vinyl} & \xrightarrow{k_1} \text{ cyclopentane} + \text{ cyclohexane} \quad (8) \\
\text{ vinyl} & \xrightarrow{k_2} \text{ cyclohexane} + \text{ cyclohexane} \quad (9)
\end{align*} \]

\[ \frac{k_1}{k_2} \approx 50 \]
b. Six-Membered Rings

Six-membered-ring formation takes place when structural features in a radical inhibit forming a five-membered ring. Possible inhibiting factors include: a) greater ring strain at the transition state for forming a five-membered ring as opposed to a six-membered one; b) steric hindrance that is sufficient to make bonding difficult at the carbon atom of the multiple bond needed to form a five-membered ring; c) structure and reactivity associated with the radical center that favors six-membered-ring formation.²²

Reactions of the phenyl thionocarbonates 7 and 9 illustrate the importance of ring strain in determining the size of a ring being formed by radical cyclization. Compound 7 undergoes the expected cyclization to give a product (8) with a five-membered ring (eq 12), but similar reaction of 9 forms only a compound (10) with a six-membered ring (eq 13).²² Reaction producing the larger ring does so because forming a five-membered ring would introduce the substantial strain at the transition state inherent in a reaction leading to a product (11) with a pair of trans-fused, five-membered rings.

Steric effects can have a powerful, modifying influence on the cyclization of simple organic radicals; thus, the 5-hexenyl radical preferentially forms a five-membered ring (eq 7, R = H), but the 5-methyl-5-hexenyl radical, more hindered at C-5, regioselectively generates a product with a six-membered ring (eq 7, R = CH₃).¹⁴,¹⁶ Steric effects do not exercise the control shown in eq 7 in determining ring size in the cyclization reaction pictured in eq 12, where the C-5 substituents do not force formation of any product with a new six-membered ring; in fact, study of 7 and similar compounds shows that the steric effects associated with C-5 substitution are unable, by themselves, to promote any six-membered-ring formation.²²
Clear examples of steric effects controlling radical cyclization in the reactions of carbohydrates are lacking, but the reactions shown in Scheme 6 suggest a steric component to regioselectivity. Formation of the spiro compound 15 takes place when R=CH₃ or OBz, but when R is a hydrogen atom, products 16 and 17 are formed (Scheme 6).²³ One proposal is that larger substituents favor formation of the spironucleoside 15 by sterically hindering reaction at C-2', but when the C-2' substituent is a hydrogen atom, reaction takes place to form products 16 and 17, compounds with new six-membered rings. Regioselectivity in this reaction also could be explained by product-radical stability; that is, compound 15 forms only when the intermediate radical 12 has stabilizing substituents at C-2'.

The nature of the radical center also can have an effect on the regioselectivity of ring formation. The intermediate primary radical in the reaction shown in eq 12 forms a product with a new, five-membered ring, but the analogous vinylic radical cyclizes to form products with new six-membered rings (Scheme 7).²² The possibility exists that, as shown in Scheme 7, a five-membered ring does form, but it then rearranges to a more stable six-membered-ring radical. If such a transformation takes place, it would be reminiscent of the silyl-ether rearrangement pictured in Scheme 3.
2. Six-Membered Versus Seven-Membered Ring Formation

When constructed from carbon, nitrogen, and oxygen atoms, six-membered rings form more rapidly than seven-membered ones, but sometimes ring formation is not fast enough to prevent hydrogen-atom abstraction prior to cyclization. The reaction shown in eq 11 is one in which internal radical addition to a multiple that is not electron-deficient is too slow for ring formation to compete with simple reduction. In contrast, cyclization involving a similar double bond (i.e., one that also is not electron-deficient) does take place in the reaction shown in eq 3 because the rate of
competing hydrogen-atom abstraction is reduced to an insignificant level by maintaining a low Bu₃SnH concentration during the reaction.⁵

As long as the only atoms in the ring are second row elements, radical cyclization typically produces a six-membered, rather than a seven-membered ring (eq 3). If an atom of the third-row element silicon is present, a seven-membered ring can be produced (eq 14).²⁴ This change in regioselectivity can be explained, at least in part, by longer bond lengths to silicon making approach of the radical center to the terminal carbon atom in the double bond the lower energy pathway.²⁵ Seven-membered ring formation depends upon the terminal carbon atom in the double bond being unsubstituted; otherwise, steric effects raise the transition-state energy sufficiently to favor formation of a six-membered ring.²⁵

