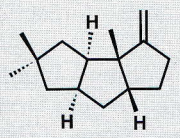
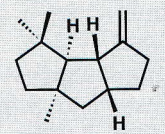


1: hirsutene



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

23

D. P. Curran (1986)

Hirsutene and $\Delta^{9(12)}$-Capnellene

23.1 Introduction

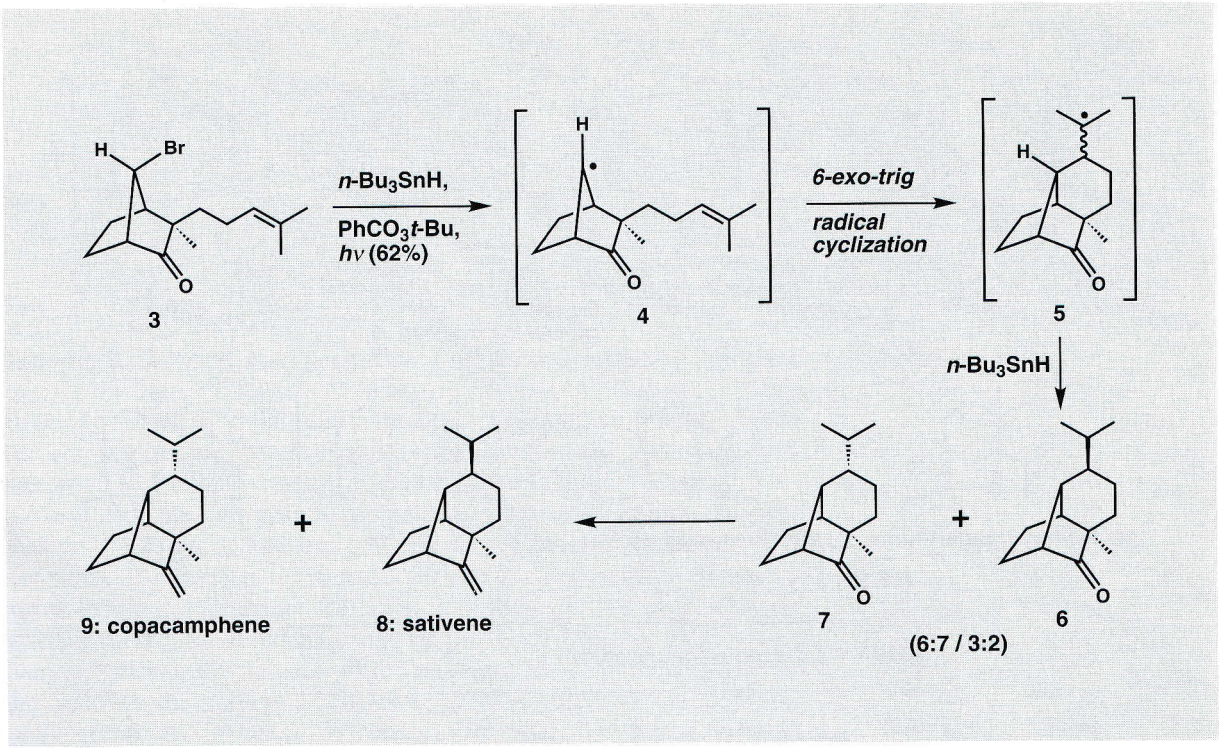
The central activity of organic synthesis is the construction of the carbon–carbon bond. For this purpose, a number of reaction processes have been developed, many of which feature the union of carbon nucleophiles (e.g. organometallic reagents) with carbon electrophiles (e.g. alkyl halides, alkyl sulfonates, epoxides, cyclic sulfates, carbonyl derivatives, and electrophilic olefins). Carbon–carbon bond constructions in the laboratory and in nature are, in fact, accomplished predominantly by polar reaction processes. In this regard, the central role of the carbonyl group as an electrophile and as an activator for the generation of nucleophilic enolate ions is particularly noteworthy. But in addition to polar processes, there are many nonpolar reactions that are indispensable as methods for carbon–carbon bond formation in organic synthesis. These include pericyclic reactions (i.e. electrocyclizations, sigmatropic rearrangements, and cycloadditions), photochemical reactions, and free radical reactions.[1]

Although the value of polar processes and pericyclic reactions in the synthesis of carbon-containing molecules has long been recognized, synthetic organic chemists have been much more hesitant in the use of radical reactions for the construction of carbon–carbon bonds. It appears that much of this disinclination can be attributed to the notion that free radicals, because of their high reactivity, react in unselective, unpredictable ways. In most applications, the desired reaction course is but one of several competing paths. In radical chain processes, premature chain terminations

such as radical–radical couplings and hydrogen atom transfers are obvious alternative pathways by which a radical intermediate can react. The reaction pathway taken by a transient free radical intermediate is determined by a subtle balance of reaction rates.

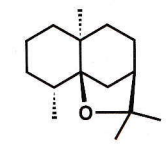
Nonetheless, the pioneering contributions of Walling, Ingold, Beckwith, Barton, Julia, Giese, and Stork, amongst others, have done much to debunk the myth that free radical reactions are too unmanageable to be of use in the synthesis of complex organic molecules.[2] Indeed, these pioneers have stimulated an explosive growth in the number of applications of radical-mediated carbon–carbon bond forming processes in organic synthesis.[1,3] Although many intermolecular radical addition processes are successful and very useful, intramolecular radical additions or radical cyclizations have been shown to be of particular value in the arena of natural product total synthesis. Intermolecular radical addition processes that are plagued by rate problems can often be conducted, with much success, in the intramolecular mode. For example, intramolecular additions of carbon-centered radicals to substituted carbon–carbon, carbon–oxygen, and carbon–nitrogen multiple bonds can all be performed efficiently since the activation entropies of intramolecular radical additions are less negative than those of their intermolecular counterparts.[3a] A decisive advantage of the intramolecular reaction mode is that highly hindered carbon–carbon bonds and quaternary stereogenic centers can be constructed through radical chemistry. In this chapter, the utility of radical reactions for the synthesis of structurally complex organic molecules is addressed, with an emphasis on some of the elegant synthetic work by D. P. Curran and his group at the University of Pittsburgh. Although only a few of the many noteworthy achievements in synthetic radical chemistry are discussed, we direct the readers' attention to some excellent, more substantial reviews of this important subject.[1,3a,b,d]

An early example of a free radical cyclization in natural product synthesis is found in the synthesis of the sesquiterpenes sativene (**8**) and copacamphene (**9**) by Bakuzis *et al.* (see Scheme 1).[4] In the event, subjection of bromoketone **3** to the tin hydride method for radical generation results in the formation of a separable 3:2 mixture of diastereomeric tricyclic ketones **6** and **7** (62% total yield). In this transformation, the tri-*n*-butyltin radical (n-$Bu_3Sn^{\bullet}$) generated *in situ* abstracts the bromine atom ($Br^{\bullet}$) from **3** to give the transitory carbon-centered radical **4**. With a suitable radical acceptor six atoms removed, **4** can participate in a 6-*exo-trig* radical cyclization to give a new carbon-centered radical **5**, after which a terminating hydrogen atom transfer affords the two stereoisomeric products and regenerates n-$Bu_3Sn^{\bullet}$. Although the stereoselectivity of the radical cyclization is poor, it is noteworthy that a rather crowded carbon–carbon bond is constructed under mild, neutral reaction conditions. Ketone olefinations allowed the conversion of **6** and **7** to sativene (**8**) and copacamphene (**9**), respectively.

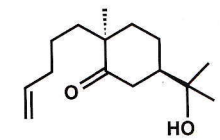


Scheme 1. Radical cyclization strategy for the synthesis of sativene (**8**) and copacamphene (**9**) by Bakuzis and coworkers.

A challenging bond construction was also achieved in Büchi's synthesis of dihydroagarofuran (**15**), a constituent of galbanum resin (see Scheme 2).[5] The action of phosphorus pentachloride on hydroxy ketone **10** in carbon tetrachloride results in the formation of bicyclic chloroether **11** in 64 % yield. With a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) as the radical initiator and tri-*n*-butyltin hydride (1.13 equiv), **11** is converted to a 3:7 mixture of diastereoisomeric substances, dihydroagarofuran (**15**) and isodihydroagarofuran (**16**) (67 % total yield). Uncyclized reduction product **13** is formed to the extent of 20 %. Under the reaction conditions, AIBN decomposes to two isobutyronitrile radicals [$(CH_3)_2C^{\bullet}CN$] that abstract a hydrogen atom from tri-*n*-butyltin hydride, thus giving *n*-$Bu_3Sn^{\bullet}$; this is the initiation step. Once formed, *n*-$Bu_3Sn^{\bullet}$ abstracts the chlorine atom from **11** to give the putative bridgehead radical **12**. The latter species has two options available: **12** can abstract a hydrogen atom from tri-*n*-butyltin hydride to give the uncyclized reduction product **13**, or it can engage the pendant alkene in a radical cyclization to give a new carbon-centered radical **14**. Abstraction of a hydrogen atom from tri-*n*-butyltin hydride by **14** then affords the epimeric tricyclic products **15** and **16** and regenerates *n*-$Bu_3Sn^{\bullet}$. Not surprisingly, the ratio of uncyclized reduction product **13** to the cyclized products increases with increasing tri-*n*-butyltin hydride concentration.



15: dihydroagarofuran



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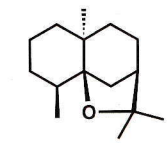
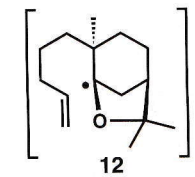


16: isodihydroagarofuran



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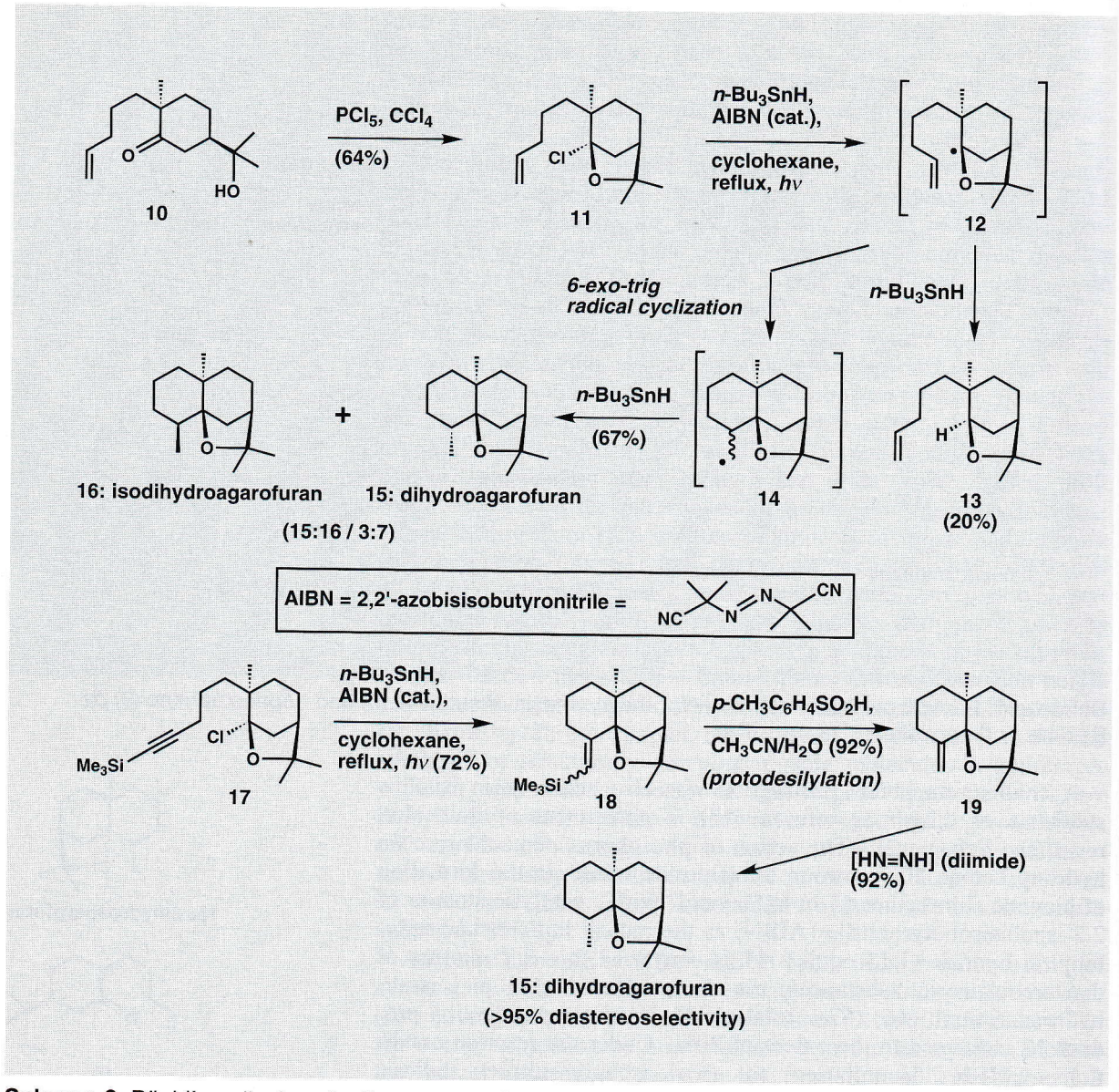
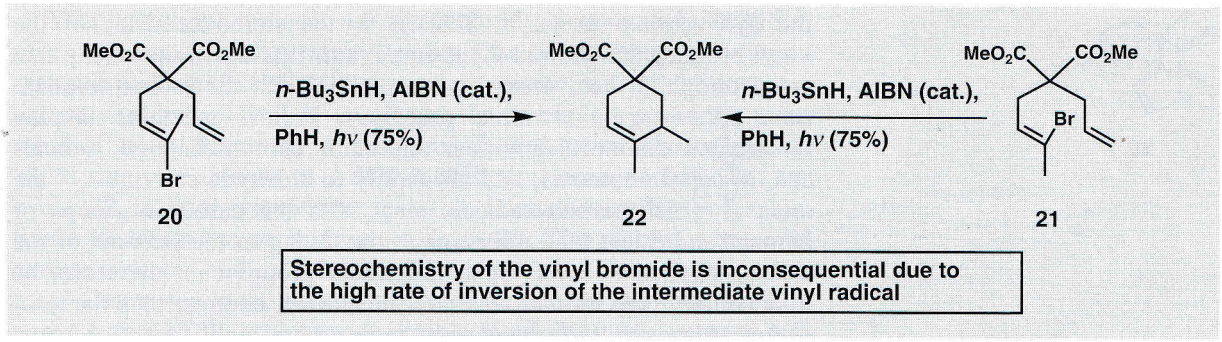


Scheme 2. Büchi's radical cyclization strategy for the synthesis of dihydroagarofuran (**15**).

