Radical Reactions in Natural Product Synthesis

CRAIG P. JASPERSE*

Department of Chemistry, University of North Dakota, Box 7185, University Station, Grand Forks, North Dakota 58202

DENNIS P. CURRAN*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

THOMAS L. FEVIG*

Schering-Plough Corporation, B-8-325, 60 Orange Street, Bloomfield, New Jersey 07003

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I. Introduction

The use of radicals[1] in organic synthesis has increased dramatically within the last decade. At the beginning of the 1980's, the place of radical reactions in natural products total synthesis was limited to a few important functional group transformations (such as the Barton–McCombie reaction[2]). However, during the past decade, radical carbon–carbon bond-forming reactions have grown in importance to the point where they are now routinely considered in strategy level planning of complex targets.[3] Recent progress in radical chemistry has been thoroughly reviewed from the standpoint of structure, reactivity, and synthetic methods.[4-9] The subject of the present review is the use of radical reactions in natural product synthesis. By summarizing accomplishments of the last decade, we hope to further expose the unique features of radical reactions for synthetic applications and to encourage the development of new, more sophisticated applications.

The review will emphasize issues of reactivity, chemoselectivity, regioselectivity, and stereoselectivity. We focus heavily on the synthesis of carbon–carbon bonds, although we do also cover several important methods that form carbon–heteroatom bonds. We do not discuss simple reduction and deoxygenation reactions, nor is there any coverage of photochemical reactions or of diradicals. We also do not cover $S_{RN}1$ reactions (although one should not overlook the beautiful cephalotaxine synthesis of Semmelhack[10]). The article is organized according to the methods by which radical reactions are conducted.[4,6] This is because, although all radical methods can effect similar transformations (radical additions and cyclizations), the success of a given transformation and the functionality contained in the final product depend heavily on the method chosen. Indeed, the choice of a method can influence synthetic planning at the strategy level. We assume that readers will be generally familiar with the key features of radical chemistry that pertain to preparative applications, although some basic features of each

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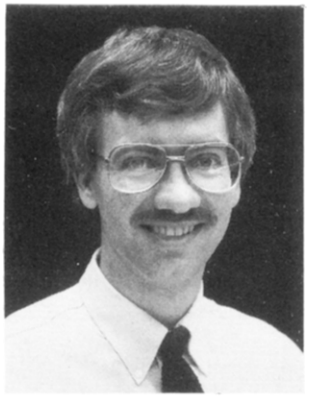


Craig Jasperse was born in 1960 in Sheboygan, WI. His undergraduate degree is from Calvin College and his Ph.D. (1987, Hans Reich) is from the University of Wisconsin—Madison. After postdoctoral study at the University of Pittsburgh (1987–1989, Dennis Curran), he became an assistant professor at the University of North Dakota. His research interests include ketyl radical anion rearrangements and oxidative ring expansion of bicyclic alcohols.

Dennis P. Curran received his B.S. in 1975 from Boston College (magna cum Laude). His Ph.D. was granted from the University of Rochester in 1979 where he worked under Andrew S. Kende and was the recipient of both Sherman Clark and Elon Huntington Hooker fellowships. After a two-year postdoctoral stay with Barry M. Trost at the University of Wisconsin as a National Institutes of Health (National Cancer Institute) postdoctoral fellow, Dr. Curran joined the faculty of the Chemistry Department at the University of Pittsburgh in September, 1981. He was promoted to the rank of Associate Professor in 1986, and Professor in 1988. Dr. Curran has been the recipient of Camille and Henry Dreyfus "Young Faculty" and "Teacher–Scholar" Awards, an Alfred P. Sloan Foundation Fellowship, an Eli Lilly Granteeship, a Merck Faculty Development Award, and a National Institutes of Health Research Career Development Award. In 1988, the American Chemical Society named Dr. Curran as a recipient of the Cope Scholar Award. Most recently, he has received an ICI Pharmaceuticals Group Award for Excellence in Chemistry, and, at the University of Pittsburgh, he has received the President's Distinguished Research Award. Dr. Curran's research interests lie in the area of natural products synthesis and the development of new synthetic methods. Programs are active in the areas of use of isoxazolines as aldol equivalents, and in the application of free-radical reactions to problems in organic synthesis.

method will be discussed. Those with little or no exposure to radical chemistry are encouraged to consult prior relevant treatments of radical chemistry.[3-9,11-14] About half of the review deals with chain reactions of metal hydride reagents; the other half is divided between addition–fragmentation chain reactions, atom-transfer chain reactions, and nonchain reduction and oxidation methods. We have tried to cover the literature through mid-1990.

Thomas L. Fevig was born in Kalamazoo, MI in 1958. He received degrees in mathematics (BA) and chemistry (BS) from Adrian College in Adrian, MI in 1981, and then entered graduate school at the University of Illinois at Champaign-Urbana. In 1986, he was awarded a Ph.D. degree in organic chemistry, working under the direction of John A. Katzenellenbogen. After a two year postdoctoral stint with Dennis P. Curran at the University of Pittsburgh, he joined Schering-Plough Corporation, where he is currently a senior scientist in Chemical Research. His research interests include medicinal chemistry and organic synthesis, especially that involving free-radical chemistry.

Radical reactions have a number of synthetic advantages which will become manifest throughout the review:

1. *Carbon-centered radicals are extremely reactive.* Nevertheless, radical addition reactions proceed under mild, neutral conditions, and the reactivity of radicals does not compromise a high level of chemo-, regio-, and stereoselectivity. Conformational restrictions often increase the rates and intensify the stereoselectivity of radical cyclizations in complex natural product syntheses. By contrast, problems of reactivity and especially chemoselectivity are often magnified by molecular complexity for ionic reactions.

2. *Radical additions to C=C bonds are usually exothermic and irreversible, with early, reactant-like transition states.* Reactions under kinetic control with early transition states often afford unique products that are unavailable by traditional ionic methods. Because transition states are early, ground-state structures of radicals often make good transition-state models, and ground-state structures of complex radicals can often be deduced from simple analogues.

3. Because radicals are not cluttered with counterions or aggregation spheres, because they are highly reactive, and because their reactions have early transition states, *radical intermediates are ideally suited for the synthesis of crowded bonds.* The facile formation of quaternary and neopentyl centers will be seen repeatedly throughout the review.

4. *Carbon-centered radicals are inert toward OH or NH groups.* Radical reactions do not need to be dry, and the protection of alcohols, amines, and related functional groups is often unnecessary. The same is rarely true for reactions involving carbanions (organometallics) or carbocations due to their respective basicity and electrophilicity.

5. In contrast to carbanions, *carbon radicals are not subject to β elimination of OR or NR_2 groups.* In contrast to carbocations, *carbon radicals are subject neither to capture by β-OR or -NR_2 groups nor mi-*

gration or elimination of β-H or -CR_3 groups. However, carbon radicals are subject to β elimination of SR, SO_nR, and SnR_3 groups, and these eliminations are key steps in some useful radical chains.

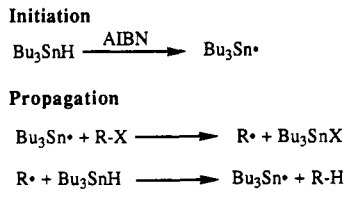
6. Most alkyl and alkenyl radicals have negligible barriers to inversion, such that *radical centers do not usually retain stereochemistry.* Stereochemical lability is not all bad, however, because it simplifies the synthesis of radical precursors.

II. The Tin Hydride Method

A. Introduction

Tributyltin hydride[15] is the reagent most commonly used to conduct free-radical reactions. Simple reduction of an organic halide by tin hydride involves a controlled chain reaction, as illustrated in Scheme 1. A site-

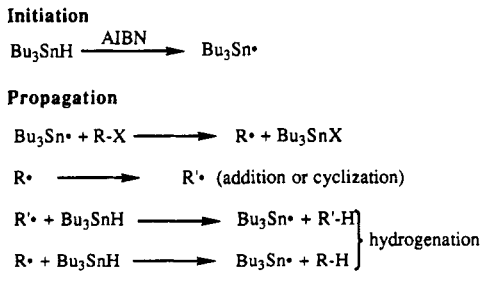
SCHEME 1



specific radical R• is generated from an organic substrate RX by atom or group abstraction. The radical R• then reacts with tin hydride to generate the reduced product RH and to regenerate Bu_3Sn•. The overall reaction is driven by the exchange of an R–X bond for a strong R–H bond, and the exchange of a Sn–H bond for a relatively strong Sn–X bond. The transferability of various atoms and groups X to tin radicals is generally in the order I > Br > SePh ≈ OC(S)SMe > Cl > SPh.[16,17] The reactivity of various R• toward tin hydride is aryl ≈ vinyl > alkyl > allyl ≈ benzyl. Primary, secondary, and tertiary alkyl radicals show very little difference in their reactivity toward tin hydride. At present, it is often assumed that carbonyl- or heteroatom-substituted radicals react with tin hydride at similar rates to alkyl radicals, although there is no hard evidence to support this assumption.

A carbon-centered radical R• can undergo reactions other than hydrogen atom abstraction (Scheme 2).

SCHEME 2



Addition to a multiple bond generates a new radical R'•, and intramolecular addition (cyclization) is particularly fast. If intra- or intermolecular radical addition is faster than hydrogen abstraction, then the initial radical R• is indirectly converted to R'H via R'•. If radical addition (or cyclization) and hydrogen atom abstraction are competitive, mixtures of RH and R'H result. Thanks to extensive physical studies, the absolute rates and the structural factors that affect the rates (and stereochemistry) of simple radical additions and rearrangements are well-understood.[9,18-20] A knowledge of the rates with which a radical R• is generated, rearranged, and trapped by tin hydride now permits the rational planning of such free-radical reactions.

The tin hydride method has several virtues compared to other radical reaction methods. Tin hydride is extremely mild and selective, so that carbonyl groups and alcohols do not need to be protected. The laboratory simplicity and sophisticated kinetic understanding of the tin hydride method also make it accessible and easy to use. A comparable knowledge of the rates of radical generation and of radical trapping is not presently available for any other radical method. Most important, the kinetic behavior of tin hydride is such that, when a radical R• is generated from a reactive radical precursor in the presence of a low concentration of tin hydride, it has a reasonably long lifetime within which to react (R• → R'•) before being trapped (R• → R–H). Tin hydride is excellent in generating a radical R•, allowing it a finite lifetime within which to react, but still eventually trapping the adduct radical R'•. The window of lifetime of a radical can be varied over a wide range simply by changing the tin hydride concentration.

A limitation of the method is that tin hydride is by nature a reducing agent. Under normal circumstances both a C–X functional group and a carbon–carbon π bond are sacrificed. A second limitation is that initial radicals R• as well as adduct radicals R'• are susceptible to hydrogen atom transfer. Tin hydride must react with R'• fast enough to maintain an effective chain reaction, but at the same time it must not trap R• prior to radical rearrangement. Although tin hydride allows R• a reasonably flexible window of reactivity, slow reactions sometimes cannot compete with direct reduction, so that desired products R'H are often contaminated by reduced starting material RH. Complete removal of tin-containing byproducts from desired products is frequently a problem, and several available solutions are discussed in reviews.[6,15] At the writing of this review, tris(trimethylsilyl)silicon hydride [$(TMS)_3SiH$, Chatgilialoglu's reagent] is emerging as a potential useful substitute for tin hydride[21] which has its own unique features as well.[22] It seems likely that the use of this reagent (or others like it) will increase.

B. Carbacycle Formation with Tin Hydride

1. Introduction

Although the tin hydride method was first applied in natural product synthesis to the construction of a 6-membered ring, radical cyclization reactions[23] are most often applied to the synthesis of 5-membered rings. There are three good reasons for this:

1. Cyclizations are usually faster for the formation of 5-membered rings than for any other ring size. The simple 5-hexenyl radical cyclizes 20 times faster than does the 6-heptenyl radical, for example.[19,20] Five-membered ring forming reactions are thus least subject to competitive formation of reduced, uncyclized byproducts.

2. The regioselectivity for 5-exo cyclizations is often outstanding.[19,20,23] For the parent 5-hexenyl radical, 5-exo cyclization is 50 times faster than 6-endo cycli-

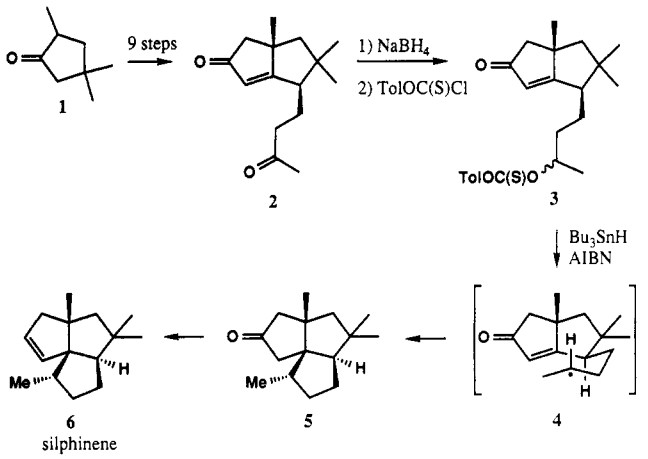
zation. Substituted examples often show higher selectivities.

3. Radical cyclizations giving 5-membered rings can be highly stereoselective.[19,20,24,25] The major product in a 5-exo radical cyclization can generally be predicted by using the Beckwith transition state model.[24] According to this model, the early transition state of a 5-exo radical cyclization resembles a cyclohexane ring, prefers the chair over the boat form, and prefers that substituents be pseudoequatorial rather than pseudoaxial.[19,20,24] Simple model studies show that substitution at C-1 or C-3 of the 5-hexenyl radical gives primarily cis-disubstituted cyclopentanes, whereas substitution at C-2 or C-4 gives primarily trans-disubstituted cyclopentanes. Stereoselectivity is highest for C-1 and C-4 substituted systems. A body of theoretical treatments[19,20] and experimental results now aid in the planning of highly stereoselective reactions, and allow "exceptions" to Beckwith's guidelines to be anticipated.[25]

2. 5-Membered Rings

A typical tin hydride promoted radical cyclization is central to Nagarajan's synthesis of the angular triquinane silphinene (6, Scheme 3).[26] Upon treatment

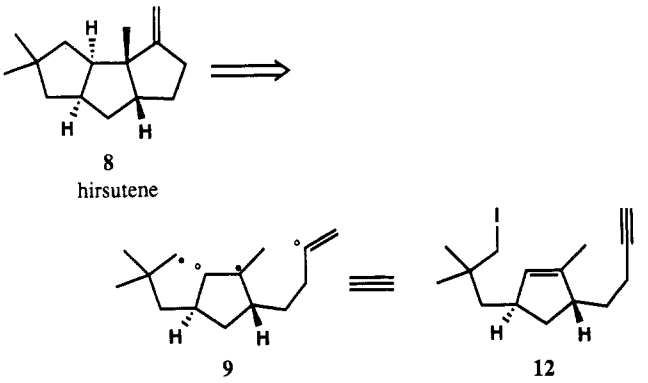
SCHEME 3



with tin hydride, the *p*-tolyl thionocarbonate **3** cyclized to give **5**, in 75% yield, as a single isomer. The stereochemistry of **5** follows from the chair-like transition state **4**. Both a neopentyl/tertiary and a neopentyl/quaternary center are produced in the cyclization reaction, illustrating the ability of radical cyclizations to create extremely hindered bonds. The cyclization is facilitated by carbonyl activation of the alkene. Cyclohexyl radical has been shown to add to methyl vinyl ketone more than 2500 times faster than to 1-hexene, for example.[27] This rate accelerating effect of electron-withdrawing substituents is explained by frontier orbital theory. Reactions of carbon-centered radicals with olefins are usually dominated by SOMO–LUMO mixing; in other words, the alkyl or vinyl radical is "nucleophilic" and the olefin is "electrophilic". The electron-withdrawing carbonyl substituent lowers the LUMO of the olefin and accelerates the radical addition. Frontier orbital theory also explains the experimental observation that increasing alkyl substitution on a radical normally increases its rate of cyclization (in the absence of overriding steric effects), because alkyl substituents raise the energy of the SOMO.[27] "Inverse-demand" reactions in which SOMO–HOMO mixing is more important are also known, however.[27]

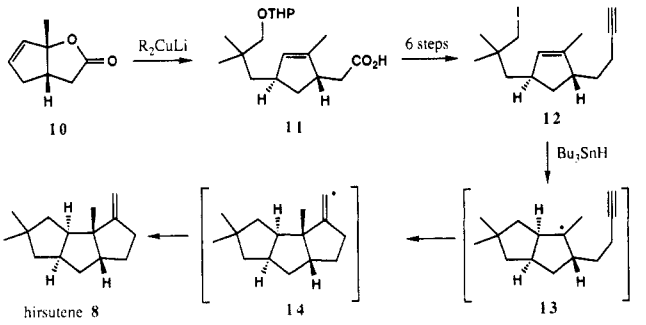
Although the adduct radical following a radical cyclization usually abstracts a hydrogen atom from tin hydride, it can cyclize again if another double or triple bond is appropriately positioned. The "tandem radical cyclization" strategy has been developed by Curran as a general approach to the triquinanes,[28] whose cis-fused 5-membered rings are suited to synthesis by radical methods. A retrosynthetic analysis of hirsutene (8) is shown in Scheme 4.[29]

SCHEME 4



According to a recently introduced notation, in which a closed dot "•" represents a radical and an open dot "∘" designates a site which reacts with a radical,[3,30] two rings can be attached to a central ring by a chain-to-ring cyclization followed by a ring-to-chain cyclization. In other words, the real synthetic equivalent of imaginary synthon **9** will have a central 5-membered ring containing a double bond and two side chains, one containing a radical precursor and the other containing an unsaturated bond as a radical acceptor. The actual radical precursor was assembled from the readily available lactone **10** (Scheme 5), which underwent anti

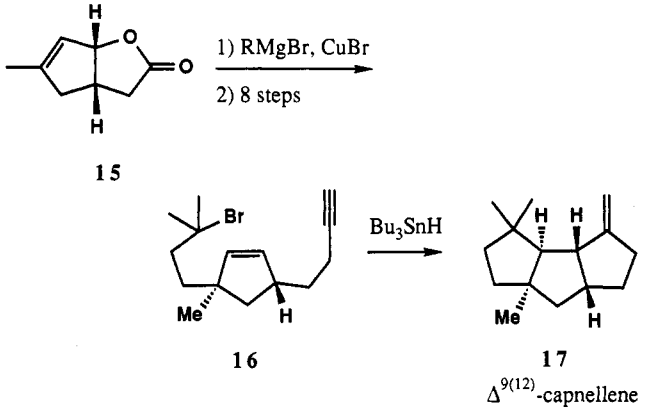
SCHEME 5



S_N2' cuprate addition to give **11**, with the desired trans relationship between the side chains. Routine elaboration provided the radical precursor **12**, and tandem radical cyclization gave hirsutene (**8**) in 65% isolated yield. In the second cyclization, the tertiary radical **13** cyclized to produce vinyl radical **14**. This might seem to be an unfavorable process because tertiary alkyl radicals are more stable than vinyl radicals. But the cyclization remains exothermic and fast because a σ bond is formed at the expense of a π bond. This success is in contrast to anion and cation cyclizations, where the stability of the anion or cation in the product relative to that in the starting material often plays a central role in determining the rate.

The synthesis of $\Delta^{9(12)}$-capnellene (17), summarized in Scheme 6, is similar to that of hirsutene.[31] Cuprate

SCHEME 6



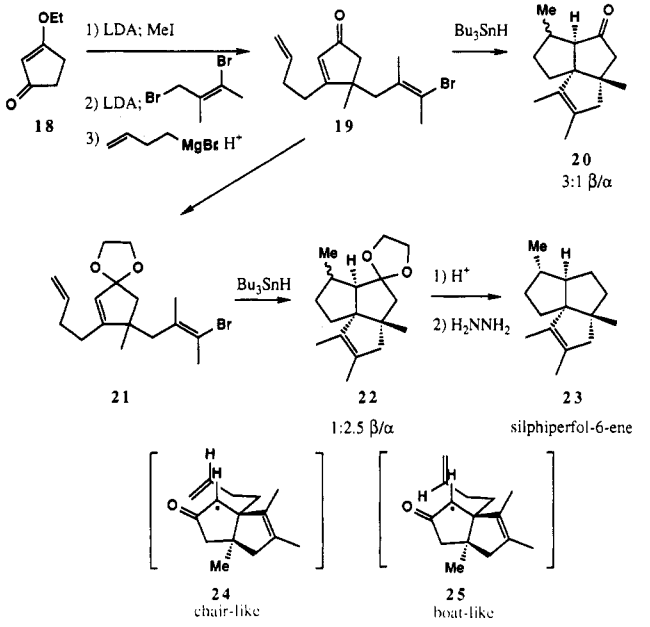
15 16 17

$\Delta^{9(12)}$-capnellene

addition to 15 was regio- and stereoselective, and side-chain elaboration provided the tertiary bromide 16, which cyclized to 17 in 61% isolated yield. Curran has also used the tandem radical cyclization strategy to make the more complex oxygenated linear triquinanes coriolin and hypnophilin by using SmI_2 methods in place of tin hydride (see section VI.B).

The angular triquinane silphiperfol-6-ene (23) has been prepared by a related tandem radical cyclization sequence (Scheme 7).[32] The cyclization precursor 19

SCHEME 7



18 19 20 (3:1 β/α) 21 22 (1:2.5 β/α) 23 (silphiperfol-6-ene)

24 (chair-like) 25 (boat-like)

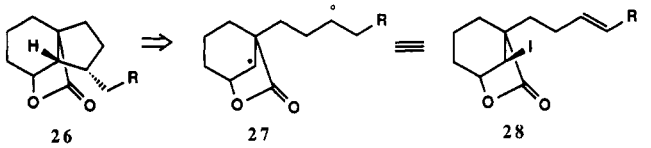
was rapidly assembled (three steps) in 45% overall yield from 18. Radical cyclization of 19 provided a 3:1 mixture of isomers 20 in 66% yield, but in the major stereoisomer the methyl group was β, contrary to the target product. The stereochemistry probably resulted from the chairlike transition state 24 in which the olefin terminus orients itself endo rather than exo relative to the existing ring, leading to the thermodynamically less stable product. In order to disfavor transition state 24 relative to boatlike transition state 25, the carbonyl group was sterically "enlarged" by conversion to the ketal 21, which cyclized in 65% overall yield. A 1:2.5 mixture of isomers formed, with the desired α-methyl isomer predominating. Meyers and Lefker have enhanced the attractiveness of this strategy by introducing a concise asymmetric synthesis of 19.[32b]

That comparable yields were observed by using either ketone 19 or ketal 21 shows that carbonyl activation of the alkene in the first cyclization is not crucial. The first cyclization certainly benefited from use of a vinyl radical, however. Vinyl radicals are much more reactive toward cyclization than are alkyl radicals; 5-exo cyclizations by vinyl radicals are ≥1000 times faster than cyclizations involving analogous alkyl radicals.[33,34] That the precursors (19 or 21) have the "wrong" geometry of the vinyl bromide for radical cyclization is not a problem. The observed stereochemical inversion of the vinyl radical is typical. Most vinyl radicals have low inversion barriers and equilibrate rapidly at normal operating temperatures. These features of vinyl radical cyclizations were first described by Stork.[33] The tandem radical cyclization involved in the formation of 22 again demonstrates the ability of radical cyclizations to generate very crowded bonds. In the first cyclization step, a quaternary center and a tetrasubstituted olefin formed, and in the second step, two tertiary centers formed, one of them neopentyl on two sides! The rational control of stereochemistry in this synthesis is also interesting. That the thermodynamically disfavored endo product 22β formed significantly, even in the presence of the ketal, emphasizes the bias for the chair-like transition state 24 rather than the boat-like 25.

Some other applications of tandem radical reactions that use the tin hydride method include Fraser-Reid's synthesis of (−)-α-pipitzol (further discussed in Scheme 14),[35] Kilburn's synthesis of isoiridomycin,[36] Parson's approach to pyrrolizidine alkaloids,[37] Parson's approach to the hexahydrobenzofuran portion of the avermectins,[38] Ferrier's approach to azadirachtin and bissetone,[39] Stork's synthesis of (+)-prostaglandin $F_{2\alpha}$ (further discussed in Scheme 36),[40] Maillard's synthesis of steroids,[41] Corey's biomimetic synthesis of 8-*epi*-prostaglandin $F_{2\alpha}$,[42] Nagano's synthesis of 1-*epi*-magydardienediol,[43] and Parson's approach to lysergic acid derivatives.[44]

Hart's clever approach to *trans*-perhydroindans involving a stereoselective radical cyclization is shown in Schemes 8 and 9.[45,46] In this analysis (Scheme 8) a

SCHEME 8

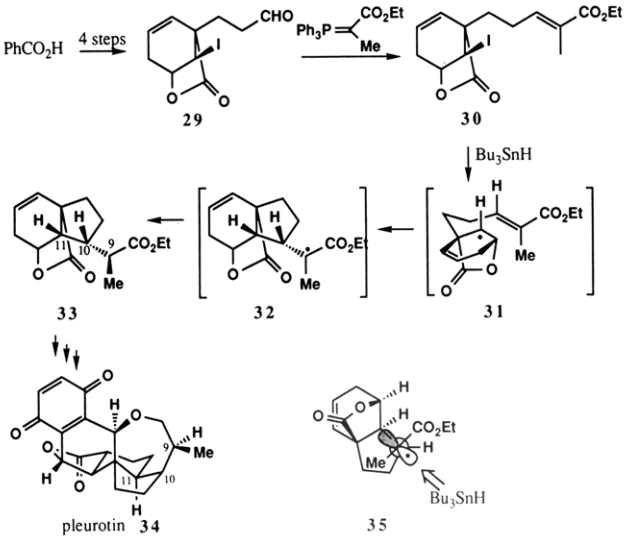


26 27 28

trans-perhydroindan 26 is disconnected to give the imaginary radical synthon 27. The reagent equivalent to 27 is the iodolactone 28.

In the elegant synthesis of the quinonoid antitumor antibiotic pleurotin (34, Scheme 9),[47] reductive alkylation of benzoic acid followed by iodolactonization gave 29 in 54% overall yield. Stereoselective Wittig olefination then gave the cyclization precursor 30 in 94% yield. Radical cyclization of 30 gave an 81% yield of *trans*-perhydroindan 33, in which three new stereocenters were established. Both a 5,5 and a 5,6 ring fusion formed; the smaller, less flexible 5-membered ring lactone dictated ring fusion stereochemistry so that

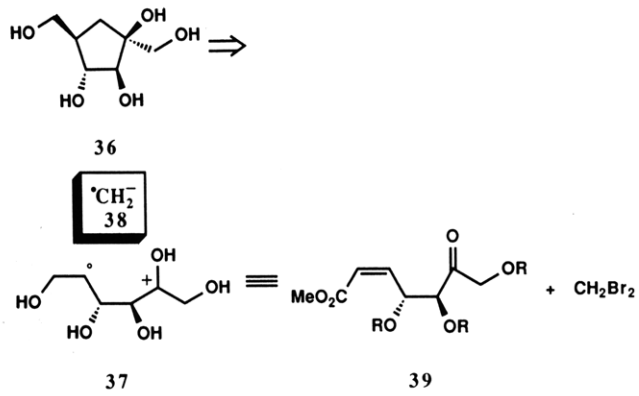
SCHEME 9



the 5,5 ring juncture formed cis and the 5,6 juncture was forced to be trans. The bridged lactone ring thus served as a powerful stereocontrol element to overcome the normal preference for *cis*-perhydroindan formation. The stereochemistry of C-10 was also established in the cyclization step. Formation of the less stable isomer in which the side chain occupies the convex position follows the guideline that 1-alkyl-5-hexenyl radicals generally give 1,5-cis-disubstituted cyclopentanes and is consistent with the chairlike transition state **31**. The high stereocontrol of C-9 was more surprising (the C-9 stereoisomer of **33** formed in only 4% yield). The C-9 stereochemistry was determined not in the cyclization step but during subsequent hydrogen transfer to radical **32**. Formation of isomer **33** may result from approach of tin hydride to the less hindered face of the delocalized radical in conformation **35** (A-strain is minimized). The stereochemical result did not depend on the stereochemistry of the starting olefin nor on the presence of the lactone carbonyl. Hart has shown that ester activation of the alkene in radical **31** is critical;[46] an unsubstituted olefin cyclized more slowly and with modest regioselectivity.

Because radical cyclizations proceed under mild, neutral conditions, and because oxygen functionalities do not trap, protonate, or β-eliminate from radicals, radical methods are nicely suited to applications in sugar chemistry. Wilcox's synthesis of carba-D-fructofuranose (**36**), the carbacyclic analogue of the enzyme regulator fructose 2,6-diphosphate, is illustrative.[48,49] The retrosynthetic analysis, shown in Scheme 10, depended on the use of a nucleophile–radical donor synthon **38** and an electrophile–radical acceptor synthon **37**.

SCHEME 10



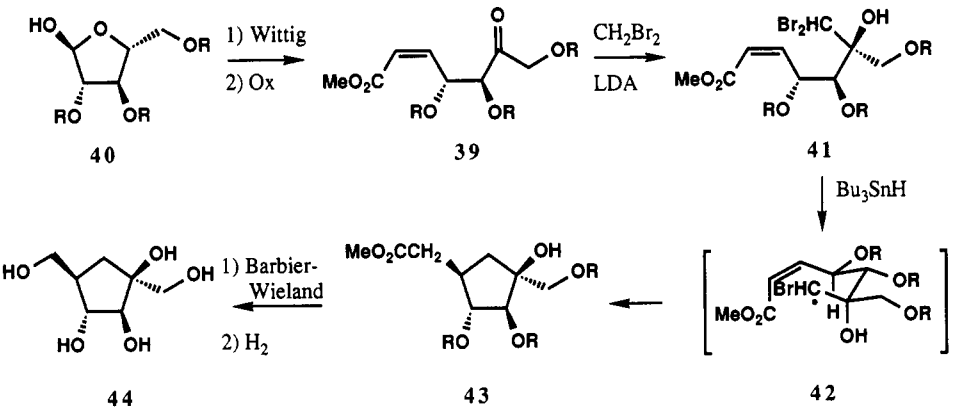
The actual synthesis (Scheme 11) began with the D-arabinose derivative **40**, which upon Wittig olefination and Swern oxidation was converted to the ketone, **39**, whose ketone and alkene groups make it the synthetic equivalent of synthon **37**. Nucleophilic addition of (dibromomethyl)lithium, the synthetic equivalent of synthon **38**, provided radical cyclization precursor **41** as a single isomer. The crucial radical cyclization was carried out by using an excess of tin hydride and provided **43** in 85% yield also as a single isomer. An intermediate cyclopentanoid bromohydrin probably formed, but it was debrominated under the reaction conditions. The "extra" bromine in this synthetic sequence is a coincidental result of the use of dibromomethyl lithium for the one-carbon synthon **38**, but it is interesting to speculate that it might improve the odds of cyclization, (there are two chances to cyclize, rather than one) and might also affect the stereoselectivity of cyclization. This radical cyclization proceeded chemoselectively in the presence of several ethers, an ester, and a free hydroxyl group. The hydroxyl group did not undergo β elimination from the radical **42**, and no racemization occurred. This selectivity shows that radical reactions can reduce numbers of protection and deprotection steps often required during carbohydrate manipulations.

The stereochemistry of the product is consistent with the chair-like transition state **42**. Wilcox has also found for cyclizations of this type that stereoselectivity is poorer when *E* olefins are used instead of *Z* olefins.[50] The superior stereoselectivity of radical cyclizations involving *Z* rather than *E* olefins is general and is most pronounced when the allylic position (C-4 in the 5-hexenyl radical numbering system) is substituted. These trends presumably result from normal allylic conformational effects and varying degrees of allylic 1,3-strain in competing transition states.[51] An approach similar to Wilcox's has been used by Jones and Roberts in their synthesis of the carbacyclic nucleotide (−)-5′-homoaristeromycin from L-ribonolactone.[52]

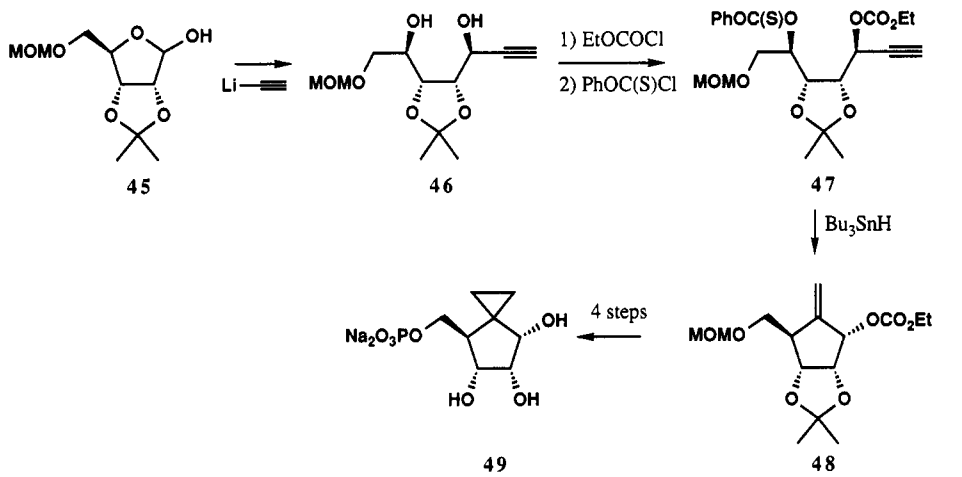
Wilcox has synthesized **49**, a carbacyclic analogue of 5-phospho-α-D-ribofuranose, from ribose by using a different but equally concise strategy (Scheme 12).[53] Stereoselective alkylation of **45** and alcohol differentiation provided **47**, which cyclized in 63% yield to give **48** as a 6.4:1 mixture of diastereomers.