3. Three- and Four-Membered Ring Formation

Forming a three-membered ring is not a promising beginning for radical cyclization because the strained, cyclic radical produced would open readily to its more stable, acyclic counterpart (eq 15).²⁶ Although ring strain also hinders formation of products with four-membered rings, the lesser
magnitude of the strain increases the possibility for isolating a cyclic product;\textsuperscript{27,28} thus, the reaction shown in Scheme 8 produces a compound with a four-membered ring.\textsuperscript{27} This reaction is kinetically controlled; otherwise, it would lead to a less strained, five-membered ring, one that contains an oxygen-stabilized radical.

\[
\begin{align*}
\text{R} & = \text{O} \\
\text{Scheme 8}
\end{align*}
\]

Radical philicity, which often is a significant factor in determining regioselectivity in kinetically controlled reactions, rationalizes the direction of ring closure in the reaction shown in Scheme 8. The nucleophilic, carbon-centered radical adds to the electron-deficient, β carbon atom in the α,β-unsaturated ester portion of the molecule. Frontier-orbital interactions, also useful in explaining kinetically controlled reactions, make the same prediction; that is, reaction should occur at the β carbon atom in an α,β-unsaturated ester (see Section II.B.2 of Chapter 18).

4. Seven-Membered and Larger Ring Formation

Radical cyclization can be surprisingly effective in forming rings with seven,\textsuperscript{24,29,30} eight,\textsuperscript{31–37} nine,\textsuperscript{36,38–43} ten,\textsuperscript{44} or even eleven\textsuperscript{45} members. Generating these larger rings from carbohydrates often is associated with the linking together of two monosaccharide units by a tether containing silicon and oxygen atoms.\textsuperscript{31–36,37–42} An example of such a reaction is shown in Scheme 9, where cyclization produces an eight-membered ring.\textsuperscript{35} Although the most common method for joining a
radical forming group and a multiple bond is by a silicon–oxygen tether, other connecting linkages are possible. These other tethers include phosphoramic (nine-membered ring formed) and ketal (nine-membered ring formed) connectors, as well as bridging units consisting of pyranoid (eleven-membered ring formed) and furanoid (eight-membered ring formed) rings.

C. Stereoselectivity

1. Five-Membered Ring Formation

   a. Chair-Like Transition States

   Even though the complex substitution patterns present in many carbohydrates introduce a variety of possibilities for steric and polar interactions, the chair-like, transition-state model typically predicts the primary stereocchemical outcome of a cyclization reaction forming a five-membered ring (Scheme 10). The lowest energy transition state for such a reaction has as many pseudoequatorial “ring substituents” as possible. An example is shown in Scheme 11.
where if one assumes the reaction passes through a chair-like transition state that maximizes pseudoequatorial substituents, it is possible to explain the stereochemistry in the final product.
b. Boat-Like Transition States

Although chair-like, transition-state structures can be used to rationalize the stereoselectivity in most radical cyclization reactions, calculations indicate that boat-like structures should be included as possibilities.\(^{16}\) In the reaction shown in Scheme 12,\(^{50}\) for example, the minor product can be explained by invoking a boat-like transition state. With the structural complexity of carbohydrates and the general similarity in energies between boat-like and chair-like transition states, it is not surprising to find that the major stereoisomer in the cyclization reaction pictured in Scheme 13 appears to arise from a boat-like transition state.\(^{19,51}\)

c. Factors Affecting Transition-State Stability

(1.) Pseudo-1,3-Diaxial Interactions

In the reaction shown in Scheme 13 it is possible to identify a pseudo-1,3-diaxial interaction\(^ {52}\) in the intermediate radical 19 and the associated, chair-like transition state 21.\(^{19,51}\) In the conformationally isomeric radical 18 and its associated, boat-like transition state 20 this desta-
bibilizing interaction is absent. The stereochemistry of the product from ring formation indicates that 1,3-diaxial interaction is the primary factor causing reaction to occur by the pathway passing through the boat-like transition state 20 (Scheme 13). 19,51

Scheme 13

\[
\begin{align*}
\text{Bu}_3\text{Sn} & \quad \text{Bu}_3\text{SnSC(=O)Im} \\
\text{C}_6\text{H}_5 & \quad \text{O} \quad \text{OCIm} \\
\text{BnO} & \quad \text{BnO} \\
\end{align*}
\]