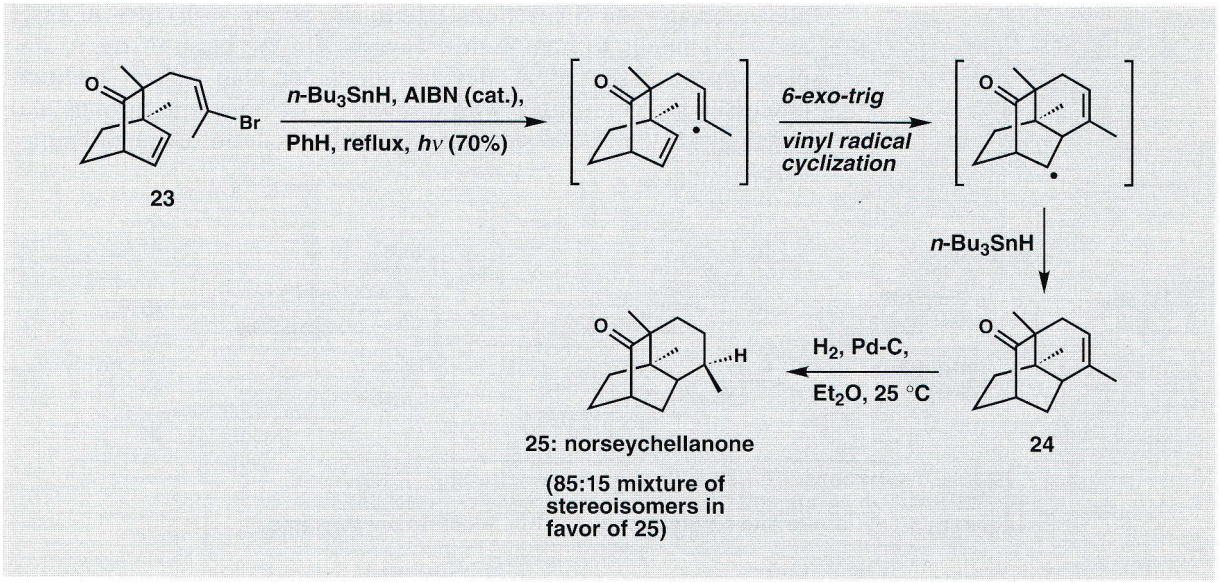
In an effort to identify a more stereoselective route to dihydroagarofuran (**15**), trimethylsilylated alkyne **17** was utilized as a substrate for radical cyclization (Scheme 2). Treatment of **17** with a catalytic amount of AIBN and tri-*n*-butyltin hydride (1.25 equiv) furnishes a mixture of stereoisomeric vinyl silanes **18** (72 % combined yield) along with an uncyclized reduction product (13 % yield). The production of stereoisomeric vinyl silanes in this cyclization is inconsequential because both are converted to the same alkene **19** upon protodesilylation. Finally, a diastereoselective diimide reduction of the double bond in **19** furnishes dihydroagaro-



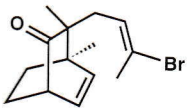
Scheme 3. Selected vinyl radical cyclizations developed by Stork and coworkers.

furan (**15**) in 92 % yield, contaminated with less than 5 % of epimer **16**. The impressive stereoselectivity exhibited in this reduction was attributed to the directing effect of the proximal ether oxygen.[6]

Vinyl radicals can also participate in 6-*exo* cyclizations. In pioneering work, Stork and his group at Columbia University showed that stereoisomeric vinyl bromides **20** and **21** (see Scheme 3) can be converted to cyclohexene **22**.[7] The significance of this finding is twofold: first, the stereochemistry of the vinyl bromide is inconsequential since both stereoisomers converge upon the same product; and second, the radical cyclization process tolerates electrophilic methoxycarbonyl groups. The observation that the stereochemistry of the vinyl bromide is inconsequential is not surprising because the barrier for inversion of most vinyl radicals is very low.[8] This important feature of vinyl radical cyclization chemistry is also exemplified in the conversion of vinyl bromide **23** to tricycle **24**, the key step in Stork's synthesis of norseychellanone (**25**) (see Scheme 4).[9] As in



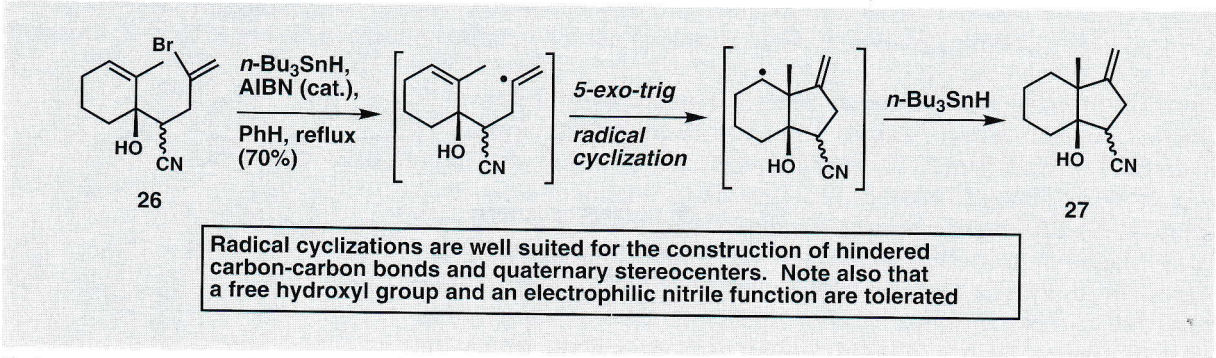
Scheme 4. Stork's vinyl radical cyclization strategy for the synthesis of norseychellanone (**25**).



23

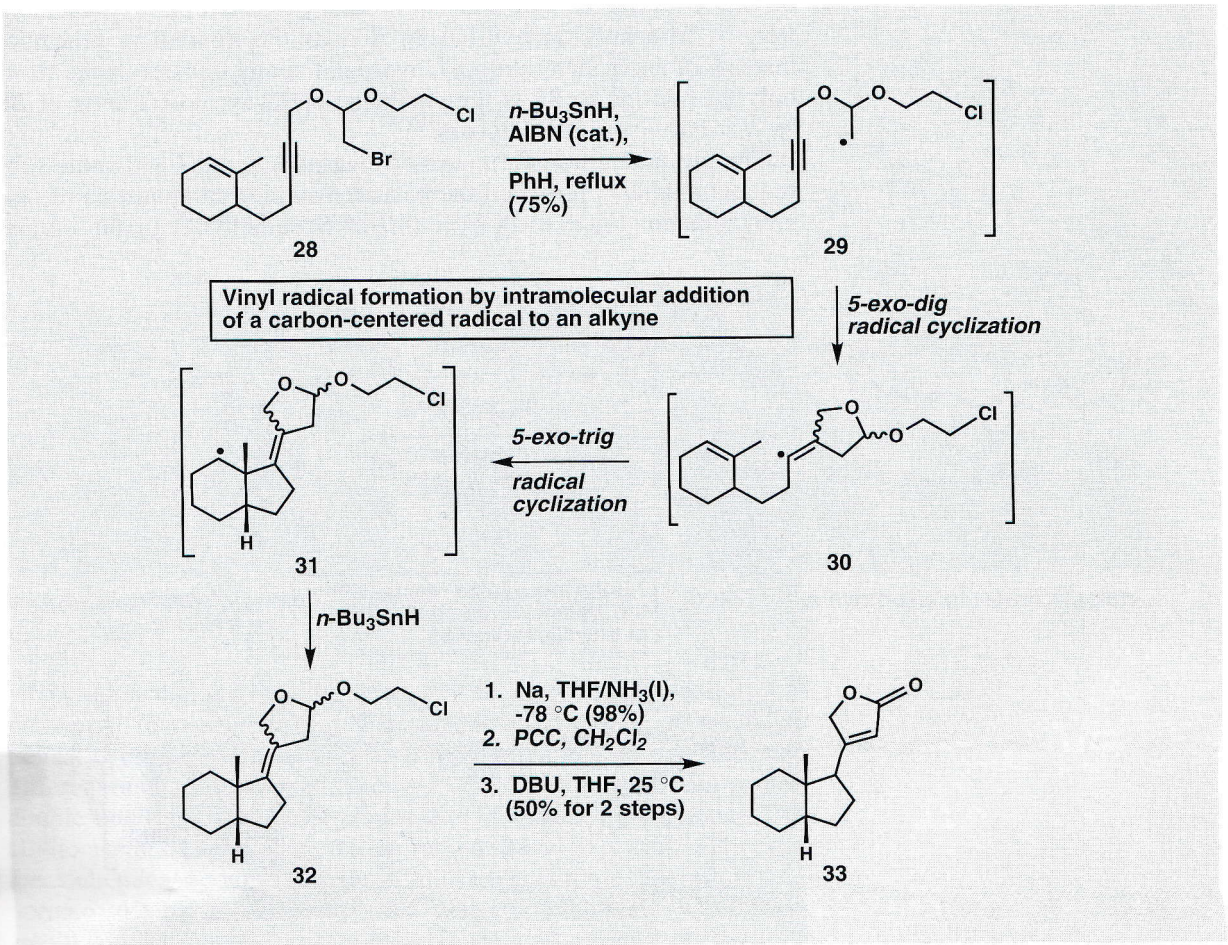
the cyclizations shown in Scheme 3, the stereochemistry of the vinyl bromide function in **23** is irrelevant. It is also noteworthy that an electrophilic keto group is compatible with the radical cyclization. By contrast to ionic processes, radical reactions display remarkable chemoselectivities. Although carbon-centered radicals can, in certain contexts, add efficiently to aldehyde carbonyls,[10] the rates at which carbon radicals react with the carbonyl groups of ketones and esters tend to be very slow owing to the strength of the carbon–oxygen π bond. Such functional groups can, therefore, be tolerated in most radical reactions in marked contrast to polar processes. Although carbon-centered radicals are highly reactive intermediates, high levels of chemo-, regio-, and even stereoselectivity can be achieved because radical additions proceed under mild reaction conditions.[3d]

The reactions of carbon-centered radicals are also tolerant of free hydroxyl or amino groups. In a historically significant example, the Stork group demonstrated that vinyl bromide **26** (see Scheme 5), on treatment with tri-*n*-butyltin hydride and a catalytic amount of AIBN in refluxing benzene, is converted to methyleneindanol **27** in 70 % yield. In this transformation, the vinyl radical derived from **26** engages the double bond in the proximate ring in a radical cyclization; a crowded carbon–carbon bond and a quaternary stereocenter are formed smoothly. Indeed, one of the most valuable assets of radical cyclization methodology is that hindered carbon–carbon bonds and quaternary stereocenters can be constructed efficiently. It is also noteworthy that the carbon–carbon double bond of the newly formed ring occupies a predefined position and is poised for further elaboration if desired. Moreover, neither the electrophilic nitrile function, nor the free hydroxyl group interferes with the desired radical cyclization. Free hydroxyl and amino groups are preserved in radical reactions due to the strong resistance of O–H and N–H bonds to homolytic cleavage. On the basis of the examples surveyed so far, it may be concluded that radical addition processes are compatible with a diversity of functional groups and are thus ideally suited for the synthesis of multifunctional molecules.

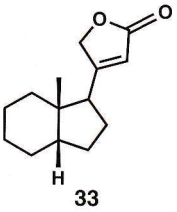


Scheme 5. Stork's construction of methyleneindanol **27**.

Although vinyl radicals are conveniently generated by reaction of a vinyl halide with a stannyl radical, the Stork group reported an intriguing alternative that features the intramolecular addition of a carbon-centered radical to an alkyne. In an elegant example, treatment of mixed acetal **28** (see Scheme 6) with tri-*n*-butyltin hydride and a catalytic amount of AIBN in refluxing benzene furnishes tricycle **32** in 75% yield.[11] In this transformation, *n*-$Bu_3Sn^{\bullet}$ selectively abstracts the bromine atom from **28**. The resulting transient carbon-centered radical **29** then adds regioselectively to the proximate alkyne function, generating vinyl radical **30**. Despite the hindered nature of its cyclohexene double bond, **30** participates in a 5-*exo-trig* radical cyclization to give cyclohexyl radical **31**. Finally, abstraction of a hydrogen atom from tri-*n*-butyltin hydride by **31** produces tricycle **32** and regenerates *n*-$Bu_3Sn^{\bullet}$. Two carbon–carbon bonds, two rings, and a congested quaternary stereocenter are created in this productive tandem radical bicyclization. Reductive cleavage of the chloroethyl protecting group in **32** with sodium in



Scheme 6. Stork's synthesis of butenolide **33**.

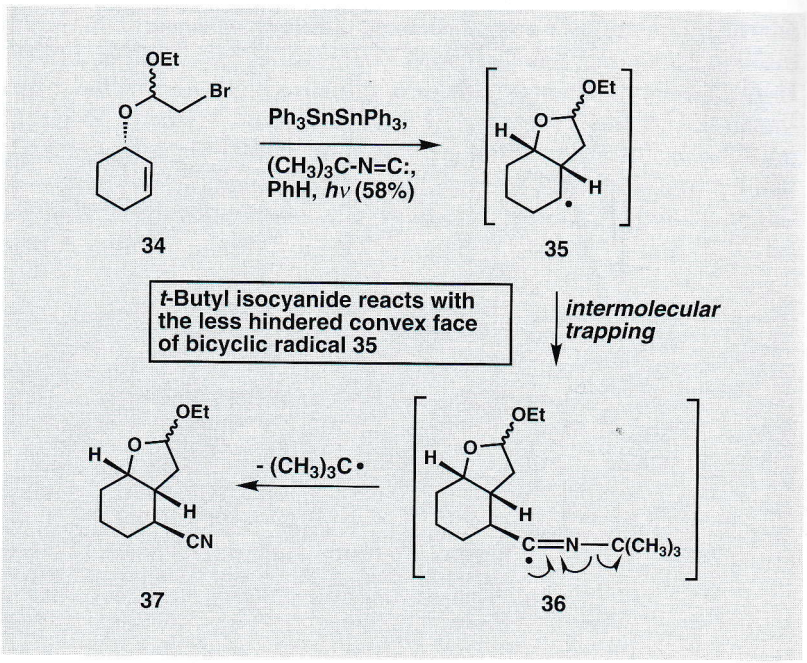


33

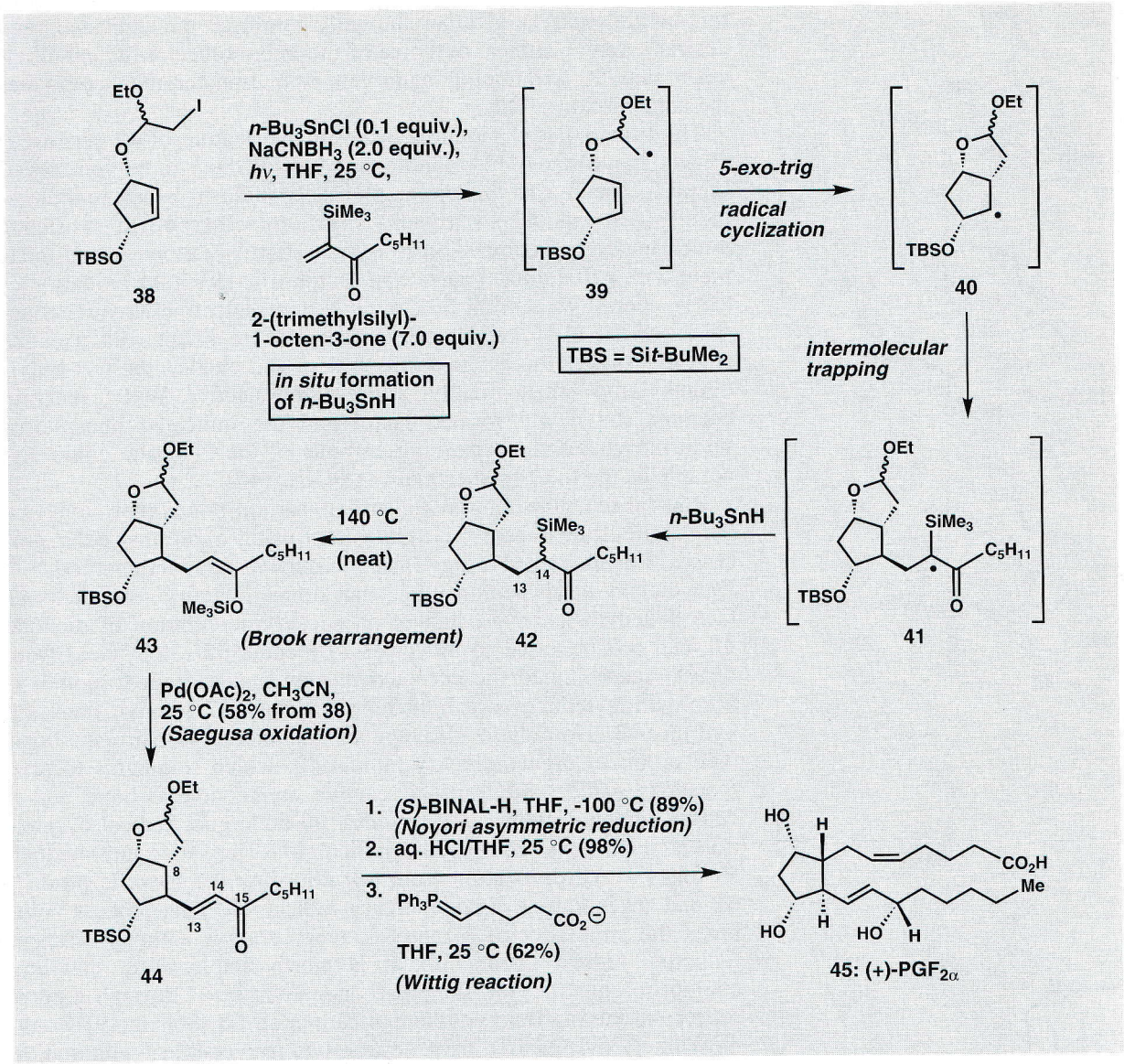
THF/liq. NH_3, followed sequentially by oxidation and base-induced double bond isomerization, provides butenolide **33**, a compound that possesses the lactone system of the steroidal cardiac aglycones.