The synthesis of carbacycles from carbohydrates by using radical cyclizations has been studied in depth by RajanBabu.[25] These studies have provided new insights on the importance of "chairlike" relative to "boatlike" transition states. RajanBabu's synthesis of Corey's lactone **54**, a well-documented prostanoid intermediate, is illustrative of this chemistry (Scheme 13).[25b] 3-Deoxyglucose **50** was converted to a mixture of enol ethers **51** in 7 steps. Radical cyclization of **51** gave **53** as the exclusive cyclization product, in 58% yield.[54] This cyclization illustrates several important principles. First, it shows radical deoxygenation of alcohols[2] via thiocarbamates (thiocarbonates, xanthate esters, and other analogues are also useful). Second, it demonstrates that a 6-membered ring radical does *not* need an axial radical acceptor in order to undergo cycliza-

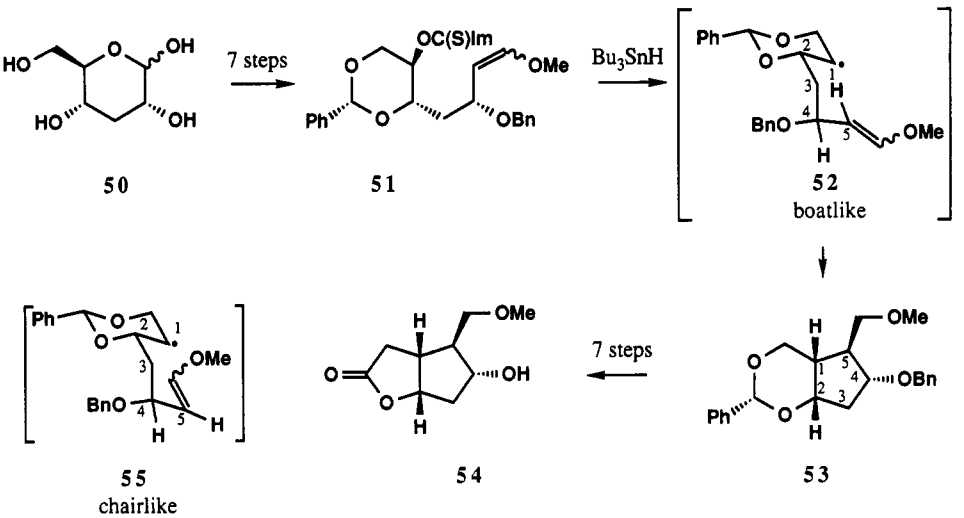
SCHEME 11



SCHEME 12

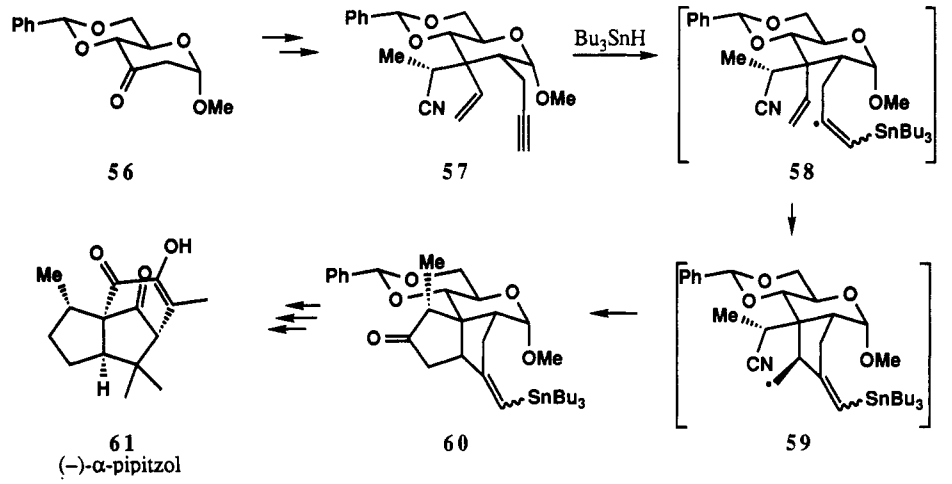


SCHEME 13

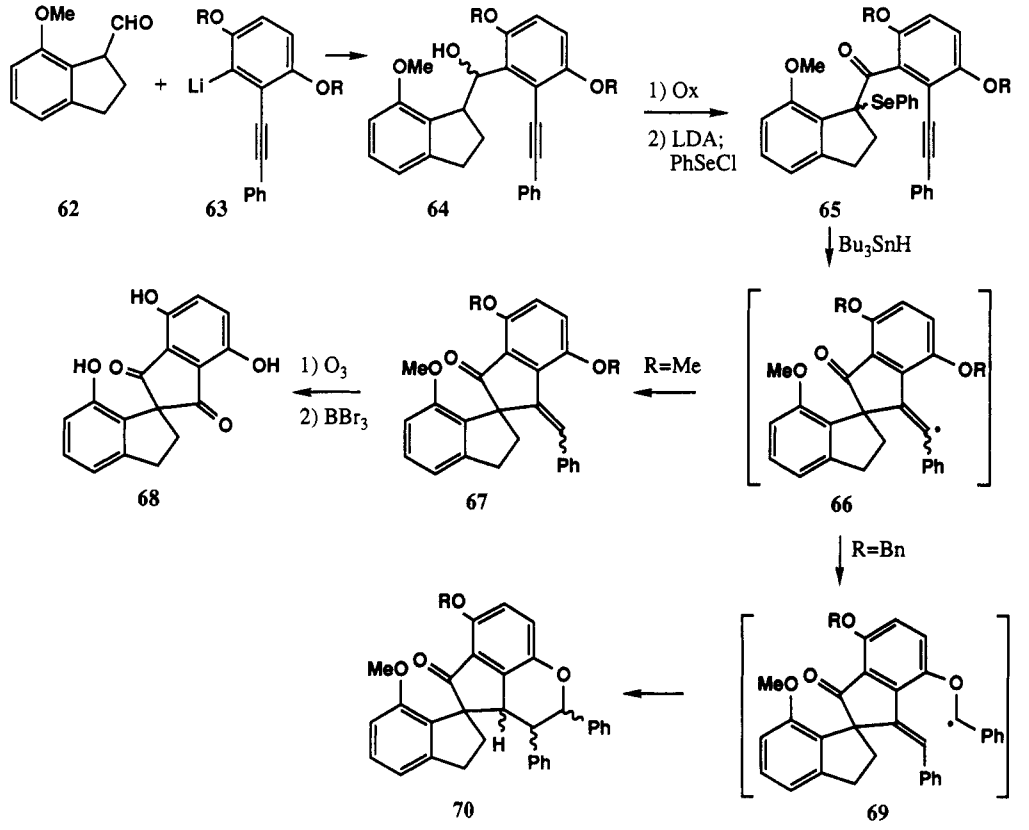


tion.[25c] The phenyl group anchored the 6-membered ring of **52** such that the side chain was held in an equatorial orientation. Third, the cyclization resulted in trans C4–C5 and trans C1–C5 stereochemical relationships relative to the newly formed 5-membered ring (see boat-like transition state **52**). This stereochemical result was dictated by the configuration of C4; if the benzyloxy group was either removed or inverted, the normal (according to Beckwith's guidelines) C1–C5 cis relationship resulting from a chairlike transition state was restored. The chairlike transition state **55** is presumably disfavored because of the local allylic conformation (C3–C6); the benzyloxy group in **55** would be pseudoaxial, and the local allylic conformation would be destabilized by $A^{1,3}$ strain. Thus, emerging general guidelines are that 4-substituted 5-hexenyl radicals give predominantly 4,5-trans-substituted rings and that *Z*-substituted olefins are more selective than *E* olefins. The first guideline takes priority even when in conflict with the normal preference for chairlike transition states.[25,55] Miwa has used a deoxygenation–cyclization strategy related to that of RajanBabu in the synthesis of the chiral iridoid glycoside aglycone 1-α-*O*-methylloganin from 2,3-anhydro-α-D-lyxopyranoside.[55]

SCHEME 14



SCHEME 15



Fraser-Reid has used an interesting tandem radical cyclization in his carbohydrate-to-carbacycle synthesis of (−)-α-pipitzol **61** (Scheme 14).[35] The pyranoside **56** was converted to **57**, which reacted with tin hydride to give **60** in 65% yield. Product **60** was readily destannylated by treatment with acid. In the context of the tin hydride method, the reaction is unusual in that the radical was generated by a stannyl radical addition, rather than an atom or group abstraction. The mechanism involves addition of tin radical to the alkyne, stereoselective cyclization of the vinyl radical **58**, and addition of alkyl radical **59** to the nitrile. The addition of tin radicals to alkenes or alkynes is normally reversible with an unfavorable equilibrium, but in the present case the vinyl radical **58** is trapped selectively and irreversibly by cyclization.[56] Alkynes have also been used as vinyl radical precursors in Oshima's syntheses of dehydroiridodiol and isodehydroiridodiol,[57] and in Subba Rao's synthesis of seychellene.[58]

Clive has applied the ability of radical cyclizations to generate quaternary centers toward the synthesis of the spiro-fused ring system present in fredericamycin A.[59] The synthesis, shown in Scheme 15, uses an alkyne as a radical acceptor and as a carbonyl synthon.[60] Addition of the aryllithium reagent **63** to the aldehyde **62** gave the alcohols **64**. Oxidation and selenation of **64** gave the radical precursor **65**, and radical spirocyclization of **65** (R = CH_3) provided **67** in 85% yield. Olefin oxidation and ether deprotection gave **68**, the central portion of fredericamycin A. A tertiary, benzylic, keto-stabilized radical was converted into a vinyl radical in the cyclization reaction, again clearly demonstrating the inherent exothermicity of cyclization whereby a π bond is converted to a σ bond. Alkynes

and nitriles are common equivalents of a carbonyl radical acceptor (O=C°); of the two radicophilic equivalents, activated alkynes are more reactive toward radical addition than are nitriles. An interesting product was originally obtained involving benzyl rather than methyl ethers. In that case, the intermediate vinyl radical **66** underwent a 1,6-hydrogen transfer from the benzyl ether, and the resulting radical **69** added back (in 6-endo fashion) to give **70** in 62% yield! This process was suppressed when methyl ethers were used, probably because of the greater bond dissociation energy of methoxy C–H bonds.

Many other 5-membered carbacycles have been made by using the tin hydride method. Examples include Curran's synthesis of the fused triquinane modhephene (further discussed in Schemes 49 and 50),[30] Sha's synthesis of modhephene and epimodhephene,[61] Parson's synthesis of quadrone,[62] Noyori's synthesis of isocarbacyclin,[63] Gais's synthesis of isocarbacyclin,[64] MacLeod's synthesis of *cis*- and *trans*-trikentrin A,[65] Srikrishna's synthesis of laurene,[66] Maillard's synthesis of steroids,[41] Jones's synthesis (–)-5′-homoaristeromycin,[52] Miwa's synthesis of 1-α-*O*-methylloganin,[55] and Kilburn's synthesis of isoiridomymecin.[36]

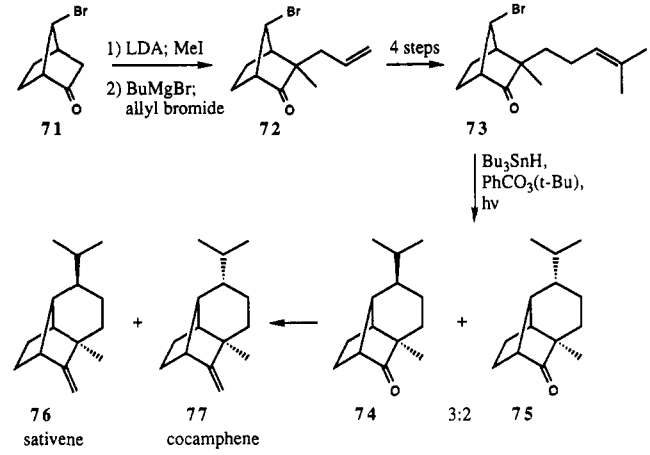
3. 6-Membered Rings

As discussed earlier, radical cyclizations leading to 6-membered rings are less general than cyclizations leading to 5-membered rings; however, they still have an important place in synthesis. Because 6-membered ring forming reactions are slower, they are more subject to competitive formation of reduced, uncyclized byproducts. Many 6-heptenyl radicals are also subject to intramolecular 1,5-hydrogen atom transfer. Such 1,5-hydrogen transfers are usually exothermic, (because they form allylic radicals), and they can sometimes be very fast. Simple 6-exo radical cyclizations are also less regioselective than are 5-exo cyclizations. For the 5-hexenyl radical, 5-exo cyclization is 50 times faster than 6-endo cyclization, but for the 7-heptenyl radical, 6-exo cyclization is only 6 times faster than 7-endo cyclization.[19,20] In addition to diminished reactivity, diminished chemoselectivity, and diminished regioselectivity, known 6-heptenyl radical cyclizations also show diminished stereoselectivity relative to 5-hexenyl radical cyclizations. Despite these limitations, radical cyclizations using the tin hydride method can often be successfully applied to the synthesis of 6-membered rings. Indeed, the earliest applications of radical cyclizations in natural product synthesis involved construction of 6-membered rings.

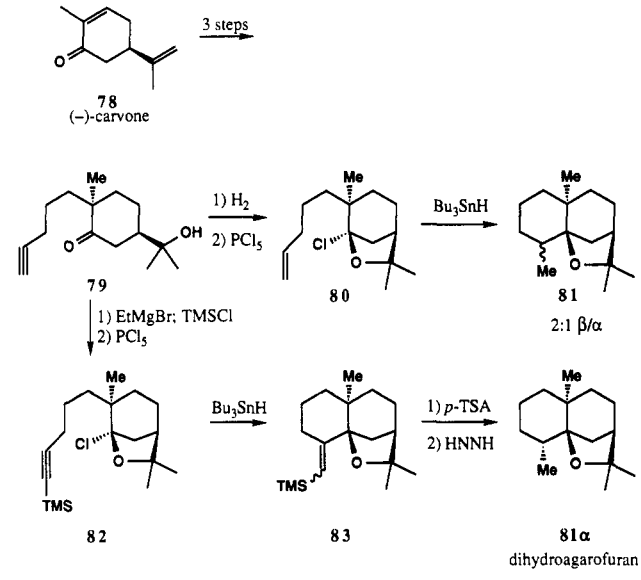
The first application of the tin hydride method in a natural product synthesis, shown in Scheme 16, did not appear until 1976.[67] The radical precursor **73** was prepared from 7-bromonorbornanone (**71**) by enolate alkylation and side-chain elaboration. Radical cyclization was carried out at room temperature with dilute tin hydride (photolytic initiation), and gave the 6-membered rings **74** and **75** in 62% yield. The stereoselectivity of the cyclization was poor, giving only a 3:2 mixture of diastereomers, but the separable diastereomers were readily converted to the natural tricyclic sesquiterpenes sativene (**76**) and cocamphene (**77**).

The second total synthesis using the tin hydride method was reported by Buchi in 1979, and again involved 6-membered ring formation (Scheme 17).[68]

SCHEME 16

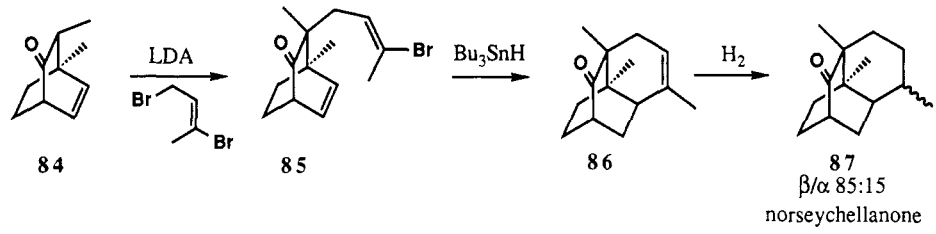


SCHEME 17

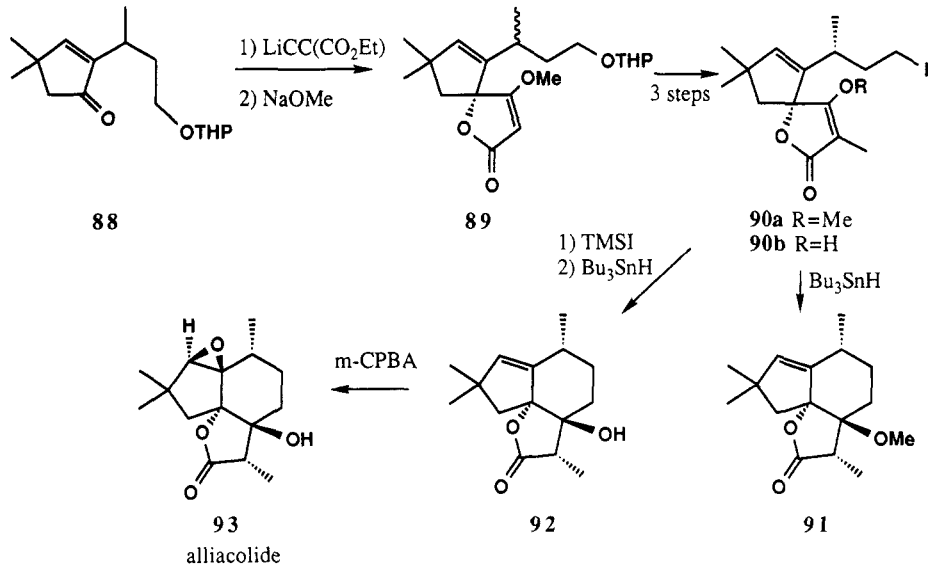


(–)-Carvone was converted to the chloro ether **80**. Radical cyclization of **80** gave a 67% yield of cyclic products **81** and a 20% yield of the uncyclized, reduced product. The poor stereoselectivity in the cyclization of **80** was circumvented by using an alkyne rather than an alkene as the radical acceptor. Radical cyclization of acetylenic silane **82** gave a mixture of vinyl silanes **83** in 72% yield, accompanied by 13% of the uncyclized, reduced product. Acidic desilylation and stereoselective diimide reduction from the less hindered β face gave dihydroagarofuran (**81α**) exclusively. The higher ratio of cyclized to uncyclized products by using alkyne **82** rather than alkene **80** suggests that the silylacetylene moiety is more radicophilic than the simple alkene. Normally radical addition to an alkyne is slower than addition to an alkene, presumably because alkynes usually have higher LUMOs (and perhaps also because a less-stable vinyl radical results).[69] When the terminal acetylene was used rather than the silylacetylene **82**, reaction with tin hydride was not clean, and unidentified high molecular weight products formed. These results show the value of the silyl group as a handy, disposable activator of the alkyne, readily introduced and readily removed after serving its purpose. However, the level of activation provided by the silyl group is probably relatively modest.

SCHEME 18



SCHEME 19

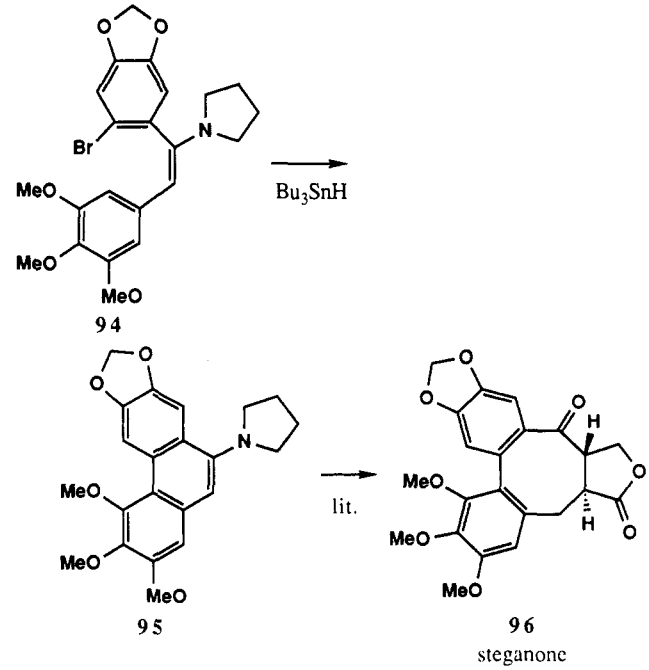


Chemists did not report the use of 6-exo radical cyclizations in natural products total synthesis again until a 1985 formal synthesis of seychellene (Scheme 18) that was a part of Stork's pioneering work on vinyl radical cyclizations.[70] Stereoselective alkylation of ketone **84** gave vinyl bromide **85**, which cyclized to **86** in 70% yield. Hydrogenation from the less-hindered face then gave predominantly norseychellanone (**87**β), which has been converted to seychellene. By using a vinyl radical in the cyclization, stereocontrol over the methyl group was deferred until the hydrogenation step. The stereochemistry of the starting vinyl bromide was irrelevant for the cyclization reaction. A similar 6-exo cyclization with a vinyl radical has also been used in Subba Rao's synthesis of seychellene.[58] Stork's seychellene synthesis illustrates one powerful way to extend the scope of 6-exo cyclizations: to use reactive vinyl (or aryl) radicals for cyclization. However, vinyl radicals are good hydrogen abstracters, and competing hydrogen transfer can be a problem in substrates with appropriately located allylic hydrogens.[71]

Pattenden's construction of the neopentyl quaternary center in his synthesis of the tetracyclic lactone alliacolide (**93**) (Scheme 19) illustrates a second approach to improving 6-exo cyclizations: to use activated radical acceptors.[72] The enone **88** was converted to optically active iodide **90**, which cyclized to give **91** as a single isomer in 97% yield. The efficient addition to the fully substituted terminus of the alkene was aided by the lactone activation of the alkene. Once again, the reaction conditions were compatible with a highly oxygenated skeleton, and β elimination of the methoxy group from "Michael adduct" **91** was not a concern. Unfortunately, deprotection of the tertiary methyl ether in **91** proved very troublesome, and when methyl tetronate **90a** was deprotected first, and then cyclized, **92** formed in only 30% yield. It is not clear why the cyclization of **90b** was so much poorer than that of **90a**. The tetronic acid may have been so acidic that it was incompatible with tin hydride, a weak hydride donor.[73]

Narasimhan has recently used a tin hydride-mediated biaryl coupling reaction in a formal synthesis of steganone **96** (Scheme 20).[74] The aryl bromide **94** cyclized

SCHEME 20



in 66% yield to provide **95**. This cyclization reaction formed a 6-membered ring by radical addition to an aryl ring, all without recourse to high dilution of the tin hydride. Inter- and intramolecular radical additions to

aromatic systems are normally slower than analogous additions to alkenes and alkynes, presumably for conformational reasons and because of the necessary loss of aromatic resonance.[75] The cyclization of **94** was facilitated by the use of an aryl radical; like vinyl radicals, aryl radicals are much more reactive than alkyl radicals.[76] The cyclization is analogous to the Pschorr reaction[77] and depended on the molecular conformation. When a ketone was used rather than the enamine, for example, no coupling occurred.[78] Furthermore, the conversion of **94** to **95** was not actually a reduction; a net loss of HBr was accomplished rather than the usual substitution of H for Br. A reoxidation step must have followed the original homolysis of the C–Br bond, but the timing and nature of the reoxidation step are unclear.

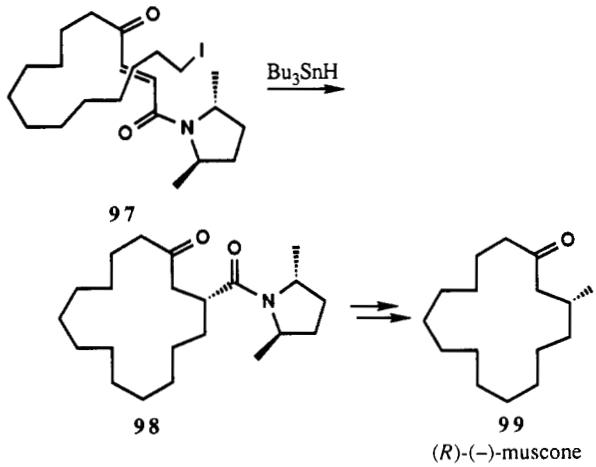
In addition to the examples already discussed, 6-membered carbacycles have been made by using the tin hydride method in Snider's syntheses of β-copaene, β-ylangene, and lemnalol,[79] in Subba Rao's seychellene synthesis,[58] in Crich's approach to vitamin D_3,[80] and in Parson's approaches to the avermectins[38] and the lysergines.[44]

4. Large Rings

The tin hydride method has recently been applied to the synthesis of large rings. An intramolecular radical cyclization to make a large ring differs significantly from both intramolecular cyclizations that make 5- and 6-membered rings and from intermolecular additions (see section II.F). As in any intramolecular reaction, the ratio of radical cyclization to hydrogen transfer can be enhanced by diluting the tin hydride. However, radical macrocyclizations usually show endo selectivity rather than exo. Furthermore, in macrocyclizations the effective molarity of the alkene is not very high, so that radical cyclization can be dangerously slow. As a result, a radical macrocyclization requires activation of the alkene. In contrast to intermolecular addition, however, polymerization is never a problem; the concentration of the macrocyclization precursor must be kept low to prevent bimolecular reaction of a radical with an activated alkene in another molecule.

The synthesis of large rings by using tin hydride has been developed primarily by Porter,[81] and a recent synthesis of (*R*)-(–)-muscone (**99**) illustrates some important features (Scheme 21).[82] Under dilute tin hydride conditions, the iodide **97** cyclized in 40–45% yield

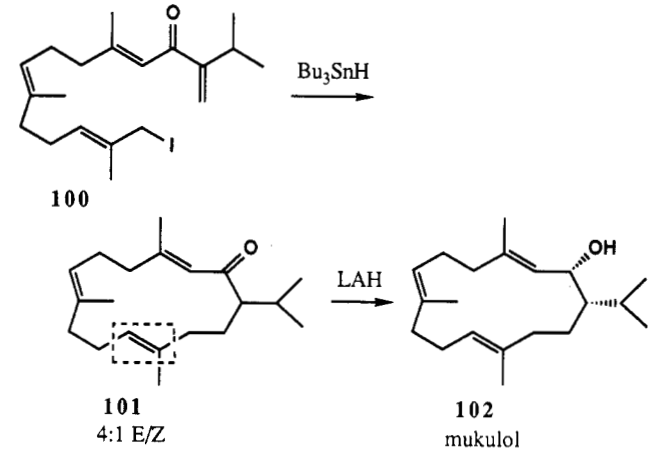
SCHEME 21



to give a 14/1 endo/exo mixture of regioisomers. When the analogous ethyl ester was used instead of the amide, the regioselectivity was even higher, ≥98:2. The regioselectivity originates from the intramolecular nature of the cyclization, because intermolecular additions to analogous olefins were not regioselective. The chiral amide also induced a high degree of stereoselectivity. The 15-endo product **98** formed as a 13:1 mixture of diastereomers, the result of radical addition to the less-hindered face of the olefin. Porter and Giese have shown comparable stereoselectivity in analogous intermolecular additions.[83]

Pattenden has used a 14-endo radical cyclization in his synthesis of mukulol (**102**) (Scheme 22).[84] The

SCHEME 22

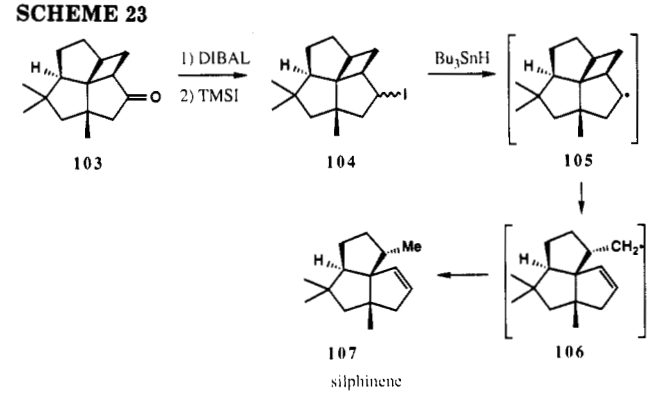


allylic iodide **100** was derived from farnesol in four steps, and was reacted with dilute tin hydride to give a 4:1 isomeric mixture of **101** in 40% yield. The partial loss of alkene stereochemistry shows that bond rotation of the intermediate allylic radical occurred faster than radical cyclization. That cyclization occurred at all is impressive, because allylic radicals are relatively stable and they do not show a good reactivity profile when compared to alkyl radicals.[85] Pattenden has more recently used a 14-endo allyl radical cyclization to synthesize (–)-zearalenone.[86] Tris(trimethylsilyl)silane was used rather than tin hydride as the chain carrier, simplifying purification without significantly decreasing the yield. This recently developed silane has reactivity similar to tributyltin hydride but it is nontoxic and has superior physical properties.[21]

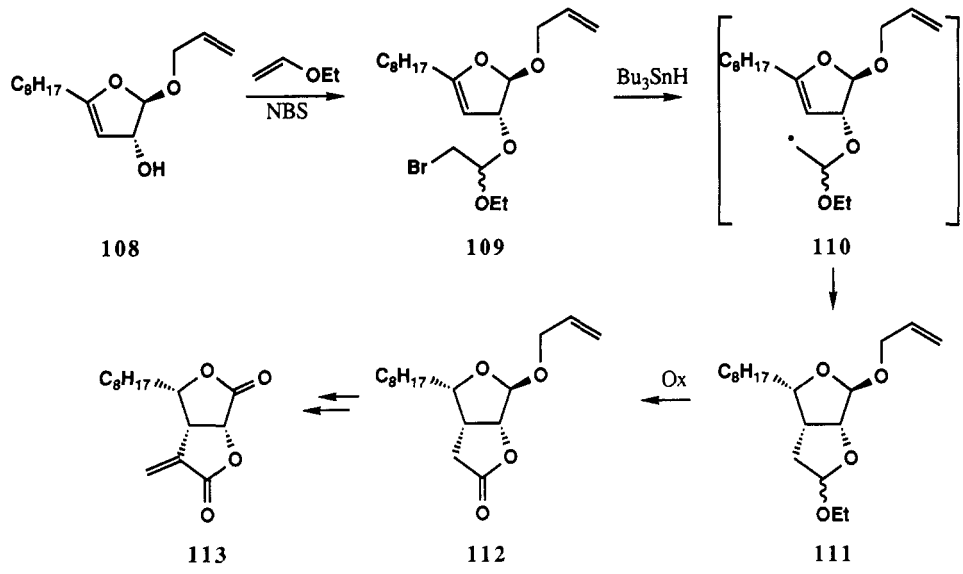
C. Carbacyclic Ring Opening with Tin Hydride

The addition of radicals to carbon–carbon multiple bonds is normally exothermic and irreversible because

SCHEME 23



SCHEME 24



(−)-isoavenaciolide

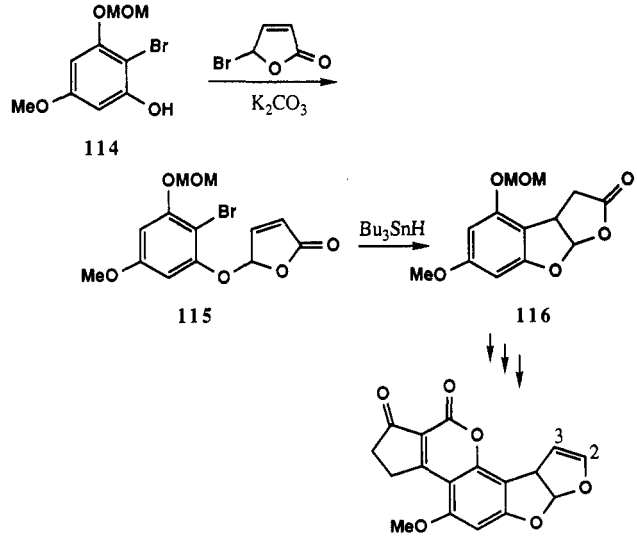
σ bonds form at the expense of π bonds. When σ bonds are highly strained, however, as in the case of cyclopropyl and cyclobutyl rings, ring opening becomes thermodynamically preferred. The opening of the cyclopropylmethyl radical, for example, is extremely fast.[9] The opening of cyclobutylmethyl radicals is not fast,[19,20] but it is exothermic and essentially irreversible. Crimmins has taken advantage of this opening in the synthesis of silphinene (**107**) (Scheme 23).[87] The ketone **103** was converted to the iodide **104**, which upon treatment with tin hydride gave silphinene in 95% yield. Syringe-pump addition of tin hydride was used so that the intermediate radical **105** had time to fragment before being captured by tin hydride.