1,3-diaxial interaction

\[
\begin{align*}
\text{Im} &= \text{N} \quad \text{N} \\
\text{Bu}_3\text{Sn} & \quad \text{Bu}_3\text{Sn} \\
\end{align*}
\]
Another phenomenon that is credited with affecting transition-state stability is allylic strain, which can be defined in terms of the partial structures shown in eq 16. Conformation 23 is favored energetically over 22 because the destabilizing steric interaction between \( R_1 \) and \( R_3 \) in 22 is greater than the corresponding interaction between \( H \) and \( R_3 \) in 23. Such interaction also affects the transition-state energies for reactions from these two conformers; thus, reaction occurs preferentially, sometimes exclusively, from 23. In the reaction shown in Scheme 14 allylic strain destabilizes conformation 24, but bond rotation to give conformer 25 relieves this strain. In a similar manner strain relief causes the reaction shown in Scheme 15 to occur primarily via a boat-like transition state derived from 26.
(3.) Hydrogen Bonding \(^{56,57}\)

The energies of the transition states in the reactions shown in Scheme 16 depend upon whether \(R\) is a hydrogen atom or a trimethylsilyl group. When the trimethylsilyl group is in place, the chair-like transition state 28 is preferred because it places all substituents in pseudoequatorial positions. \(^{56}\) If the trimethylsilyl groups are replaced by hydrogen atoms, a different, chair-like transition state (27), one that has two pseudoaxial substituents but is stabilized by hydrogen bonding, has lower energy. The reactions described in Scheme 16, therefore, illustrate the power of hydrogen bonding in influencing reaction stereoselectivity.
(4.) Conformation of an Existing Ring

The reactions shown in eq 17 illustrate the effect that the stereochemistry of a remote ring substituent can have on reaction stereoselectivity. It is unlikely that the C-4 benzyloxy groups in the radicals formed from the allyl ethers 29a and 29b are close enough to the radical center or the multiple bond to influence reaction directly. A more likely possibility is that substituent stereochemistry affects pyranoid-ring conformation in the intermediate radicals and that differences in conformation (or in the mixture of accessible conformations) determine reaction stereoselectivity. The idea that inversion of configuration at C-4 can change intermediate-radical conformation in these reactions (eq 17) is supported by the observation that other pyranos-1-yl radicals that are epimeric at C-4 adopt quite different radical conformations.
2. Six-Membered Ring Formation

Chair-like transitions states also provide a basis for understanding stereoselectivity in six-membered ring formation. In the cyclization reaction shown in Scheme 17, product formation can be explained by assuming that two chair-like transition states (30 and 31) are accessible during reaction. The difference in energy between these two depends primarily on steric interactions involving the CH$_2$CO$_2$CH$_3$ group. The transition state 31 with its pseudo-1,3-diaxial interaction would be expected to be higher in energy than the transition state 30, which avoids such interaction. The highly stereoselective formation of 32 is consistent with this proposed difference in transition-state energies (Scheme 17).
3. Seven-Membered and Larger Ring Formation

In the reaction shown in Scheme 18 the size of the \( t \)-butyldimethylsilyl groups causes the pyranoid ring in the phenyl selenide 34 to adopt a \( ^1C_4 \) conformation. If this conformation is maintained during cyclization, as appears to be the case, radical addition to the vinyl group will occur exclusively from the \( \alpha \) face of the pyranoid ring in the radical 35 to give, after hydrogen-atom abstraction, the cyclic silyl ether 36.\(^{24,29b}\) When protection is provided by the less sterically demanding benzyl groups, more conformational flexibility exists in the pyranoid ring (\( ^1C_1 \) and \( ^1C_4 \) interconvert more easily) and radical addition occurs from either face of the ring system (Scheme 19).\(^{24,29b}\)

Further indications exist of the importance of radical conformation in forming rings with seven or more members. In the reaction shown in eq 18 the rigidity of the radical derived from the iodide 37 reduces the number of conformations possible but includes one that holds the radical center and the double bond in close enough proximity that cyclization gives the major product; in contrast, in the reaction shown in eq 19 the greater flexibility of the radical generated from the iodide 38 changes the opportunity for interaction between reactive centers to the point that a complex mixture of products is formed.\(^{61}\)
Scheme 19

Bu₃Sn⁺ - Bu₃SnSeC₆H₅

Bu₃SnH - Bu₃Sn⁻

KF, KHCO₃, H₂O₂, MeOH, THF

64%

16%

Me₂C⁺

Me₂C⁺

CMe₂

CMe₂

OH

OH

OH

OH

I

Me₂C⁺

Me₂C⁺

CMe₂

CMe₂

OH

OH

OH

OH

37

50%

(18)
IV. Unsaturated Carbohydrates That Undergo Radical Cyclization

The unsaturated carbohydrates that undergo radical cyclization are an eclectic mixture of compounds in which the reactive multiple bond in each typically is electron-deficient. Reduced electron density in the multiple bond can be caused either by conjugation of this bond with a carbonyl group or by having an electronegative substituent attached to it. Ring formation still can occur when a double or triple bond is not electron-deficient, but as described earlier in this Chapter (Section II), in such a situation cyclization is slower and less able to compete with other radical reactions.