The finding that a carbon-centered radical produced by a radical cyclization can be intercepted intermolecularly by an entity other than hydrogen constitutes a major development in synthetic radical chemistry. In many cases, it would be desirable to terminate a radical chain process with a grouping that would be amenable to future synthetic manipulations. In a pioneering example, Stork and Sher demonstrated that carbon-centered radical **35** (see Scheme 7), the product of a 5-*exo-trig* radical cyclization of bromoacetal **34**, can be trapped with *tert*-butylisocyanide.[12] As expected, *tert*-butyl isocyanide engages the less hindered convex face of bicyclic radical **35**. Presumably in the manner shown, a chemically versatile cyano group is introduced and *tert*-butyl radical is eliminated. The overall process accomplishes a tandem vicinal difunctionalization of an alkene, and its productivity is analogous to the familiar conjugate addition of a carbon nucleophile to an enone, followed by trapping of the resulting enolate ion by a suitable electrophile.[13] Incidentally, if tri-*n*-butyltin hydride is used as the tin radical precursor instead of hexaphenylditin, a hydrogen atom transfer from tri-*n*-butyltin hydride to **35** is the exclusive pathway; no trapping of **35** by *tert*-butylisocyanide occurs.

The promising transformation shown in Scheme 7 and some subsequent studies[14] provided the basis for an elegant synthesis of (+)-prostaglandin $F_{2\alpha}$ [(+)-$PGF_{2\alpha}$] (**45** in Scheme 8).[15] In the crucial

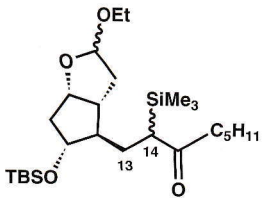


Scheme 7. Stork's tandem vicinal difuctionalization strategy.



Scheme 8. Stork's tandem radical cyclization/trapping strategy for the synthesis of (+)-prostaglandin $F_{2\alpha}$ (**45**).

step, iodoacetal **38**, readily available in optically active form, is converted to α-trimethylsilylated ketone **42** by way of a tandem radical cyclization/intermolecular trapping process. In one step, two differentiated carbon appendages are added across a carbon–carbon double bond in a completely regio- and stereoselective manner. The allylic acetal oxygen of the initial radical **39** controls the regio- and stereochemical course of the radical cyclization to **40**. Once formed, **40** reacts efficiently and diastereoselectively with 2-(trimethylsilyl)-1-octen-3-one, a reactive radical acceptor, to give **41**; the cup-shaped structure of bicyclic radical **40** and the α-disposed



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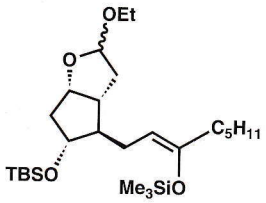

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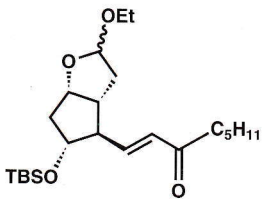

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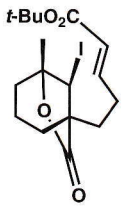
tert-butyldimethylsilyl ether mutually reinforce the indicated (and desired) stereochemical outcome of the intermolecular radical alkylation step. A terminating hydrogen atom transfer then completes the construction of **42**.

The trimethylsilyl grouping is a valuable feature of **42** because it allows the *trans*-$\Delta^{13,14}$ double bond of $PGF_{2\alpha}$ to be introduced regiospecifically. To this end, a thermally induced Brook rearrangement[16] converts **42** to trimethylsilyl enol ether **43**, a substance which undergoes conversion to α,β-unsaturated ketone **44** on treatment with palladium(II) acetate in acetonitrile (Saegusa oxidation)[17] (58 % overall yield from **38**). After a stereoselective Noyori reduction[18] of the C-15 ketone carbonyl in **44**, treatment with aqueous acid hydrolyzes the cyclic acetal moiety and cleaves the *tert*-butyldimethylsilyl ether. Finally, a *cis*-stereoselective Wittig reaction between the newly formed lactol and the indicated phosphorus ylide introduces the remaining carbons of the C-8 side chain and completes the total synthesis of (+)-$PGF_{2\alpha}$ (**45**).

Radical reactions can create carbon–carbon bonds that would be very difficult or impossible to construct using traditional polar processes. For example, using Giese's reductive mercury method,[3a,19] Danishefsky et al. demonstrated that organomercury compound **47** (see Scheme 9), the product of an acetoxymercuration of dienone **46**, can be converted to bicyclo[3.3.0]octane **52** (58 % yield from **46**).[20] According to the accepted mechanism, sodium trimethoxyborohydride reduces organomercuric acetate **47** to give mercuric hydride **48**. Homolytic cleavage of the mercury–hydrogen bond then produces organomercury radical **49**, which fragments to give β-acetoxy radical **50**. With a reactive enone double bond and a carbon-centered radical in proximity, **50** undergoes radical cyclization to a new carbon-centered radical **51**. The latter intermediate abstracts a hydrogen atom from **48**, affording the bicyclic product **52** and regenerating organomercury radical **49**. This process combines the simplicity of alkene solvomercuration with an efficient reductive radical cyclization. It is worth emphasizing that any attempt to construct the same carbon–carbon bond through a polar process involving the hypothetical carbanion **53** (Scheme 9) would most likely by thwarted by a destructive, irreversible β-elimination of the newly introduced acetoxy function to give **46**. A valuable attribute of radical reactions is that OR and NR_2 groups in the β-position are not eliminated.

The success of intramolecular conjugate additions of carbon-centered radicals in multifunctional contexts is noteworthy. Compound **57** (see Scheme 10), prepared by an interesting sequence starting from *meta*-toluic acid (**54**) (see **54** → **55** → **56** → **57**), can be converted to the highly functionalized perhydroindane **58** through an intramolecular conjugate addition of a hindered secondary radical.[21,22] This radical cyclization actually furnishes a 6:1 mixture of perhydroindane diastereoisomers, epimeric at C-7, in favor of **58** (96 % total yield). It should be noted that a substantially less strained *cis*-fused bicyclo[4.3.0] substructure is formed in this cyclization.



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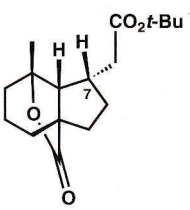

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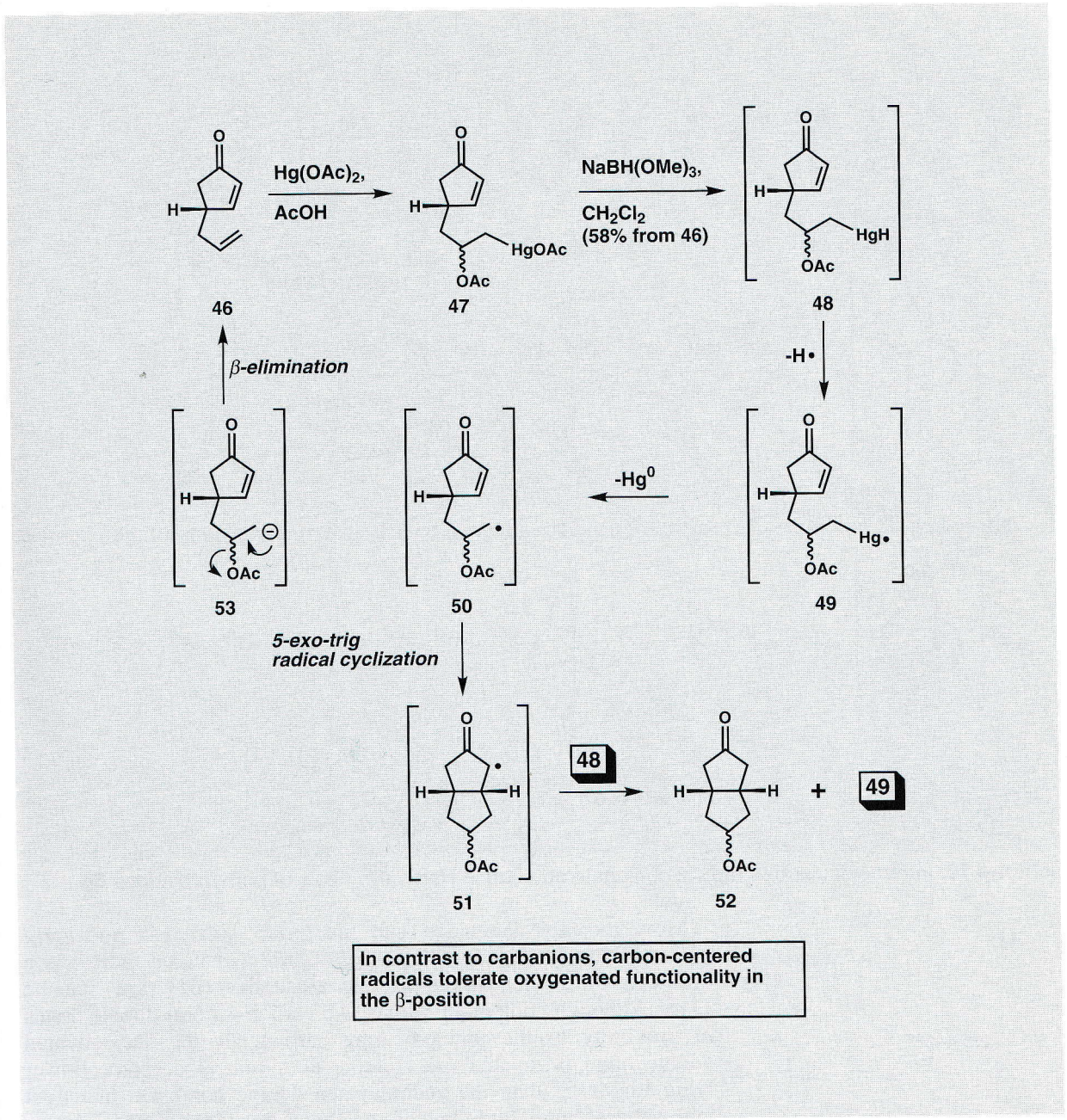
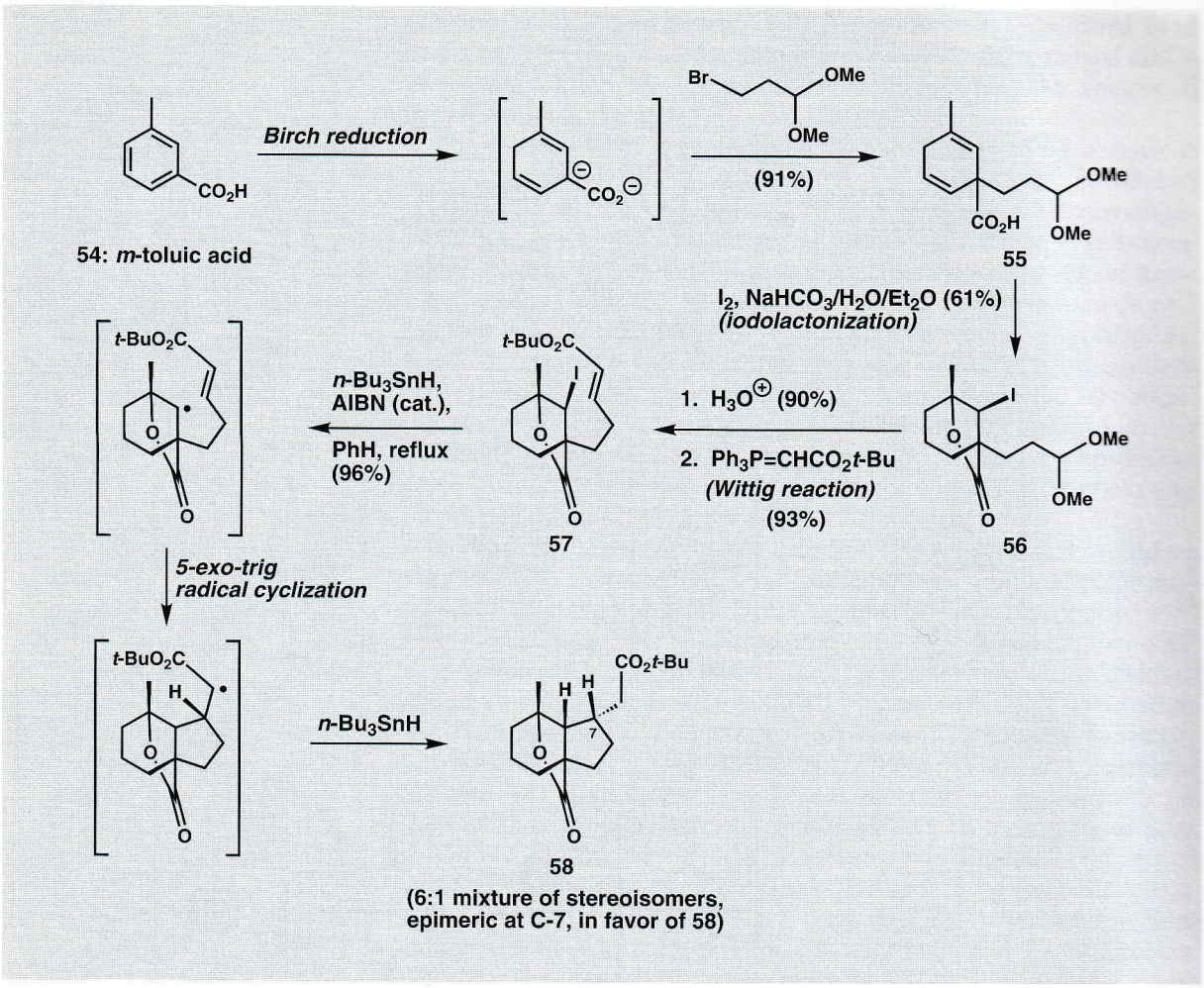
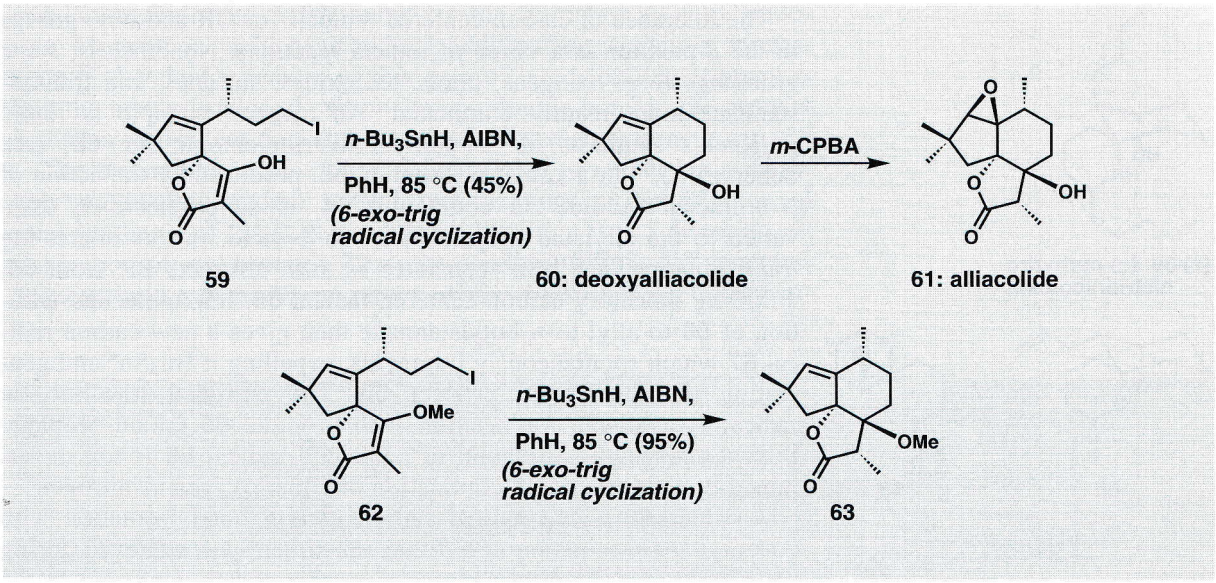


Scheme 9. Danishefsky's synthesis of bicyclo[3.3.0]octane **52** using Giese's reductive mercury method.