D. Oxacycle Formation with Tin Hydride

The tin hydride method has been used extensively for the synthesis of oxygen-containing rings. The conversion of allylic alcohols into γ-lactones, a method originally developed by Stork[88a] and Ueno,[88b] has seen repeated application in natural product synthesis.[89] The straightforward procedure is illustrated in Dugger's synthesis of (−)-isoavenaciolide (**113**, Scheme 24).[90,91] The allylic alcohol **108** derived from D-ribose was alkylated by 1,2-dibromomethyl ethyl ether (which is usually prepared in situ from ethyl vinyl ether and NBS or bromine) to give the bromoacetal **109**. Radical cyclization gave the ethyl lactols **111** in 76% overall yield from the allylic alcohol. Collins oxidation provided the lactone **112**, which was carried on to the natural product. The cyclizations of radicals such as **110** are unusually rapid. From simple model studies, it is known that substitution of oxygen (or nitrogen) for carbon at the 3 position of 5-hexenyl radicals accelerates cyclization more than 10-fold.[9] The accepted explanation for this acceleration is that the shortened C–O bonds and the smaller C–O–C angle lead to better overlap in the transition state. A rate increase of this magnitude makes 5-exo radical cyclization so fast that hydrogen transfer does not compete, even at high concentrations of tin hydride. Regioselectivity is also improved, as 6-endo cyclization is not comparably accelerated.[92] The overall conversion of allylic (as well as propargylic or homoallylic) alcohols to oxacycles is popular not only because of the speedy radical cyclizations, but also because of the ready availability of cyclization precursors. Allylic alcohol → γ-lactone conversions have been applied in Stork's elegant synthesis of (+)-prostaglandin $F_{2\alpha}$ (discussed later, see Scheme 36),[93] in Holton's synthesis of taxusin (discussed later, see Scheme 27),[94] in Yadav's synthesis of (+)-eldanolide,[95] and in Pattenden's approach toward ginkgolide ring systems.[96]

Radical cyclizations of allyl *o*-bromoaryl ethers have been used to make dihydrobenzofurans. An example is Snieckus's formal syntheses of aflatoxins B_1 and B_2 (**117** and **118**, respectively) (Scheme 25).[97] The con-

SCHEME 25



117 aflatoxin B_1
118 aflatoxin B_2 (2,3-dihydro)

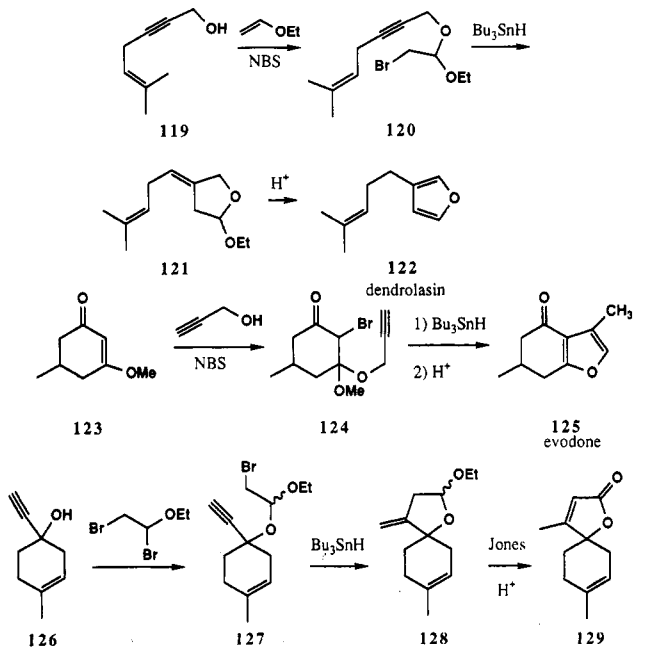
tiguously substituted bromophenol **114** was prepared by using Snieckus's directed metallation tactics. A very similar approach to aflatoxins was used by Hoffmann, but, in contrast to Snieckus's results, he encountered difficulties when the aryl ring was increasingly oxygenated.[98] Hoffmann eventually dismissed the tin hydride mediated cyclization in favor of a Pd(0)-catalyzed cyclization. Balasubramanian has also used radical

cyclizations of *o*-bromoaryl allyl ethers in the synthesis of pterocarpans.[99]

A variety of other cyclizations involving allyl ethers have been reported, and the requisite cyclization precursors have been prepared by varying methods. Srikrishna used bromo etherification of allyl alcohol itself, followed by radical cyclization, in the synthesis of marmelo oxides A and B,[100] and Ferrier used a trans etherification in an approach to azadirachtin and bissetone.[39] When allylic alcohols are alkylated by 2,3-dibromopropene, subsequent radical cyclization generates methylene-substituted tetrahydrofuran derivatives. This approach has been applied by both Hanessian[101] and Parsons[38] toward the hexahydrobenzofuran subunit present in the avermectins. Parsons has also generated a methylene-substituted tetrahydrofuran by using a propargyl allyl ether as a cyclization precursor in the synthesis of the phyllanthocin spiroacetal ring system.[102]

Propargylic alcohols can be easily *O*-alkylated and converted to substituted furans or lactones as shown in Scheme 26.[88a,103,104] In the first example, alkylation

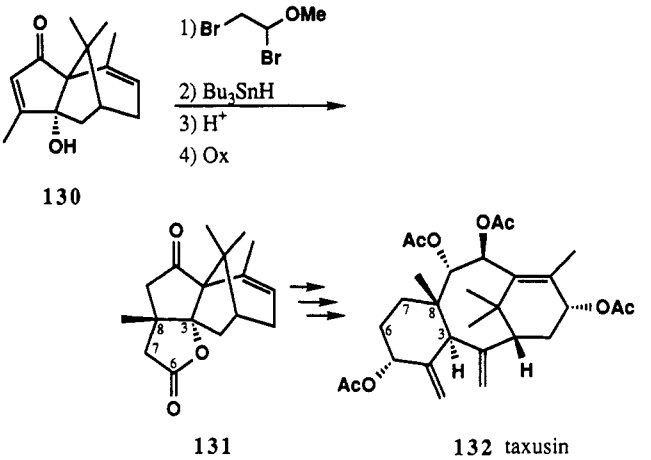
SCHEME 26



of propargyl alcohol **119** and cyclization by using catalytic tin hydride gave **121**, which upon treatment with acid gave the naturally occurring furan dendrolasin (**122**). The synthesis of evodone (**125**) made use of a somewhat more complex bromoacetal **124** and illustrates the facile assembly of 3-acyl-2-alkyl furans from 1,3-dicarbonyl compounds. In the synthesis of andirolactone (**129**), the radical derived from **127** chose 5-exo spirocyclization onto an alkyne over 6-exo bridged cyclization onto an alkene.[105] Radical additions to alkenes are faster than comparable additions to alkynes, but the rate of 5- versus 6-membered ring formation is a much more important consideration.[106] Balasubramanian has used a similar approach to make dihydrofurans in an approach to the pterocarpans,[99,107] and related cyclizations involving propargyl ethers were central to Clive's synthesis of frullanolide,[108] Srikrishna's synthesis of bulletenone,[109] and Sharma's synthesis of avenaciolide.[110]

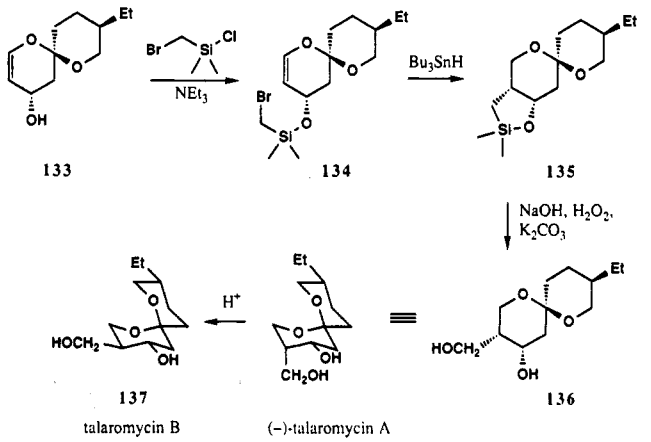
The facility of the alcohol alkylation–cyclization sequence makes it an attractive method to regio- and stereoselectively alkylate alkenes, even when the oxacycle is subsequently cleaved. This powerful strategy was introduced and popularized by Stork.[88a,112] In Holton's synthesis of taxusin (**132**, Scheme 27), for example, alkylation, radical cyclization, hydrolysis, and oxidation converted tertiary allylic alcohol **130** to lactone **131** in 82% overall yield.[94] The lactone ring in **131** is a temporary device in this synthesis, and only vestiges of it remain in the final product **132**. From a strategic perspective, the radical lactonization used the alcohol to dictate the configuration at C8 of taxusin. The ability of radical cyclizations to generate crowded bonds, in this case a neopentyl quaternary center, is again evident. The lactone group also served to temporarily protect the tertiary alcohol, which upon timely liberation induced ring fragmentation to expose the taxane skeleton.

SCHEME 27



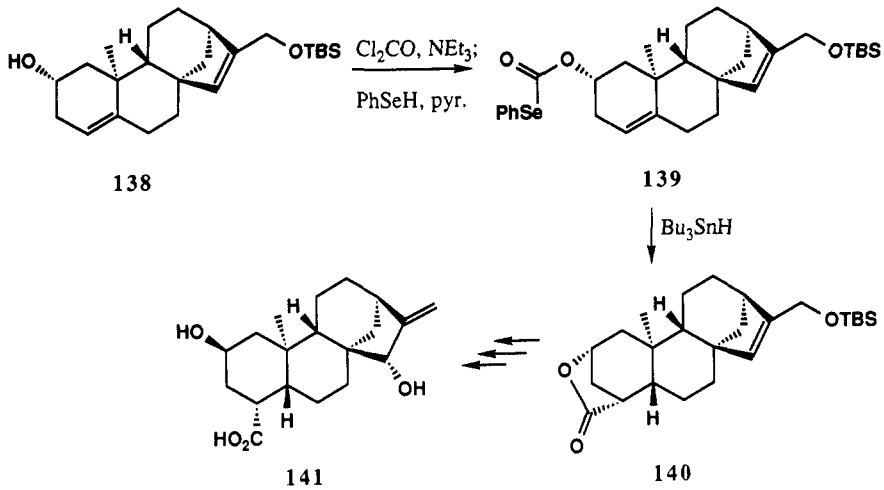
The ability of alcohols to direct alkene alkylations is also nicely illustrated in Crimmins's synthesis of the toxic metabolite (–)-talaromycin A (**136**, Scheme 28).[111]

SCHEME 28



Talaromycin A contains an axial hydroxymethyl group and is less stable than talaromycin B (**137**) in which the hydroxymethyl group is equatorial. Under the acidic conditions required for ketal formation, talaromycin A indeed rearranges to the more stable talaromycin B. Thus a synthesis of the less stable **136** requires its formation under nonacidic, nonequilibrating conditions. This was accomplished from the alcohol **133** by silylation, regio- and stereoselective radical cyclization, and oxidation of the carbon–silicon bond. The yield for the

SCHEME 29

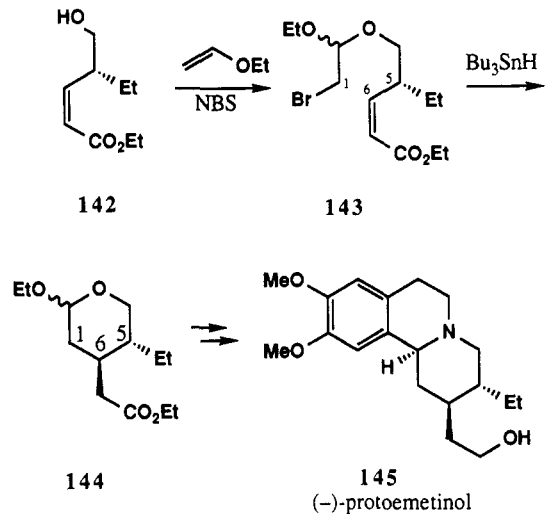


entire sequence from the starting alcohol **133** to talaromycin A (**136**) was 78%. The synthesis again illustrates the mild, neutral reaction conditions of radical cyclizations, and the ability of the hydroxymethylation process to faithfully translate stereochemistry from the preexisting alcohol to the alkylation product. It is interesting that the radical cyclization of **134** involved addition to an enol ether. An alkene is normally viewed as electrophilic in a radical cyclization, so it might be anticipated that an enol ether would have diminished reactivity. However, enol ethers often show comparable reactivity to unsubstituted alkenes. The directed hydroxymethylation method was originally developed by both Stork[112] and Nishiyama,[113] and has also been applied by Wicha[114] and Koreeda[115] in the context of steroid synthesis, and by Majetich in the synthesis of 14-deoxyisoamijol.[116]

Not only allylic but also homoallylic alcohols can be used in directed alkylations, as shown by Corey in his synthesis of atractyligenin (**141**, Scheme 29).[117] The homoallylic alcohol **138** was converted to the selenocarbonate **139**, which cyclized to give the bridged lactone **140** in 73% yield. Slow addition of tin hydride was needed to suppress formation of an isomeric δ-lactone, which formed in about 10% yield even under dilute conditions. This observation is interesting, because a mechanism for isomerization between the products is not obvious. Regardless of the mechanism, however, the homoallylic alcohol served nicely to deliver the one-carbon alkylating agent to the olefin in regio- and stereocontrolled fashion, a transformation not readily available by ionic methods. The synthesis also demonstrates the utility of formyl radicals in cyclization reactions and provides an example of bridged ring formation. In contrast to the previously discussed oxacycle formations, in which oxygen occupied the 3-position of the 5-hexenyl type radicals, the cyclization of **139** involved a radical with oxygen in the 2-position. In a recent synthesis of albidin, Wege has also used an interesting aryl radical cyclization in which oxygen occupied the 4-position,[118] and Murphy has reported a synthesis of lilac alcohols by using a cyclization of an alkoxy radical, where oxygen is in the 1-position.[119]

Six-membered oxacycles can also be prepared by radical cyclization, usually from homoallylic alcohol precursors.[120-124] An example is shown in Scheme 30.[125]

SCHEME 30



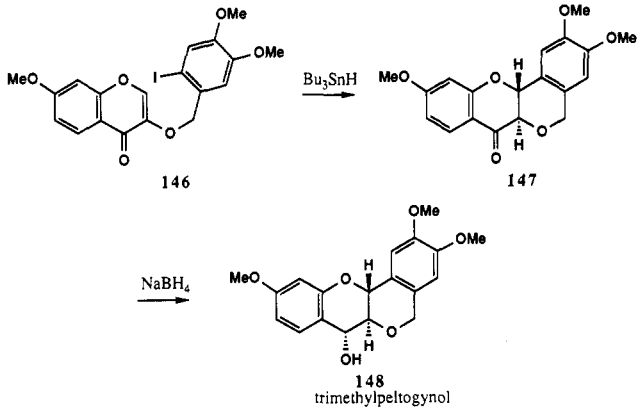
Alkylation of the optically active homoallylic alcohol **142** followed by radical cyclization gave in 88% yield the product **144**, in which the two alkyl ring substituents were trans. The lactol ether **144** was subsequently converted to (-)-protoemetinol (**145**), (-)-protoemetine, (-)-emetine, (-)-tubulosine, and dihydrocorynantheol. The strategic function of the radical cyclization was to establish the trans stereochemistry between the ring substituents. The formation of 6-membered rings by radical cyclization is not always highly stereoselective, but 1,2-chirality transfer from the allylic carbon (C-5) generally remains high because the ground-state preference for an allylic hydrogen to eclipse the double bond is retained in the transition state. The *E* olefin isomer of **143** was less discriminating than the *Z* isomer, and it gave only a 4:1 trans/cis mixture of **144**.

In Scheme 30 (as in Schemes 24 and 27), a bromoacetal was used in the radical cyclization reaction rather than a bromoacetate, even though the lactol ether **144** was promptly oxidized following the cyclization. When the bromoacetate analogue of **143** was reduced with tin hydride, radical cyclization proceeded in only 35% yield. Radical cyclizations in which esters (or amides) are part of the forming ring are generally quite slow and

are only marginally useful under tin hydride conditions. Presumably the transition state for a radical cyclization is substantially destabilized by distortion of an ester relative to its ground-state s-cis conformation.[126,127] However, a recent study has shown that substrates that fail to undergo cyclization at room temperature may succumb simply by heating.[128] Radical cyclizations involving bromoacetals have also been used to make 6-membered rings in Watt's synthesis of (+)-picrasin B, (+)-Δ^2-picrasin B, and (+)-quassin,[129] in Takano's synthesis of (−)-methyl elenolate,[130] and in Stork's approach to gelsemine.[123] In each of these examples, as in Scheme 30, the alkene was activated by an electron-withdrawing group. When oxygen is present in the chain, it is not clear whether activation of the alkene is actually required.

Six-membered rings have occasionally been made by 6-endo cyclizations of appropriately substituted 5-hexenyl radicals. The high 5-exo regioselectivity of 5-hexenyl radical cyclizations is suppressed by substitution at the 5-position. For example, 5-exo cyclization of the 5-methyl-5-hexenyl radical is 25 times slower than that of the parent 5-hexenyl radical, and the regioselectivity reverses from 50:1 to 1:2.[19,20] When the 5-position is substituted, conformational or electronic bias is usually required for regioselective formation of either 5- or 6-membered rings. An example of a useful 6-endo cyclization is Whiting's synthesis of trimethylpeltogynol (148, Scheme 31), where the carbonyl sub-

SCHEME 31

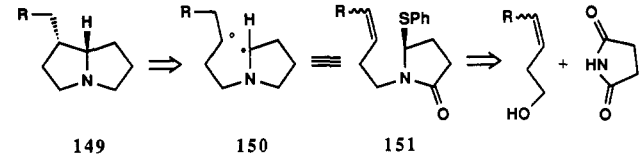


stituent in **146** favors 6-endo cyclization.[131] Cyclization occurred in 42% yield. Only a trace amount of the cis stereoisomer was observed, but the origin of this interesting stereochemical outcome is obscure. Related 6-endo cyclizations have been used in Whiting's synthesis of dehydroisorotenone[132] and in Thomas's approach to the bryostatins.[133,134] In both examples, an electron-withdrawing group on the 5-position helped dictate the regioselectivity. Parsons's lysergine approach provides a recent example of a 6-endo cyclization in which the 5-position is not substituted.[44]

E. Nitracycle Formation with Tin Hydride

By analogy to the alkylation–radical cyclization strategy involving unsaturated alcohols, nitrogen-containing heterocycles can also be made from unsaturated amines.[37,135,137] Hart's concise syntheses of pyrrolizidine alkaloids by using α-acylamino radicals was historically the first comprehensive synthetic strategy that was founded on radical cyclizations.[138–140] The approach is illustrated in Scheme 32. According to Hart's analysis,

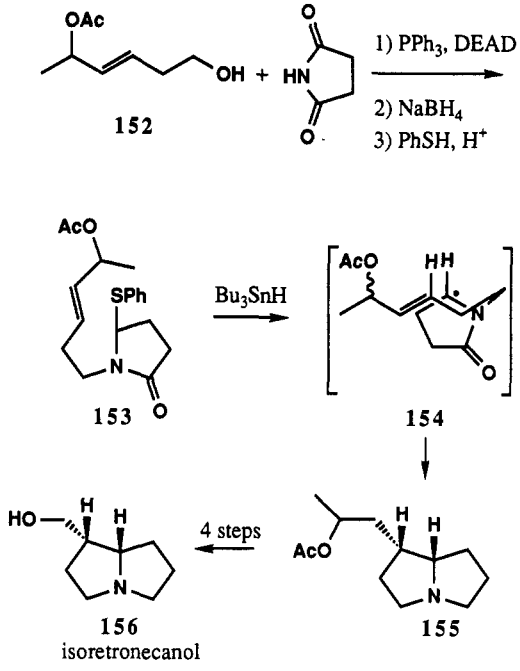
SCHEME 32



dissection of a simple pyrrolizidine at the bridgehead gives an imaginary synthon **150**. The reagent equivalent to the synthon **150** is the readily available unsaturated sulfide **151**.

The synthesis of isoretronecanol (**156**, Scheme 33),

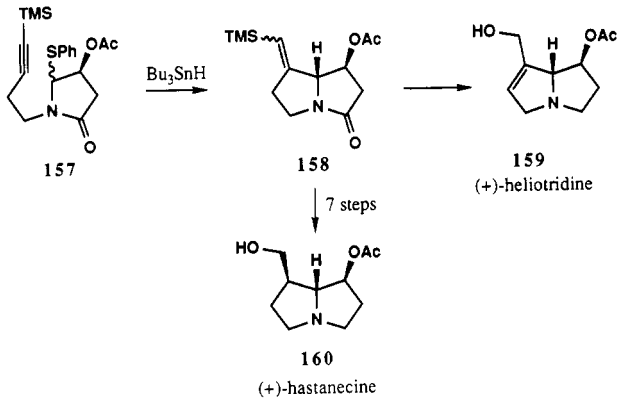
SCHEME 33



reported in 1984, is illustrative of the execution of this strategy.[138] N-Alkylation of succinimide with **152** under Mitsunobu conditions introduced the side-chain olefin, and reduction and hydroxy–thiophenoxy exchange gave the radical precursor **153** in 73% overall yield. Radical cyclization gave a 9:1 mixture of pyrrolizidinone **155** and its diastereomer (in which the side chain is β rather than α) in 86% yield. The stereochemistry of the cyclization is consistent with chairlike transition state **154**, in which the alkene orients itself on the concave face of the forming bicycle. Two other byproducts formed, the indolizidinone resulting from 6-endo cyclization (in 4% yield), and the uncyclized reduced product (in 5% yield). Slow, syringe-pump addition of tin hydride was required in order to minimize formation of the uncyclized reduced byproduct. The strategic beauty of the synthesis is the ready assembly of the cyclization precursor, the regioselectivity of the cyclization, and the stereoselective formation of the thermodynamically disfavored product.

An alkyne was used as the α-acylamino radical acceptor in Hart's syntheses of (+)-heliotridine and (+)-hastanecine (**159** and **160**, Scheme 34).[140] Radical cyclization of optically active **157** gave a mixture of vinylsilanes **158** in 70% yield, accompanied by 22% of the uncyclized reduced product. The TMS substituent was crucial, activating the alkyne as a radical acceptor

SCHEME 34



and ensuring 5-exo regioselectivity in the cyclization.[68] In the absence of the silyl group, even lower ratios of cyclized to reduced products were observed, and when the methyl substituted alkyne was used, the cyclization proceeded in 6-endo fashion. In addition to alkenes and alkynes, Hart has also used an allene as the α-acylamino radical acceptor in the synthesis of (±)-supinidine.[139]

Despite their accessibility and successful applications in synthesis, α-acylamino radicals cyclize more slowly and less selectively than most 5-hexenyl radicals.[138-40] Hart found that not even recourse to high dilution (syringe-pump addition of tin hydride) was able to prevent formation of significant quantities of uncyclized reduced byproducts in some cases. The 5-exo:6-endo ratios were also unusually low. In Scheme 33, the exo:endo ratio was good (9:1) with a substituted olefin, but when the analogous terminal olefin was used, only a 2:1 ratio was observed. The diminished reactivity and regioselectivity is due to acylamino substitution of the radical. An alkyl radical is stabilized by orbital overlap with an α-heteroatom.[141] Since this stabilization is diminished or lost in the cyclization transition state, the activation energy for cyclization may increase. Stereoelectronic effects may also come into play since overlap between the SOMO of the radical and the LUMO of the olefin may be disfavored by resonance. While the effect of an α-acylamino substituent is bad, the effect of an α-amino substituent is worse. Padwa has found that cyclization of α-amino 5-hexenyl radicals are too slow to be useful under tin hydride conditions.[142]

Hart has recently applied an interesting α-acylamino radical cyclization in an approach to the gelsemine skeleton (Scheme 35; gelsemine has structure **168**).[143] A Diels-Alder reaction generated the bicyclic template **161**, and modification of the imide and elaboration of the side chain provided the radical precursor **162**. A key reaction in this sequence was a regioselective reduction that differentiated the two imide carbonyl groups. Radical cyclization of **162** by using slow addition of tin hydride gave **166** in 60–90% yield as a 12:1 mixture (major stereoisomer shown). Unfortunately **166** was not the isomer desired for gelsemine. The major stereoisomer presumably resulted from cyclization of conformation **164** in which the "5-hexenyl radical" portion is boatlike, whereas the minor stereoisomer resulted from the chairlike **165**.[25] The stereochemical outcome follows the guideline (derived from A-strain) that 4-substituted 5-hexenyl radicals give 4,5-trans-substituted rings. The reactive conformation **164** was not the major equilibrium conformation, suggesting that conformational interconversion of **163** to **164** was faster than loss of radicals (by radical–radical or radical–solvent reactions). Activation of the radical acceptor alkene was crucial; when the CO_2Et group was replaced with hydrogen, no cyclization occurred under the same reaction conditions. Barbier–Wieland degradation of **166** and isomerization led in six steps to the gelsemine substructure **167**.

α-Acylamino radicals have also been used by both Beckwith[144] and by Bachi[145] in syntheses of fused bicyclic β-lactams, by Fliri and Mak in a synthesis of 4-allylazetidinones,[146] by Keck in a synthesis of isoretronecanol,[147] and by Corey in a synthesis of (+)-biotin.[92b]

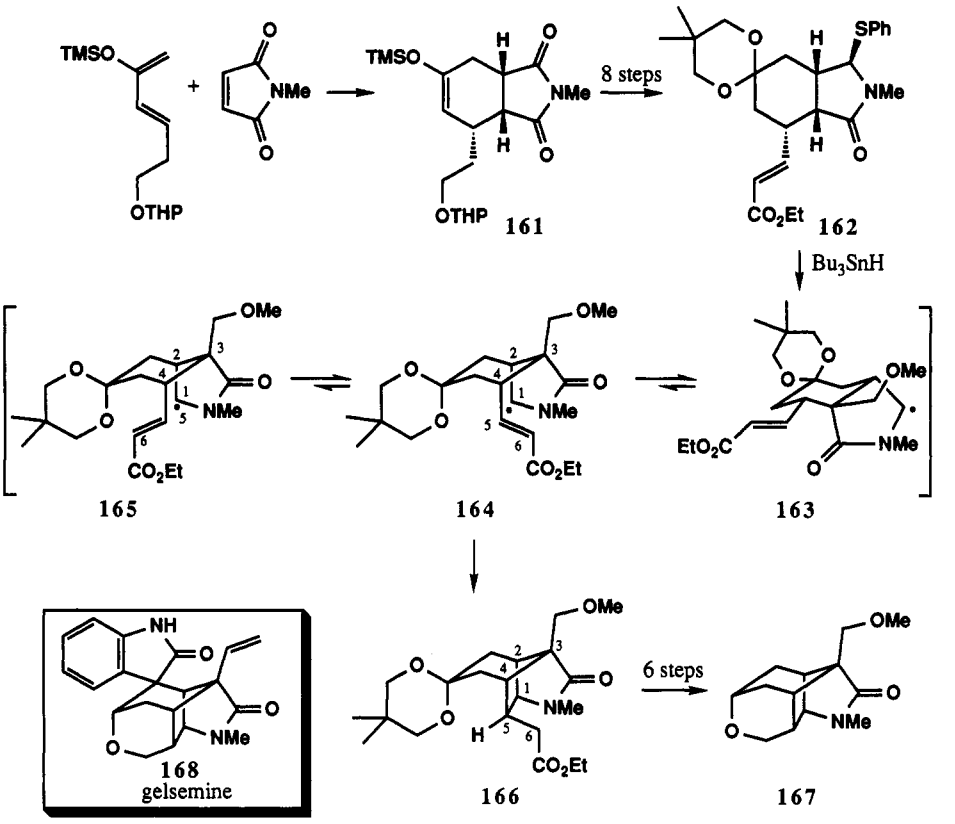
Although the accessibility of α-acylamino radicals from imides underlies their popularity, allylic amines have also been used in the synthesis of 5-membered nitrogen heterocycles. Allylic amines are actually better suited to radical cyclizations, because nitrogen incorporation in the 3-position of 5-hexenyl type radicals accelerates cyclization, whereas in the 2-position nitrogen decelerates cyclization. Two examples in which allylic amines are used, Danishefsky's synthesis of 3-demethoxyerythratidinone (Scheme 46)[136] and Boger's synthesis of (+)-CC-1065 and various analogues (Schemes 47 and 48),[137,148] are discussed later in different contexts. Parsons has also used cyclization of an allylic amine in an interesting tandem hydrogen atom transfer-radical cyclization approach to pyrrolizidine alkaloids,[135] Ishibashi has used cyclization of an allylic amide in the synthesis of mesembranol,[149] and Jones has used cyclization of a related amide in the formal synthesis of geneserine.[150] An enamine, in which the nitrogen occupies the 4-position of a 5-hexenyl type radical, has been used by Yamaguchi in an approach to the benzo[*f*]indolizidine ring system,[92c] but the electronic effect of nitrogen makes cyclizations involving enamines less efficient than all-carbon analogues.[151]

A number of 6-membered nitrogen heterocycles have been prepared by using radical cyclizations. Examples include Hart's approach to the manzamine alkaloids,[152] Beckwith's synthesis of epilupinine,[151] Prabhakar's synthesis of phenanthridines,[153] Simpkin's approach to histrionicotoxin,[154] Ueda's synthesis of carbon-bridged cyclonucleosides,[155] Yamazaki's approach to emetine,[164] Parsons's synthesis of carbapenams,[135] Takano's synthesis of xylopinine,[156] Kano's synthesis of morphine analogues,[157] and Takano's synthesis of bharatamine.[130] The last three of these applications involved 6-endo cyclizations.

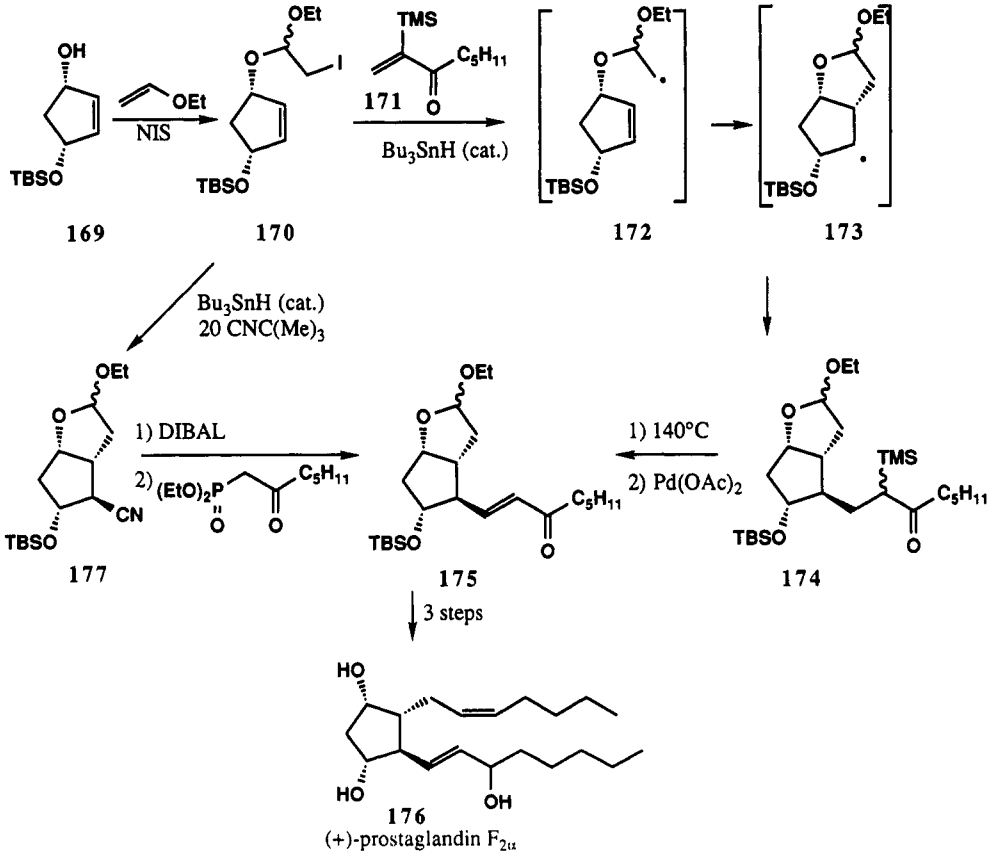
F. Intermolecular Radical Additions with Tin Hydride (Giese Reactions)

Intermolecular radical addition reactions are much more difficult to conduct by the tin hydride method than intramolecular reactions.[6,7,15,27] Radical addition must compete favorably with hydrogen abstraction, so activated alkenes such as β-unsubstituted acrylates, acrylonitriles, and vinyl ketones are usually required. The rate of addition is enhanced experimentally by using excesses of the olefin. Reaction chains are still usually short, however, and addition products may be contaminated either with reduced starting material, with telomers, or with both. Despite these limitations, the unique features of radical additions make them

SCHEME 35



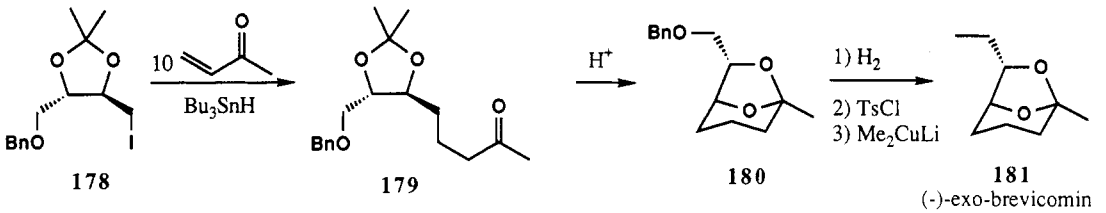
SCHEME 36



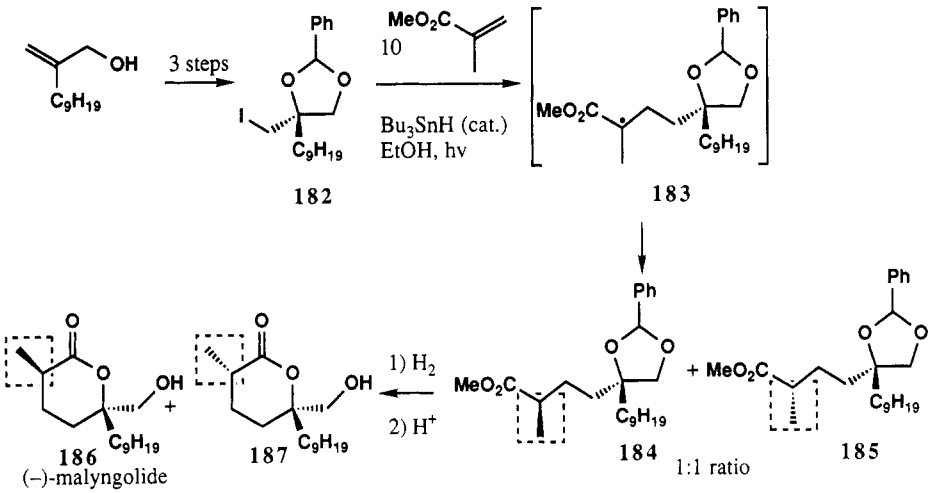
useful, and several intermolecular radical alkylations have been used in natural product synthesis.