A. α,β-Unsaturated Carbonyl Compounds

The electron-deficient double bond in an α,β-unsaturated ester is an attractive target for internal addition of a carbon-centered radical. The majority of reactions of this type produce five-membered rings, fewer, but still a significant number, form six-membered rings. Formation of smaller and larger rings also takes place, but such reactions are far less common. (Examples of internal radical addition in α,β-unsaturated esters are found in the reactions shown in Schemes 8, 16, and 17.) The radicals that participate in this type of reaction usually are generated from halogenated carbohydrates but also can be formed from reaction of carbohydrates containing O-thionocarbonyl, cyclic O-thionocarbonyl, O-thionocarbamoyl, phenyl seleno, aryl telluro, O-acyl-N-hydroxy-2-thiopyridonyl, and vinyl groups.

Other α,β-unsaturated carbonyl compounds that undergo radical cyclization include nucleosides that have a carbon-centered radical in the sugar portion of the molecule. In these reactions
cyclization occurs by internal radical addition to a carbon–carbon double bond in the nitrogenous base.\textsuperscript{95–101} Since the substrate in most of these reactions is a derivative of uridine, cyclization is, in effect, an internal addition to an α,β-unsaturated lactam (eq 20).\textsuperscript{96}
Other cyclization reactions of carbonyl compounds include internal addition to α,β-unsaturated aldehydes, ketones, and lactones, and to lactams that are α,β- and γ,δ-unsaturated. Reaction of the unsaturated lactam pictured in Scheme 20 begins with halogen-atom abstraction that is followed by 1,5-transfer of a hydrogen atom to give the interconverting radicals 39α and 39β. New rings form when these radicals react to give the cyclic, stereoisomeric radicals 40α and 40β, respectively. The stereoselectivity of this reaction depends upon the stereochemistry of the C-2' substituent and changes when the configuration at C-2' is inverted.

**B. Silyl Ethers and Silaketals**

One method for connecting a radical forming group and a multiple bond is with a silicon–oxygen tether. In some compounds of this type (e.g., the substrate in the reaction pictured in eq 6) the multiple bond is located in a substituent group, while in others (eq 21) it is part of a ring system. As mentioned earlier in the chapter (Section III.B.4), connecting the reacting segments of a molecule through a silicon–oxygen bond is particularly useful in producing larger (seven-, eight-, and nine-membered) rings. An example of a reaction that forms a larger ring is shown in Scheme 18, where an allyl group is tethered to the 2-position in the phenyl selenide 34. A similar tether connects the two saccharide units in the radical 41, an intermediate destined to form an eight-membered ring that then is converted into a partially protected C-disaccharide (Scheme 21). The carbon-centered radicals in these reactions usually are generated by treating phenyl selenides with tri-n-butyltin hydride.

Having a vinyl group tethered to a radical-forming substituent through a silyl ether linkage can provide the structure needed to form either a five-membered or a six-membered ring. It is worth recalling (Section III.B) that in compounds of this type the size of a ring formed can depend on the concentration of the hydrogen-atom donor; thus, in the reaction shown in eq 6, higher Bu₃SnH concentration causes formation of a five-membered ring, but lower concentration favors a six-membered one. Scheme 3 contains a rationalization for this concentration dependence.

In the radical reactions of the unsaturated silyl ethers pictured in Schemes 18, 19, and 21 and eq 21, the final step is hydrogen-atom abstraction from Bu₃SnH. When the substrate is an unsaturated iodide and no Bu₃SnH is present in the reaction mixture, the cyclic product is a silyl ether that contains an iodine atom (Scheme 22). Reaction of this product with fluoride ion eliminates...
both the silicon-containing group and an iodide ion and introduces additional unsaturation into the final product.