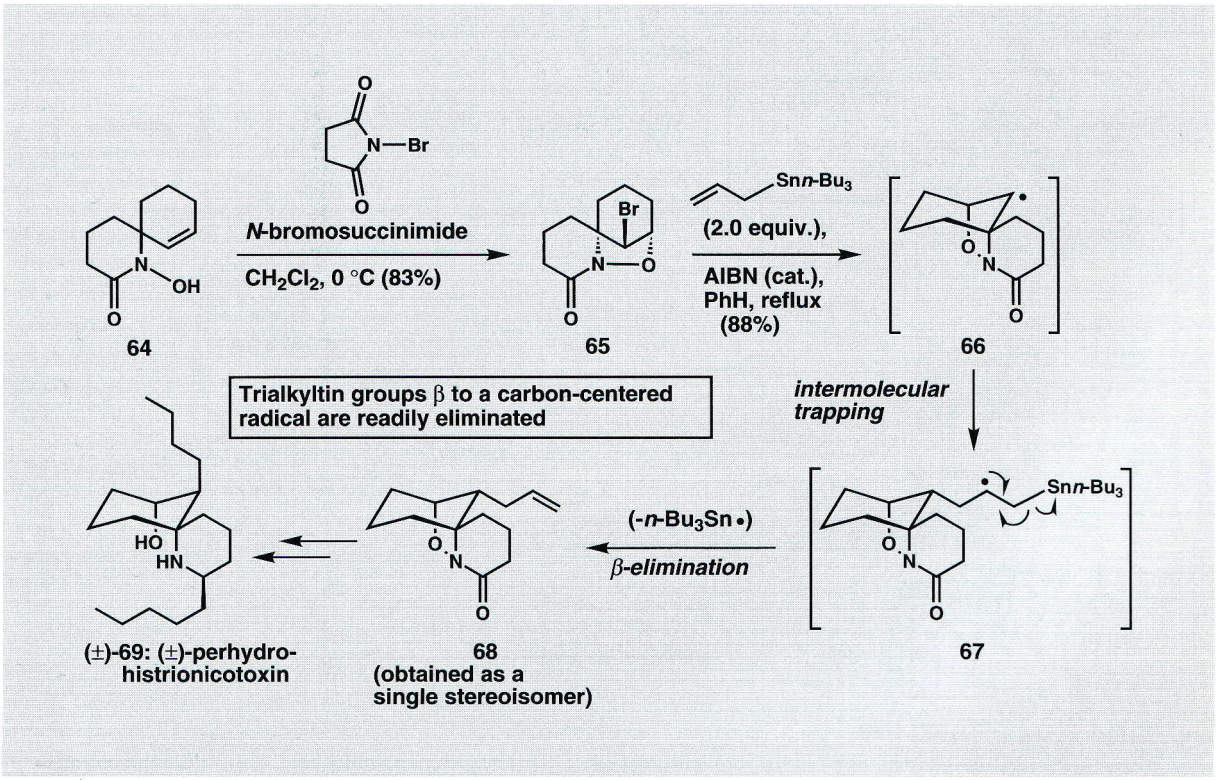


Scheme 10. Intramolecular free radical conjugate addition in Hart's synthesis of perhydroindane **58**.

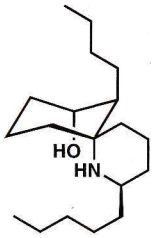
More recently, Pattenden and his group utilized a 6-*exo-trig* intramolecular conjugate addition of a carbon-centered radical in a synthesis of the tetracyclic lactone alliacolide (**61**) (see Scheme 11).[23] Although compound **59** has two carbon–carbon double bonds in proximity to the iodine-bearing carbon, the lactone-activated double bond is much more reactive as a radical acceptor (lower lying LUMO)[24] than the unconjugated double bond. On treatment with tri-*n*-butyltin hydride and AIBN in benzene at 85 °C, compound **59** is converted diastereoselectively to deoxyalliacolide (**60**) (45 % yield). Interestingly, compound **62** cyclizes much more smoothly than **59**, affording tricyclic lactone **63** as a single diastereoisomer in 95 % yield. It is noteworthy that lactone activation of the rather hindered double bond permits the smooth formation of a fully substituted stereogenic center in this transformation. Moreover, the neutral reaction medium tolerates oxygenated functionality and does not induce a destructive β-elimination of the methoxyl group.



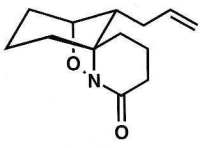
Scheme 11. Intramolecular free radical conjugate addition in Pattenden's synthesis of alliacolide (**61**).



Scheme 12. Intermolecular radical trapping–fragmentation in Keck's synthesis of (±)-perhydrohistrionicotoxin [(±)-**69**].



(±)-69: (±)-perhydrohistrionicotoxin



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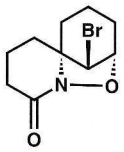
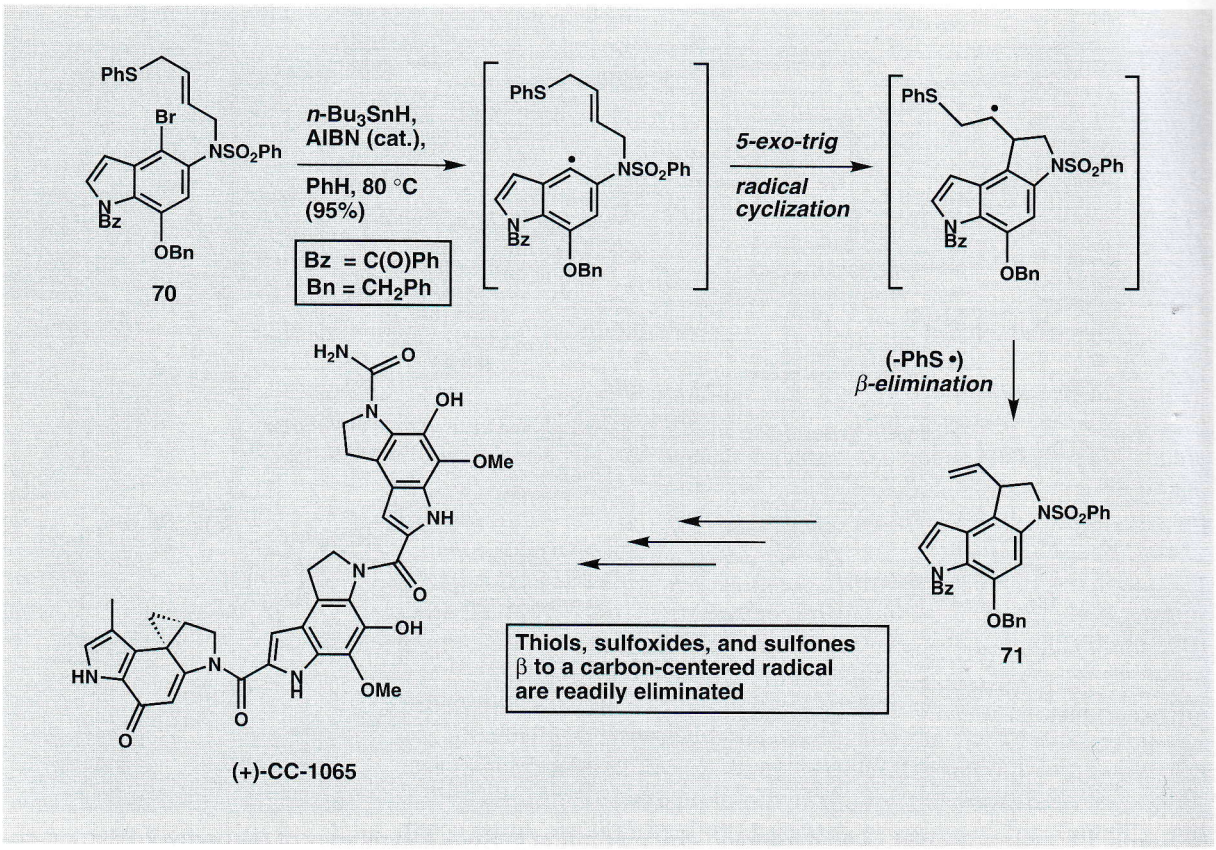


65

The tolerance of carbon-centered radicals for OR and NR_2 groups in the β-position is a virtue of radical reactions. Nonetheless, some groupings (e.g. halogens, thiols, sulfoxides, sulfones, and trialkylstannanes) are readily eliminated. An elegant example is found in Keck's synthesis of (±)-perhydrohistrionicotoxin [(±)-**69**] (see Scheme 12).[25] In a key step, bromide **65**, produced by the action of *N*-bromosuccinimide on compound **64**, is stereoselectively converted to the allylated tricycle **68** in 88 % yield. In this interesting transformation, *n*-$Bu_3Sn^{\bullet}$ generated *in situ*, abstracts $Br^{\bullet}$ from **65**, affording transitory carbon-centered radical **66**. Intermolecular addition of **66** to allyl tri-*n*-butylstannane then gives a new carbon radical **67** which spontaneously fragments, expelling *n*-$Bu_3Sn^{\bullet}$ and generating the C-allylated product **68**. The extruded tri-*n*-butyltin radical is available for reaction with bromide **65** (chain propagation). Gratifyingly, allylation of neopentyl radical **66** is not undermined by a destructive β-elimination of either oxygen or nitrogen.

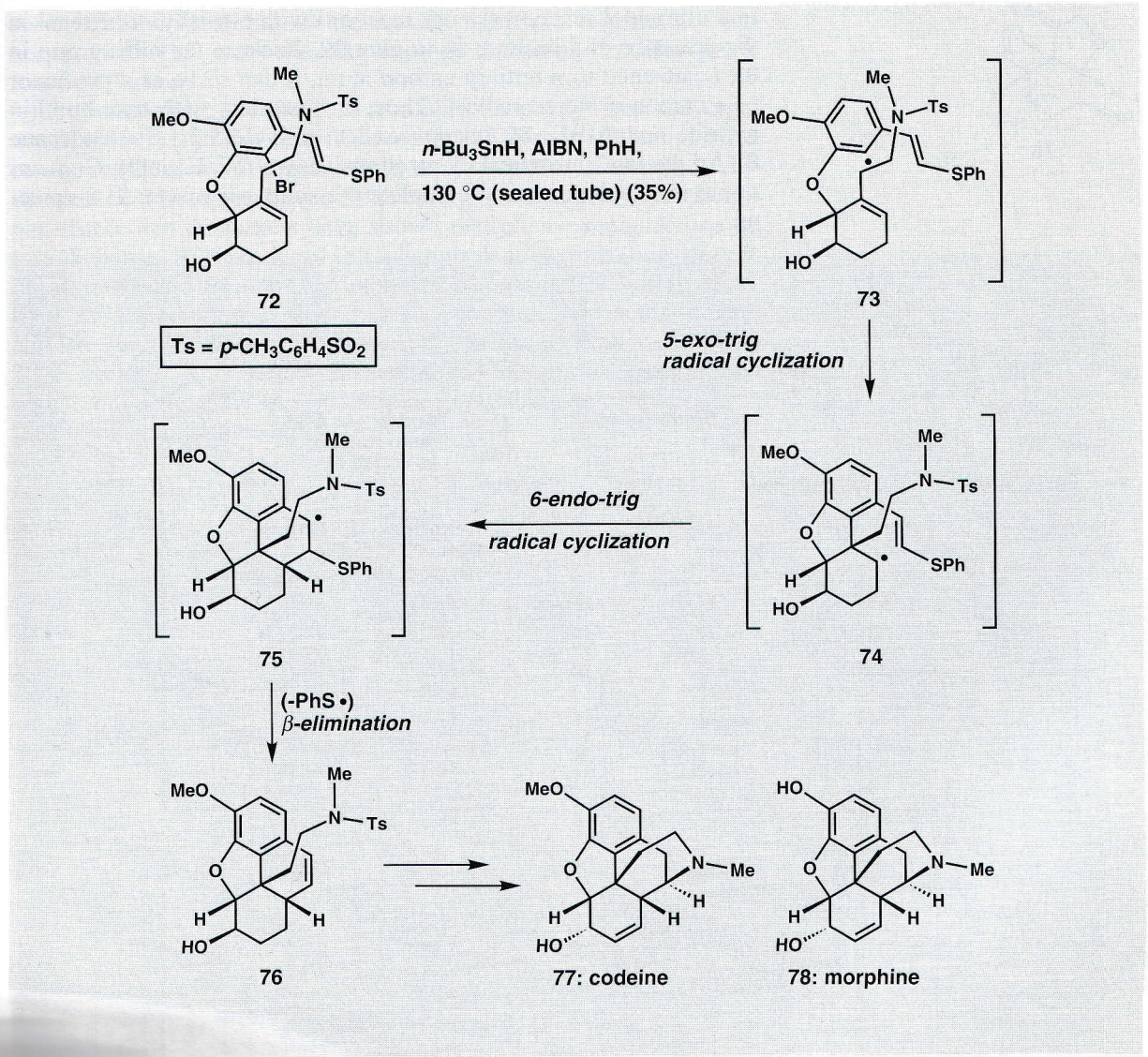
An interesting free radical carbon–carbon bond formation with concomitant elimination of a β-thio substituent was achieved during the course of Boger's impressive synthesis of CC-1065.[26,27] In the event, treatment of aryl bromide **70** (see Scheme 13) with tri-*n*-



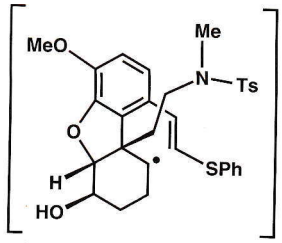
Scheme 13. Intramolecular radical addition/fragmentation in Boger's synthesis of (+)-**CC**-1065.

butyltin hydride and AIBN results in the formation of vinyl indoline **71** in 95% yield by a radical addition/fragmentation mechanism.[28] A valuable feature of this type of bond-forming strategy is that the newly fashioned carbon–carbon double bond in the product provides convenient opportunities for further elaboration.