The most elegant example is the tandem intramolecular cyclization-intermolecular alkylation reaction used by Stork in the synthesis of (+)-prostaglandin $F_{2\alpha}$ (176, Scheme 36).[40] The optically active allylic alcohol 169 was converted to the iodoacetal 170. When the iodide was treated with a catalytic amount of tin hy-

SCHEME 37



SCHEME 38

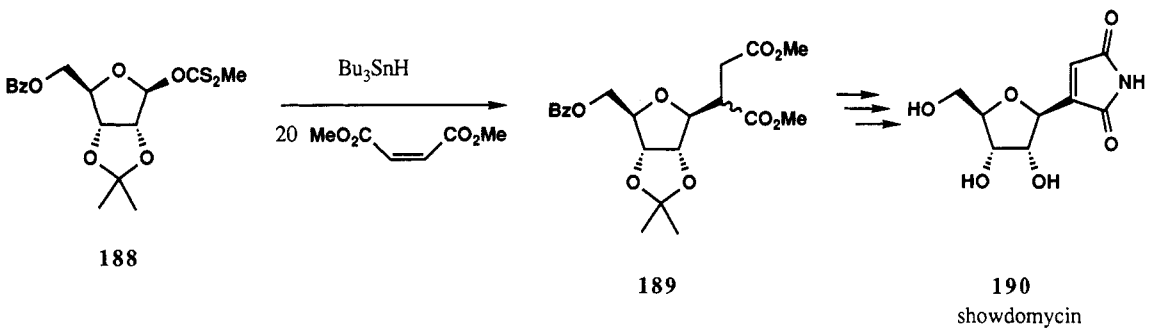


dride and an excess of the α-silyl-substituted vinyl ketone **171**, cyclization and intermolecular trapping produced **174**, in which two new alkyl groups were added across a double bond with complete control of stereochemistry. Thermal rearrangement of the α-silyl ketone and oxidation of the resulting silyl enol ether gave **175** in 58% overall yield from the radical precursor **170**. A variation used an excess of *tert*-butyl isocyanide as the intermolecular radical acceptor. Cyclization of **170** and addition to *tert*-butyl isonitrile, again by using catalytic tin hydride, provided **177** in 71% yield. Reduction of the nitrile and Horner–Emmons olefination of the resulting aldehyde gave **175** in 78% yield. The original hydroxy group permits the introduction of the two prostaglandin side chains with complete stereocontrol.

Stork's prostaglandin synthesis features a variety of significant chemistry. First, it was in this context that the allylic alcohol → γ-lactol method was originally developed. Second, the tandem cyclization–addition reaction highlights the difference between the rates of intra- versus intermolecular addition reactions. Not even a large excess of the vinyl ketone, which is activated toward radical addition, could compete with cyclization to an unactivated olefin (**172** → **173**). Third, the use of the α-silyl enone served to provide a "site-specific enol". Whereas anionic Michael additions provide regiospecific enolates (which can be further functionalized), in the tin hydride method, "radical Michael additions" normally lead to saturated ketones. If the ketone **174** had not been silylated, subsequent regioselective oxidation would have been extremely difficult. Fourth, the use of the isocyanide is an alternative to the use of an excess of olefin when the olefin is valuable. Fifth, the use of catalytic tin hydride (Bu_3SnH, $NaBH_3CN$, *tert*-butyl alcohol as solvent) is an important method for carrying out slow radical reactions. Under these reactions conditions, tin hydride is continuously regenerated by reduction of tin halide as it forms during the radical chain reaction. Tin hydride must often be dilute in order for slow radical reactions to occur, and Stork's catalytic tin hydride conditions provides an alternative to syringe pump addition. The catalytic method also obviates the formation of stoichiometric amounts of tin byproducts. This is a significant advantage both because tin reagents are toxic and because the removal of tin byproducts is sometimes difficult. Sixth, the reaction again demonstrates the stability of radicals β to heteroatoms. Neither the acetal (**172**) nor the OTBS groups (**173**) suffer from having neighboring radicals formed in the β position. A closely related tandem cyclization–addition sequence has recently been applied to the synthesis of 1-*epi*-magydardienediol by Nagano.[43]

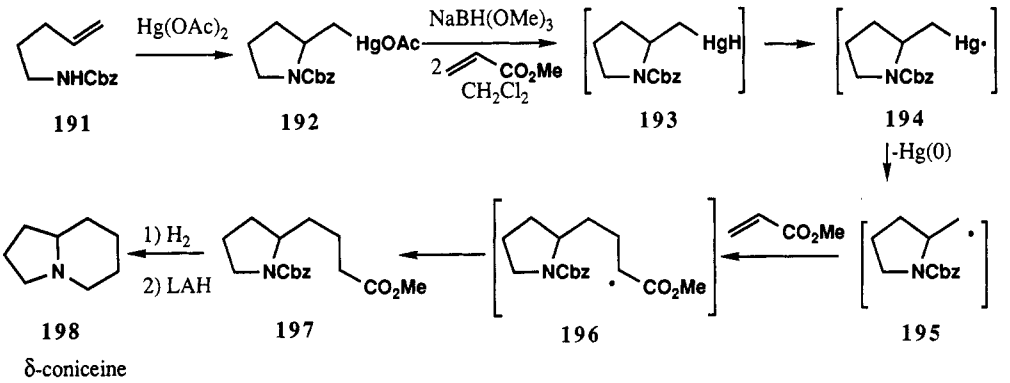
Giese has used intermolecular radical alkylations in syntheses of (−)-*exo*-brevicomin (**181**)[158] and (−)-malyngolide (**186**),[159] as shown in Schemes 37 and 38. In the brevicomin synthesis, the optically active iodide **178** derived from D-tartaric acid was alkylated in 53% yield by using 10 equiv of methyl vinyl ketone and with slow addition of Bu_3SnH. Clearly, anionic Michael addition conditions could not have done the same job because of β elimination. In the enantiospecific synthesis of malyngolide, Sharpless epoxidation was used to give the optically active radical precursor **182**, which was alkylated in 70% yield by methyl methacrylate. Catalytic tin hydride conditions ($NaBH_4$, EtOH, Bu_3SnH)[160] slightly different from those used by Stork minimized the tin hydride concentration. A 1:1 mixture of diastereomers was produced, the result of nonselective hydrogen transfer to the intermediate radical **183**. The two isomers were carried on to the separable lactones **186** and **187**. By using the opposite tartrate in the Sharpless epoxidation reaction, the chirality of **182** was reversed and the other two stereoisomers of malyngolide were prepared. Giese and others have also developed conditions for the alkylation of glycosyl and furanosyl

SCHEME 39



188 189 190
showdomycin

SCHEME 40



191 192 193 194 195 196 197 198
δ-coniceine

radicals.[161] An application of this method was the key to Araki's synthesis of *dl*-showdomycin (**190**, Scheme 39).[162] Dropwise addition of tributyltin hydride to the xanthate **188** and 20 equiv of dimethyl maleate gave the alkylation product **189** in 62% yield. The product was accompanied by traces of the starting xanthate as well as 10% of the dithiocarbonyl isomer of **188**. This reaction is unusual in that intermolecular addition to the substituted terminus of a double bond was accomplished.

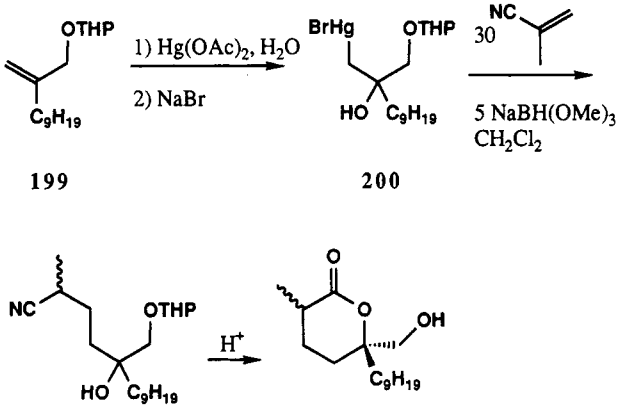
Intramolecular alkylations using tin hydride have also been used in Nagarajan's approach to pseudomonic acid C from D-xylose,[163] in Takahata's formal synthesis of slaframine,[164] and in Maillard's approach to steroids.[41]

III. The Mercuric Hydride Method

Reductive addition reactions conducted by the mercury method are also called Giese reactions. The mercuric hydride method for conducting radical reactions is very similar in principle to the tin hydride method, and it has been used for intermolecular radical additions.[165-167] Although the mercury method has been surpassed in popularity by the tin method, it retains many nice features including the ease of synthesis of precursors and the ease of conducting reactions at lower temperatures. The mercury method predated the tin method,[168] and it is thus a very important step in the historical development of synthetic applications of radical reactions.

Danishefsky's synthesis of δ-coniceine (Scheme 40) is a good example of synthesis by the "mercury method".[169a] Ureidomercuration of **191** gave the organomercurial acetate **192**, which was alkylated with excess methyl acrylate in 64% overall yield. In the accepted mechanism,[168] the borohydride converts the organomercuric acetate **192** into the mercuric hydride **193**. Hydrogen atom transfer (to **196**) produces mercury

SCHEME 41

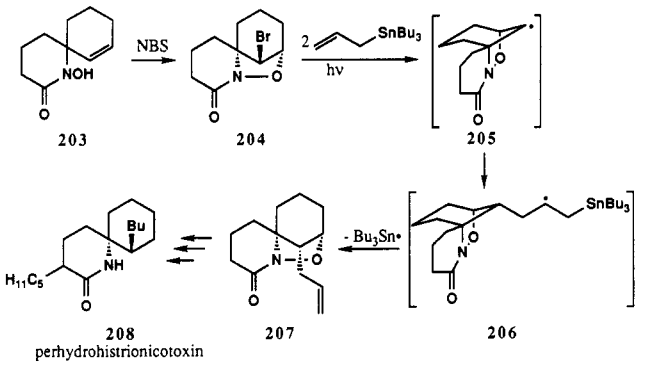


199 200 201 202
1:1 mixture malyngolide

radical **194**, fragmentation gives alkyl radical **195**, intermolecular alkylation gives **196**, and hydrogen abstraction (from mercuric hydride **193**) provides product **197** (and another molecule of **194** which continues the chain).

Kozikowski has used the mercuric hydride method to synthesize (±)-malyngolide **202** (Scheme 41).[169b] Oxymercuration of allylic ether **199** followed by ligand exchange gave the organomercurial bromide **200**. This was alkylated by a large excess of methacrylonitrile, giving adduct **201** as a 1:1 mixture of diastereomers in 49% yield, accompanied by 19% reduced nonalkylated material. Upon treatment with acid, **201** gave a separable mixture of (±)-malyngolide **202** and its diastereomer. The particular utility of the mercury method derives from the ready access to functionalized organomercurials, as demonstrated in both of these syntheses. However, the method has a drawback: or-

SCHEME 42



ganomercuric hydrides are better hydrogen atom donors than are tin hydrides.[168b] Thus it becomes increasingly difficult for intermolecular additions of an alkyl radical (**195** → **196** in Scheme 40) to compete with direct reduction of the alkyl radical. In Kozikowski's malyngolide synthesis, even with a 30-fold excess of methacrylonitrile, the ratio of alkylation to reduction was only 3:1.

The mercuric hydride method has seen surprisingly little application in intramolecular cyclization reactions. An exception was Corey's interesting biomimetic synthesis of 8-*epi*-prostaglandin $F_{2\alpha}$. An intramolecular peroxymercuration was followed by a tandem radical sequence in which a stereoselective cyclization gave an alkyl radical which was trapped intermolecularly by oxygen.[42]

IV. The Fragmentation Method

A. Intermolecular Reactions with the Fragmentation Method

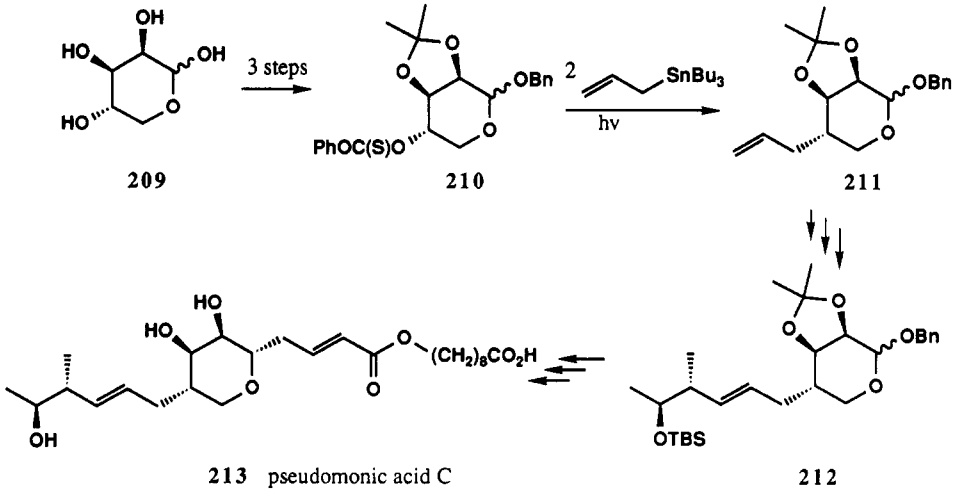
The problem with conducting intermolecular reactions by the tin hydride method is that the initial radical must add to an alkene and not be trapped by tin hydride, whereas the adduct radical must be trapped by tin hydride and not add to the alkene. The fragmentation method is a clever alternative that avoids this selectivity problem.[170] The fragmentation method also differs from the tin hydride method in that the net effect is substitution rather than reduction. In this method, chain carriers (like $Bu_3Sn^•$) are generated in a fragmentation step rather than an atom-transfer step.

Fragmentation methods based on allyltrialkyltin reagents are especially useful. Keck first applied such a method to the synthesis of (±)-perhydrohistrionicotoxin **208** (Scheme 42), a potent neurotoxin.[171] Radical allylation of bromide **204** proceeded in 88% yield to give the isomer **207** exclusively. The mechanism involves intermolecular addition of radical **205** to allyl tin to give **206** followed by β fragmentation of tin radical to give the product. β fragmentation of tin radicals is exothermic and is extremely fast. The tin radical that is extruded then propagates the chain reaction. Because tin hydride is not used, alkylation is the only available fate for the alkyl radical **205**, and the competition between alkylation and hydrogenation that troubles the tin hydride method does not interfere.[172] The lack of competition for the allylation reaction is critical, because addition reactions to allyl tin are only about 10 times faster than addition to ordinary alkenes.[173] Keck's allylation reactions are particularly useful in light of the synthetic versatility of allyl groups. The facial selectivity in the alkylation of **205** resulted from equatorial attack by the allyl tin. Unfortunately the isomer obtained was not the one desired for the natural product target, although oxidative degradation and isomerization were successfully accomplished. Nevertheless, the high-yielding alkylation of a neopentyl center β to both nitrogen and oxygen, without destruction of the hydroxamic ester, is impressive. Anionic nucleophiles might not have been so chemoselective.

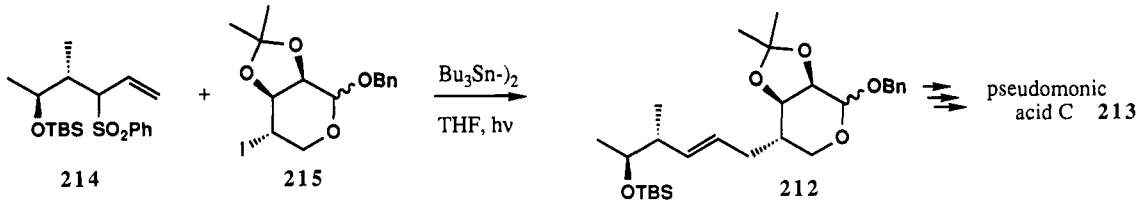
Keck has also used the fragmentation method in the synthesis of the antibiotic pseudomonic acid C (**213**, Scheme 43).[174] Lyxose was converted to the thionocarbonate **210**, and photolytic allylation with 2 equiv of allyltributyltin gave **211** in 80–93% yield as a single pair of anomers. The allyl group was elaborated by ozonolysis and subsequent olefination to give **212**, which was carried on to pseudomonic acid C. The oxygenated ring system **210** was quite sensitive to the radical precursor used. Synthesis of the analogous bromide or selenide proved troublesome, and the methyl xanthate and thiocarbonyl imidazolide gave inferior results to the phenyl thionocarbonate in the allylation reaction. Chemical initiation with AIBN also proved less satisfactory than photolysis.

Allylic sulfides or sulfones can also be used in radical allylation reactions,[175] as demonstrated in Keck's second

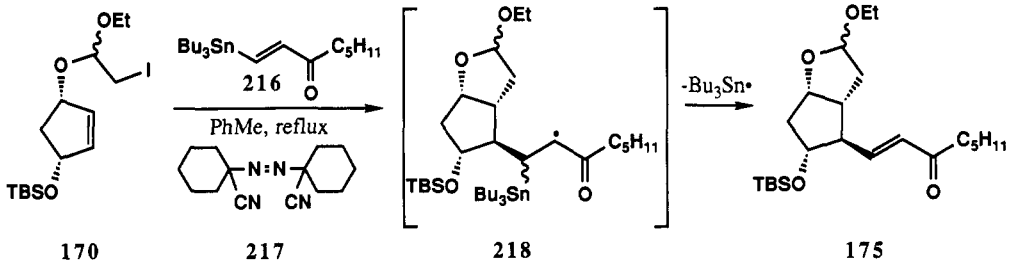
SCHEME 43



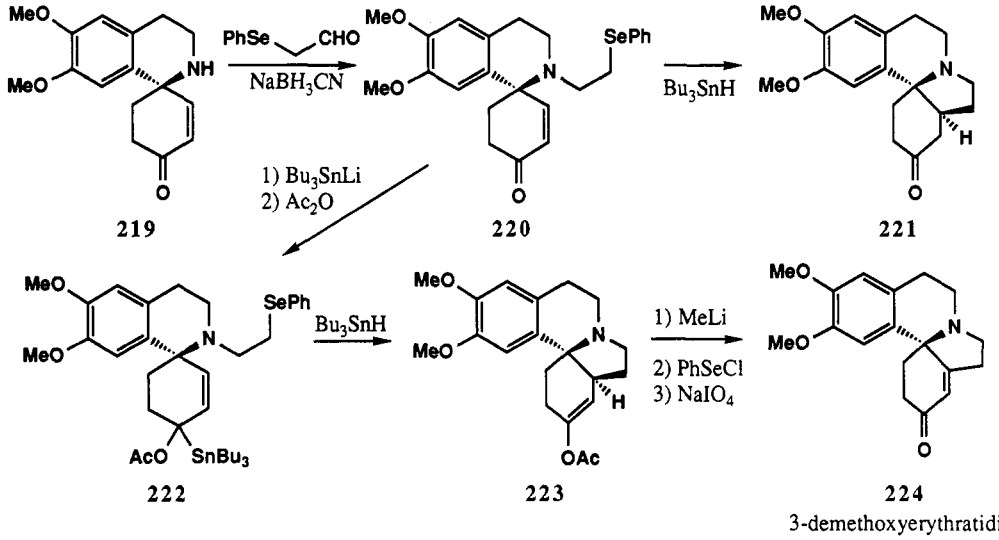
SCHEME 44



SCHEME 45



SCHEME 46



generation synthesis of (+)-pseudomonic acid C (213, Scheme 44).[176] Although the alkylation of 215 was very sensitive to the reaction conditions, optimization allowed formation of 212 in 74% yield. Analogous radical allylations with 1- or 3-substituted allylic stannanes are complicated by competitive isomerization of the reagents. The use of the complex allylic sulfone 214, which does not isomerize, allowed a much more convergent route to pseudomonic acid C than when the simple allyl stannane was used (compare Schemes 43 and 44). This synthesis nicely illustrates the potential for assembling two large, complex pieces of a molecule by a radical addition.

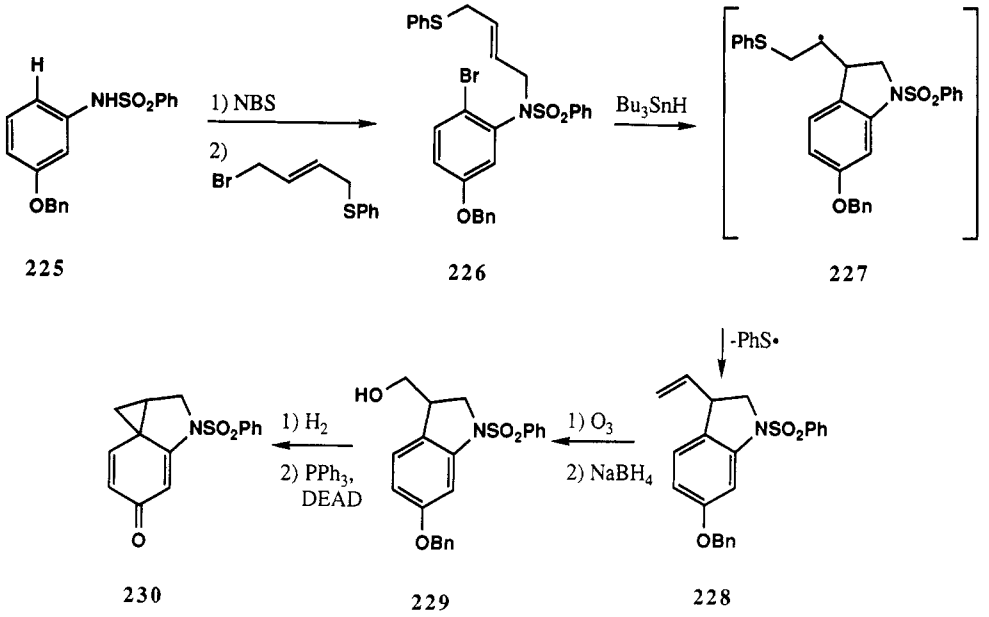
Other applications of radical allylation reactions that use the fragmentation method have appeared. Examples involving simple allylations include Kano's synthesis of the unusual amino acid statine,[177] Tam's synthesis of AZT analogues,[178] and the facile syntheses of 6-α-allylpenam derivatives by Hanessian and Just.[179,180] Toru has also used a 2-substituted allylic stannane to synthesize 6-oxoprostaglandin E_1.[181]

Vinyl stannanes can also be used in intermolecular alkylation reactions, as demonstrated by Keck's tandem cyclization–alkylation synthesis of $PGF_{2\alpha}$ (Scheme 45; for the structure of $PGF_{2\alpha}$ see 176, Scheme 36).[182] The radical precursor 170 is the same one used in Stork's synthesis (Scheme 36).[40] Reaction with 4 equiv of the β-stannyl vinyl ketone 216 directly provided Stork's intermediate 175, in 72% yield. The intermolecular addition takes advantage of the relatively high reactivity of α,β-unsaturated ketones. The ketone also ensures that the radical adds α and not β to the tin. Even with the ketone activation, the reaction required the use of high temperature (refluxing toluene rather than benzene), and accordingly, the use of a more stable radical initiator (217) than usual. At lower temperatures, increased amounts of reduced material which had cyclized but did not alkylate were observed. Baldwin, who pioneered the use of vinyl stannanes in the fragmentation method, has also used this methodology in the synthesis of 1270′, an antibiotic metabolite of fungi.[183]

B. Intramolecular Cyclizations with the Fragmentation Method

The fragmentation method has found several applications in intramolecular cyclization reactions. Danishefsky has used a radical cyclization to form the 5-membered nitrogen containing ring of the erythrina alkaloid 3-demethoxyerythratidinone (224, Scheme 46).[136] The allylic amine 219 was converted to the selenide 220 by reductive amination, and tin hydride

SCHEME 47

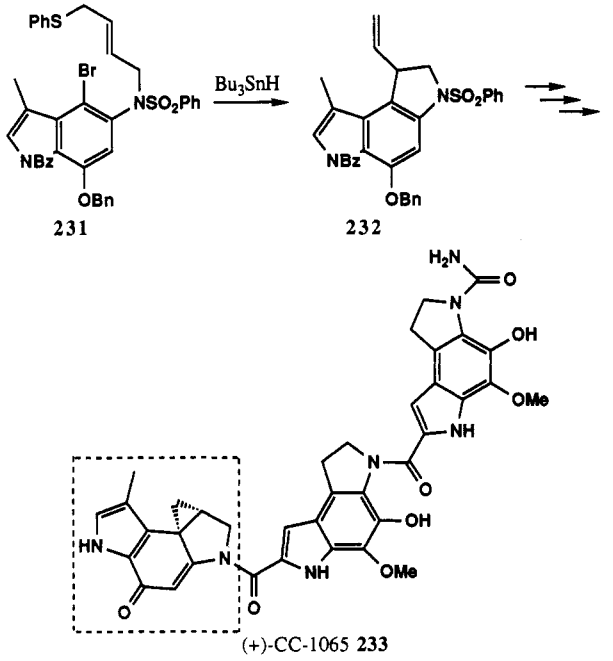


225 226 227 228 229 230

mediated cyclization gave an 88% yield of the cyclized product **221**. However, conversion of **221** to the natural product **224** requires regioselective introduction of unsaturation on the more substituted side of the ketone, a very difficult task. As mentioned earlier, whereas anionic Michael additions generate enolates which can be further functionalized, tin hydride mediated Michael additions give ketones that "forget" their original sites of unsaturation. Two solutions to this problem have been discussed already. Stork used an α-silyl enone to "remember" the regiochemistry of unsaturation (Scheme 36),[40] and Keck used a β-stannyl enone to regenerate the alkene (Scheme 45).[182] Danishefsky used a third option, as shown in Scheme 46. The enone **220** was readily converted to the acetoxystannanes **222** in 83% yield. Radical cyclization then gave the enol acetate **223**, in 65% yield. Having "remembered" the original site of unsaturation, the enol acetate was readily converted to the desired product **224**. A principle advantage of the Danishefsky method is the facility with which the enone was converted to the allylic acetoxystannane. A potential drawback is that the olefin is no longer activated by the ketone (that is, **220** has a more reactive radical acceptor than **222**). Keck has also used an intramolecular radical allylation in the synthesis of isoretronecanol.[147]

Boger used a somewhat different fragmentation reaction in his synthesis of the indoline portion of the antitumor–antibiotic (+)-CC-1065 (**233**) and various analogues (Schemes 47 and 48).[137,148] The key to the biological activity of (+)-CC-1065 is the substructure **230**, because the electrophilic cyclopropane ring alkylates DNA. Because of the lability of the cyclopropylcyclohexadienone ring system, the cyclopropane ring must be synthesized at the end of any projected total synthesis. In Boger's strategy, the cyclopropane is "protected" as a hydroxymethyl/phenol system (see **229**). In the representative model system (Scheme 47), the *N*-arylsulfonamide **225** was brominated and the nitrogen alkylated to give **226**. Radical cyclization proceeded in 91% yield by an addition/fragmentation mechanism to give the vinyl indoline **228**. Although β fragmentation of thio radicals is fast, 2 equiv of tin

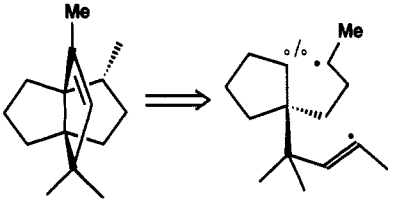
SCHEME 48



231 232 (+)-CC-1065 233

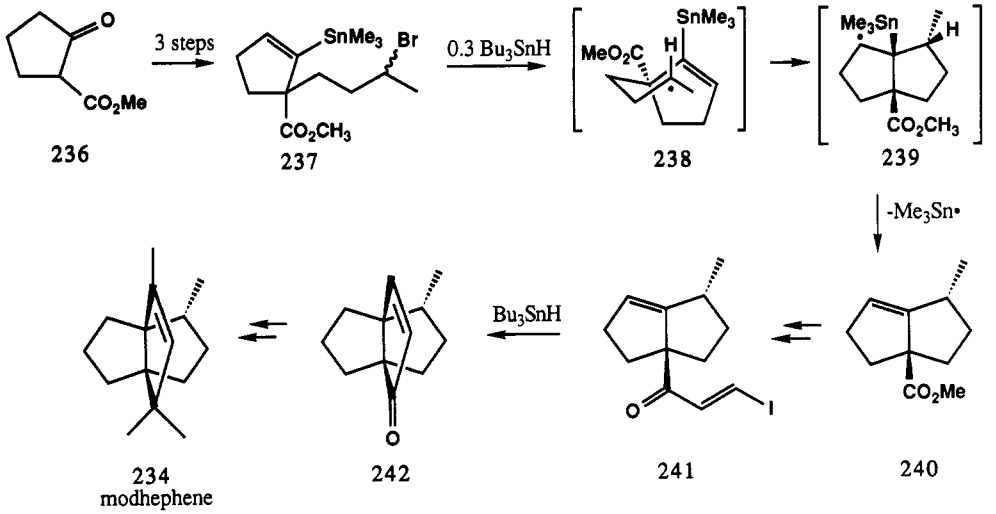
hydride was still required. After fragmentation, PhS• abstracts a hydrogen atom from tin hydride to give a tin radical (which can propagate the chain), and the PhSH so formed may react with a second equivalent of tin hydride to generate H_2 and $PhSSnBu_3$. Although fragmentation involving an allylic sulfide does not remove the need for tin hydride, it retains the advantage that the cyclized radical (**227**) is not simply reduced but is instead converted to a synthetically useful alkene

SCHEME 49



234 235

SCHEME 50



functional group. An analogous pathway was followed in the actual synthesis of (+)-CC-1065 (Scheme 48). Aryl bromide **231** underwent radical cyclization–fragmentation in 95% yield. Boger has used this approach for the synthesis of a broad series of CC-1065 analogues, which have helped to elucidate the structural features important for the biological activity of these important molecules.

An intramolecular fragmentation reaction using a vinyl stannane has recently been applied by Curran and Jasperse in the synthesis of the fused triquinane modhephene (**234**, Schemes 49 and 50).[30] Their retrosynthetic approach to a fused triquinane was to dissect two of the 5-membered rings at the bridgehead, as shown in Scheme 49. A number of alternate permutations involving ring to side chain cyclizations could also be envisioned, but any successful synthesis of modhephene must control the methyl-bearing stereocenter.

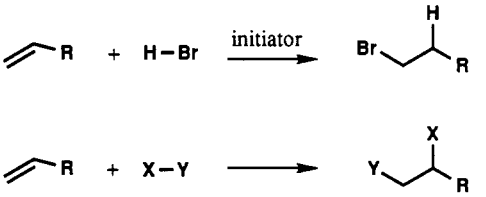
The synthetic solution (Scheme 50) used two independent 5-exo radical cyclizations onto the preexisting ring. The keto ester **236** was converted in three steps and 68% yield to the vinyl stannane **237**. Radical cyclization of **237** proceeded efficiently to give the bicycle **240** in 90% yield, as a single diastereomer. The β stereochemistry of the methyl group is consistent with the usual chairlike transition state **238**, but the stereoselectivity is unusually high. When the $SnMe_3$ group was replaced by H, the stereoselectivity dropped to 3:1. The $SnMe_3$ substituent probably intensifies the stereoselectivity for steric reasons; the pseudoaxial trimethyltin substituent destabilizes the alternate transition state with the methyl group eclipsed to tin. 5-Hexenyl radical cyclizations onto substituted alkene termini are normally slow, and often require some sort of activation. However, radical **238** was not highly reactive (like an aryl or vinyl radical), the olefin was not activated by an electron-withdrawing group, and the cyclization was not facilitated by oxygen or nitrogen incorporation in the 3-position. Although tin hydride was used in the reaction, it served only as an initiator and not as a chain-transfer reagent, and thus it was used at very low concentration. The use of the fragmentation method undoubtedly contributed to the high yield of this transformation. The fragmentation step was also necessary because it regenerated the double bond for later use. After the bicyclic ester **240** was converted to the iodoenone **241**, another radical cyclization onto the double bond gave the propellane enone **242** in 88% yield. Neopentyl quaternary centers formed in each of the two radical cyclizations, again showing the power of radical cyclizations to make hindered bonds. A recent synthesis of modhephene by Sha has used a ring to side chain radical cyclization conducted by the tin hydride method.[61]

V. The Atom/Group Transfer Method

A. Introduction

Although most of the radical additions and cyclizations described above have been terminated by reduction or fragmentation, it is also possible to terminate radical reactions by reaction of the final radical with the initial radical precursor. This sets off a classical chain reaction, often called a Kharasch reaction, which is exemplified by the peroxide initiated, anti-Markovnikov hydrobromination of olefins illustrated in Scheme 51.