Scheme 21

Scheme 22

\( \text{Ar} = \text{C}_6\text{H}_5 \)
A process similar to that shown in Scheme 22 takes place in the reaction pictured in Scheme 23, where homolytic cleavage of the C–Se bond is followed by ring formation to generate the cyclic radical 44. If diphenyl diselenide (C₆H₅SeSeC₆H₅) is added to the reaction mixture, the yield of the unsaturated nucleoside 45 increases from 47% to 77%. Diphenyl diselenide reduces competing radical reactions (e.g., hydrogen-atom abstraction) by rapidly reacting with 44 to form an intermediate selenide from which the product 45 is produced by an elimination reaction.\(^{115b}\)

C. Alkenyl and Alkynyl Ethers, Esters, Acetals, and Alcohols

A molecule with an \(O\)-allyl\(^{5,9,45,58,134-146}\) or an \(O\)-propargyl\(^{21,147-157}\) group and a properly positioned, radical-forming substituent will react to form a new ring system. Equations 22\(^{136}\) and 23\(^{152}\) describe reactions of compounds of this type. These reactions take place even though ring formation produces highly reactive radicals, a primary radical from an allyl ether (eq 24) and a vinylcic one from a propargyl ether (eq 25). Not surprisingly, ring formation takes place readily in compounds where cyclization does not need to produce such reactive radicals; in fact, as long as reactive centers can come within bonding distance, radical cyclization occurs in a wide variety of unsaturated radicals.\(^{158-186}\) Some specific examples are shown in equations 26 and 27, where ring formation takes place in molecules in which the multiple bond is located in an existing ring system (eq 26)\(^{159}\) or is part of an acyclic structure (eq 27).\(^{185}\)
Cyclization takes a different course in its final stage when a radical is formed by electron transfer from samarium(II) iodide. In such a reaction the cyclic radical reacts with additional SmI₂ to form an organosamarium intermediate that undergoes elimination to produce a carbon–carbon double bond (Scheme 24). In the reaction shown in Scheme 24 an O-acetyl group is eliminated, but even a hydroxyl group (presumably complexed with SmI₂) can depart in forming the double bond (eq 28).
The course of radical cyclization in allyl ethers and related compounds sometimes is altered by internal hydrogen-atom abstraction.\(^{58,88,134,138,171,172,185}\) Hydrogen-atom abstraction by a carbon-centered radical from a C–H bond does not take place readily. The best possibility for this type of reaction occurs when a radical is particularly reactive [e.g., the primary radical produced from an allyl ether (eq 24) or the vinyl radical from a propargyl ether (eq 25)] and the abstraction is internal. Such reaction happens following cyclization of the pyranos-1-yl radical 46 (Scheme 25).\(^{58,134,138}\) Although the radicals 47 and 48, produced in this reaction, are both primary, only 48 has the proper stereochemistry for internal hydrogen-atom abstraction. In a similar reaction the vinylic radical 49, produced during ring formation, abstracts a hydrogen atom from the
neighboring O-benzyl group in route to formation of a mixture of cyclic compounds (Scheme 26).\(^{172}\)

**D. Compounds with Terminal Triple Bonds**

A triple bond in a molecule can have more than one role in a radical cyclization reaction. In addition to being the multiple bond that combines with a radical centered on a carbon atom elsewhere in the molecule, as occurs in the reaction shown in eq 27, a triple bond also can be the source for a carbon-centered radical that adds to another multiple bond.\(^{188}\) When a radical (usually the tri-n-butyltin radical) reacts with the triple bond in a compound such as the propargyl ether 50 to form a vinylic radical, rapid internal reaction of this radical takes place if there is a second multiple bond within bonding distance (Scheme 27\(^{190}\)).\(^{189-200}\)

Although the tri-n-butyltin radical also can add to a double bond,\(^{75}\) triple bond addition is a far more likely beginning step in a cyclization reaction.\(^{193,201}\) The difference in reactivity between a double and a triple bond is apparent in the reaction shown in eq 29,\(^{193}\) where a triple bond reacts in preference to a similarly positioned double bond. These differences in reactivity between double and triple bonds are determined by the rate of radical cyclization rather than stannyl radical addition. The stannyl radical actually adds more rapidly to a double bond than to triple bond, but the
adduct radical from addition to a double bond reverts more rapidly and cyclizes more slowly than that from addition to a triple bond.\textsuperscript{201}