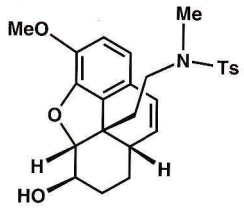
The β-elimination of a thiyl radical (RS•) terminated a remarkably productive tandem radical bicyclization in Parker's formal total syntheses of (±)-codeine and (±)-morphine (see Scheme 14).[29] Subjection of aryl bromide **72** to the conditions indicated generates transient aryl radical **73**, an intermediate which engages the substi-



Scheme 14. Tandem radical bicyclization–fragmentation in Parker's synthesis of intermediate **76** en route to codeine (**77**) and morphine (**78**).



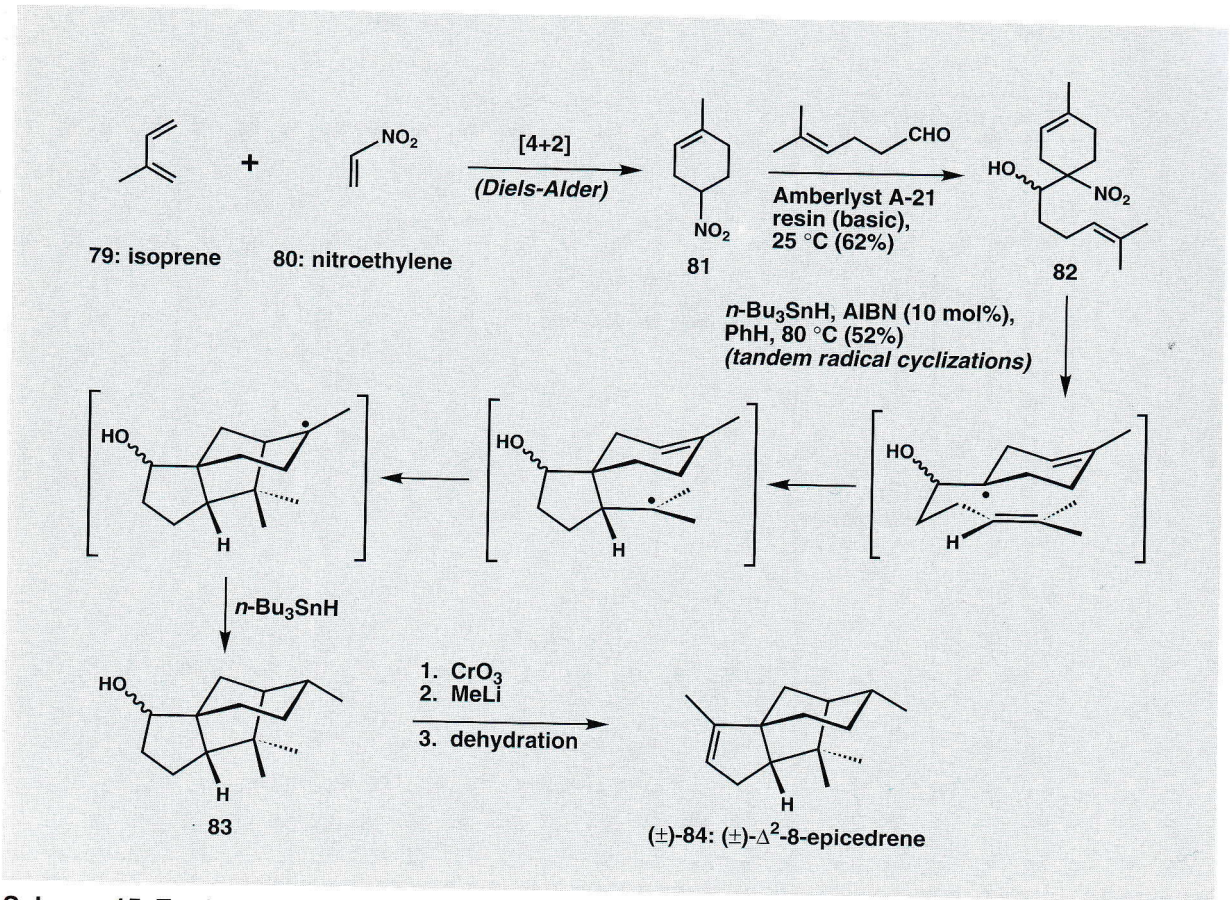
74



76

tuted cyclohexene double bond in a stereo- and regioselective 5-*exo*-*trig* radical cyclization. This event creates a new carbon-centered radical **74** which then participates in a 6-*endo*-*trig* cyclization with the pendant styryl double bond to give benzylic radical **75**. Finally, spontaneous β-elimination of PhS$^{\bullet}$ occurs, affording key intermediate **76** (35 % yield). Two rings, a critical quaternary stereocenter, and a strategically placed carbon–carbon double bond are all formed in this elegant sequential transformation.

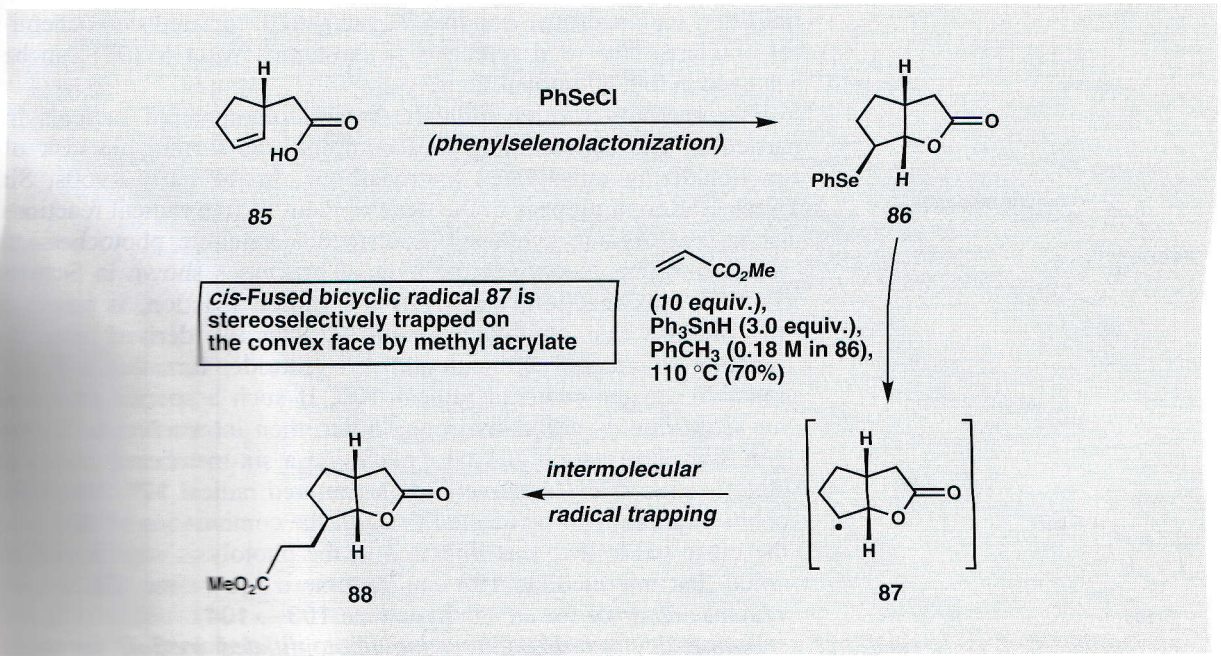
Sequential radical cyclizations are also featured in an efficient and clever synthesis of the cedrane framework **83** (see Scheme 15).[30] Compound **81**, the product of a regioselective Diels–Alder reaction between isoprene (**79**) and nitroethylene (**80**), participates in a nitroaldol reaction (Henry reaction) with 5-methyl-4-hexenal in the presence of a basic resin to give **82**. Because the nitro group in **82** is attached to a tertiary carbon atom, it can serve as a precursor to a carbon-centered radical. Thus, on treatment with tri-*n*-butyltin hydride and AIBN, **82** is converted to tricyclo[5.3.1.0^{1,5}]undecane **83** by the tandem radical cyclizations shown (52 % yield). Conventional manipulations then complete the synthesis of (±)-Δ^2-8-epice-



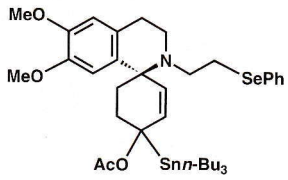
Scheme 15. Tandem radical cyclizations in Chen's synthesis of (±)-Δ^2-8-epicedrene [(±)-**84**].

drene [(±)-**84**]. This impressively short synthesis of a small, yet complicated, tricycle (see **83**) takes full advantage of the versatile nitro group.[31] In the first step, isoprene (**79**) and nitroethylene (**80**) combine smoothly in a Diels–Alder reaction[32] to give adduct **81**; in this pericyclic reaction, the nitro group activates the dienophile (nitroethylene) and guides the regioselective formation of the *para*-substituted [4+2] adduct **81**. The second step (see **81** → **82**) takes advantage of the capacity of the nitro group to stabilize an adjacent negative charge; by way of a base-induced nitroaldol or Henry reaction,[33] compound **81** is joined through a carbon–carbon bond with the indicated γ,δ-unsaturated aldehyde (a polar reaction). Finally, the nitro grouping in **82** can serve as a convenient precursor to a carbon-centered radical since it is affixed to a tertiary carbon atom.[34] This work cleverly exploits the properties of a single functional group.[35]

The wide variety of methods available for the synthesis of organoselenides,[36] and the observation that the carbon–selenium bond can be easily cleaved homolytically to give a carbon-centered radical creates interesting possibilities in organic synthesis. For example, Burke and coworkers have shown that phenylselenolactone **86** (see Scheme 16), produced by phenylselenolactonization of γ,δ-unsaturated acid **85**, can be converted to free radical intermediate **87** *with triphenyltin hydride. In the presence of excess methyl* acrylate, **87** is trapped stereoselectively, affording compound **88** in 70% yield;[37] it is noteworthy that the intermolecular carbon–carbon bond forming event takes place on the less hindered convex face of bicyclic radical **87**.



Scheme 16. Burke's two-step carbolactonization process.



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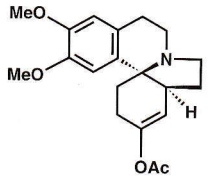
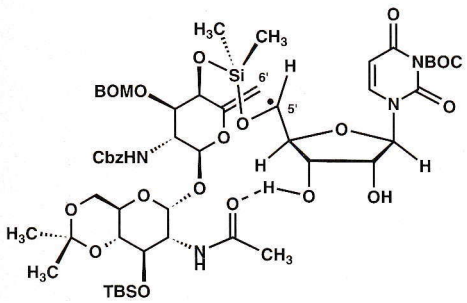


92



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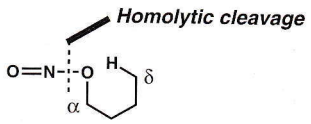

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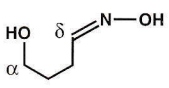


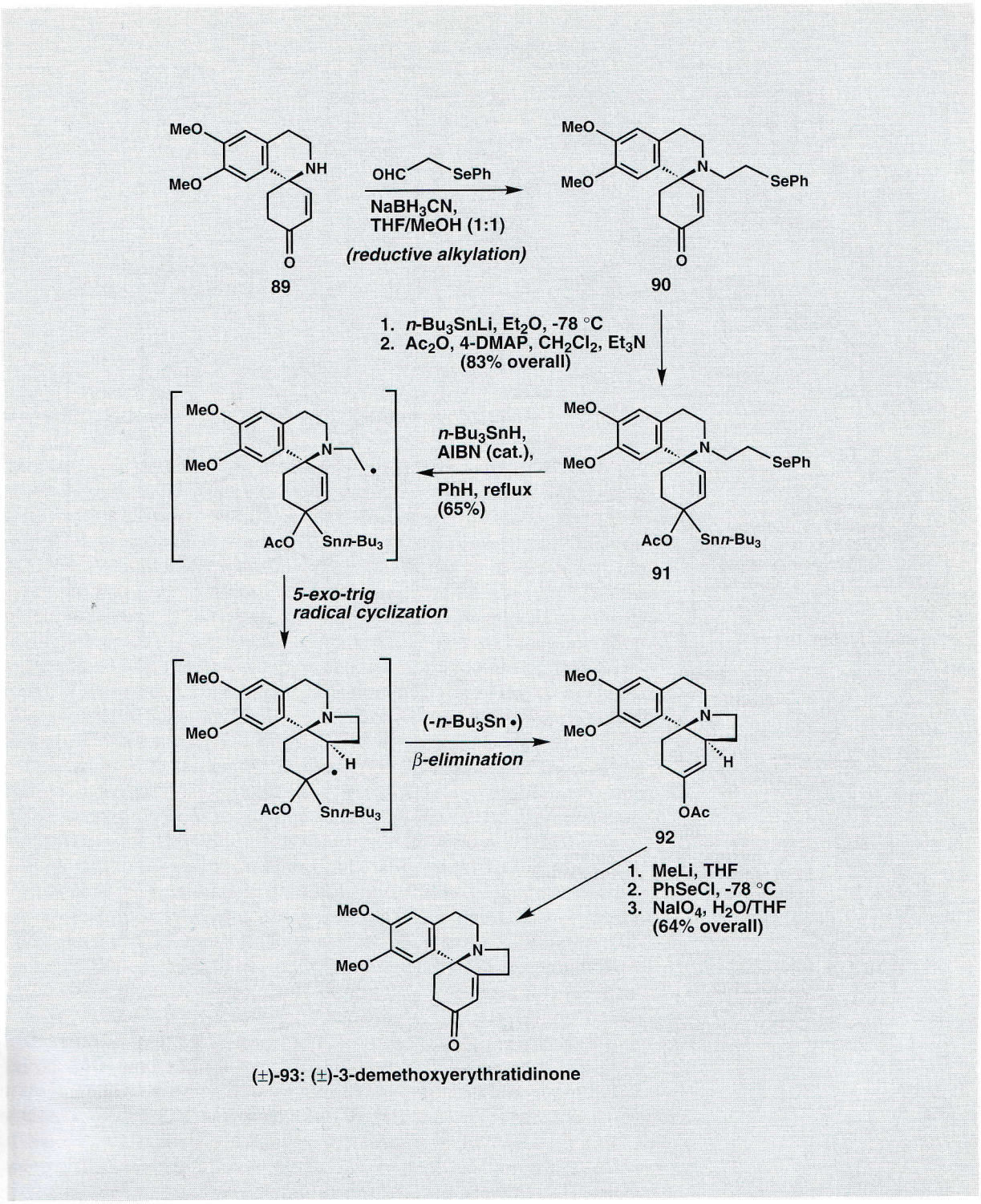
103

During the course of Danishefsky's elegant synthesis of the erythrina alkaloid (±)-3-demethoxyerythratidinone (**93**) (see Scheme 17), it was found that organoselenide **90**, prepared by reductive alkylation of amine **89**, can be converted to allylic geminal acetoxystannane **91** in two straightforward steps.[38] This tactic is noteworthy because radical cyclization of **91**, with concomitant fragmentation, furnishes enol acetate **92** regiospecifically, thereby allowing a controlled introduction of the requisite enone double bond in the natural product (see **92** → (±)-**93**).