SCHEME 51



In this reaction, the atom undergoing addition to the olefin (bromine) is generated directly by hydrogen atom abstraction from the starting material (HBr), giving rise to the term "atom-transfer addition". Fortunately for synthetic chemists, many molecules X–Y can be readily employed in this scheme. Of most interest are reagents where Y = carbon or heteroatom and X = H, halogen, or heteroatom-containing groups (group-transfer additions).

The fundamental aspects of this type of reaction have been recently reviewed,[6,7,184] so discussion here will be very brief. For an atom-transfer chain to succeed, both the initial addition (or cyclization) reaction and the atom-transfer step must be relatively rapid, exothermic reactions in order to compete with standard chain-

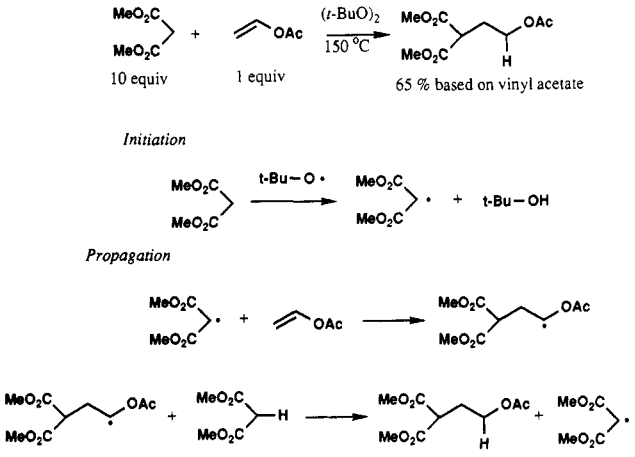
termination steps. The addition–cyclization step often meets this criterion because a strong σ bond is formed at the expense of a π bond. However, the atom-transfer step generally only succeeds when the initial radical site is more stable (from a resonance energy standpoint) than the adduct radical site. The initial radical can undergo a wide variety of addition or cyclization reactions (or combinations of the two), as long as these reactions are faster than the final atom- (or group-) transfer step.[184]

This section is divided into two main subsections, atom- (H, halogen) and group- (–SR, $-CoR_n$) transfer reactions, and the halogen-transfer section is subdivided according to the atom bonded to the halogen (carbon or heteroatom).

B. Hydrogen Transfer

One of the major advantages of the atom-group-transfer method is that the product generally retains useful functionality as a result of the transfer. The hydrogen atom transfer reaction lacks this potential advantage because the reactions are terminated by formation of a C–H bond. Scheme 52 illustrates a

SCHEME 52

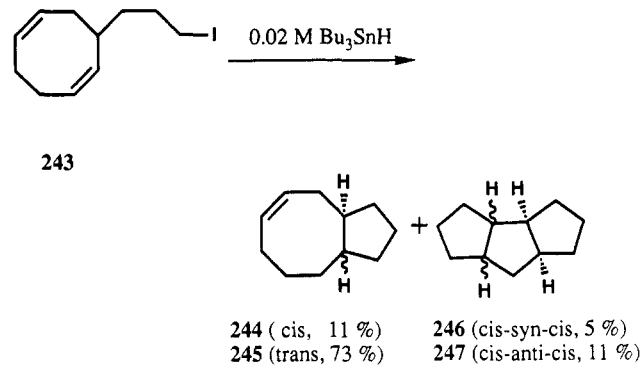


typical hydrogen atom transfer reaction and shows the accepted mechanism.[185] Even the most reactive C–H bonds barely react fast enough to maintain a viable chain reaction. Consequently, the hydrogen-donor substrate is typically used in large excess in the absence of solvent. Large amounts of initiator are also required.

Because of these limitations, the hydrogen atom transfer method is generally useful only in the construction of simple molecules. Complex natural products contain many C–H bonds (often many activated ones) so that site selectivity can be a serious problem. Nevertheless, in one interesting example, a hydrogen atom transfer cyclization reaction was critical to the success of the entire strategy. In an approach to the linear triquinane class of natural products, Winkler and Sridar[186] performed the model tandem radical cyclization shown in Scheme 53. Reduction of **243** under standard tin hydride conditions produced the desired cis–anti–cis tricyclic product **247** in only 11% yield. A stereoisomeric tricyclic product **246** also formed in 5% yield. The major product was the cyclopenta-fused cyclooctane **245**.

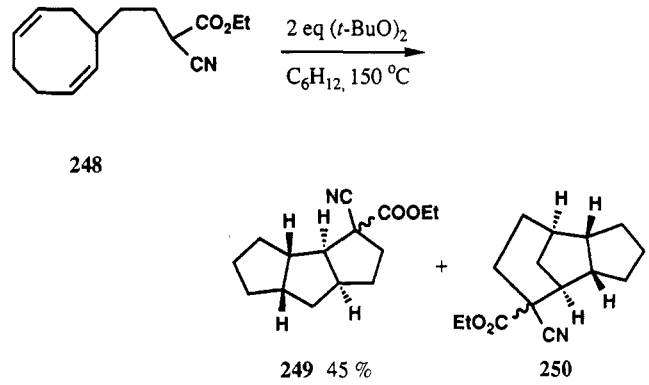
The low yield of tricyclic products was ascribed to the undesirable stereochemistry of the initial, irreversible cyclization. The major, trans-fused product radical

SCHEME 53



cannot undergo transannular cyclization fast enough to compete with hydrogen transfer from tin hydride because a strained, trans-fused [3.3.0] system would be formed. On the other hand, cyclization of cyano ester **248** by the hydrogen atom transfer method, as shown in Scheme 54, gave only tricyclic products **249** and **250**.

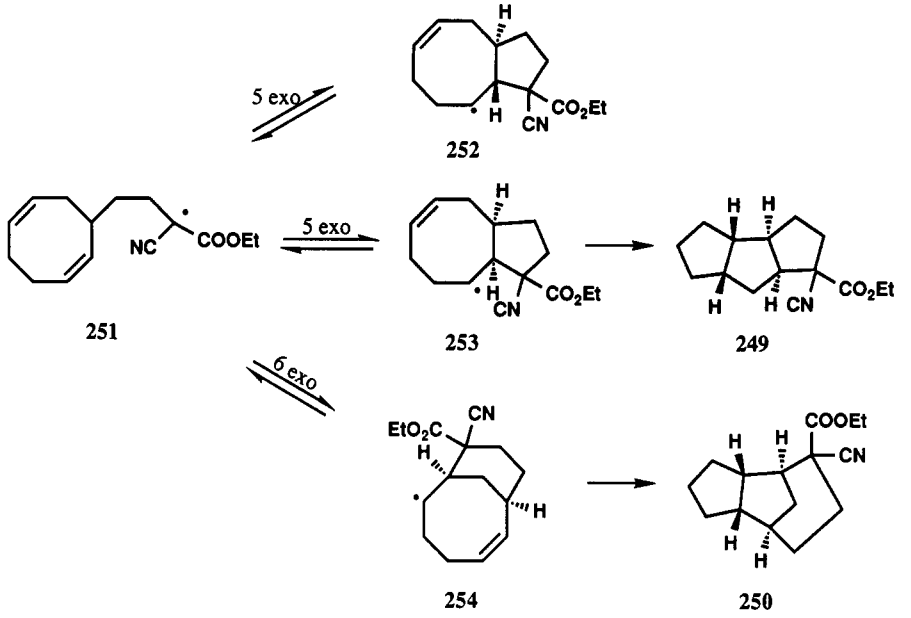
SCHEME 54



The striking contrast between Schemes 53 and 54 is an example of what can happen when radical cyclizations are reversible. Pioneering work on reversible radical cyclizations was conducted by Julia.[186b]

The important features leading to this much improved result are the absence of tin hydride, and the highly stabilized nature of the initial radical. Now, the first cyclization becomes reversible, as illustrated in Scheme 55.[23] In the absence of tin hydride, all of the intermediate radicals have relatively long lifetimes, so that reversion to starting radical **251** or transannular cyclization to **249** are undisturbed by competing hydrogen transfer to give bicyclic products. Thus, radical **252**, which cannot undergo annulation because of the strain energy mentioned earlier, simply reverts to starting radical **251**. The other two intermediate radicals (**253** and **254**) cyclize irreversibly to the observed products. The cyano ester functionality is critical to the reverse cyclization.[23] Without such stabilizing groups, radical cyclizations are typically irreversible under any conditions. Even with these stabilizing groups, the hydrogen-transfer method is often the only reliable option for approaching thermodynamic product distributions (**249** and **250**). As an added bonus, the bulk of the ester and cyano substituents increases the inherent preference for the required cis–anti–cis ring fusion. Unfortunately, these thermodynamic conditions also allow kinetically slow but thermodynamically acceptable processes (like the 6-exo cyclization of **251** → **254**) to compete.

SCHEME 55

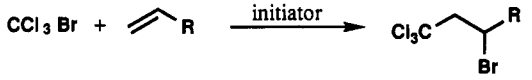


C. Halogen Atom Transfer

1. Introduction

The halogen atom transfer method is far more synthetically useful than the hydrogen atom transfer method for several reasons. First, a versatile halogen atom is retained in the product. Second, the atom-transfer step is often very rapid, leading to an efficient chain process. Finally, site specificity is seldom a problem because the carbon- (or heteroatom-) halogen bond is usually by far the weakest bond in the molecule. This method is quite old, dating to the pioneering work of Kharasch[187] on the addition of polyhaloalkanes across olefins. Scheme 56 illustrates a typical Kharasch reaction with bromotrichloromethane.

SCHEME 56

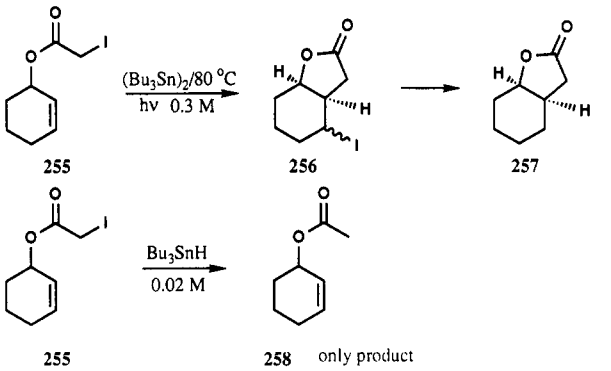


The propagation sequence for this reaction is analogous to that described above for the hydrogen-transfer reactions. As with hydrogen-transfer reactions, most chlorine and bromine transfer reactions are not rapid, and for some time, synthetic use of the halogen atom transfer method was restricted to specialized atom donors like polyhaloalkanes. Fortunately, the scope of such atom-transfer reactions can be dramatically extended by using a low-valent metal promoter, although the precise role of the metal promoter (initiator? source of halogen?) is sometimes unclear.

Iodides are fantastic atom donors, and almost any exothermic iodine transfer reaction will be sufficiently rapid to propagate a chain. A recent example from the labs of Curran[128,188] demonstrates an intramolecular reaction (atom-transfer cyclization) and illustrates some important aspects and advantages of modern applications of the atom-transfer method (Scheme 57).

Sunlamp irradiation of iodo ester **255** with a catalytic amount (5–10%) hexabutylditin at high iodo ester concentration (0.3 M) afforded bicyclic iodide **256**. Reduction of **256** provided lactone **257**. By contrast, reduction of **255** with tin hydride at moderately low

SCHEME 57



concentration (0.02 M) gave none of the lactone **257**, and only reduced product **258** was obtained. Since the same initial radical is formed in each case, the difference in its behavior is a result of the different reaction conditions. In the atom-transfer method, tin hydride is not present, and the ester-substituted radical has a sufficient lifetime to undergo the slow cyclization. However, the resulting secondary radical has a very short lifetime because it reacts rapidly with starting iodide to generate a more stable radical. In the presence of tin hydride at 0.02 M, radical lifetimes are shorter, and reduction of the initial radical proceeds to the exclusion of cyclization. It is likely that lower concentrations of tin hydride could be used, and that some lactone **257** could be formed.[89] But it is unlikely that the tin hydride method could equal the atom-transfer method in practicality and yield for this reaction.

The two halogen atom transfer reactions shown above succeed because the initial and final radicals are allotted different solution lifetimes; the initial radical has a long lifetime because no reductant is present, and the final radical has a short lifetime because of the rapidity of halogen transfer. Such differentiation is not possible in the tin hydride method because alkyl radicals react with tin hydride at similar rates. In the examples shown, the stabilization is provided by the polyhaloalkyl and the carbonyl group, respectively. Other useful stabilizing groups include cyano, vinyl and aryl, and heteroatoms. It is also possible to use unstabilized alkyl

iodides as long as the final radical is even less stable (vinyl).

In recent years, applications toward natural products synthesis have appeared. These have exploited the unique advantages of the halogen atom transfer method, namely:

(1) Only an initiator, and no external chain-transfer agent (Bu_3SnH), is required. This reduces or eliminates the amount of toxic, difficult to remove tin compounds that need be employed.

(2) Because there is no good hydrogen atom donor (Bu_3SnH) present, the initial radical has a long solution lifetime in which to undergo productive reactions. This is especially useful in conducting slow radical cyclizations to form 6- and 7-membered rings, and bridged ring systems. It is also advantageous in sequencing radical reactions.

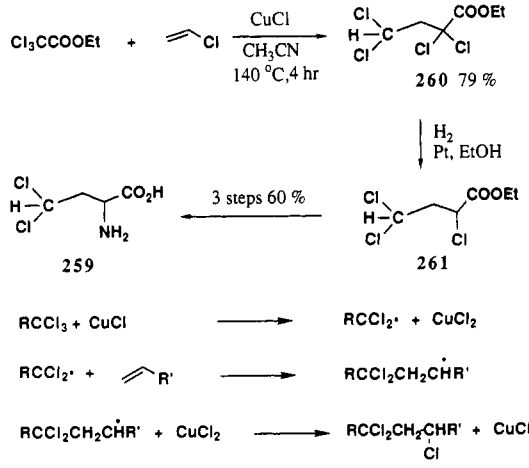
(3) The formation of the simple reduction products, which are sometimes difficult to separate from desired product, is minimized.

(4) The products retain a versatile halogen at a predictable site. The halogen atom can, among other things, be reduced, eliminated, displaced, converted to a Grignard reagent, or serve as a radical precursor.

2. Carbon–Halogen Bonds

Several natural product syntheses that use a halogen atom transfer reaction have been reported recently. For the most part, the initial radicals formed have been stabilized by adjacent chlorine atoms, carbonyl groups, or both. Chlorine atom stabilization is normally somewhat disadvantageous in that the chlorines can be difficult to introduce and usually require subsequent removal. However, Bellus has recently described[189] a synthesis of the naturally occurring amino acid antibiotic *d,l*-armentomycin (**259**), in which the chlorine atoms are actually required in the final product (Scheme 58).

SCHEME 58

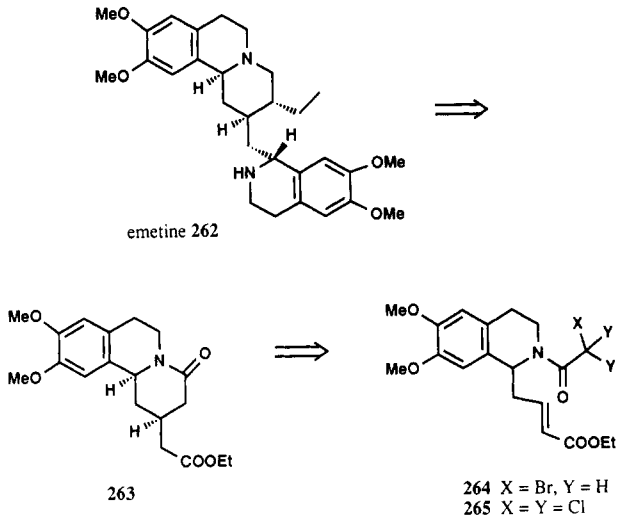


Copper(I)-promoted addition of ethyl trichloroacetate to vinyl chloride furnished tetrachloro adduct **260** in high yield. Selective monodechlorination (82%) gave α-chloro ester **261**, which was readily transformed into the natural product **259** by standard manipulations. Thus, an isolated $CHCl_2$ group, which is normally difficult to incorporate, was readily introduced through the halogen atom transfer addition reaction performed on a simple substrate. Bellus has provided a number of other interesting and useful examples of this reaction,[189] which are characterized by the ready availability of starting materials, and the high degree of functionality in the products.

A few comments on this type of coupling reaction are warranted. While all the mechanistic details are not fully understood,[189,190] the high yields of 1:1 adducts that are formed even when a 1:1 ratio of starting materials is employed suggests that standard "Kharash-type" chain reactions may not be involved, and that the metal may be more than just an initiator. Bellus has suggested that the radicals remain coordinated to the copper during the entire course of the reaction (other transition metals may also be used[190]). Redox chains like that shown in the lower part of Scheme 58 are also often proposed.[5] Whatever the case, the reactivity profile imposed by the metal is useful, and several workers have used the intramolecular version of the reaction in syntheses of, or approaches to, natural products.

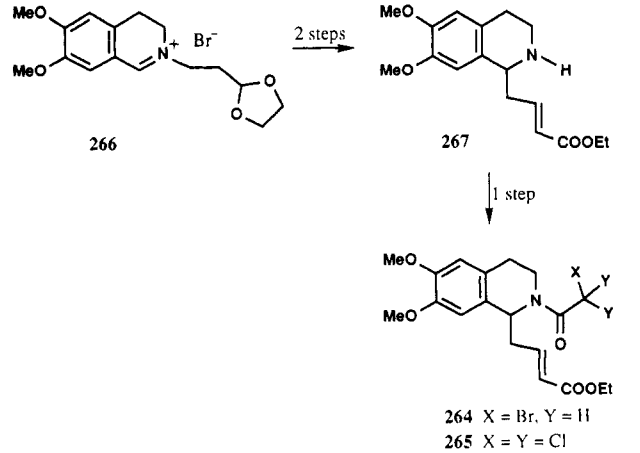
Yamazaki and co-workers[191] have recently described an approach to the naturally occurring alkaloid emetine (**262**) which features formation of a 6-membered ring by halogen atom transfer cyclization. Their plan, summarized in Scheme 59, called for preliminary con-

SCHEME 59



struction of tricyclic lactam ester **263** with subsequent elaboration of the tetrahydroisoquinoline moiety. The lactam ring was to be formed by a 6-exo radical cycli-

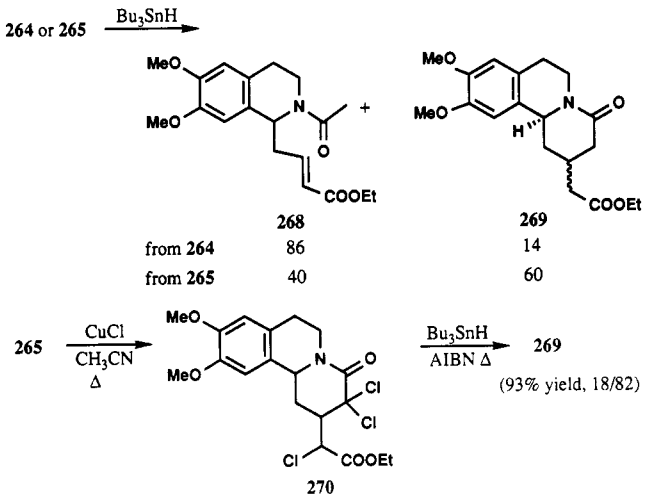
SCHEME 60



zation performed on either of the substrates **264** or **265**. The synthesis of these radical precursors is outlined in Scheme 60.

Two factors would appear to mitigate against the success of the proposed cyclization. First, 6-membered ring formation by radical chemistry is generally more difficult than 5-membered ring formation. Second, the substrates likely exist as pairs of amide rotamers, with the most populated rotamers having geometries unsuited for cyclization. Tin hydride reduction of bromide **264** gave only a 14% yield of cyclic product **269** alongside 86% of **268** (Scheme 61). Trichloride **265**

SCHEME 61



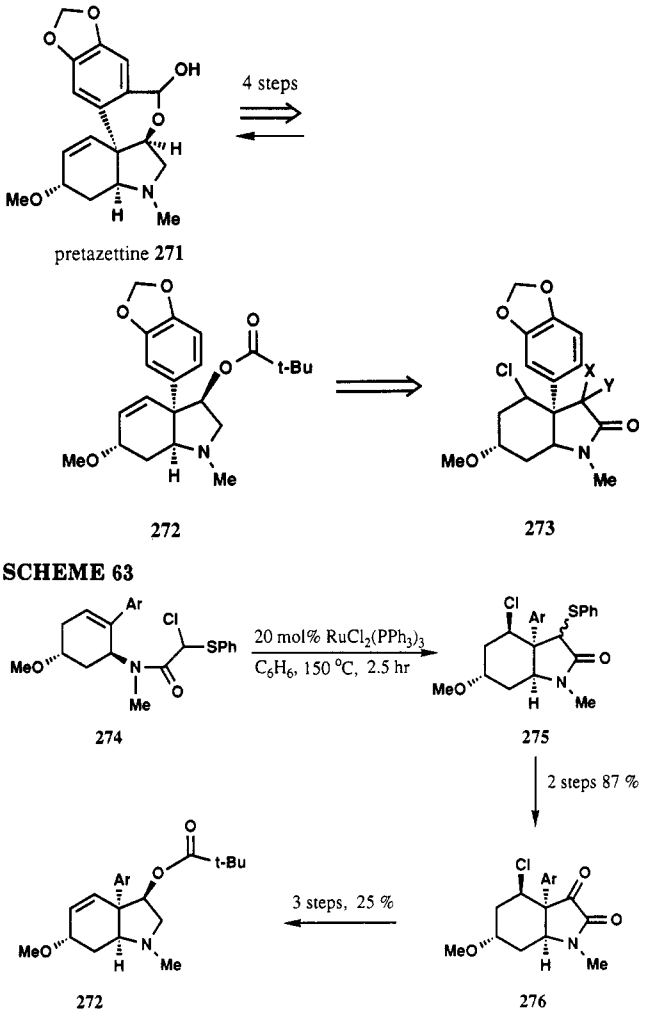
gave an improved cyclization yield of 60%, perhaps because there are three opportunities for the initial radical to be generated (3 chlorines).

By contrast, treatment of the trichloroacetamide **265** with 0.3 mol % CuCl in CH_3CN in a sealed tube at 140 °C, followed by reductive removal of the chlorine atoms, afforded **269** in 93% yield as an 82/18 mixture of α and β epimers. There are several possible reasons why the atom-transfer technique gave superior results. First, because of the absence of a reducing agent, the initial radical has a long solution lifetime such that the 6-exo cyclization is kinetically feasible. Second, this radical is stabilized, so that a driving force for allylic hydrogen atom abstraction does not exist (or is at least diminished). Third, because of the high reaction temperature, the interconversion of amide rotamers may be facilitated (unfavorable rotamers can rotate and cyclize).[128] Finally, it is possible that the metal participates in the reaction, thereby altering the structure of the reacting radical.

Ishibashi and Ikeda[192] have reported a similar lactam-forming cyclization in their formal synthesis of (±)-pretazettine (**271**). The strategy is summarized in Scheme 62. The actual target was pivalate ester **272**, which had been converted into (±)-pretazettine (**271**) in 4 steps. The ester **272** was attainable from a precursor such as **273**, which has sufficient functionality (depending on the choice of X and Y) for conversion into **272** and is the product of a chlorine atom transfer cyclization of a chloro acetamide. This approach has good precedent in Itoh's[193] previous synthesis of the mesembrane ring system.

In the present example, the actual cyclization substrate was readily available chloro sulfide **274**, as shown in Scheme 63. Treatment of **274** with 20 mol % of

SCHEME 62

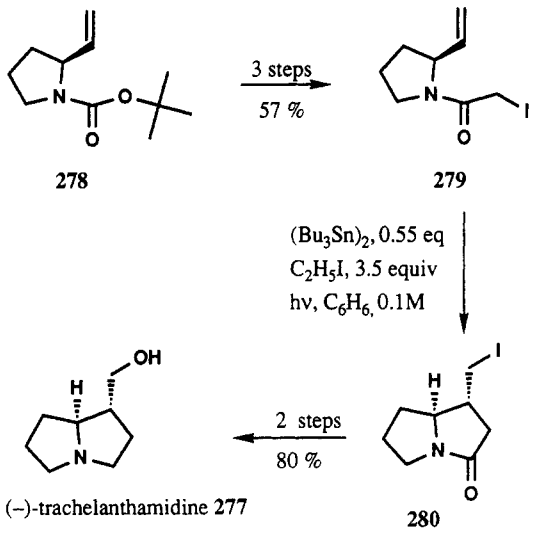


$RuCl_2(PPh_3)$[190] produced the lactam **275** in 57% yield. Sulfide oxidation and Pummerer rearrangement/hydrolysis gave ketolactam **276**. This was dehydrochlorinated, reduced to the amino alcohol, and acylated to give the target **272**. In the key radical cyclization, the transferred chlorine atom serves to install the requisite olefin. The sulfur substituent serves a triple role in (1) facilitating introduction of the chlorine, (2) stabilizing the initial radical (and perhaps facilitating the chlorine transfer), and (3) providing an easy way to introduce the required oxygen functionality.

Livinghouse and Jolly[194] have synthesized (−)-trachelanthamidine (**277**) by using yet another lactam forming reaction (Scheme 64). The known vinyl proline derivative **278** was readily transformed into iodoacetamide **279**. Cyclization of **279** was conducted by a modification of Curran's[195] standard atom-transfer conditions (0.55 equiv hexabutyl ditin, 3.5 equiv CH_3CH_2I, light), and gave **280** in 58% yield with excellent stereoselectivity (30/1). The synthesis was completed by displacement of iodide with cesium propanoate, followed by $LiAlH_4$ reduction of the ester and amide groups.

Recently, Curran and Tamine[128] have proposed that the modified conditions introduced by Jolly and Livinghouse may not be effective for the reasons that these workers proposed.[194] Instead, because of the amide rotational barrier, the important variable for a successful cyclization is temperature. In related cycliza-

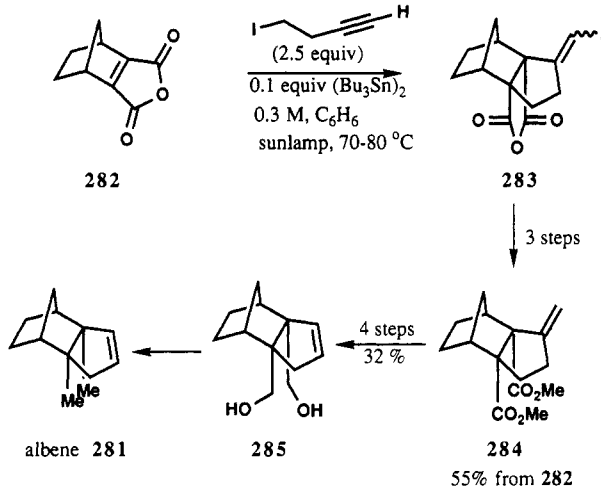
SCHEME 64



tions, Curran's standard conditions can be used provided that the reaction is heated during the irradiation.[128]

Curran and Chen[196] have recently developed an iodine atom transfer annulation protocol in which two radical reactions, an addition and a cyclization, occur between the radical-generation and atom-transfer steps. This process relies on the high reactivity of vinyl radicals, which abstract iodine atoms rapidly even from simple alkyl iodides (lacking any radical stabilizing group). The utility of the procedure was demonstrated by the synthesis of the simple natural product albene (**281**, Scheme 65). Atom-transfer annulation of **282** and

SCHEME 65



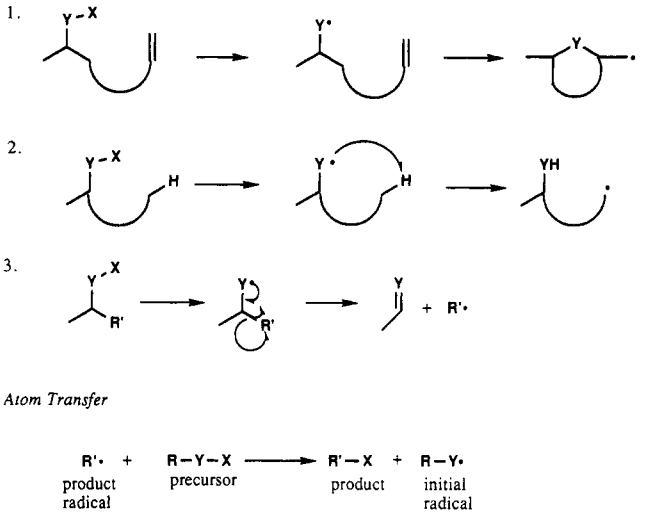
iodobutyne gave the annulation product **283**, which was not purified, but instead directly processed to **284**. Conversion of **284**, via **285**, to albene (**281**) was straightforward.

Although these atom-transfer annulations usually give modest yields (40–60%), they represent a very direct, one-pot synthesis of substituted (methylene)cyclopentanes from simple precursors. Atom-transfer annulations based on electrophilic radicals have also been developed.[197]

3. Heteroatom–Halogen Bonds

Heteroatom–halogen bonds are very weak and are easily homolytically cleaved. The resulting heteroatom centered radicals typically react via three general pathways (Scheme 66): (1) addition to suitably situated

SCHEME 66

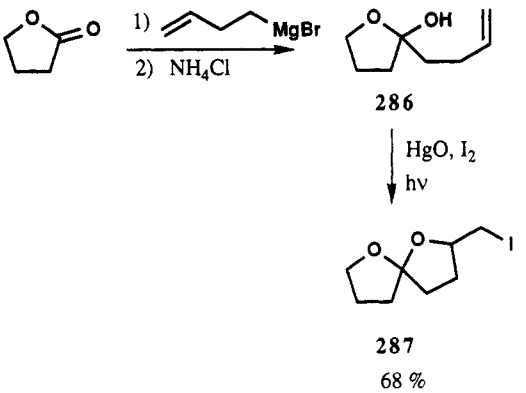


multiple bonds, (2) hydrogen atom abstraction, or (3) formation of a carbon–heteroatom double bond with simultaneous carbon–carbon bond cleavage (β fragmentation). In each case, a subsequent halogen atom transfer propagates a chain reaction.

Each of the reactivity patterns in Scheme 66 has been exploited in natural product syntheses. The first two processes are useful in the formation of heterocycles (5- or 6-membered, Y = O or N), the latter case requiring a subsequent, ionic ring closure. The third pathway is especially useful in ring expansion schemes. These reactions seldom involve carbon–carbon bond formation, so only representative examples of each type will be given. The discussion will focus on the cleavage of nitrogen–halogen and oxygen–halogen bonds.

Kraus and Thurston[198] have developed an alkoxy radical cyclization method in connection with an approach to ginkgolides. They required a route to spiroketals, and lactol **286** was prepared and subjected to various conditions known to generate alkoxy radicals (Scheme 67). Only the conditions developed earlier by

SCHEME 67

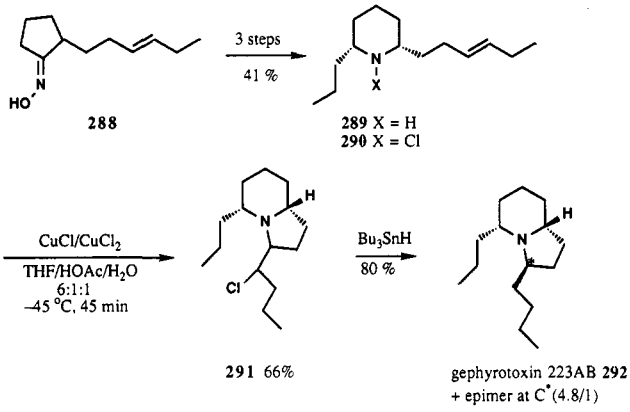


Barton and Akhtar (HgO, I_2, hν)[199] proved successful, giving the desired iodomethyl spiroketal **287** in good yield. The alkoxy radical cyclization may prove to be a useful alternative to the much more common iodo etherification reaction, especially when reactivity (electron-deficient olefins) or regioselectivity is a problem.

Alkoxy radicals are much more reactive than carbon radicals. In contrast, aminyl radicals are less reactive. This reactivity can be increased by rendering the aminyl radical more electrophilic by protonation, metal complexation, or attachment of an electron-withdrawing group to the nitrogen (carbonyl, NO_2). The fragmentation reaction (type 3 above) rarely occurs with aminyl radicals, presumably because the C=N bond is much weaker than a C=O bond. The other two reaction types do occur;[200] the hydrogen atom abstraction pathway is a component of the well-known Hofmann–Löffler–Freytag reaction.