\textbf{Scheme 26}

\textbf{Scheme 27}

E. Compounds in Which the Multiple Bond is not Electron-Deficient

If a carbon-centered radical and a multiple bond are in separate molecules, radical addition only competes effectively with other radical reactions (e.g., hydrogen-atom abstraction) when the
multiple bond is electron-deficient. If this bond is not electron-deficient, successful addition is rare and requires conditions that minimize competing reactions. When the two reactive centers are in the same molecule and can come into close proximity, cyclization can be competitive when the multiple bond is not electron-deficient (eq 35\(^{5,183,202-210}\)). In fact, even if this bond is electron-rich, ring formation can take place (eq 30\(^{211-221}\)).

\[
\begin{align*}
\text{Et}_3\text{B} - \text{O}_2 & \quad \text{Bu}_{3}\text{SnH} \\
& \quad \text{C}_6\text{H}_5\text{CH}_3 \\
\text{OEt} & \quad \text{H} \\
(\text{C}_5\text{H}_3)_2\text{Sn} & \quad \text{(29)} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{Si}(\text{C}_6\text{H}_3)_{2\dagger}\text{-Bu} & \\
\text{C}_6\text{H}_5 & \\
\text{OEt} & \\
\text{Br} & \\
\text{OEt} & \\
\text{C}_6\text{H}_5 & \quad \text{(30)} \\
\end{align*}
\]

The framework in a typical sugar has one of the three structural types shown above. (A hexose is used as an example.) A framework radical is one centered on a numbered carbon atom, and a framework multiple bond is one involving at least one of these atoms.

**Figure 1.** Possible carbohydrate frameworks

V. An Organization for Carbohydrates That Undergo Radical Cyclization

It is useful in organizing radical cyclization reactions to divide them into groups that have common features. One method for doing this places radicals of similar structure together. Where carbohydrates are concerned, such a plan can be based on the location of the radical center and the multiple bond. A radical center can exist on an atom that is part of the molecular framework...
(Figure 1) or part of a substituent group. The same possibilities exist for the multiple bond. Cyclization reactions of carbohydrates then naturally divide into the four basic types shown in Figure 2. (A short-hand terminology describing these four types has been proposed and is included in Figure 2.) This division provides the basis for constructing Tables 1-4. In addition to these four tables, two smaller ones are included in recognition of the importance of radical cyclization reactions in the synthesis of nucleosides (Table 5) and carbon-linked disaccharides (Table 6.)

---

**VI. Summary**

Forming a new ring by internal addition of a carbon-centered radical to a multiple bond is a powerful tool in carbohydrate synthesis. Regioselectivity and stereoselectivity are vital aspects of
this type of reaction. Being able to predict regioselectivity is critical because a cyclization reaction potentially can form rings of two sizes. Since the newly formed ring nearly always has an additional chiral center (sometimes two), understanding stereoselectivity is essential in predicting stereochemistry in the cyclic product.

Compounds with five-membered rings are the ones most often produced by radical cyclization. Reactions that form five-membered rings are capable of generating six-membered rings also, but rarely do so because the transition state leading to the larger ring has greater ring strain. Compounds with six-membered rings are the major products when cyclization is capable of forming either six- or seven-membered rings consisting only of second row elements. Larger rings (seven or more members) are created when a radical center and a distant multiple bond are linked by a tether, usually one containing a silicon–oxygen bond.

The stereoselectivity of reactions that produce five- and six-membered rings usually can be rationalized by assuming that the reaction passes through a chair-like transition state. The lowest energy transition state for such a reaction has as many substituents as possible in pseudoequatorial positions. A variety of factors (pseudo-1,3-diaxial interaction, allylic strain, hydrogen bonding, conformation of an existing ring) affect transition-state energy and can, on occasion, cause a boat-like transition state to be more stable than a chair-like one.

Various types of unsaturated carbohydrates, often α,β-unsaturated esters, undergo radical cyclization. Also prominent among reactive compounds are those in which the radical-forming part of the molecule and the portion containing the multiple bond are connected by a silicon–oxygen tether. A third group of compounds that cyclize readily includes allyl and propargyl ethers and related compounds.
Table 1. Framework Radical Reacting With a Framework Multiple Bond

<table>
<thead>
<tr>
<th>radical forming substituent</th>
<th>type of multiple bond</th>
<th>number of atoms in the new ring</th>
<th>references</th>
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<td>−CH=CHCH2O−</td>
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<td>CH2=CHCH−O−</td>
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<td>168</td>
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<tr>
<td>I</td>
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<td>−CH=CHCO2Me</td>
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<td>61</td>
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<td>186</td>
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<tr>
<td>I</td>
<td>HC≡CH−O−</td>
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</tr>
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<td>87, 89</td>
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<td>Br</td>
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Table 1. Framework Radical Reacting With a Framework Multiple Bond (Continued)