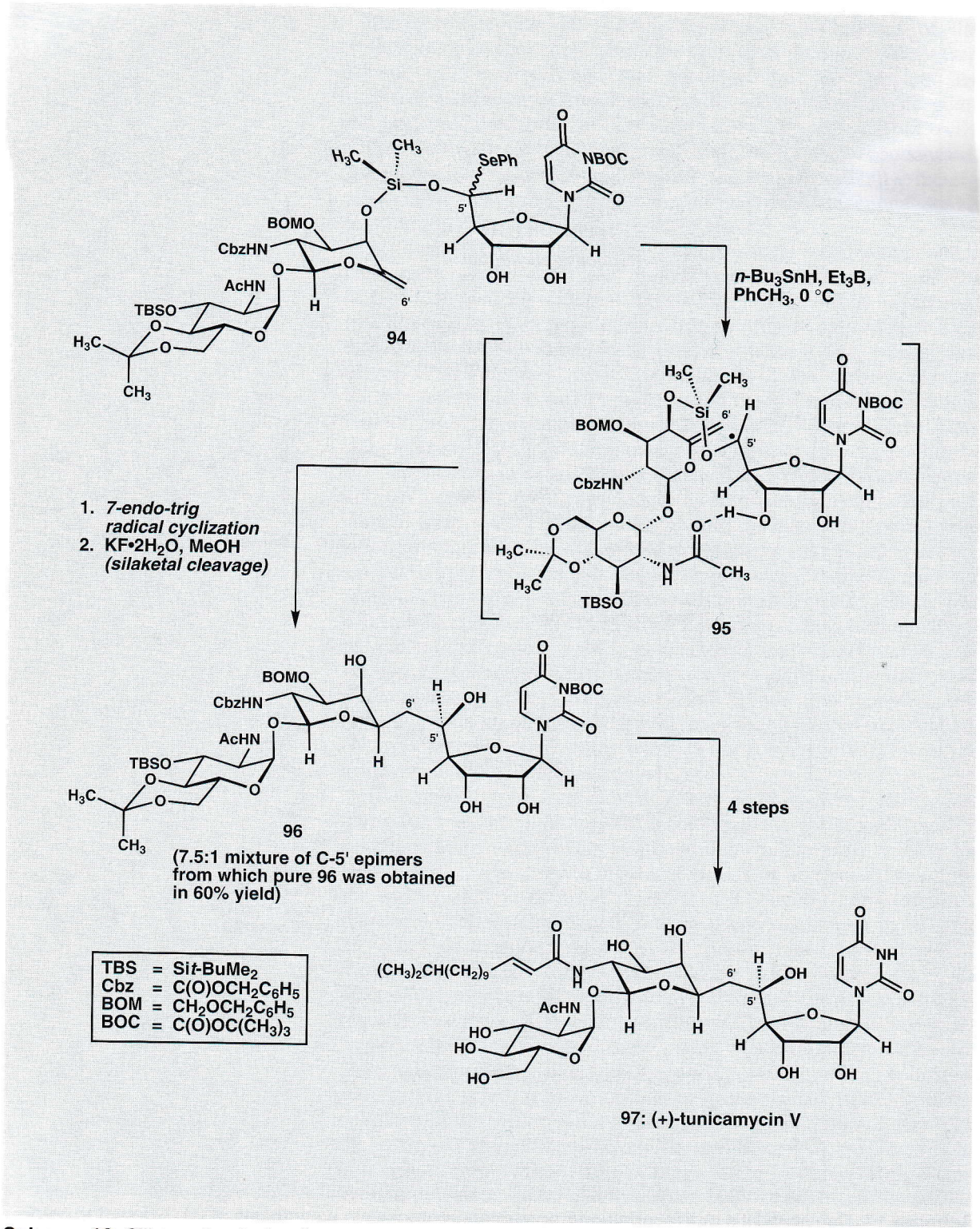
A novel organoselenide radical precursor is the key intermediate in convergent syntheses of the tunicamycin antibiotics (e.g. **97**) by A.G. Myers and his group at the California Institute of Technology (see Scheme 18).[39] In this elegant work, two functionalized sectors are united through a mixed-silaketal (see intermediate **94**), a group that serves as a temporary tether.[40] Homolysis of the carbon–selenium bond in **94** with tri-*n*-butyltin hydride and the low-temperature radical initiator triethylborane brings about a 7-*endo-trig* ring closure. Fluoride-induced cleavage of the silaketal then furnishes a 7.5:1 mixture of C-5′ epimers in favor of **96**. This radical cyclization establishes the C5′–C6′ bond and the C-5′ stereocenter of the tunicamycins. The preferential formation of **96** is consistent with the hydrogen-bonded transition structure **95**. The silicon bridge brings the carbon-centered radical and the carbon–carbon double bond into proximity, and the indicated hydrogen bond stabilizes transition structure **95**; the desired configuration at C-5′ emerges from this arrangement. Incidentally, if the radical cyclization of **94** is conducted in a protic solvent such as methanol, compound **96** is obtained with significantly diminished stereoselectivity (1.6:1). This observation supports the hypothesis that transition state hydrogen bonding is crucial to the desired stereochemical outcome. The total synthesis of (+)-tunicamycin V (**97**) can be achieved in four additional steps.

The reactivity of free radicals, heteroatom-centered radicals in particular, can be exploited to accomplish the formidable task of functionalizing unactivated hydrocarbons. In the early 1960s, Sir Derek Barton, a pioneer in the development of free radical reactions for use in organic synthesis, described a valuable photochemical reaction which comprises the general processes shown in Scheme 19.[41,42] This reaction, known as the Barton reaction, is based on the premise that photolysis of nitrite ester **99**, derived from the reaction of alcohol **98** with nitrosyl chloride, furnishes a highly reactive oxygen-centered radical **100**. If such a species possesses an accessible δ-carbon–hydrogen bond, then intramolecular hydrogen atom abstraction can take place via a six-membered transition state to give a less reactive carbon-centered radical **101**. Nitrosoalcohol **102** can then be formed through the combination of **101** with the nitric oxide that was liberated in the photolysis step. It will be noted that intermediate **102** can tautomerize to oxime **103**, a convenient precursor for an aldehyde (see **103** → **104**).

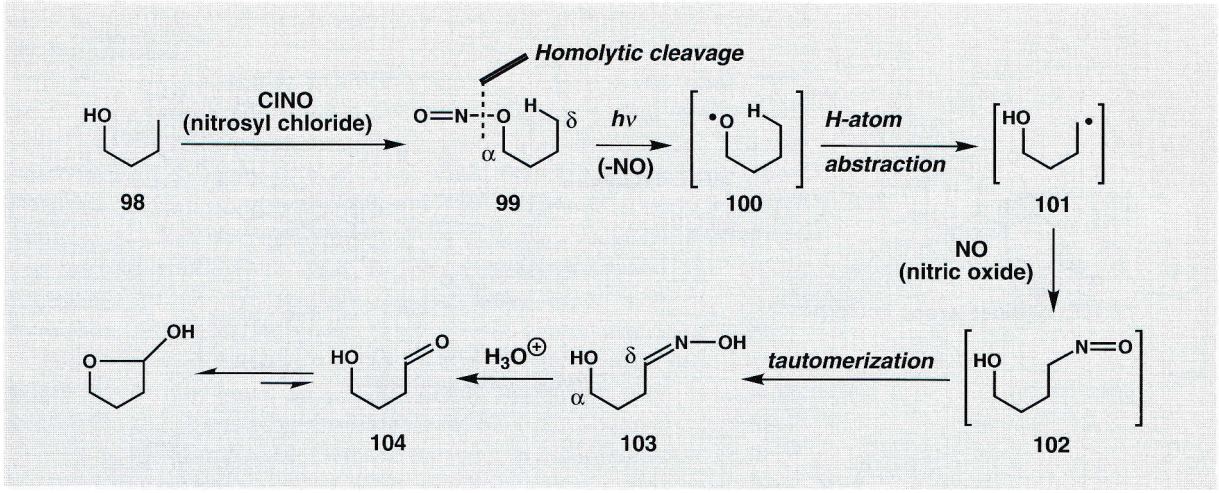
Barton devised this interesting photoinitiated method for functionalizing unactivated carbon–hydrogen bonds in response to a



Scheme 17. Danishefsky's radical addition/fragmentation process in a synthesis of (±)-3-demethoxyerythratidinone [(±)-**93**].

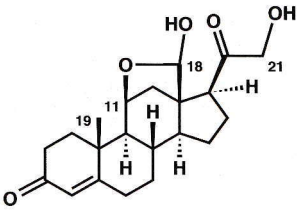


Scheme 18. Silicon-directed radical cyclization in Myers's synthesis of (+)-tunicamycin V (**97**).

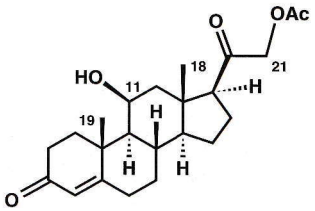


Scheme 19. Nitrite ester photolysis: the Barton reaction.

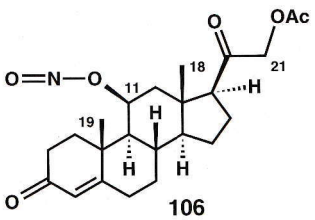
very difficult problem that emerged in the steroid field. In 1954, the structure of aldosterone (**112** see Scheme 20) was revealed as a result of the brilliant research of Reichstein and his colleagues.[43] A novel feature of aldosterone (**112**) is the masked aldehyde function at C-18. Although it would have been desirable to devise a feasible synthetic pathway to aldosterone starting from an abundant steroid precursor (partial synthesis), the state of the art in organic synthesis methodology at the time was not equal to the task of functionalizing an angular C-18 methyl group, a characteristic feature of many steroids. It was in this context that Barton conceived of the clever solution shown in Scheme 20. In 1960, Barton and his group reported that corticosterone acetate (**105**), a readily available steroid, can be converted to aldosterone 21-acetate (**111**) through application of the Barton reaction.[44] This interesting transformation commences with the conversion of corticosterone acetate (**105**) into the corresponding nitrite ester **106** with nitrosyl chloride in pyridine. When a solution of **106** in toluene is irradiated, alkoxyl radical **107** is generated. In **107**, the oxygen-centered radical and the C-18 angular methyl group occupy neighboring regions of space, a circumstance which favors an intramolecular hydrogen atom abstraction to give carbon-centered radical **108**. The latter intermediate then captures nitric oxide (NO), the other photolysis product, furnishing a nitroso alcohol (see **109**), which finally tautomerizes to the crystalline oxime **110**. Aldosterone 21-acetate (**111**) is produced upon treatment of oxime **110** with nitrous acid [ca. 20% yield from corticosterone acetate (**105**)]. Competitive hydrogen atom abstraction from the similarly placed C-19 methyl group in **107** decreases the efficiency of the desired pathway. Although the overall yield is not high, it is noteworthy that this photoinitiated free radical reaction allowed the synthesis of approximately 60 grams of aldosterone 21-acetate (**111**), thus permitting the biological activity of this compound to be fully studied. It should be noted that an improved synthesis of



112: aldosterone



105: corticosterone acetate



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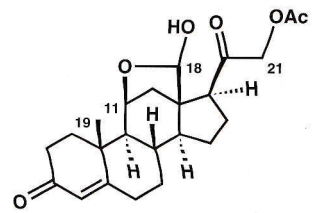
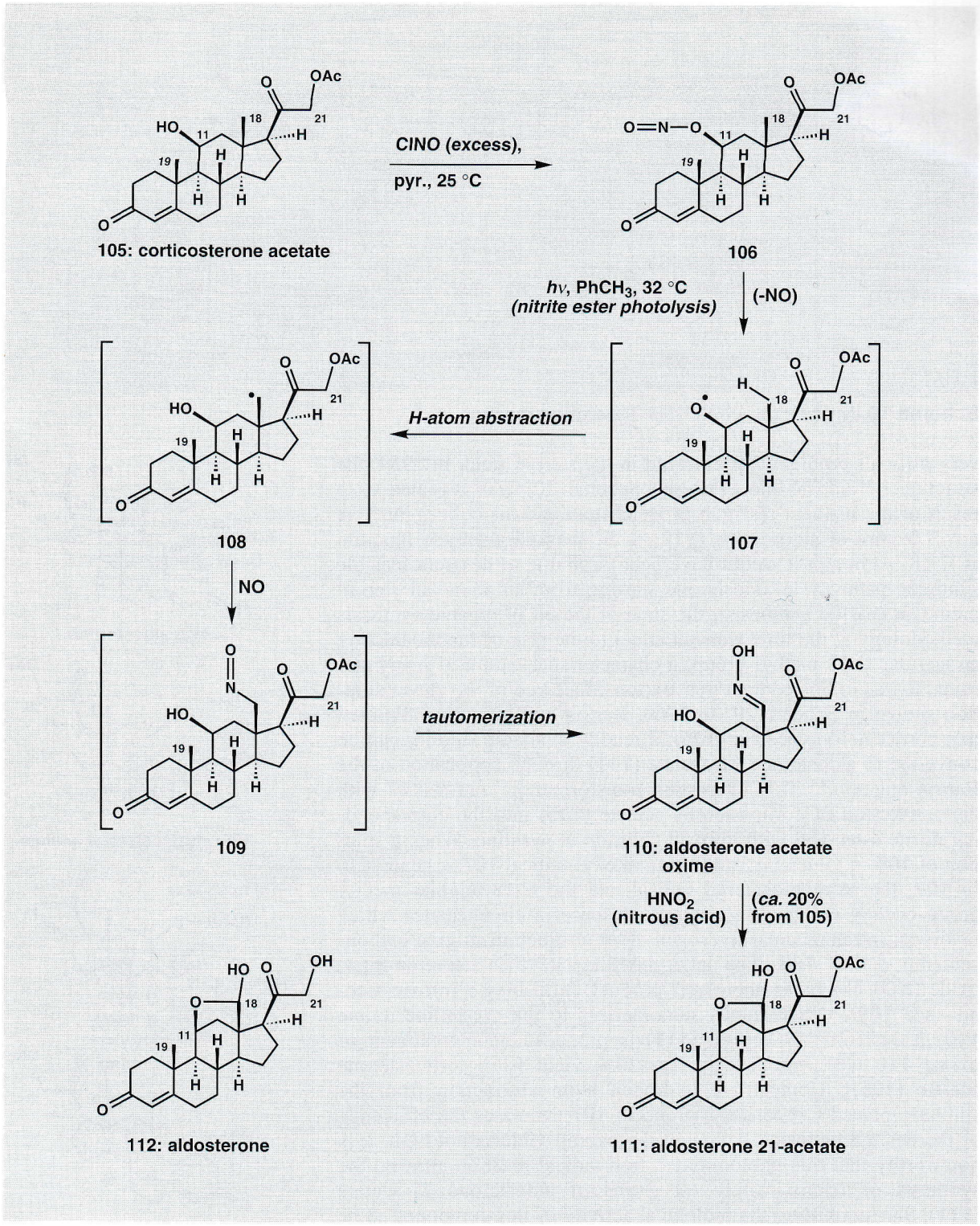


111: aldosterone 21-acetate

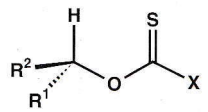


Scheme 20. The Barton synthesis of aldosterone 21-acetate (**111**).

aldosterone featuring the Barton reaction was subsequently reported by Barton et al.[45]

The use of the Barton reaction is not restricted to steroidal structures. For example, during the course of Magnus's total synthesis of grandisol (**117**) (see Scheme 21), it was found that alcohol **113** can be converted to lactol **116** in 51 % yield through the application of Barton's nitrite photolysis method (see **113** → **114** → **115** → **116**, Scheme 21).[46,47] A good substrate for a Barton reaction is one having a rigid framework with a carbon–hydrogen bond situated in proximity to an oxygen radical precursor (e.g. a nitrite ester); hydrogen atom abstraction occurs via a six-center transition state.