Broka has used an aminyl radical cyclization en route to gephyrotoxin 223AB (**292**),[201] a constituent of the skin extracts of poison-dart frogs. The required substrate **290** was synthesized as outlined in Scheme 68,

SCHEME 68

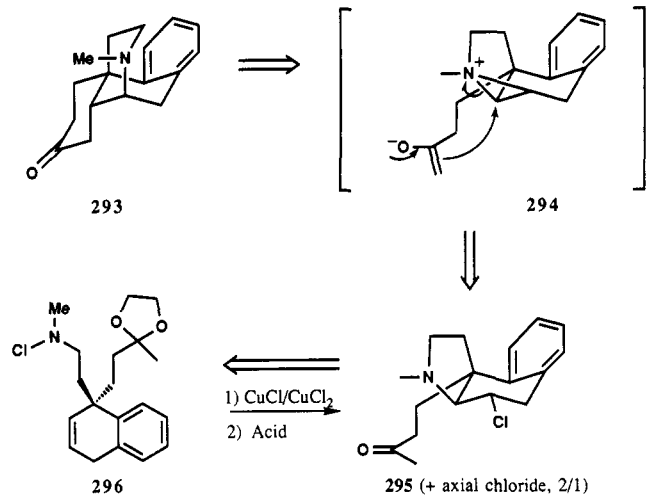


by a Beckmann rearrangement/imine reduction sequence starting from oxime **288**. After chlorination of **289**, treatment of **290** with CuCl (0.1 equiv) and $CuCl_2$ (1.0 equiv), followed by Bu_3SnH reduction of the resulting chloride **291**, gave the target **292**. In principle, the same product could have been obtained by using the Hofmann–Löffler–Freytag reaction on a saturated side chain substrate; however, the presence of γ-hydrogens on both side chains would have led to regiochemical problems in the H-abstraction step.

In a second example, Broka and Gerlits[202] have taken advantage of the reactive nature of the product of a chlorine atom transfer aminyl radical cyclization, a β-chloroamine (nitrogen mustard). Intramolecular displacement of chloride by nitrogen gives rise to an aziridinium cation, which is highly susceptible to nucleophilic attack. Thus, the retrosynthetic analysis of the morphinan ring system **293** shown in Scheme 69 was conceived. The plan called for a radical cyclization to construct a fused ring system (**295**) and subsequent intramolecular nucleophilic attack by a ketone enolate (or equivalent) on the aziridinium cation (see **294**). This would effect a 1,2 migration of the nitrogen atom, so that the bridged ring system would be formed.

The cyclization substrate **296** was readily synthesized from 1-naphthoic acid. Treatment of **296** with CuCl/$CuCl_2$ furnished the two epimeric chlorides (**295** and epimer) and a dehydrochlorination product. The chlorides **295** were also obtained when $FeCl_2/FeCl_3$ or $TiCl_3$ were employed, but the amount of axial epimer was increased. This suggests that the metal plays some role in the chlorine-transfer step, either by donating the chlorine atom directly, or by complexing to the aminyl radical. Only the major product **295**, with the equatorial

SCHEME 69



chloride anti to the nitrogen, underwent efficient aziridinium ion formation with subsequent closure to give **293**. This closure was accomplished on an enol silyl ether derivative of **295**.

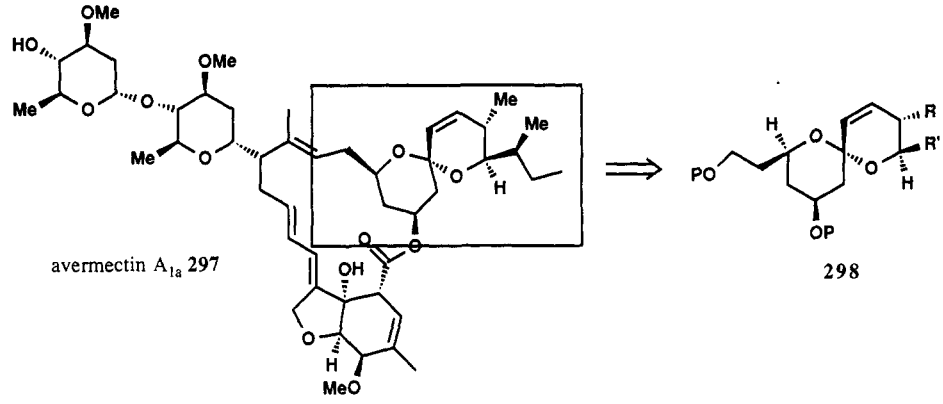
The second reaction associated with heteroatom-centered radicals is hydrogen abstraction, which is often followed by atom/group transfer and ionic ring closure. For a nitrogen-centered radical, this is called the Hofmann–Löffler–Freytag reaction.[199] However, oxygen-centered radicals are also potent hydrogen atom abstractors, and analogous transformations work when hydrogen abstraction is faster than β-fragmentation reactions. Indeed, the well-known Barton[203] reaction for remote functionalization of steroids and terpenoids is a famous example of hydrogen abstraction by alkoxy radicals. Because of the high reactivity of alkoxy radicals, the hydrogen abstraction is only useful when the reacting centers are held in close proximity and are 6 atoms distant from one another (as in the Barton reaction), or when the hydrogen to be abstracted is activated (that is, the resulting radical is stabilized).

A single example from the recent work of Danishefsky[204] demonstrates the synthetic potential of this method for heterocycle synthesis. In an approach to the naturally occurring insecticide avermectin A_{1a} (**297**), Danishefsky and co-workers required a synthetic route to the spiroketal portion, represented by **298** (Scheme 70).

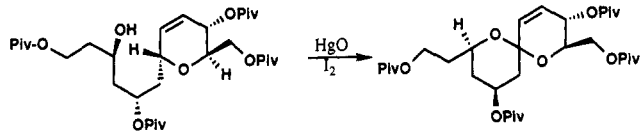
The cyclization substrate **299** (Scheme 71) was prepared in 11 steps from triacetylglucal. The key steps were formation of a new dihydropyran by a diene–aldehyde cycloaddition, and its cleavage to give the side chain with its attendant stereocenters correctly installed. Treatment of **299** with HgO/I_2 in CCl_4 afforded the desired spiro ketal **300** as a single stereoisomer. Central to the success of this reaction is that 1,6-hydrogen transfer of the doubly activated hydrogen (allylic ether) was more rapid that 1,5-hydrogen transfer of unactivated hydrogens.

The last reactivity pattern of heteroatom-centered radicals is β fragmentation. This cleavage often occurs with oxygen-centered radicals to give a carbonyl group, or with iminyl radicals to give a nitrile. This transformation is very useful in ring enlargement processes, as generalized in Scheme 72. The atom Y can be either carbon, oxygen, or nitrogen giving ketones, lactones, or amides respectively.

SCHEME 70

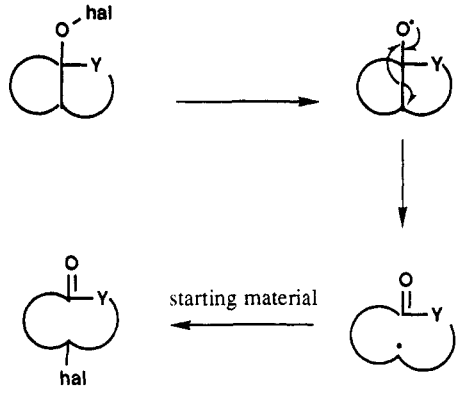


SCHEME 71



299 300

SCHEME 72



Because of the current interest in synthesizing medium- and large-ring compounds, the fragmentation method has been used with some frequency in natural product synthesis. Notable efforts have come from the groups of Suginome and Suárez, who have systematically explored the potential of the method. A single example from each group will be given.

Suginome and Yamada[205a] have synthesized the naturally occurring 15-membered cyclic ketones exaltone and (±)-muscone from commercially available cyclododecanone as shown in Scheme 73.

Starting from **301**, a straightforward sequence of reactions produced ketones **302a,b**. These were cyclized to the tertiary alcohols **303a,b** by treatment with SmI_2 in THF/HMPA. Reaction of **303a,b** with HgO and I_2, with in situ photolysis, provided ring-expanded iodoketones **304a,b**. Bu_3SnH reduction then furnished the natural products **305a,b**.

Suárez and co-workers have reported an approach to the synthesis of the A ring of vernolepin (**306**),[205e] a cytotoxic, antitumor sesquiterpene. Their plan was to generate the lactone ring and the angular vinyl group by fragmentation of a lactol derived alkoxy radical. As a model, Suárez et al. studied the fragmentation chemistry of the steroidal lactols **307a,b** (Scheme 74). Reaction of **307a,b** with iodosobenzene diacetate (IBDA) and I_2 under UV irradiation produced lactone **308**. In this reaction, the sulfur and tin groups behaved similarly, and served two purposes: (1) to direct β-bond cleavage (in their absence, fragmentation was not regioselective), and (2) to introduce the double bond.

There are other methods to generate alkoxy radicals. Nitrite esters (RONO)[203] and peroxides also serve as oxy radical precursors. However the reactivity of these species can differ from the hypohalites because chain reactions do not occur. For example, peroxides do not give group-transfer (OH) products. Instead, the normal reaction course is fragmentation (to ketones) followed by oxidation (with olefin formation) or other reactions of the resulting radical. Schreiber's concise synthesis of recifiolide[206] is a beautiful illustration of a method based on hydroperoxide reduction.

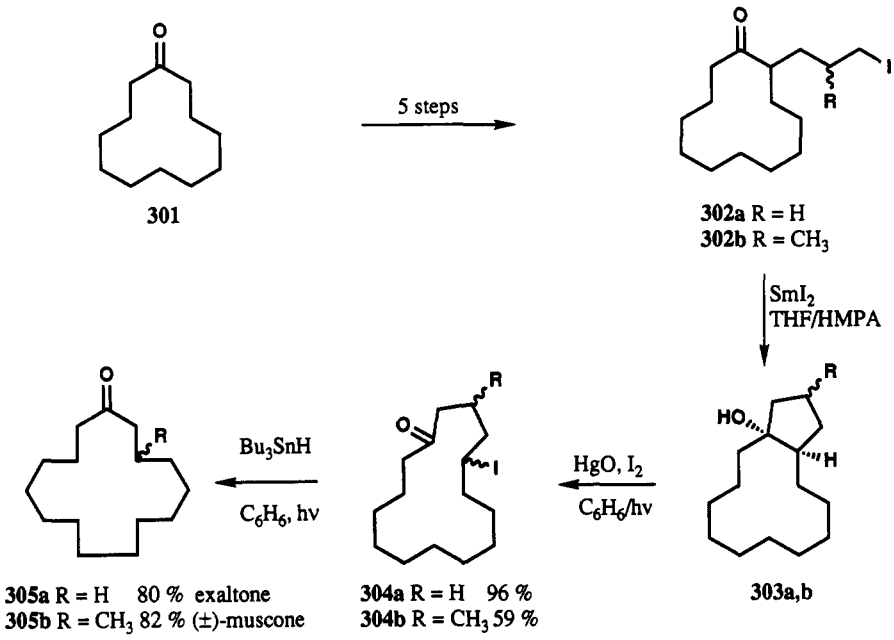
4. Group Transfers

In addition to simple halogen and hydrogen atoms, functional groups can also be transferred during radical reactions. The most important of these functional groups are various organocobalt complexes (cobalt group transfer method) and the thiopyridyl group (Barton thiohydroxamate method). These processes are formally related to atom-transfer reactions because of the nature of the transformations that they effect, but there are significant mechanistic differences. Fundamental aspects of each of these methods have been reviewed,[4,6,7,207,208] so only brief introductions will be given here.

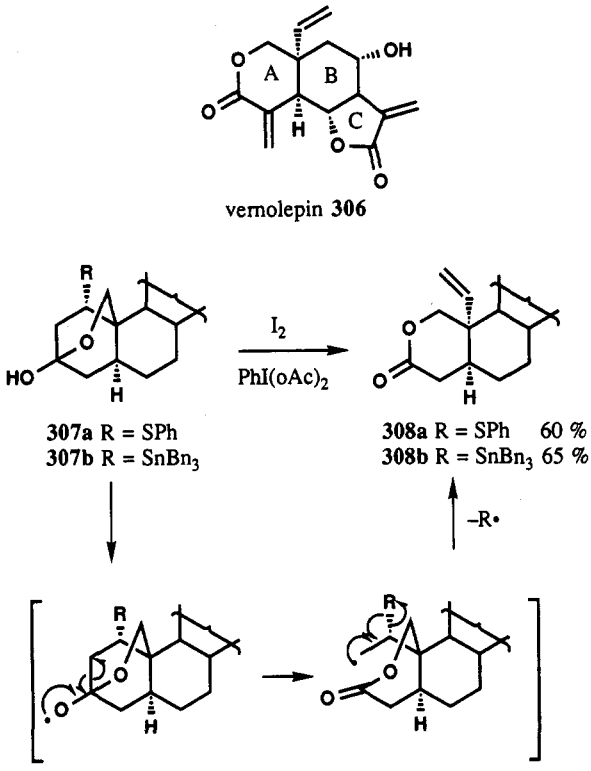
Organocobalt(III) complexes such as Co(salen), Co(dmgH)$_2$, and vitamin B_{12} can be reduced to the corresponding Co(I) species by Na, NaHg, Zn, or $NaBH_4$, or at an electrode (Scheme 75). These powerful nucleophiles react with primary or secondary alkyl halides or tosylates to give alkyl Co(III) complexes **309**. The carbon–cobalt bonds in these complexes are weak (25–35 kcal/mol) and are easily homolyzed by heat or light to generate alkyl radicals. The radicals are truly "free" and undergo reactions characteristic of radicals generated by other means.[207d] Reaction of the resulting radical with the persistent Co(II) radical (present in relatively high concentration) generates the new organocobalt(III) complex **310**, the product of a cobalt group transfer reaction (Scheme 75). Tertiary alkyl, aryl, and vinyl radicals can also be produced, but in these cases the reaction is probably an electron-transfer process that does not involve formation of an aryl (vinyl) cobalt bond.

The cobalt group transfer method is formally analogous to the halogen atom transfer method. Although it appears that the cobalt method requires an extra step

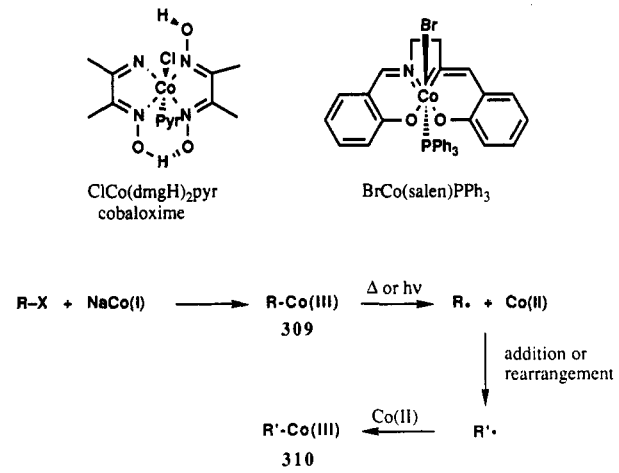
SCHEME 73



SCHEME 74



SCHEME 75

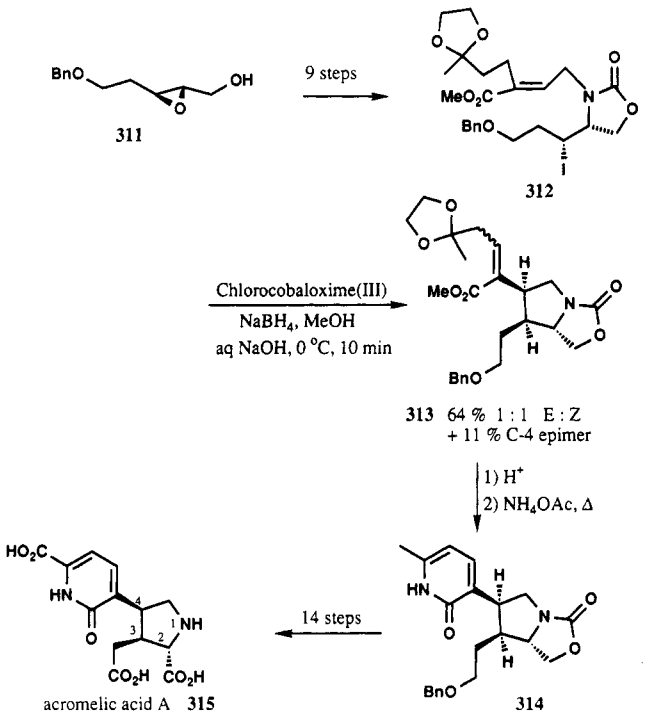


to prepare the initial radical precursor, the organocobalt(III) precursor need not be isolated, and is often generated and photolyzed in situ. As in the halogen atom transfer method, a versatile functional group is retained in the product. The cobalt group can be replaced by many of the same functional groups as halogen can (SPh, SePh, OH, elimination of HCo to olefin), and in addition can be replaced directly by an oxime group. Despite these similarities, the two processes differ fundamentally in mechanism. Atom-transfer reactions are chain processes, but organocobalt reactions are nonchain processes that rely on persistant radical (Co(II))/transient radical coupling.

A significant advantage of the cobalt group transfer method is the ability to induce elimination of cobalt hydride from the product. This reaction is especially facile when the initial radical adds to an activated olefin. It is not always clear whether this rapid elimination proceeds through an intermediate having a fully formed carbon–cobalt bond or through a disproportionation. A key consequence is that cobalt-transfer reactions occur where halogen atom transfers would probably fail (because they are endothermic). Another advantage of the cobalt method is that toxic tin compounds are not required. Indeed, vitamin B_{12} is a positively healthy reagent!

Baldwin and Li have recently completed an enantiospecific total synthesis of acromelic acid A (**315**), a potent neurotoxin obtained from poison mushrooms.[209] The key step in their plan was a cobalt-mediated radical cyclization of substrate **312**. As summarized in Scheme 76, this was prepared in optically active form starting from epoxy alcohol **311**. Treatment of **312** with sodium cobaloxime provided **313**, the stereoisomer expected from Beckwith's guidelines. A small amount of the C-4 epimer was also formed, however. After deketalization and pyridone formation, the synthesis of **315** was completed with a series of oxidation and protection–deprotection steps.

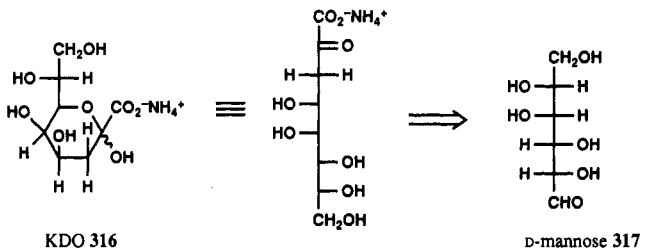
SCHEME 76



311 312 313 64 % 1 : 1 E : Z + 11 % C-4 epimer 314

Cobalt group transfer reactions can also be conducted intermolecularly, as exemplified by Branchaud's recent synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO, **316**),[210] an important constituent of the outer membrane of gram-negative bacteria. The synthetic plan called for deoxygenative attachment of a 2-carbon unit onto the hydroxyl-bearing terminus of D-mannose (**317**), as outlined in Scheme 77. This plan is hard to execute

SCHEME 77

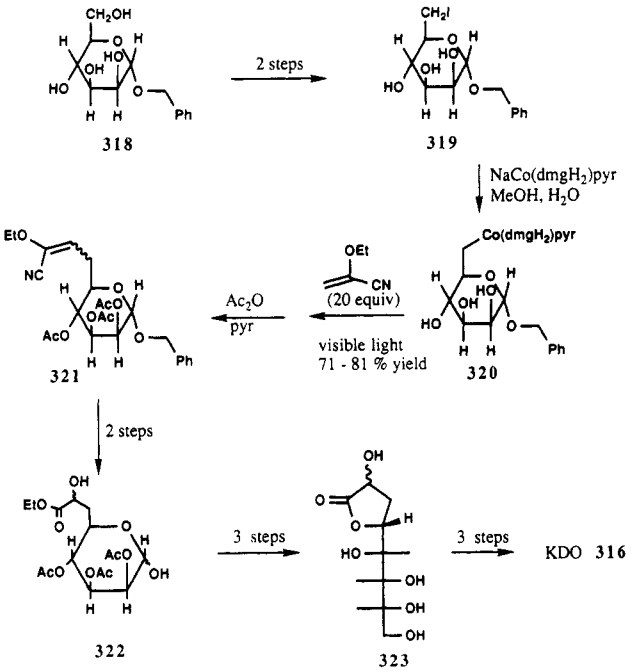


KDO 316 D-mannose 317

by traditional polar methods. Use of the sugar as a carbanion equivalent is not possible because β elimination of alkoxide would compete with intermolecular addition. The opposite polar approach would require reaction of an acyl anion equivalent with a functionalized, hydroxyl-protected sugar. The use of radical chemistry solves both of these problems; β elimination does not occur, and protecting groups are not required.

The synthesis was carried out from the known benzyl pyranoside **318** as shown in Scheme 78. Conversion of **318** into the corresponding iodide **319** was followed by displacement with $NaCo(dmgH)_2pyr$ to give **320**. Reaction of **320** with an excess of α-ethoxyacrylonitrile under the influence of visible light provided the two carbon chain extension product **321** after acylation. The synthesis was completed by vicinal hydroxylation of the olefin and debenzylation to give hydroxy ester **322**. This was deprotected, reduced, and lactonized to give **323**. Finally, hydrolysis of the lactone, selective oxidation of the α-hydroxy acid, and ion exchange afforded KDO (**316**).

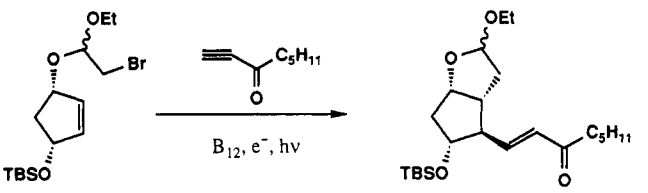
SCHEME 78



318 319 320 321 322 323

The use of vitamin B_{12} in organic synthesis has been pioneered by Scheffold.[207b,c] Vitamin B_{12} itself can be reduced either electrochemically (–0.8 V) or chemically (Zn/NH_4Cl) to give the nucleophilic cob(I)alamin (B_{12a}), which can be introduced into organic molecules in the same way as described above. Vitamin B_{12} is used only in catalytic quantities, and Scheffold et al. have used it to prepare several simple natural products.[207b] A potential advantage of B_{12} over the other cobalt complexes is its optical activity; a potential disadvantage is that the final product usually results from reduction and does not contain cobalt.[207b] All in all, this method represents a good alternative to reactions that might be conducted by tin hydride chemistry, as illustrated by Scheffold's variant on the prostaglandin synthesis outlined in Scheme 79[207c] (see Schemes 45 and 36 for related approaches).

SCHEME 79

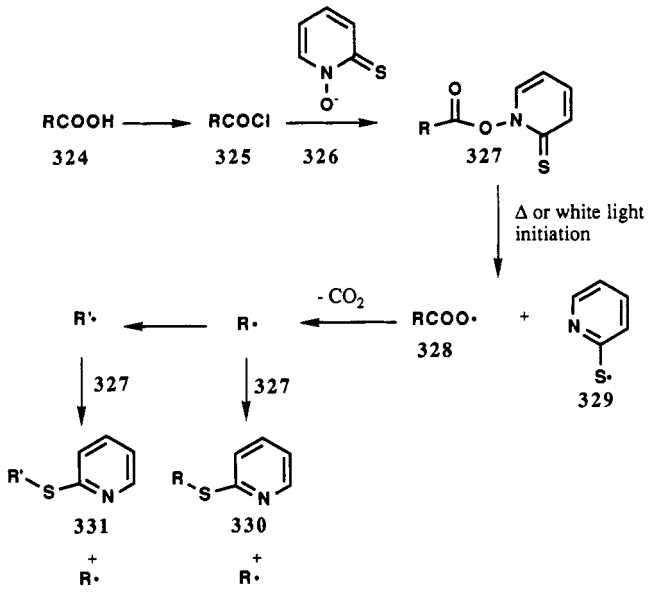


170 175 55%

Besides cobalt complexes,[211] the other group frequently transferred is the thiopyridyl group. The thiohydroxamate method, developed by Barton and co-workers, has many useful permutations. A recent, thorough review provides detailed information.[208] The basic reaction is outlined in Scheme 80.

Acid chlorides **325** react with the salt of *N*-hydroxypyridine-2-thione **326** to give *O*-acyl thiohydroxamate esters **327**. These are cleaved homolytically by heat or light to afford the carboxy radical **328** and thiopyridyl radical **329**. Decarboxylation provides radical R• which can react with starting thiohydroxamate ester **327**

SCHEME 80

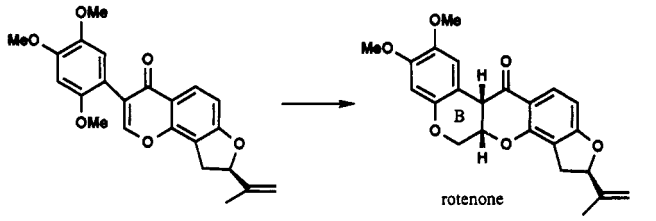


(chain transfer), or more usefully, suffer rearrangement or addition to give the new radical R′·. Reactions to form R′· must necessarily be faster than the reaction with **327**, and, like other chain methods, optimum reaction conditions can readily be selected.

The Barton thiohydroxamate method benefits from the same advantages as the atom and cobalt group transfer methods. It is not reductive, so the final product is provided with versatile functionality. Furthermore, slow additions or cyclizations should be possible, and the lower limits are set by the rate of radical addition to the thiohydroxamate ester (5×10^5 to 1×10^6 M^{-1} s^{-1} for alkyl radicals) and by the concentration of the ester. Finally, the reactions are easy to run since the thiohydroxamate ester can either be isolated or generated in situ, and the decarboxylative nature of the process assures that the radical precursors (carboxylic acids as opposed to halides) will be stable. Despite these advantages, the method has scarcely been used in natural product synthesis.[212] However, a few recent synthetic endeavors will illustrate its potential.

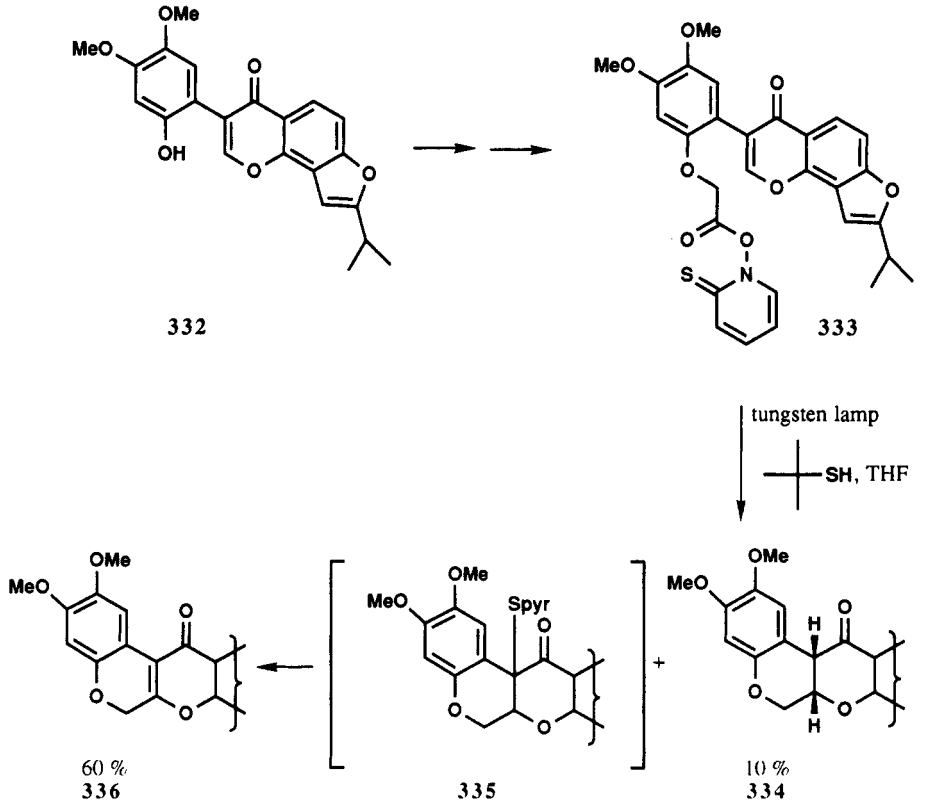
Whiting and co-workers[213] have performed a 6-endo cyclization by using the Barton method during a study designed to clarify the mechanism of rotenoid biosynthesis. The B ring of these compounds is biosynthesized by the unusual transformation shown in Scheme 81. Thinking that this cyclization may involve radical intermediates, the authors tested the feasibility of such a reaction in model systems.

SCHEME 81



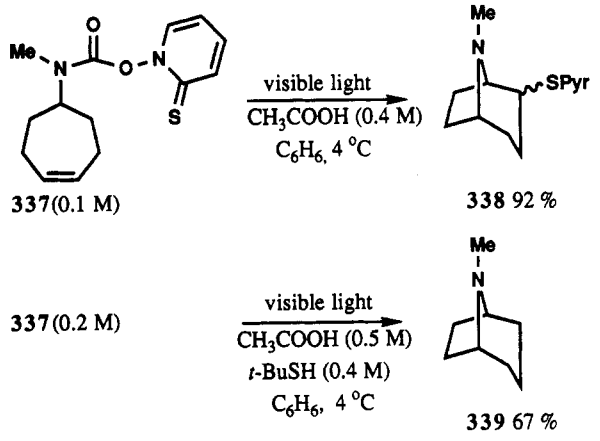
The known isoflavone **332** was prepared and converted into the required thiohydroxamate ester **333** (Scheme 82). This material was irradiated (tungsten lamp) in refluxing tetrahydrofuran solution (0.022 M) with *tert*-butyl mercaptan (0.033 M) to afford products **334** and **336**. The major product presumably formed by thermal elimination of pyridine mercaptan from the intermediate **335**. Hydrogen abstraction from *tert*-butyl mercaptan gave **334**. Thus, the free radical 6-endo cyclization represents a viable biosynthetic pathway to rotenones.[131b]

SCHEME 82



An example from the work of Newcomb[214] demonstrates that heteroatom-centered radicals can be generated by the Barton method. Cycloheptenyl amine gave carbonate **337** in 81% yield (Scheme 83). Visible

SCHEME 83



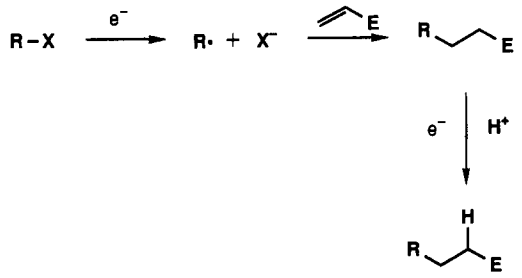
light initiated reaction of **337** in the presence of acetic acid furnished pyridylthio-substituted tropane **338** in the absence of *t*-BuSH, and reduced tropane **339** in its presence. Cyclization of the corresponding *N*-chloroamine gave the analogous chlorotropane, but in only 7.5% yield. This illustrates a major advantage of the Barton chemistry; a stable, β-protio- or β-pyridylthio amine is obtained rather than a potentially reactive nitrogen mustard.

VI. The Reductive Method

A. Introduction

Another method of conducting radical reactions involves treatment of various electrophiles, most notably carbonyl compounds and halides, with one-electron donors. Scheme 84 provides an outline of a reductive

SCHEME 84



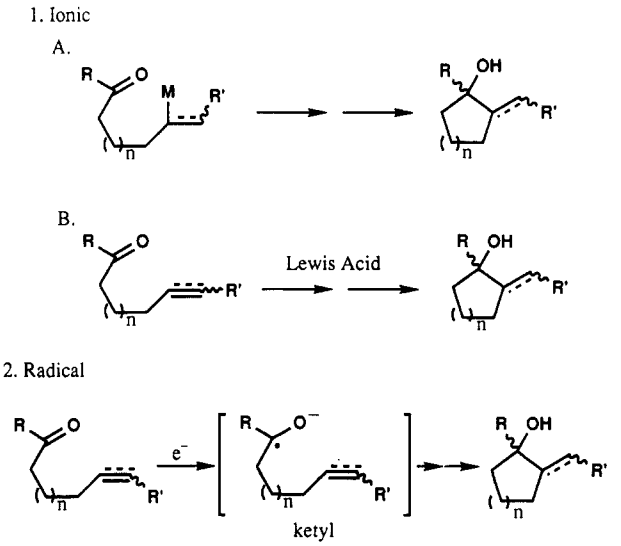
addition reaction. Reductive conditions are naturally suited to substrates that produce initial intermediates (radicals or radical anions) that are not easily reduced. The resulting radicals or radical anions can then undergo addition or cyclization reactions prior to accepting a second electron. Reactions involving ketyls are by far the most popular application of the reductive technique. Because ketyls are radical anions and not radicals, they fall outside the comprehensive scope of this review, but they are sufficiently important to merit discussion. Special attention will be given to ring-forming reactions, where the advantages of the radical approach are best illustrated. The literature examples that we have selected will serve to highlight the use of increasingly mild and chemoselective electron donors, a major area of development in the field.

B. Ketyl/Olefin Cyclizations

1. Introduction

Consider the three straightforward ring-forming routes to 2-substituted cycloalkanols shown in Scheme 85. Analysis of the three processes reveals potential

SCHEME 85

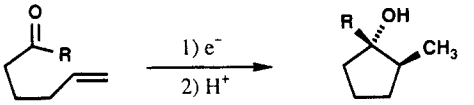


disadvantages of the ionic procedures that can be overcome by using a reductive radical method. For example, ionic procedure A involves the in situ generation and cyclization of an alkyl (or vinyl) organometallic species, an operation sometimes complicated by enolization or other competing side reactions.[215] In addition, the cyclization substrates (normally halides) are somewhat less readily prepared than those of the other two methods shown.