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<td>HCC≡CH−O−</td>
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<td>179, 180, 219</td>
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Table 1. Framework Radical Reacting With a Framework Multiple Bond (Continued)

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Table 2. Framework Radical Reacting With a Substituent Multiple Bond

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<td>CH$_2$═CHCH$_2$O$\equiv$</td>
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<td>204</td>
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<tr>
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<td>203, 206, 209</td>
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<tr>
<td>Br</td>
<td>CH$_2$═CHC(Me)$_2$O$\equiv$</td>
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<td>Br</td>
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Table 2. Framework Radical Reacting With a Substituent Multiple Bond (Continued)

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<th>number of atoms in the new ring</th>
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Table 2. Framework Radical Reacting With a Substituent Multiple Bond (Continued)

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<td>C₆H₄OC(=S)O</td>
<td>CH₂=CHCH₂O⁻</td>
<td>5</td>
<td>157</td>
</tr>
<tr>
<td>C₆H₄OC(=S)O</td>
<td>CH₂=CHO⁻N⁻</td>
<td>6</td>
<td>220</td>
</tr>
<tr>
<td>ImC(=S)O</td>
<td>CH=CHCO₂⁻</td>
<td>5</td>
<td>72, 73, 74</td>
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<tr>
<td>ArSO₂</td>
<td>CH₂=CHSiO⁻</td>
<td>5</td>
<td>117</td>
</tr>
<tr>
<td>C₆H₅SO₂</td>
<td>CH₂=CHCH₂O⁻</td>
<td>5</td>
<td>137</td>
</tr>
<tr>
<td>ArSO₂</td>
<td>RC≡CSSiO⁻</td>
<td>5</td>
<td>117</td>
</tr>
<tr>
<td>C≡CH</td>
<td>OCH=CHCO₂Et</td>
<td>5</td>
<td>199</td>
</tr>
<tr>
<td>C≡CH</td>
<td>OCH=CHCO₂Et</td>
<td>6</td>
<td>199</td>
</tr>
<tr>
<td>C≡CH</td>
<td>OCH=CHCO₂Et</td>
<td>7</td>
<td>199</td>
</tr>
<tr>
<td>C≡CH</td>
<td>OCH=CHCO₂Et</td>
<td>8</td>
<td>199</td>
</tr>
<tr>
<td>NO₂</td>
<td>HC≡CC₂H₂O⁻</td>
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<td>153</td>
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<td>C(=O)H</td>
<td>CH≡CC(=O)NH⁻</td>
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<td>101</td>
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</table>
### Table 3. Substituent Radical Reacting With a Framework Multiple Bond

<table>
<thead>
<tr>
<th>radical forming substituent</th>
<th>type of multiple bond</th>
<th>number of atoms in the new ring</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>-CH=CHCH-O-</td>
<td>5</td>
<td>21, 6, 7,109, 159</td>
</tr>
<tr>
<td>I</td>
<td>-CH=CHCO$_2$Et</td>
<td>6</td>
<td>6, 7</td>
</tr>
<tr>
<td>I</td>
<td>HC≡CCH-O-</td>
<td>5</td>
<td>185</td>
</tr>
<tr>
<td>Br</td>
<td>-CH=CHCH-O-</td>
<td>5</td>
<td>21, 81, 109,124-127, 129,132, 159, 163</td>
</tr>
<tr>
<td>Br</td>
<td>CH$_2$=CHCH-O-</td>
<td>6 + 7</td>
<td>184</td>
</tr>
<tr>
<td>Br</td>
<td>CH$_2$=CHCH-O-</td>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td>Br</td>
<td>-CH≡CCH-O-</td>
<td>6</td>
<td>130</td>
</tr>
<tr>
<td>Br</td>
<td>-C≡C-O-</td>
<td>5</td>
<td>124, 133, 183, 211, 212, 214, 218</td>
</tr>
<tr>
<td>Br</td>
<td>-CH=C-O-</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Br</td>
<td>-C≡C-O-</td>
<td>5 + 6</td>
<td>23, 215, 217</td>
</tr>
<tr>
<td>Br</td>
<td>-C≡C-O-</td>
<td>5</td>
<td>23, 216</td>
</tr>
<tr>
<td>Br</td>
<td>-CH=CCO$_2$Me</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>Br</td>
<td>-CH=CHCO$_2$Et</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Br</td>
<td>CH$_2$=CCO$_2$Me</td>
<td>9</td>
<td>94</td>
</tr>
<tr>
<td>Br</td>
<td>CH$_2$≡CCN</td>
<td>9</td>
<td>94</td>
</tr>
<tr>
<td>Br</td>
<td>-CH=CHCHO</td>
<td>5</td>
<td>109</td>
</tr>
<tr>
<td>Cl</td>
<td>-CH=CHCH-O-</td>
<td>5</td>
<td>152, 162</td>
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<tr>
<td>-C≡CH</td>
<td>-CH=CHCH-0-</td>
<td>5</td>
<td>21, 190-193, 195</td>
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<td>-C≡CH</td>
<td>-C≡C-O-</td>
<td>5</td>
<td>192, 214</td>
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<tr>
<td>-CH$_2$C≡CH</td>
<td>-CH=CHCH-O-</td>
<td>5</td>
<td>195</td>
</tr>
<tr>
<td>C$_6$H$_5$(=S)O-</td>
<td>-CH=CHCO-</td>
<td>5</td>
<td>221</td>
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### Table 4. Substituent Radical Reacting With a Substituent Multiple Bond