The affinity of a trialkyltin radical for the sulfur atom of a thiocarbonyl forms the basis of a particularly useful reaction in organic synthesis: the Barton–McCombie reaction (see Scheme 22).[48,49] In two steps, the Barton–McCombie reaction accomplishes the replacement of the hydroxyl group of an alcohol with a hydrogen, a functional group transformation of immense importance in organic synthesis. The popularity of this method derives from the facility with which secondary alcohols, even hindered secondary alcohols, can be deoxygenated. Scheme 22 illustrates the key features of the Barton–McCombie reaction. The first step is the production of a thioxoester derivative **118** through thioacylation of an alcohol with a suitable thiocarbonyl compound; a virtue of the Barton–McCombie reaction is that a variety of thioxoesters can be utilized.[50] In the second step, **118** is exposed to tri-*n*-butyltin hydride in refluxing toluene (xylene or *para*-cymene can also be used). Tri-*n*-butyltin radical, generated *in situ*, selectively attacks the thiocarbonyl sulfur atom of **118**,



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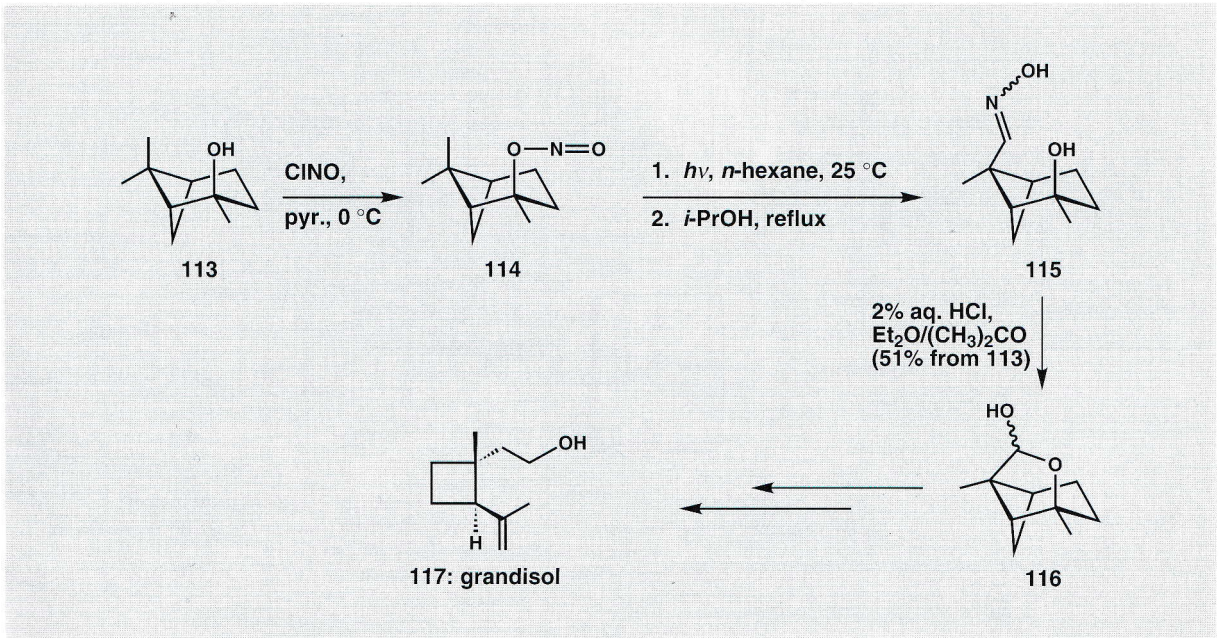
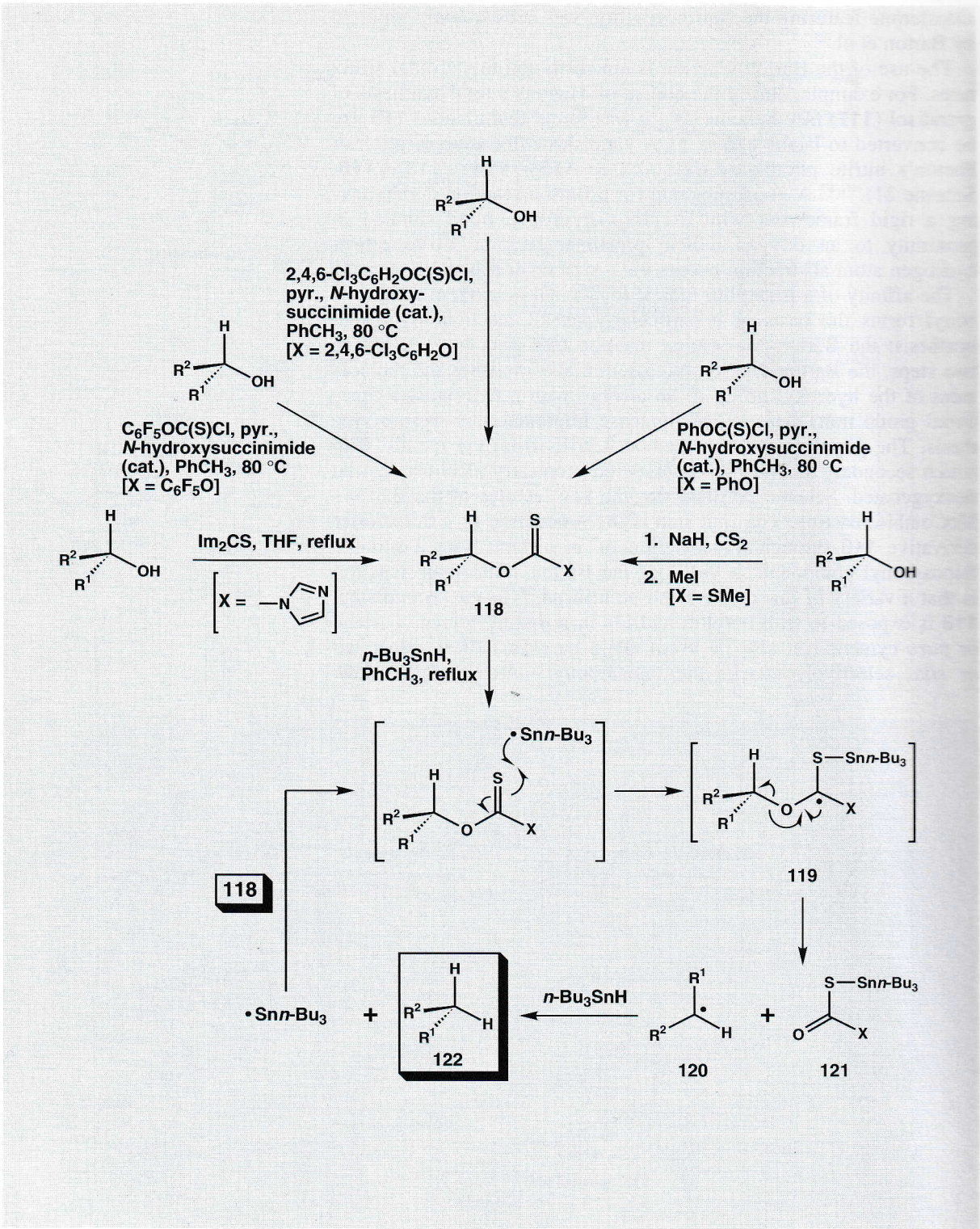


113 **114** **115** **116** **117: grandisol**

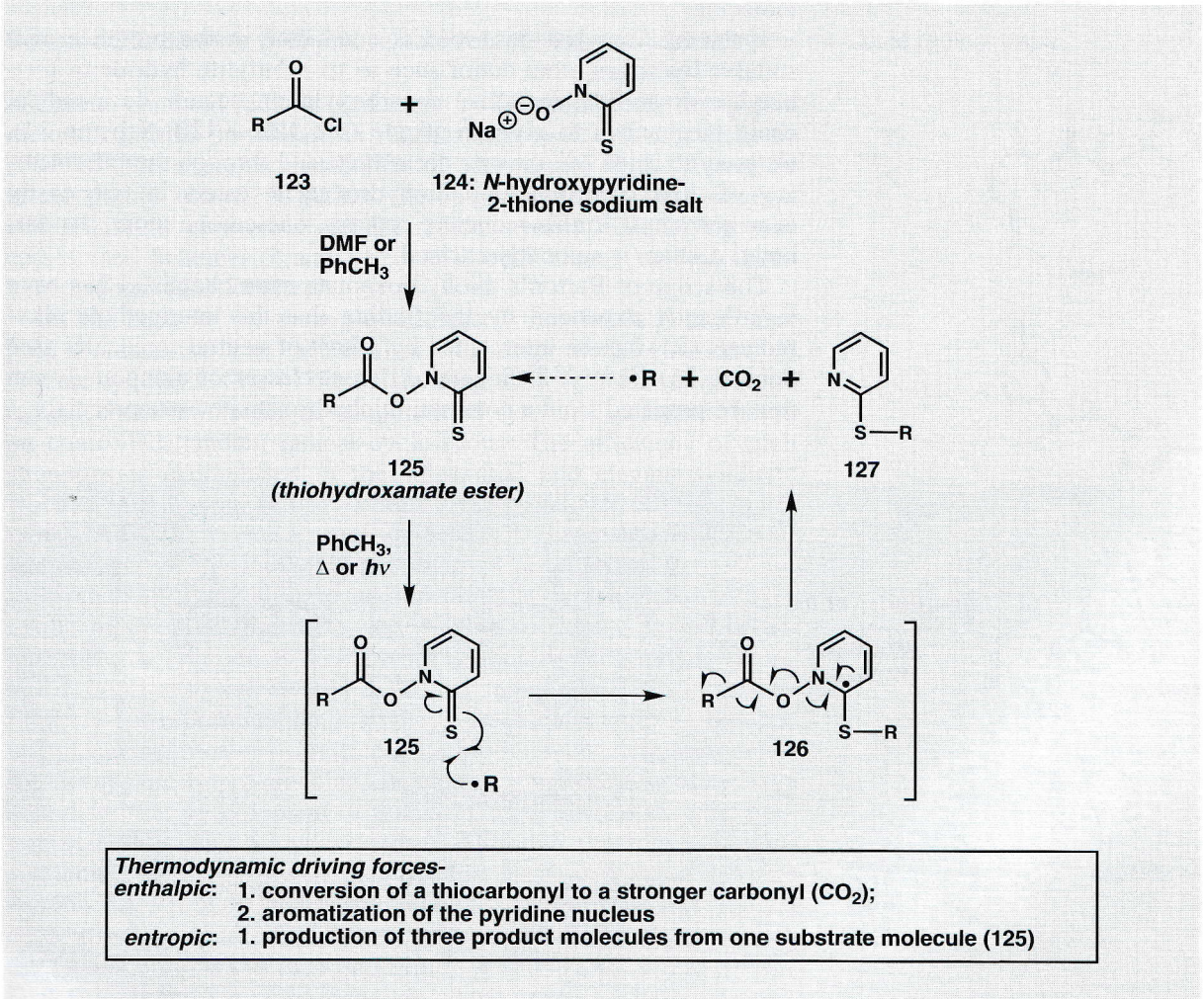
Scheme 21. The Barton reaction in Magnus's synthesis of grandisol (**117**).



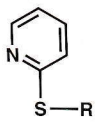
Scheme 22. The Barton–McCombie reaction [$R^1R^2CHOH \rightarrow R^1R^2CH_2$].

affording radical **119** which dissociates into two fragments, radical intermediate **120** and carbonyl compound **121**. Finally, carbon radical **120** abstracts a hydrogen atom from tri-*n*-butyltin hydride to give the reduced product **122** and n-$Bu_3Sn^{\bullet}$. The affinity of the tin radical for the thiocarbonyl sulfur atom in **118**, the overall conversion of a carbon–sulfur double bond to a stronger carbon–oxygen double bond, and the increase in entropy resulting from the dissociation of the intermediate radical **119** into two fragments are all driving forces for this valuable reaction.

In more recent studies, the Barton group has shown that *O*-acyl thiohydroxamates (thiohydroxamate esters) are convenient sources of alkyl radicals.[49c,51,52] Barton's thiohydroxamate ester chemistry is mild and easily executed, and the intermediate organic radicals are amenable to a wide variety of useful transformations. A thiohydroxamate ester of the type **125** (see Scheme 23) can be formed



Scheme 23. Barton's thiohydroxamate ester chemistry: synthesis of alkyl pyridyl sulfides (**127**).

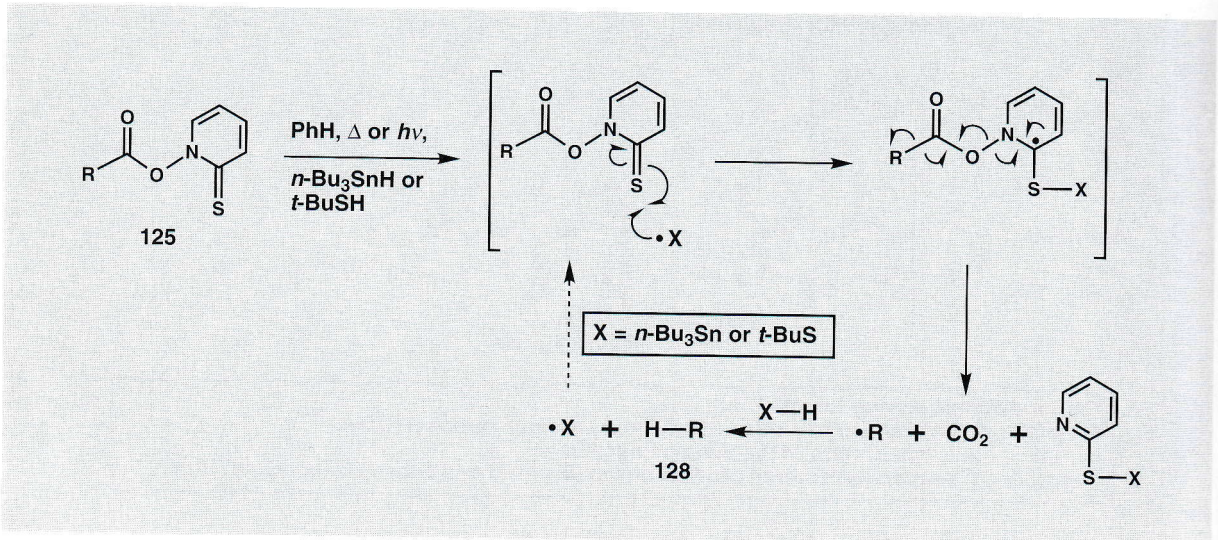


127

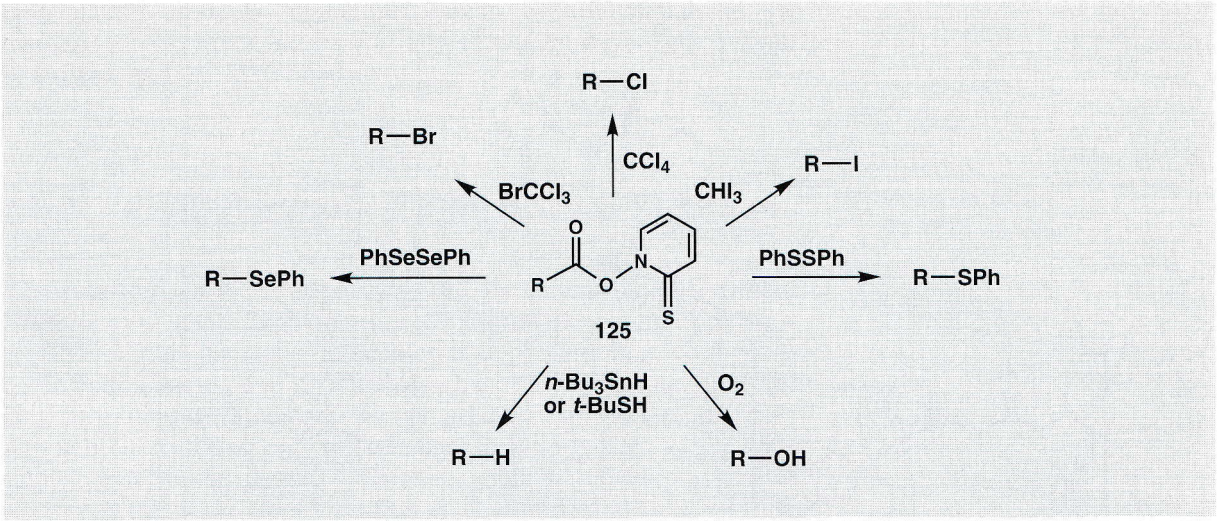
from the reaction of an activated carboxylic acid derivative, such as acid chloride **123**, with the commercially available sodium salt of *N*-hydroxypyridine-2-thione (**124**). If a solution of **125** in toluene is simply heated to reflux or irradiated with a tungsten lamp, an alkyl pyridyl sulfide of the type **127** can be produced in excellent yields. In this transformation, an alkyl radical (R•) formed by thermolytic or photolytic decomposition of thiohydroxamate ester **125** attacks the thiocarbonyl sulfur atom of **125** to give a new radical intermediate **126**. Concerted or stepwise fragmentation of **126** then results in the formation of CO_2, the alkylpyridyl sulfide **127**, and an alkyl radical (R•) which is available for reaction with another molecule of **125**. The formation of a strong carbon–oxygen π bond (CO_2) in exchange for a weaker carbon–sulfur π bond, and aromatization to the pyridine nucleus (**127**) provide powerful enthalpic driving forces for this fragmentation. The reaction is also favored entropically because three entities are formed from one substrate molecule.