Ionic approach B, the Friedel–Crafts type addition to a double or triple bond, is fraught with difficulties. Potential problems include poor reactivity and/or regiocontrol (depending on the nature of R′), the formation of double-bond regioisomers, the elimination of water from the product, and the possibility of undesired cationic rearrangements.

In the reductive method, an unsaturated carbonyl accepts an electron from the donor to give a ketyl radical anion. ESR studies[216] have shown that about 70% of the unpaired electron density of this species is carbon centered. Not surprisingly then, the ketyl can add intramolecularly to a carbon–carbon multiple bond to give the 2-substituted cycloalkanols. Ketyl radical cyclizations are governed by similar guidelines to those that apply to radical cyclizations. High regioselectivity is normal, and considerable stereoselectivity is often observed with olefinic substrates. The hydroxyl group and pendant methyl (alkyl) substituent are usually obtained trans to one another,[217] as outlined in Scheme 86.

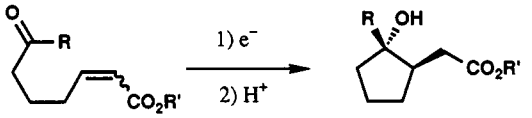
SCHEME 86



Despite similarities, there is an important difference between ketyl and radical behavior: since ketyls are charged, they are not necessarily transient. In fact, many metal ketyls can have long solution lifetimes.

Another advantage accrues from the use of electron-deficient olefins.[218] This is illustrated by the example in Scheme 87. The product, a 1,4 difunctional com-

SCHEME 87



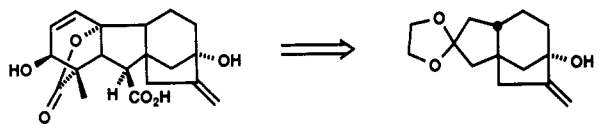
pound, results from an umpolung of normal, ionic reactivity patterns.[219] In such reactions, it is not immediately obvious which functional group (ketone or unsaturated ester) accepts the first electron. Nonetheless, either initial radical anion has the potential to produce the same product.

Of course, ketyl–olefin (acetylene) cyclizations are not without limitations. The reactions are often performed with powerful electron donors such as lithium in liquid ammonia. Under these conditions, many functional groups are at risk and must be protected. Also, side reactions such as reduction of the carbonyl (without cyclization) and pinacolization are common problems. Finally, the method is essentially limited to the formation of 5- and 6-membered rings, although a few examples of intermolecular ketyl–olefin additions have been reported.[220]

2. Examples

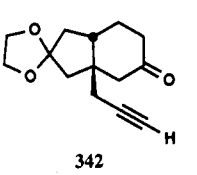
The cyclization of unsaturated carbonyl compounds by the electron-donation method was introduced by Stork and co-workers over 20 years ago in the context of a projected synthesis of gibberellic acid (**340**).[221] This complex natural product was considered to be derivable from protected tricyclic intermediate **341**, as shown in Scheme 88. In turn, **341** was envisioned to arise from

SCHEME 88



gibberellic acid (340)

341

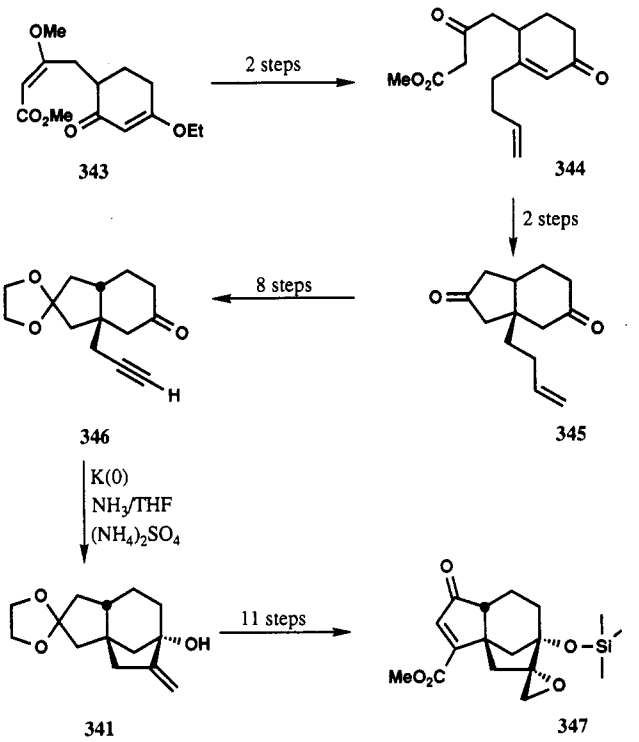


342

reductive cyclization of ketoacetylene **342**. Indeed, Stork had shown with a series of model compounds that this type of cyclization could occur.[221a,222]

The cyclization substrate was assembled as shown in Scheme 89. Alkylation of 3-ethoxy cyclohexenone with methyl 3-bromo-2-methoxycrotonate gave **343**. Treatment of this with butenylmagnesium bromide, followed by dehydration and hydrolysis of both enol ethers, afforded keto ester **344**. Intramolecular Michael addition to the enone, followed by decarbomethoxylation, afforded bicyclic diketone **345**. An eight-step sequence involving selective ketone protection and conversion of the butenyl side chain into a propargyl chain, successfully gave keto acetylene **346**.

SCHEME 89



The substrate **346** was dissolved in NH_3 containing dry THF and ammonium sulfate. Potassium metal was slowly added to the mixture by allowing the refluxing NH_3 to leach the metal from a perforated surface. This procedure afforded the tertiary alcohol **341** in 60–70% yield. This alcohol was carried on to advanced intermediate **347**, which is a typical, highly functionalized gibberelin intermediate.[223]

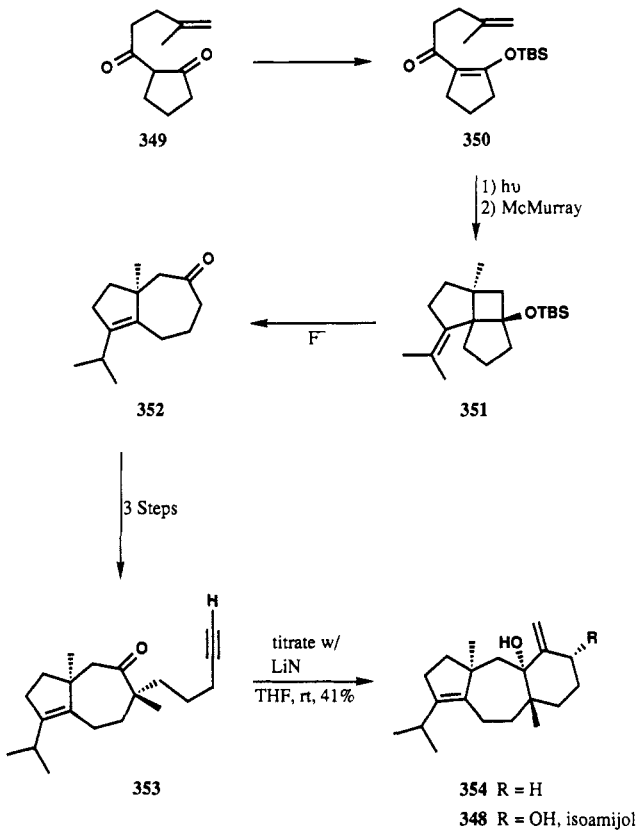
Thus, the use of ketyl–acetylene radical cyclization reaction provided a straightforward solution to a challenging synthetic problem. By using today's technology, one could probably shorten the route to the cyclization substrate and avoid the use of the strongly reducing K/NH_3 system. Current applications of ketyl cyclizations have moved away from traditional dissolving metal reduction conditions and toward more selective reductants.

Naphthalene is reduced by alkali metals to give alkali metal naphthalenides (designated $C_{10}H_8^{\bullet-}M^+$) which are, necessarily, weaker reducing agents than the metals themselves. Pradhan and co-workers[224] developed these reagents for use in ketyl–acetylene radical cyclizations in response to a problem sometimes observed with alkali metal/ammonia reductive cyclizations: overreduction (deoxygenation) of the product. The naphthalenides possess the desirable property of good solubility in ethereal solvents. Moreover, the highly colored solutions of $C_{10}H_8^{\bullet-}M^+$ are convenient to use since the very rapid radical cyclizations can be conducted titrimetrically, and the naphthalene can be used catalytically.

Pattenden et al. have very recently exploited the virtues of $C_{10}H_8^{\bullet-}Na^+$ in a total synthesis of isoamijol **348** outlined in Scheme 90.[225] As in the previous example, the bridgehead hydroxyl adjacent to an exomethylene group arises from a ketyl–acetylene radical cyclization, which in this case, formed a 6-membered ring.

Acylation of the pyrrolidine enamine of cyclopentanone with 4-methylpent-4-enoyl chloride afforded

SCHEME 90

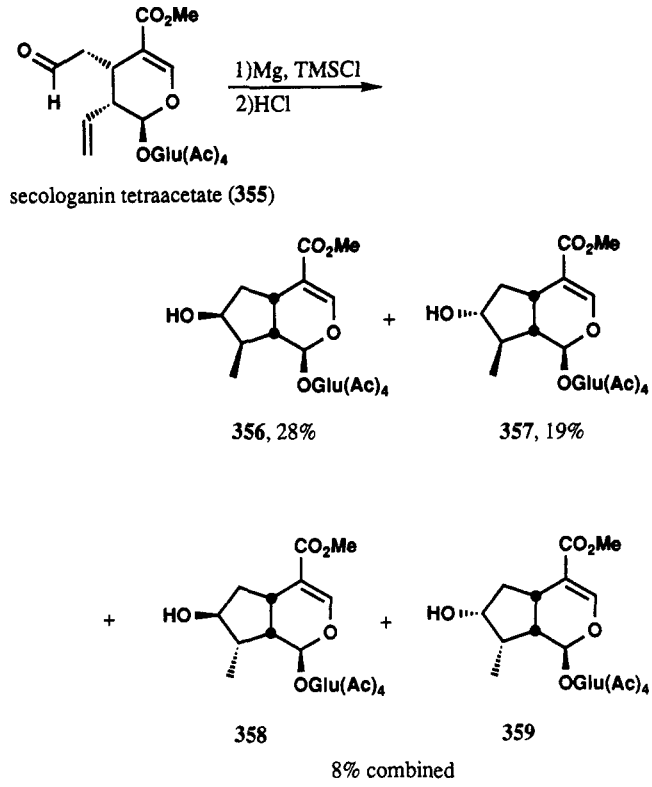


dione **349**. Treatment of **349** with TBS-Cl and Et_3N gave a mixture of silyl enol ethers which, upon photolysis, furnished only the 2 + 2 photoadduct derived from enol ether **350**. Apparently, the exo and endo enol ethers interconverted under the photolysis conditions. The carbonyl group was then converted into isopropylidine by use of the McMurray carbonyl coupling procedure (acetone, Ti(O)). In a key step in the synthesis, a fluoride-induced Grob fragmentation served to cleave the cyclobutane ring and migrate the olefin to provide **352** in essentially quantitative yield. From **352**, the cyclization substrate **353** was prepared by sequential enolate alkylations with triisopropylsilyl-protected pentynyl iodide and methyl iodide, followed by desilylation.

Treatment of keto acetylene **353** with $C_{10}H_8^{\bullet-}Na^+$ produced tertiary allylic alcohol **354**, with the required trans fusion of the 7- and 6-membered rings, in 41% yield. Oxidation of **354** with SeO_2/*t*-BuOOH provided isoamijol **348** stereospecifically, albeit in low yield. Pattenden has also synthesized capnellenediol by using a sodium naphthalenide induced ketyl–acetylene cyclization.[226]

While alkali metals of alkali metal naphthalenides can promote reductive cyclization of unsaturated carbonyl compounds, such powerful reducing agents still suffer from functional group incompatibility, and are prone to give side reactions such as overreduction or deprotonation. In a move toward alleviating these problems, Corey and Pyne[227] developed a milder reducing system, Zn/TMS-Cl/2,6-lutidine, which could still induce the reductive cyclizations.[228] The function of the lutidine is to prevent protic or Lewis ($ZnCl_2$) acid catalyzed elimination of trimethylsilanol from the product. Hutchinson and co-workers have recently used a related procedure (Mg/TMS-Cl) in a synthesis of loganin tetraacetate from secologanin tetraacetate, as outlined in Scheme 91.[217b] This work illustrates the

SCHEME 91



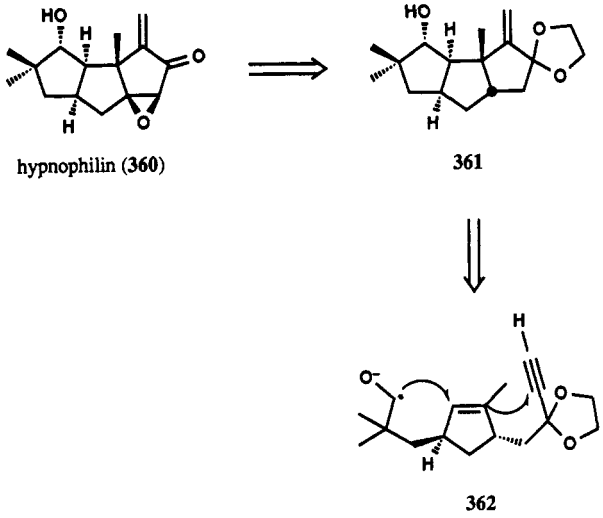
advantages and disadvantages of this type of reductive radical cyclization. Treatment of secologanin tetraacetate (**355**) with 20 equiv of magnesium metal and 6 equiv of TMS-Cl for 80 h at room temperature led to a mixture of four stereoisomers (**356–359**), in addition to 13% recovered starting material.

The main advantage of the method, the mild reaction conditions, is readily attested to by the substantial survival of the abundant functionality embodied in **355**. There are, however, two disadvantages. First, the high degree of stereoselectivity normally observed in ketyl–olefin cyclizations is absent here. Presumably, this is a consequence of silylation of the ketyl prior to cyclization. Both Shono[229] and Beckwith[230] have suggested that the high stereoselectivity obtained in ketyl–olefin cyclizations is at least partly due to electronic repulsion between the negatively charged oxygen atom and the alkene in the transition state. Silylation of the ketyl would be expected to remove or diminish this interaction, and to erode stereoselectivity. The second disadvantage of the Mg or (Zn)/TMS-Cl method is that the reactions are very slow, presumably because of the heterogeneous nature of the reaction mixture. In certain circumstances, this allows side reactions to compete with, or even completely overwhelm, the desired radical cyclization. For example, when substrate **355** was submitted to the Corey conditions (Zn/TMS-Cl/lutidine), enol silylation of the aldehyde was observed to the exclusion of cyclization. Another side reaction which can interfere with radical cyclization has been encountered during a recent synthesis of hypnophilin (see below).

Over the past several years, a relatively new one-electron donor, samarium(II) iodide (SmI_2) has been used with increasing frequency.[231] The reagent's growing popularity is attributable to its solubility in THF, its reducing ability, and its chemoselectivity (nitriles, esters, isolated acetylenes, and many other functional groups are compatible).

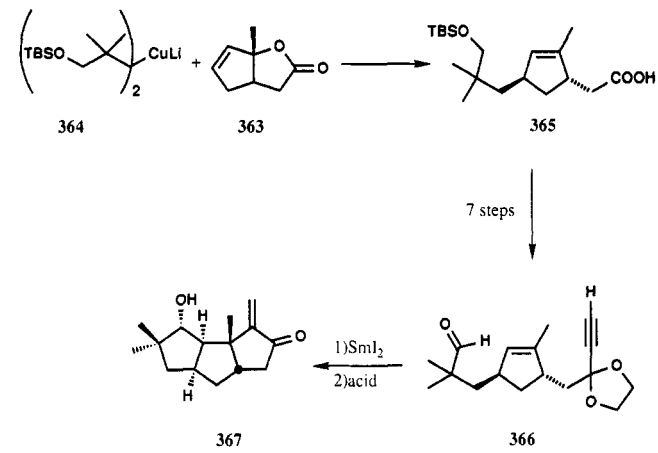
Fevig and Curran recently exploited these features by using SmI_2 in a key step of a total synthesis of the sesquiterpene natural product hypnophilin (**360**).[232] Retrosynthetically, the fused tricyclopentanoid ring system of hypnophilin could arise from a tandem radical cyclization reaction as shown in Scheme 92. The feasibility of this approach had been demonstrated earlier in syntheses of the hydrocarbons hirsutene and capnellene (see Schemes 5 and 6). To incorporate the oxygen functionality, the reaction called for a tandem radical cyclization beginning with ketyl **362**. As in the hirsutene and capnellene syntheses, the stereochemistry of the ring fusions was to be controlled by the trans disposition of the side chains in the cyclization substrate. Thus, each radical cyclization gives a cis-fused 5,5-ring system, and the trans orientation of the side chains insures the anti relationship between the two outer rings. The preference for formation of *trans*-2-alkyl-1-hydroxycyclopentanes in ketyl cyclizations boded well for controlling hydroxy group stereochemistry.

SCHEME 92



The cyclization substrate was prepared as shown in Scheme 93. Treatment of vinyl lactone **363** with cuprate **364** gave carboxylic acid **365**, the product of an S_N2' anti lactone opening, in excellent yield. From **365**, a conventional, seven-step sequence of reactions furnished aldehyde **366**. A few related aldehydes, differing only in the constitution of the acetylene-bearing side-chain, were also prepared. Early attempts at reductively cyclizing these aldehydes were unsuccessful. Reduction of one aldehyde with Li/NH_3 gave a complex reaction mixture, as did irradiation of **366** in HMPA,[233] a procedure developed by Cossy et al. (see below). Treatment of **366** with Zn/TMS-Cl according to the Corey procedure gave what was believed to be a mixture of bicyclic olefins that was unlikely to have been formed by a radical process.[234]

SCHEME 93

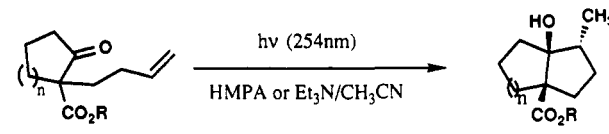


The use of SmI_2 was attractive, since this reagent is known to react readily with aldehydes, but not with isolated acetylenes. Ultimately, it was found that slow addition of a THF solution of SmI_2 to aldehyde **366** in THF containing 10% HMPA[235] allowed the cyclization to be performed as a titration (to a purple end point). Alcohol **367** was isolated in 61% yield. Under these conditions, the SmI_2 concentration is always low, so reduction of the intermediate alkyl radical cannot compete with the second cyclization. From enone **367**, completion of the synthesis required only installation of the epoxide functionality. This was achieved by a three step sequence involving formation of a silyl dienol ether (excess LDA and TBS-Cl), DDQ oxidation to the corresponding dienone, and finally, selective epoxidation of the dienone to provide the natural product hypnophilin. The penultimate dienone is also a known precursor of the natural product coriolin.

This SmI_2-promoted tandem radical cyclization, in conjunction with the pioneering contributions of Fukuzawa,[218a] Kagan,[231] Inanaga,[236] and Molander,[237] heralds SmI_2[238] as an important new reagent. It combines many of the desirable features of the previously mentioned reductants without some of their drawbacks.

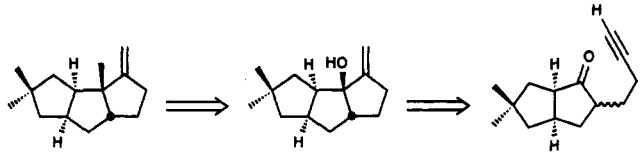
Two even milder methods for electron donation to carbonyls deserve attention. In 1986, Cossy and Portella reported the photochemical reductive cyclization of olefinic and acetylenic ketones.[233] A typical example is provided in Scheme 94. The reaction proceeds by electron donation from excited state HMPA to ground-state ketone, or by reduction of excited-state ketone by ground-state Et_3N. Good yields and stereoselectivity are observed under these very mild reaction conditions. HMPA gives better results in the cyclization of keto olefins, but the two solvent systems are equally effective with keto acetylenes. Despite the superior reactivity of HMPA, the Et_3N/CH_3CN combination is less hazardous and more volatile, allowing for an exceedingly simple reaction workup involving only evaporation of solvent.

SCHEME 94



Cossy and co-workers have recently applied this new technique in a total synthesis of (±)-hirsutene.[239] The retrosynthetic analysis (Scheme 95) first called for the

SCHEME 95



hirsutene (368) 369 370

rather unusual replacement of an angular methyl group with hydroxyl (see **369**). Once this was done, the now familiar functionality produced by a ketyl–acetylene cyclization was readily apparent (see **370**).

The bicyclic substrate was constructed as outlined in Scheme 96. Cyclopentannulation of cyclopentenone (**372**) was carried out with **371** by Trost's procedure.[240] Cyclopropanation of the resulting olefin, followed by hydrogenolysis of the 3-membered ring, furnished the required *gem*-dimethyl group in **374**. Because of the propensity of 1-bromo-3-butyne to eliminate HBr under the basic alkylation conditions, the butynyl side chain was affixed in latent form. Thus, alkylation of the potassium enolate of **374** with 1-iodo-3-chloro-2-butene, followed by reduction of the ketone, dehydrochlorination with isomerization to the triple bond, and finally, reoxidation, gave the cyclization substrate **370** as a 2.9:1 mixture of exo/endo butynyl isomers. Submission of the mixture to the photocyclization conditions afforded **376** as the only tricyclic product. The cyclization of the endo isomer was apparently so slow, for steric reasons, that it could not compete with hydrogen atom abstraction to form **375**. The synthesis was completed by reaction of the tertiary allylic alcohol **374** with methylmagnesium bromide in the presence of a Ni(II) catalyst. Cossy and co-workers have applied the technique to several other synthetic endeavors, including a total synthesis of the naturally occurring, monoterpenoid alkaloid, actinidine.[241]

The final electron-donation method to be described in this section is electrochemical reduction. This method has considerable synthetic potential because of the chemoselectivity attainable. The functional group to be reduced (the electrophore) can easily be selected merely by conducting the reaction at the appropriate voltage. Despite this advantage, electrochemistry has been applied sparingly by synthetic organic chemists, perhaps because of their lack of familiarity with the technique.

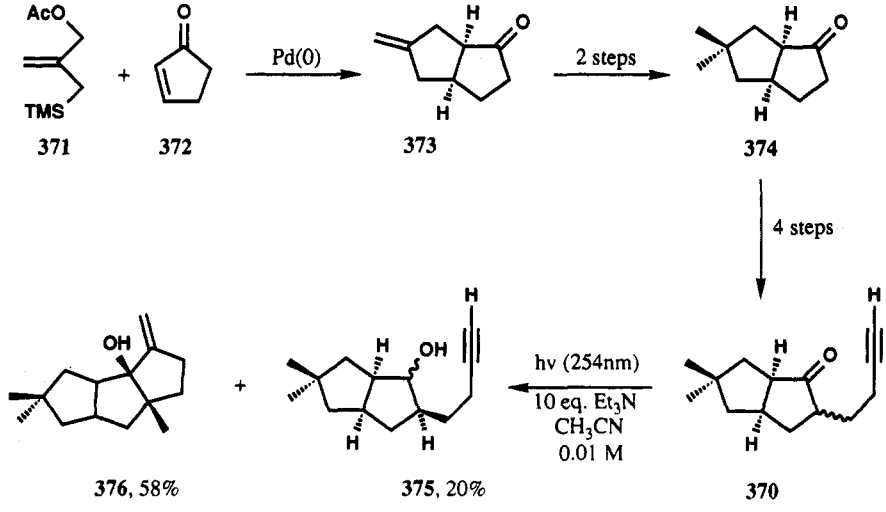
Of the several electrochemical carbon–carbon bond forming reactions that have been developed,[229] this discussion will focus on ketyl–olefin (acetylene) cyclizations. The electrochemical variant was first reported by Shono et al.[229] These workers found that electrogenerated ketyls could be induced to add to unactivated olefins, acetylenes, and even aromatic rings. In addition, the scope of the reaction was defined with respect to accessible ring sizes, stereochemistry, and certain substitution patterns; the results are in general agreement with the trends described above. In a subsequent series of papers, Kariv-Miller and co-workers have studied the mechanism of some ketyl cyclizations in considerable detail[242] under a variety of reaction conditions.

Until recently the electrochemical ketyl–olefin radical cyclization had not been successfully employed in the synthesis of a natural product.[243] However Little[244] and Shono[245] have just reported some applications which will be described here.

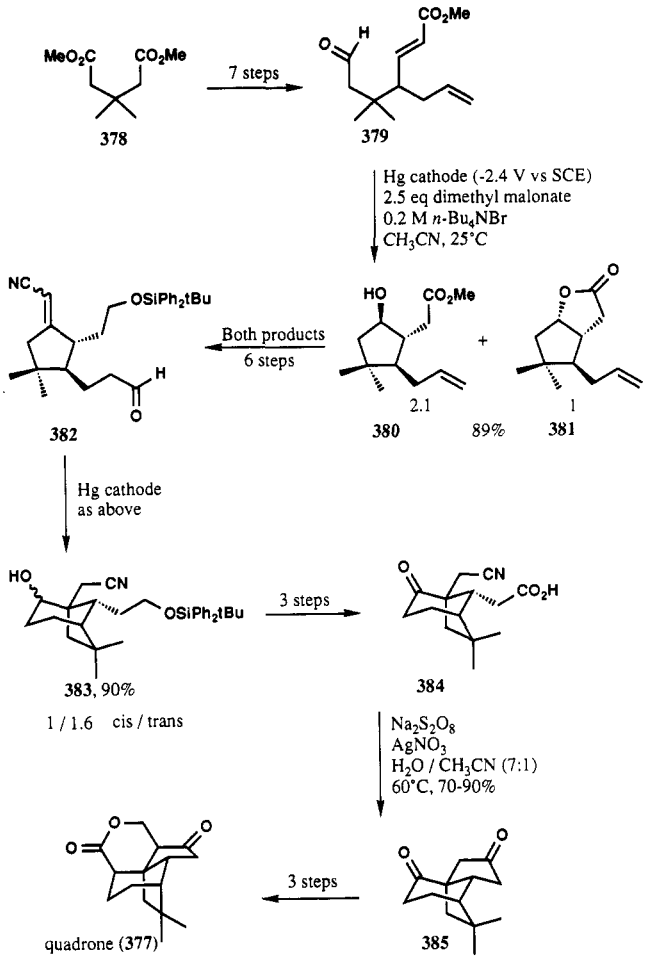
Little's approach to quadrone (**377**) is outlined in Scheme 97. This interesting synthesis employs two electroreductive cyclizations and an oxidative radical cyclization. Starting from symmetrical diester **378**, a seven-step procedure gave the first cyclization substrate **379**. Electroreduction of this material afforded trans hydroxy ester **380** and cis lactone **381** in high yield. The formation of this mixture was inconsequential, as each product could be carried on to α,β-unsaturated nitrile **382** by a six-step sequence. A second electroreductive cyclization on this substrate again provided a mixture of hydroxyl epimers **383** in excellent yield. Oxidation of the alcohols gave a single ketone, which was elaborated into cyano acid **384**. Decarboxylative radical addition to the nitrile under oxidative conditions afforded dione **385** after imine hydrolysis. (Other oxidative reactions are discussed in the next section.) The dione **385** was readily transformed into quadrone (**377**).

There are several points to be made regarding the scope and mechanism of these cyclizations.[246] First,

SCHEME 96



SCHEME 97

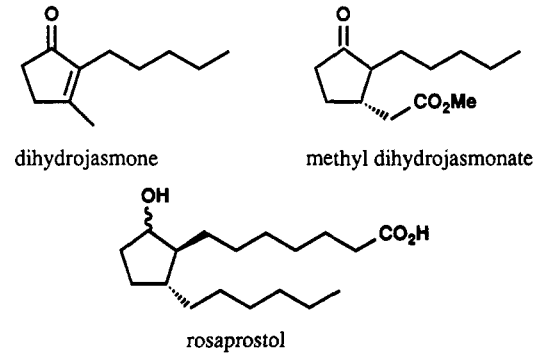


although the examples shown involve the use of aldehydes, ketonic substrates also give good results. Variations in the electron-withdrawing group on the olefin are also tolerated. The second cyclization reaction shown above, in which a 6-membered ring is formed in the process of generating a highly substituted, bridged bicyclic system, further indicates that the reaction may be of broad scope. The reaction is not without drawbacks, however. Possible side reactions include ester hydrolysis and olefin saturation. In addition, the stereoselectivity is not as high as that obtained in ketyl-unactivated olefin cyclizations, although in all but one case the selectivity occurs in the same sense.

Little has presented solid evidence that the α,β-unsaturated ester (or nitrile) is the electrophore in the reaction. Beyond this point, the precise details of the cyclization are not fully established, but may be described in general terms as follows. After the first electron is added to the α,β-unsaturated ester, a rapid and reversible cyclization ensues, producing a new radical anion. This is protonated irreversibly, and then further reduced to generate an enolate, which is subsequently protonated. It was also determined that, at least for ketonic substrates, partial *E,Z* equilibration of the olefin can precede cyclization. Each, or possibly all, of these factors (the nature of the electrophore, the reversibility of cyclization, and olefin isomerization) could contribute to the modest stereoselectivity observed. The proton donor used in the reaction can have a profound effect on the stereoselectivity. The use of dialkyl malonate, which effectively suppresses the hydrolysis and olefin saturation side reactions, leads to lower stereoselectivity (relative to H_2O), possibly by adversely influencing the equilibria mentioned above.

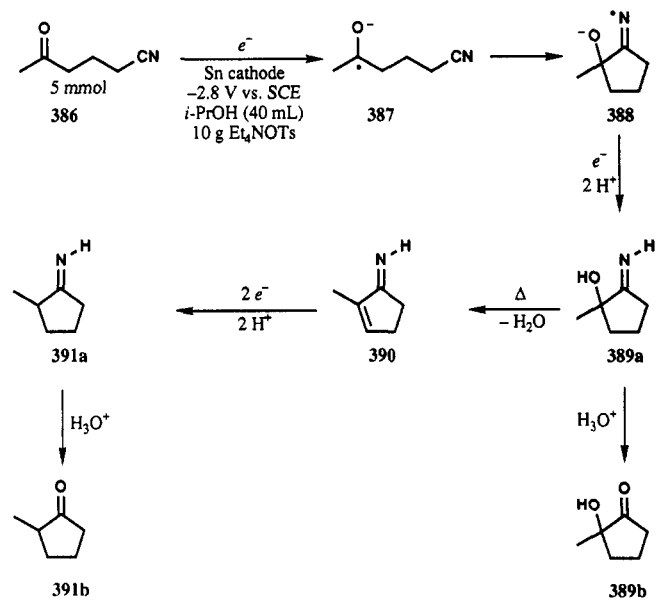
Shono and Kise have developed an electrochemical ketyl–nitrile cyclization reaction, and used it to synthesize dihydrojasmone, methyl dihydrojasmonate, and a simple prostaglandin, rosaprostol, whose structures are shown in Scheme 98.

SCHEME 98



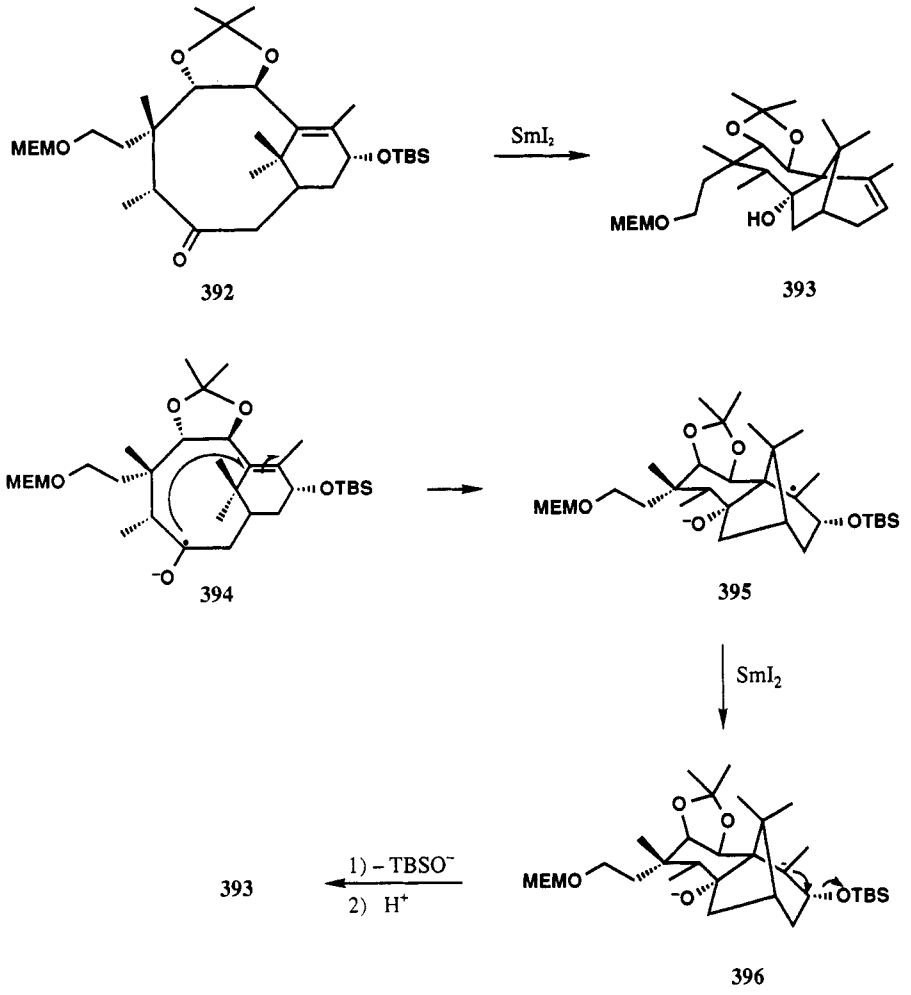
The basic reaction is shown in Scheme 99. Reduction of the ketone **386** to the ketyl **387** occurs first (isolated nitriles are inert to the reaction conditions). Addition to the nitrile gives **388**, which is reduced and protonated to provide hydroxy imine **389a**. If the reaction is run at elevated temperature (65 °C), dehydration takes place. The resulting unsaturated imine **390** is reduced and protonated to afford imine **391a**. Hydrolysis of either imine **389a** or **391a** gives the observed products **389b** or **391b**. Starting from appropriately substituted cyano ketones, Shono's method provides easy access to 2,3-disubstituted cyclopentanones such as those shown in Scheme 98.