<table>
<thead>
<tr>
<th>radical forming substituent</th>
<th>type of multiple bond</th>
<th>number of atoms in the new ring</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>-CH=CC≡O</td>
<td>5</td>
<td>110, 111</td>
</tr>
<tr>
<td>I</td>
<td>CH₂≡CH⁻</td>
<td>5</td>
<td>111</td>
</tr>
<tr>
<td>I</td>
<td>-CH=CC(=O)NH⁻</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>I</td>
<td>-CH≡CHCO₂⁻</td>
<td>10</td>
<td>44</td>
</tr>
<tr>
<td>Br</td>
<td>CH₂≡CHCH₂O⁻</td>
<td>11</td>
<td>45</td>
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<tr>
<td>Br</td>
<td>CH₂≡CH⁻</td>
<td>6</td>
<td>111, 205</td>
</tr>
<tr>
<td>Br</td>
<td>HC≡CCH₂O⁻</td>
<td>5</td>
<td>156</td>
</tr>
<tr>
<td>HC≡C⁻</td>
<td>CH₂≡CHCH₂O⁻</td>
<td>5 + 6</td>
<td>194</td>
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<tr>
<td>HC≡C⁻</td>
<td>-CH≡CH⁻</td>
<td>5</td>
<td>197, 198</td>
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<tr>
<td>HC≡C⁻</td>
<td>-CH≡CH⁻</td>
<td>5</td>
<td>197</td>
</tr>
<tr>
<td>HC≡C⁻</td>
<td>(CH₃)₂C≡CHCH₂O⁻</td>
<td>5 + 6</td>
<td>194</td>
</tr>
<tr>
<td>HC≡C⁻</td>
<td>-CH≡CHC(=O)N⁻</td>
<td>6</td>
<td>200</td>
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<tr>
<td>HC≡O</td>
<td>CH₂≡CHCH⁻</td>
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### Table 5. Nucleoside Synthesis

<table>
<thead>
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<th>type of multiple bond</th>
<th>number of atoms in the new ring</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>-CH≡CHCO₂Et</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>C₆H₅Se</td>
<td>-CH≡CHCO₂Me</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>C₆H₅OC(=S)O</td>
<td>-CH≡CHCO₂Et</td>
<td>5</td>
<td>79</td>
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</table>
Table 6. Carbon-Linked Saccharides

<table>
<thead>
<tr>
<th>radical forming substituent</th>
<th>type of multiple bond</th>
<th>number of atoms in the new ring</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CH=CHCH−O−</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>I</td>
<td>CH2=CO−</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>I</td>
<td>CF2=CO−</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>C6H5Se</td>
<td>CH2=CH−O−</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>C6H5Se</td>
<td>CH2=CH−O−</td>
<td>8</td>
<td>31, 32, 35, 38, 43</td>
</tr>
<tr>
<td>C6H5Se</td>
<td>CH2=CH−O−</td>
<td>9</td>
<td>38-41, 43, 46</td>
</tr>
<tr>
<td>C6H5Se</td>
<td>CH2=CH−O−</td>
<td>11</td>
<td>38</td>
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<td>C6H5Se</td>
<td>CH2=CO−</td>
<td>8</td>
<td>33, 34</td>
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<td>C6H5SO2</td>
<td>CH2=CH−O−</td>
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<td>5</td>
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VII. References

Comounds With Carbon–Carbon Multiple Bonds II: Cyclization Reactions

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