SCHEME 99



So far, this discussion has focused largely on the radical cyclization itself. However, each radical cyclization produces a new radical which can either undergo further radical reactions, or be reduced to the corresponding anion. This new anion in turn can undergo

SCHEME 100



further ionic reactions. Anion formation subsequent to radical cyclization is probably a common phenomenon. However, the vast majority of reductive reactions have either been performed in the presence of proton donors, or have been quenched with water. Until very recently,[247-249] the alleged anions have only been captured by protons.

Holton and Williams used the potential ionic reactivity in reductive cyclizations during a synthesis of taxusin.[250] They observed that reduction of unsaturated bicyclic ketone **392** with samarium iodide produced tricyclic alcohol **393** (Scheme 100). The reasonable mechanistic explanation that these workers postulated for the formation of the observed product **393** is shown in Scheme 100. A SmI_2-promoted 5-exo ketyl–olefin cyclization of **394** produces the new radical anion **395**. Further reduction by the excess SmI_2 affords the corresponding dianion **396**, which subsequently expels $TBSO^-$.[251] This reaction proceeds in "almost quantitative yield" even though the ketyl adds to a hindered tetrasubstituted olefin.

Unlike ketyls, which are not easily reduced, alkyl radicals produced either in ketyl cyclizations or by reduction of organo halides, are readily reduced by the reagents used to generate them. Nevertheless, with proper control of reaction conditions (maintaining a low concentration of reducing agent for example) the radicals can be provided with sufficient longevity to undergo useful reactions.[252] Among the reductants useful in initiating reductive radical cyclizations are alkali metals,[253] Zn,[254] SmI_2,[255] and Cr(II) salts. In the latter case, alkylchromium(III) species can be formed and trapped by electrophiles after radical cyclization.[248]

VII. Oxidation

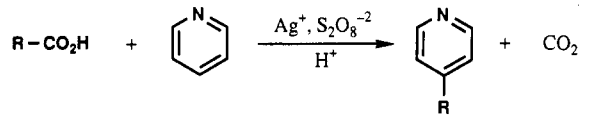
A. Introduction

While the previous section discussed the generation of radicals by donation of electrons to electron-deficient systems, one can also produce radicals by the opposite process, that is, by abstracting electrons from electron-rich species. Despite the antithetical nature of the two methods, there are several similarities. As in the reductive method, the two most common procedures are electrochemical (anodic oxidation) and chemical (oxidizing metal salts). When oxidizing metals are used, there is a possibility that the derived radicals are not truly free, but metal associated. This may account for differences in reactivity that may be observed when radicals are generated under oxidizing conditions. Also in common with the reductive method, the possibility of performing tandem radical/ionic processes (in this case, radical/cation) exists. In the oxidation method, a new radical produced by an addition or cyclization of the initial radical can be oxidized to a cation under appropriate reaction conditions. The cation can then be trapped by nucleophiles, providing in many cases the

product of an umpolung with respect to standard ionic reactivity, in addition to circumventing the loss of functionality associated with much of the reductive chemistry.

These characteristics and others combine to make oxidative free-radical reactions useful in natural product synthesis. The focus of this discussion will be mainly on electrochemical (Kolbe electrolysis) and Mn(III)-based methods. These two are by far the most frequently used oxidative free-radical methods in natural product synthesis. Another important oxidative procedure, the Minisci reaction (Scheme 101), has been

SCHEME 101

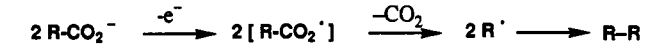


widely used in heterocyclic chemistry. This reaction, which has many useful variants, has been reviewed elsewhere[256] and will not be covered here. Other examples of oxidative free radical methods can be found in Giese's book.[6b]

B. Electrochemical Oxidation

The Kolbe electrolysis is one of the oldest known radical reactions.[257] In its simplest form (Scheme 102),

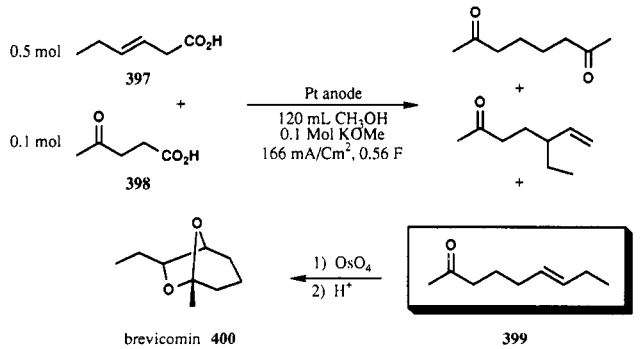
SCHEME 102



the reaction involves oxidative decarboxylation of a carboxylate salt to give an alkyl radical with one less carbon. Combination of this radical with another gives the symmetrical dimer. This simple dimerization has seldom been used in natural product synthesis.[258] However, recent developments from the labs of Schäfer and co-workers have considerably extended the synthetic utility of the process by developing procedures for cross coupling. Several natural products of diverse structure have been prepared.

One of Schäfer's early contributions in this area was a short synthesis of *exo*-brevicomin (**400**) shown in Scheme 103.[259] Recognizing that the bicyclic ketal

SCHEME 103

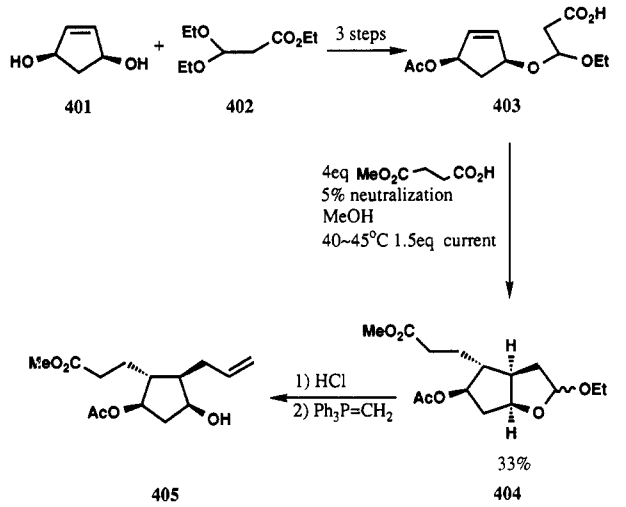


would arise by an intramolecular ketalization of a keto diol, Schäfer and Knolle synthesized its precursor, keto olefin **399**, by a mixed-Kolbe coupling of acids **397** and **398**. This gave a mixture of the desired product **399** (33%), along with several other symmetrical and cross-coupled products.

Several aspects of the coupling reaction are noteworthy. First, it allows for a fairly short synthesis, in part because the ketone need not be protected. Synthesis of keto olefin **399** through a Wittig-type approach would probably not afford this luxury. Also, the synthesis can be performed on large scale. A serious drawback is that the two carboxylic acids are of approximately equal value, but one must be used in excess in order to obtain a reasonable yield of cross-coupled product **399**. In this particular case, the yield is further compromised by the allylic and unsymmetrical nature of the radical derived from **397**. However, Schäfer and co-workers have shown in subsequent studies that syntheses can be designed such that "expendable" carboxylic acids can be employed in excess, thereby increasing the economy of the approach.[260]

More recently, Schäfer has shown that the radical–radical coupling by the Kolbe electrolysis can be preceded by a radical cyclization. Schäfer and Becking's[261] interesting variant on the popular radical approach to prostaglandins (see Schemes 36, 45, and 79), is shown in Scheme 104. The cyclization precursor **403** was

SCHEME 104



readily assembled from cyclopentenediol (**401**) and ester acetal **402**. Coelectrolysis of mixed acetal **403** in the presence of a 4-fold excess of methyl hemisuccinate afforded bicyclic acetal **404** in reasonable yield (33%), considering that two carbon–carbon bonds were formed across the double bond of **403**, and that a single diastereoisomeric product was obtained. A viable $PGF_{2\alpha}$ precursor **405** was obtained from **404** in only two steps. Schäfer and Becking have also applied this strategy toward the synthesis of pyrrolidine alkaloids.[262]

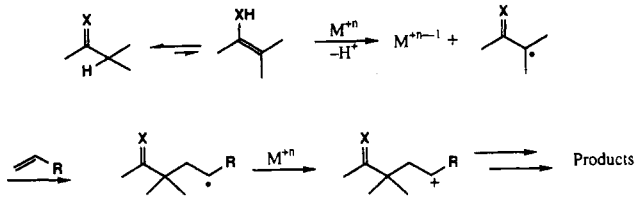
C. Chemical Oxidation

1. Introduction

Chemical oxidative methods are naturally suited for the reactions of electrophilic radicals. These initial electrophilic radicals are not easily oxidized and have time to react with nucleophilic multiple bonds. The product radicals are then usually more susceptible to oxidation than the initial radicals. Oxidations are often conducted on enol (or enolate) derivatives, and a simplified mechanism for such an oxidation is outlined in Scheme 105.

Many of the same species that suffer one-electron oxidation at the anode can be oxidized in a similar manner by chemical oxidants. Oxidants include I_2, O_2,

SCHEME 105

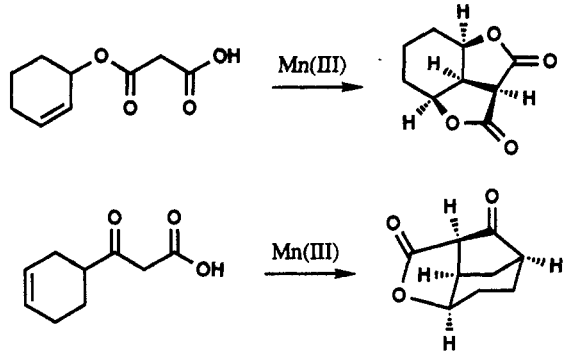


and most importantly, high-valent metal salts. In the last category, the use of Ag^{2+} salts, generated in situ, has been mentioned at the beginning of this section in connection with the Minisci reaction. Among the most widely used oxidants nowadays are Mn^{3+} salts, and this discussion will be confined to their use in natural product synthesis. However, other metal oxidants are available,[263] and they should also be useful for related reactions.

2. Manganese(III) Acetate Oxidations

Treatment of unsaturated, enolizable dicarbonyl compounds with $Mn(OAc)_3 \cdot 2H_2O$ often gives rise to the products of apparent radical cyclization followed by oxidation and nucleophilic trapping. Two representative examples are given, Scheme 106.[264] Although am-

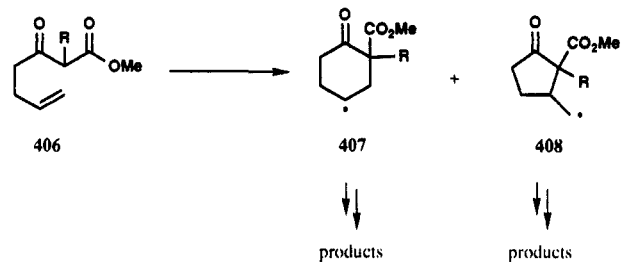
SCHEME 106



biguities still remain, informative mechanistic studies are available.[265-269]

The electrophilic radicals produced by Mn(III) oxidation have no tendency to react further with the oxidant because an unstable α-carbonyl cation would be formed.[270] Neither do the stabilized radicals tend to abstract hydrogen atoms from the medium (typically, glacial acetic acid). These two factors enable intermolecular radical additions and relatively slow radical cyclizations to be performed readily by the Mn(III) oxidative method. A third reactivity difference concerns cyclization regioselectivity. At least with β-keto ester substrates, Mn(III) radical cyclizations do not always follow the guidelines developed for unstabilized alkyl radicals. For example, oxidations of keto esters with structures like **406** (Scheme 107) typically give

SCHEME 107



about 2:1 ratios of products resulting from 6-endo (**407**) and 5-exo (**408**) cyclization modes.[267] Despite this, the regioselectivities of these cyclizations are predictable and consistent, and it now appears that these regioselectivities are due to the structures of the radicals themselves and not to the presence of a Mn-complexed radical.[271]

In addition to the reactivity differences mentioned above, the Mn(III) oxidative method exhibits a number of features which are distinctly advantageous in natural product synthesis:

(1) The reactions are performed under mild conditions, often at room temperature in glacial acetic acid. Thus, numerous functional groups are compatible.

(2) Substrates are readily assembled by using enolate and/or β-keto ester dianion alkylations.

(3) Radical additions or cyclizations can be carried out with maintenance (C=C) or introduction (C–O) of functionality.

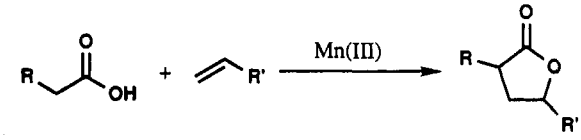
(4) 1,4-Dioxygenated compounds are formed readily, an umpolung of normal ionic reactivity.

(5) Tandem or higher order sequences (radical/radical or radical/cation) are possible.

Intermolecular Additions

Mn(III)-based natural product syntheses employing intermolecular radical additions derive from the pioneering work of Heiba and Dessau[272] and Bush and Finkbeiner.[273] These workers discovered and developed the fundamental reaction, shown in Scheme 108. Ox-

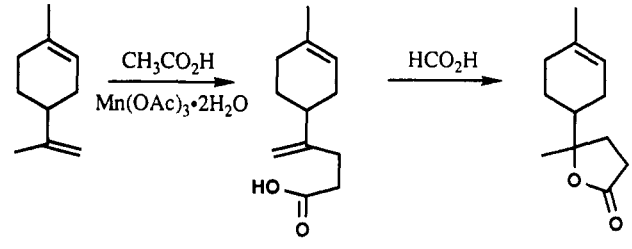
SCHEME 108



idation of a carboxylic acid with Mn(III) in the presence of a terminal alkene generates a lactone. When the oxidized species are only monocarbonyl compounds, they must virtually be used as solvents.

Variations of this intermolecular process have been employed in a few natural product syntheses. For example, Gardrat[274] has converted limonene (**409**) into the C-12 terpene lactone norbisabolide (**411**) as shown in Scheme 109. In this case, elimination of a proton from

SCHEME 109

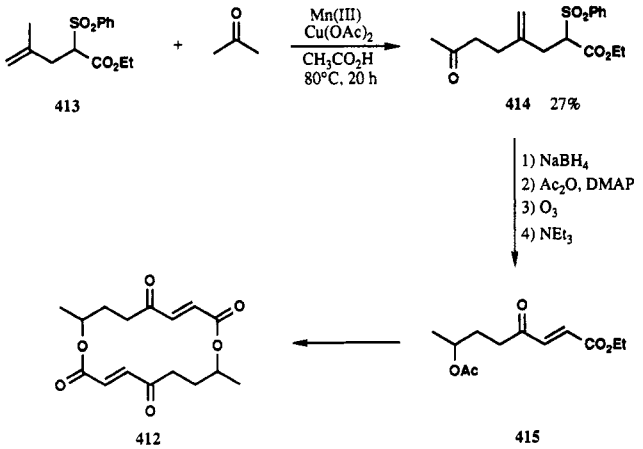


409 410 411
nor-bisabolide
43% overall

the tertiary cation was faster than lactone formation. Thus, a second step was required to convert **410** to **411**.

Uguen and Breuilles[275] have also used manganese-promoted addition in a synthesis of the natural fungicide pyrenophorin (**412**) outlined in Scheme 110. Treatment of olefin **413** with acetone (used in large

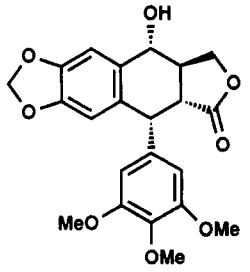
SCHEME 110



excess to prevent oxidation of **413**) and Mn(III)/Cu(II) in CH_3CO_2H afforded the coupled product **414** in modest yield (the starting olefin was also recovered in 41% yield). Cu(II) was essential in obtaining the desired regioselectivity of alkene formation. From **414**, the formal synthesis was accomplished in straightforward manner by formation of **415**.

Finally, Fristad and co-workers[276] have reported an interesting approach to the highly oxygenated, 4-arylnaphthalene family of naturally occurring lignans, as exemplified by podophyllotoxin (Scheme 111). Their

SCHEME 111



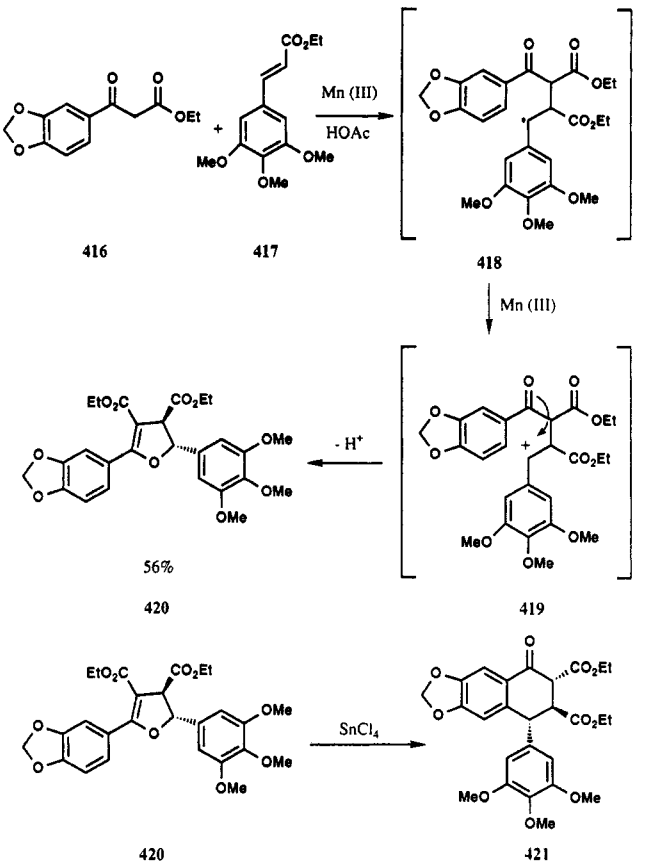
podophyllotoxin

plan was based on some earlier work by Heiba and Dessau.[277]

Oxidation of keto ester **416** in the presence of cinnamate **417** directly gave dihydrofuran **420** in 56% yield (Scheme 112). Presumably the electrophilic aroylacetate radical adds to the styrene to give a radical **418** that is stabilized by an aryl group. This regioselectivity is in keeping with the electronic nature of the two reactants (a nucleophilic radical would be expected to give the opposite regioselectivity). Next, the benzylic radical is oxidized very rapidly to cation **419**, which is then trapped by the ketone to give the dihydrofuran **420**. The trans stereoisomer was obtained exclusively. The reaction is useful because the dihydrofuran can be transformed into the desired tetralone **421** upon treatment with $SnCl_4$.

Thus, the entire carbon skeleton of podophyllotoxin can be assembled in just two steps from fairly simple precursors. The carboethoxy group adjacent to the ketone is potentially useful in completion of the synthesis, and it is necessary in the manganese oxidation because the electron-rich styrene **417** would be competitively oxidized by Mn(III) in the absence of a very acidic carbonyl component.

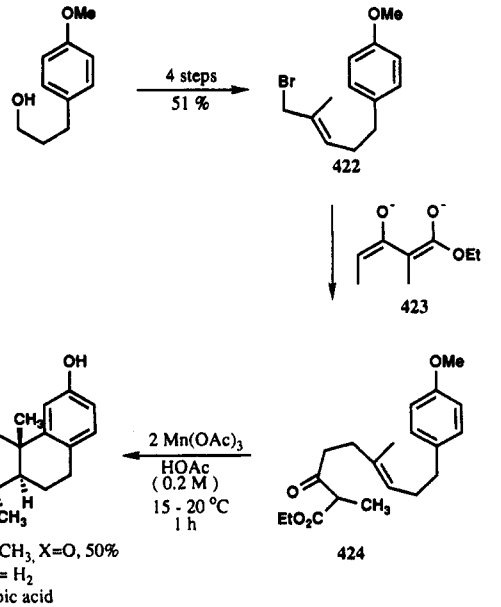
SCHEME 112



Intramolecular Additions

Recently, there has been a rapid increase in intramolecular applications of Mn(III) oxidation,[278] particularly in the natural products area. Snider, Mohan, and Kates[279] found that 6-membered rings are readily formed, and that tandem cyclizations are possible, during a very short total synthesis of podocarpic acid (**426**) shown in Scheme 113. Alkylation of readily

SCHEME 113



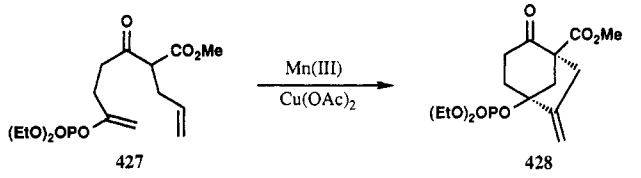
available allylic bromide **422** with dianion **423** afforded the precursor **424**. Oxidation of **424** with Mn(III) af-

forded **425** as the sole tricyclic product. Reduction of the ketone to a methylene group under Clemmensen conditions then furnished the ethyl ester of podocarpic acid (**426**).

The excellent stereoselectivity observed is typical of related cyclizations. Relative stereochemistry between the carboalkoxy-bearing stereocenter and the adjacent ring fusion stereocenter is determined in the radical cyclization, and now appears that free radicals are involved (not Mn-complexed radicals).[271a] The relative stereochemistry of the ring fusion is determined in the second cyclization. It is not clear whether closure to the aromatic ring proceeds by a free-radical mechanism, or by radical oxidation to a tertiary cation, followed by Friedel–Crafts alkylation.[280]

Snider and co-workers have also formed bridged ring systems in an approach to gibberellane and kaurane diterpenes (Scheme 114).[281] For example, Mn(III)

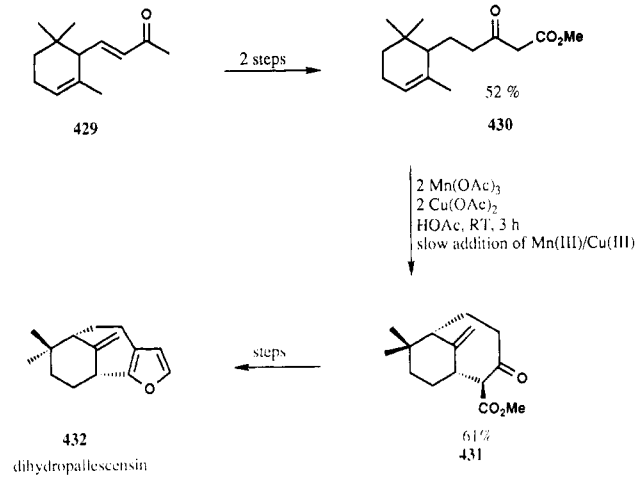
SCHEME 114



oxidation of **427** provides **428** in 77% yield. This product results from two sequential radical cyclizations.

Very recently, White and co-workers have reported a demanding oxidative cyclization en route to dihydropallescensin, a marine-derived, furanosesquiterpene.[282] Their synthetic approach, summarized in Scheme 115, deferred the formation of the furan to a late stage.

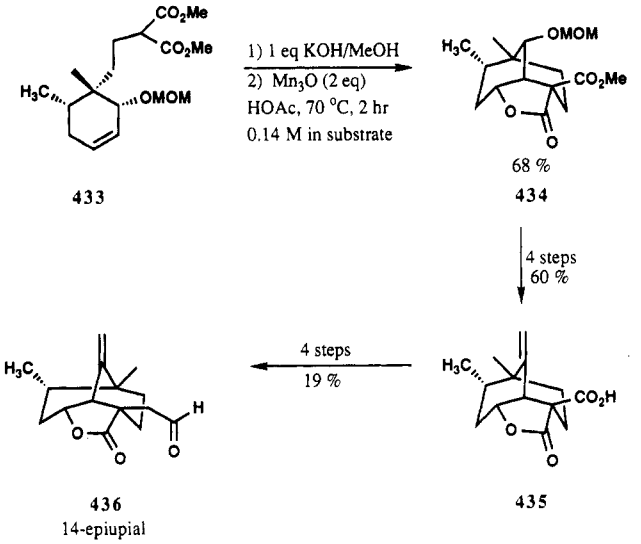
SCHEME 115



The desired keto ester **430** was generated in just two steps: Li/NH_3 reduction of the olefin **429**, and carbomethoxylation of the resulting methyl ketone. Treatment of **430** with Mn(III) and an equal amount of Cu(II) furnished the bridged bicyclic keto ester **431** in good yield. The substitution pattern of the olefin **430** dictates exclusive 7-endo cyclization. That the other olefin isomers violate Bredt's rule may be responsible for the formation of only one olefin regioisomer. The carbomethoxy group occupies the β position in the major product (a small, unspecified amount of the α isomer was obtained after purification), apparently as a result of kinetic control, since it could be subsequently equilibrated. The success of this cyclization (which forms a bridged 7-membered ring) suggests that this chemistry may be of very broad scope. From keto ester **431**, the synthesis of **432** was completed in six steps.

As a final example of Mn(III) oxidative cyclizations, we cite Paquette's recent synthesis of 14-*epi*-upial (**436**),[283] outlined in Scheme 116. Cyclization of **433**

SCHEME 116



under typical conditions proceeded in good yield (68%), considering the complexity of both substrate and product, to give the desired ring system **434**. From **434**, the methylene group was introduced by standard Wittig chemistry, and an exhaustive hydrolysis/relactonization reaction gave carboxylic acid **435**. Adjustment of oxidation level and Wittig chain extension then afforded 14-*epi*-upial (**436**).

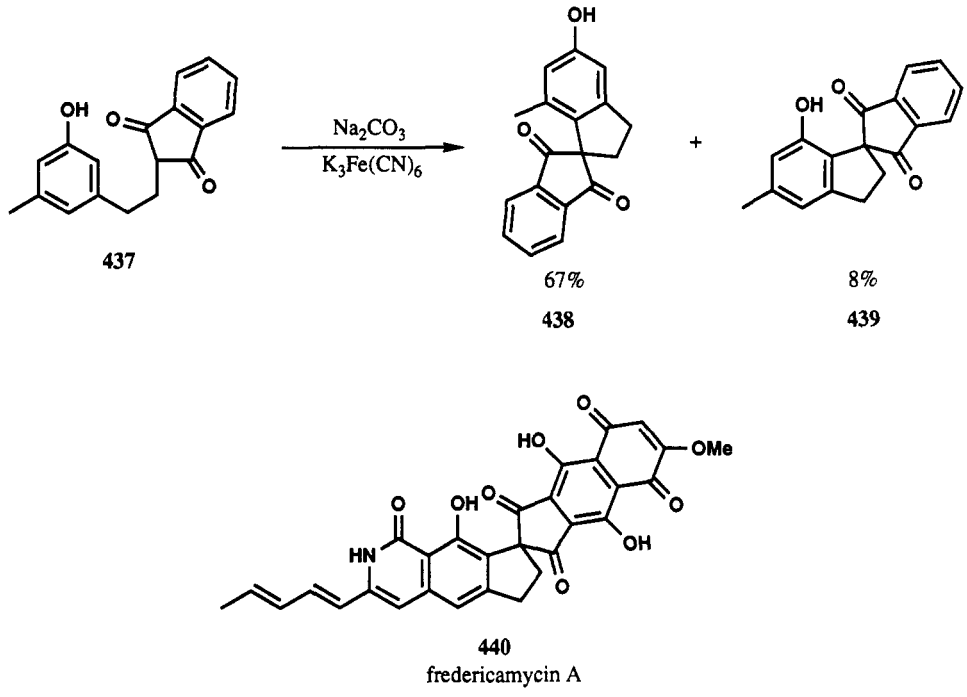
Interestingly, the three other stereoisomers of cyclization substrate **433** either gave very poor yields or completely failed in the oxidative cyclization reaction. Apparently, adverse steric interactions tip the balance in favor of oligomerization or other side reactions. An attempted iodine atom transfer cyclization of an iodomalonate was not useful either, and a synthesis of upial could not be completed.

3. Anion Oxidations

Though not involving the use of Mn(III), Kende and co-workers have developed an oxidative radical method that is representative of a class of reactions involving oxidation of anions.[284] This reaction involves oxidative coupling of phenolate-enolate systems by using either $K_3Fe(CN)_6$ or K_2IrCl_8 as oxidants. An example of the synthetic potential of the method is provided by Kende's approach to fredericamycin A (**440**)[284a] outlined in Scheme 117. In a model study, cyclization substrate **437** was treated at 0 °C with 0.5 M Na_2CO_3 and 6 equiv of $K_3Fe(CN)_6$ (0.5 M), followed by citric acid workup. This gave a mixture of products **438** and **439**. The unfavorable regiochemistry could be overcome by blocking the para position with an iodine atom, which could be reductively removed later. In this case, a 46% yield of the desired, ortho-coupled product (corresponding to **439**) was obtained.

The mild reaction conditions of Kende's method are attractive for synthetic purposes, but the reaction does

SCHEME 117



not yet seem to be of very broad scope. Spiro compounds are only attainable when a 5-membered ring is formed. Fused systems can be prepared while forming either 5- or 6-membered rings, and perhaps others. The enolate precursor is essentially restricted to cyclic diones (as above) and cyclic diamides of related structure. A few exceptions are known: nitro alkanes[284c] and a malononitrile.[284d]

VIII. Concluding Remarks

We conclude this review with a brief, admittedly subjective, look back at the field. The debt that synthetic practitioners of radical chemistry owe to their predecessors (and contemporaries!) in physical organic chemistry is difficult to overestimate. The explosion of synthetic applications during the 1980's can be attributed in good measure to the detailed understanding of structure and reactivity of many elementary classes of radicals that was already in place. The question then arises: "What sparked the synthetic application of radical reactions?" This is not an easy question for us to answer.

Sometimes radical chemists present a case that most of the key developments required for synthetic applications of radical reactions were in place in the early 1970's. If one consults Kochi's treatise[5] (published in 1973), one sees that they have a good case. Many of the most fundamental principles of organic radicals emerged during research in radical polymerizations, and these principles have been well understood for more than 30 years.[14] By 1970, Kharash reactions were so well studied that the field was declining in popularity,[187] Julia had already demonstrated many elegant examples of ring-forming reactions of electrophilic radicals,[186b] tin hydrides were emerging as useful reagents,[285] the kinetics and thermodynamics of simple hexenyl radical cyclizations were well known (if not completely understood), radical allylations with allylstannanes were known,[286] Stork had already conducted the first cyclizations of ketyls,[221a] oxidative procedures with manganese acetate were known,[272,273] and dissolving metal reductions were standard practice. To these can be added classic name reactions like the Kolbe electrolysis,[257] the Barton reaction,[194] and the Hofmann–Löffler–Freytag reaction.[200b]

Two very important classes of radical reactions that were not known at this time were Giese reactions (the reductive additions of nucleophilic radicals to electron deficient alkenes) and Barton's thiohydroxamate method. The Giese reaction first emerged in the late 1970's as the "mercury method",[168] and the more popular "tin method" was introduced shortly thereafter. Barton's thiohydroxamate method was not introduced until 1983,[208] but the era of carbon sulfur bonds as radical precursors was ushered in in 1975 with the Barton–McCombie reaction.[2] It seems unlikely that the introduction of two new preparative methods just before the synthetic explosion of free-radical reactions was a complete coincidence.

If synthetic chemists lagged behind their physical organic counterparts for a long time, they have recently more then rectified the situation. The field of organic radical chemistry is now—perhaps more so than any other subdiscipline of organic chemistry—a stimulating, productive interplay between synthetic organic chemists and physical organic chemists. Indeed, the boundary between these two groups is often so blurred that it can be difficult to determine who is in which camp. This is clearly good, and we believe that the current excitement in the field of radical chemistry will be maintained well into the 1990's.

Acknowledgments

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the Dreyfus Foundation. Finally, we would like to thank the four referees, who made some helpful comments and alerted us to a few key references.

References and Notes

(1) In this chapter, most reactions involve uncomplexed radicals that are freely diffusing in solution. These species will simply be called "radicals". The term "free radicals" will only be used to distinguish normal radicals from such entities as "metal-complexed" radicals.
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