If the reaction just described is conducted in the presence of a suitable hydrogen atom donor such as tri-*n*-butyltin hydride or *tert*-butyl hydrosulfide, reductive decarboxylation occurs via a radical chain mechanism to give an alkane (see **125** → **128**, Scheme 24). Carboxylic acids can thus be decarboxylated through the intermediacy of their corresponding thiohydroxamate esters in two easily executed steps. In this reductive process, one carbon atom, the carbonyl carbon, is smoothly excised.

The scope of Barton's thiohydroxamate ester chemistry has been significantly expanded by the finding that the intermediate alkyl radicals (R•) can be intercepted by a host of neutral molecules (see Scheme 25).[42b,49c,52,53] Several different classes of compounds can thus be prepared from a common thiohydroxamate ester precursor.



Scheme 24. Barton's thiohydroxamate ester chemistry: reductive decarboxylation.

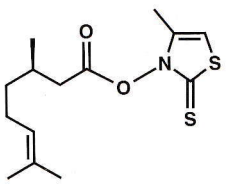


Scheme 25. Barton's thiohydroxamate ester chemistry: use of neutral molecule radical traps.

Carbon-centered radicals generated by Barton's thiohydroxamate method can also participate in ring-forming reactions (see Scheme 26).[52b,53] For example, irradiation of **129** results in the formation of compound **130** (82% yield). The outcome of this transformation is reminiscent of Stork's elegant radical cyclization/trapping processes (see Schemes 7 and 8), in that both alkene carbon atoms have become functionalized.

On the basis of the examples addressed thus far, it is clear that radical reactions can accomplish manifold transformations in organic synthesis. One of the outstanding achievements of synthetic radical chemistry is the development of synthetic strategies based on controlled, tandem radical cyclizations. The efficiency of such strategies is exemplified in the substantial and elegant synthetic work of D. P. Curran and his group.[54] The remainder of this chapter will address the concise total syntheses of (±)-hirsutene [(±)-**1**][55] and (±)-$\Delta^{9(12)}$-capnellene [(±)-**2**][56] by the Curran group.

A relatively large class of natural products is distinguished by a fusion of three cyclopentane rings. These tricyclopentanoid or triquinane natural products derive from various sources and are classified according to ring fusion as linear, angular, or propellane (see Figure 1 for representative examples). Triquinane natural products, many of which possess significant antibiotic and/or antitumor activity, occupy an important place in organic synthesis, for they have stimulated the development of numerous methods for the construction of condensed cyclopentanoids.[57] Although synthetic strategies that construct each ring of the tricyclic framework in a stepwise fashion have proven successful, those that employ tandem radical cyclizations are particularly powerful because they can accomplish the formation of more than one ring in a single step. As shown by D. P. Curran and his group, tandem radical or radical-initiated polyolefinic cyclizations are ideally suited for the synthesis of triqui-



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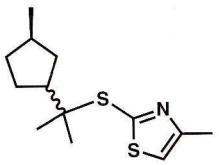

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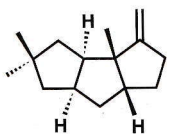
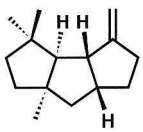
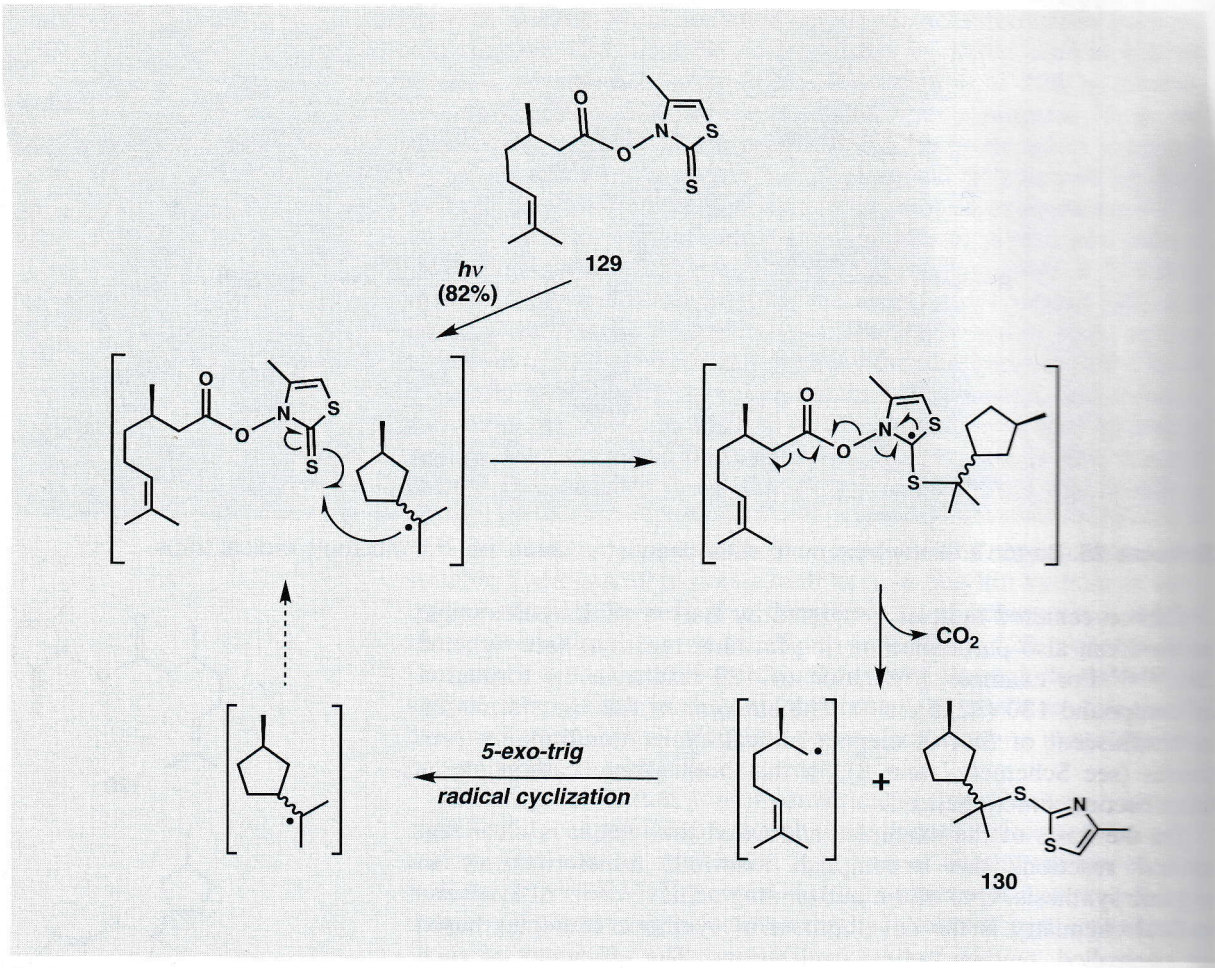


(±)-1: (±)-hirsutene



(±)-2: (±)-$\Delta^{9(12)}$-capnellene



Scheme 26. Barton's thiohydroxamate ester chemistry: construction of a carbon–carbon bond.

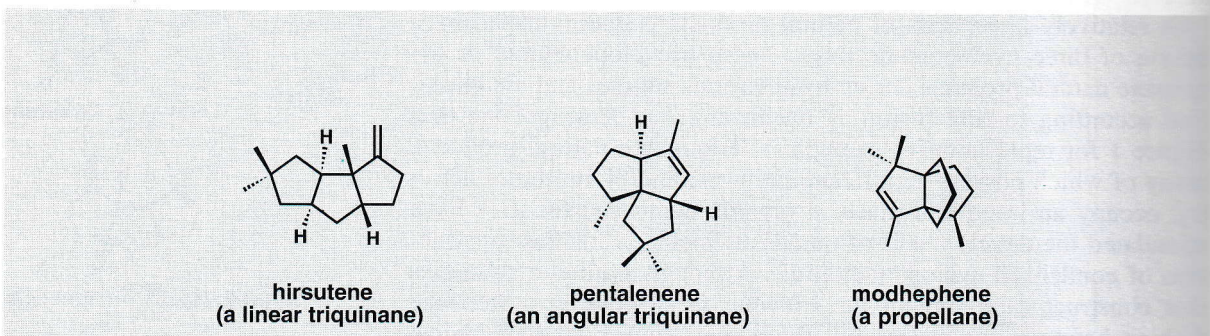
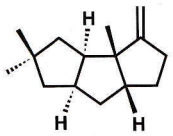


Figure 1. Representative linear, angular, and propellane triquinane natural products.

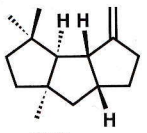
nane natural products. In the sections below, the details of the synthesis of (±)-hirsutene [(±)-**1**] and (±)-$\Delta^{9(12)}$-capnellene [(±)-**2**] by Curran et al. are described.

23.2 *Retrosynthetic Analysis and Strategy*

Hirsutene (**1**) and $\Delta^{9(12)}$-capnellene (**2**), the parent members of the hirsutane and capnellane families of triquinane natural products, respectively, are isomeric molecules that possess four contiguous stereogenic centers, one of which is quaternary. The linearly fused tricyclopentanoid frameworks of compounds **1** and **2** are obviously very similar, differing only with respect to the positions of the three methyl groups. An asset of Curran's tandem radical cyclization strategy is that it provides a unified entry into a wide variety of linear condensed cyclopentanoid natural products. As a result, it is possible to devise nearly identical retrosynthetic pathways for these structurally related molecules.

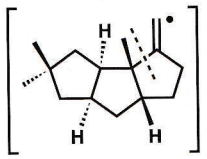


1: hirsutene



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

The key features of Curran's productive and elegant tandem radical cyclization strategy are illustrated in a retrosynthetic analysis for hirsutene (**1**) (see Scheme 27). The final synthetic event was projected to be an intermolecular transfer of a hydrogen atom from tri-*n*-butyltin hydride to the transitory tricyclic vinyl radical **131**. The latter can then be traced to bicyclic tertiary radical **132** and thence to monocyclic primary radical **133** through successive hex-5-enyl-like radical cyclizations. It was anticipated that the initial radical **133** could be generated through the abstraction of the iodine atom from **134** by tri-*n*-butyltin radical. According to this strategy, primary iodide **134**, a rather simple *trans*-disubstituted cyclopentene could be transformed directly into hirsutene by a radical-initiated tandem bicyclization process and a terminating hydrogen atom transfer. Two carbon–carbon bonds, two contiguous stereogenic centers, and two carbocyclic rings would be formed in this elegant transformation.



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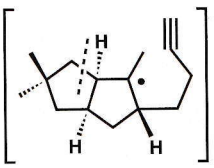

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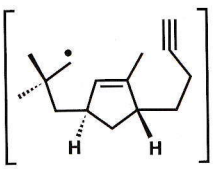
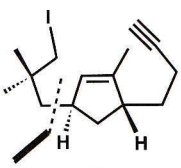


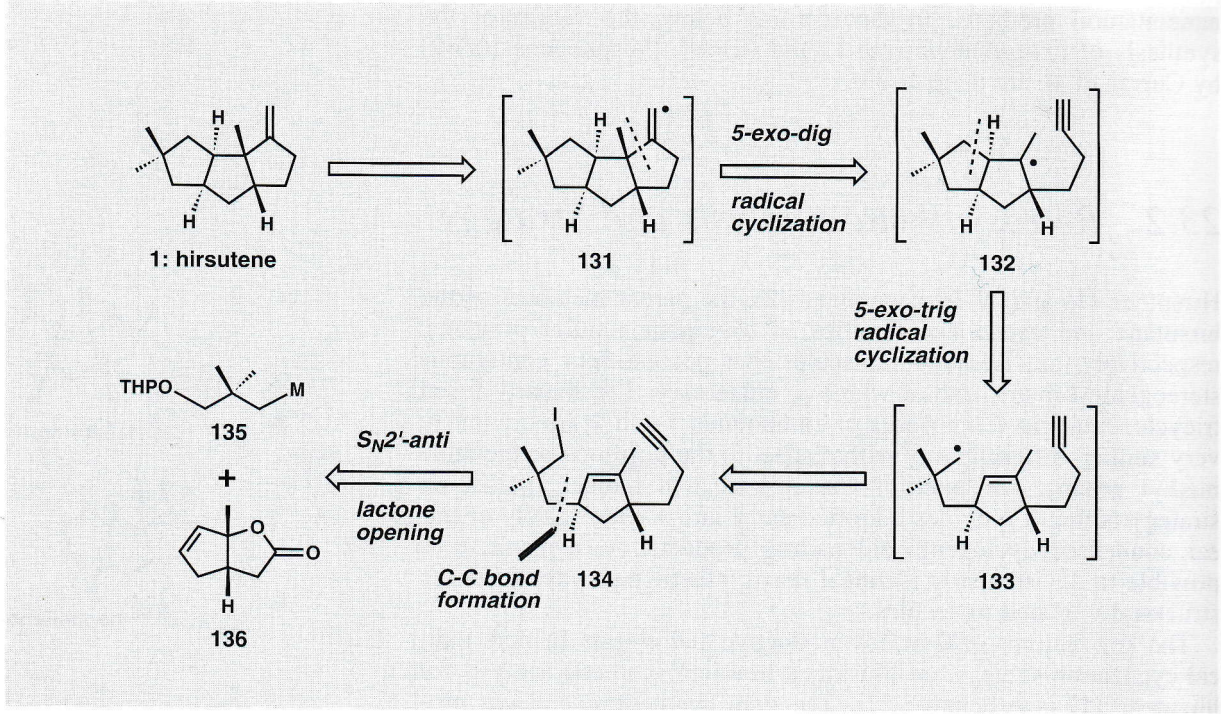
133

It is important to note here that both of the 5-*exo* radical cyclizations (**133** → **132** → **131**, Scheme 27) must proceed in a *cis* fashion; the transition state leading to a strained *trans*-fused bicyclo[3.3.0]octane does not permit efficient overlap between the singly occupied molecular orbital (SOMO) of the radical and the lowest unoccupied molecular orbital (LUMO) of the alkene. The relative orientation of the two side chains in the monocyclic radical precursor **134** is thus very significant because it dictates the relationship between the two outer rings (i.e. *syn* or *anti*) in the tricyclic product. The *cis-anti-cis* ring fusion stereochemistry of hirsutene would arise naturally from a cyclization precursor with *trans*-disposed side chain appendages (see **134**).



C-C bond formation **134**

trans-Disubstituted cyclopentene **134**, the projected radical precursor, can be traced retrosynthetically to organometallic reagent **135** and *cis*-fused bicyclic lactone **136**. In the synthetic direction,

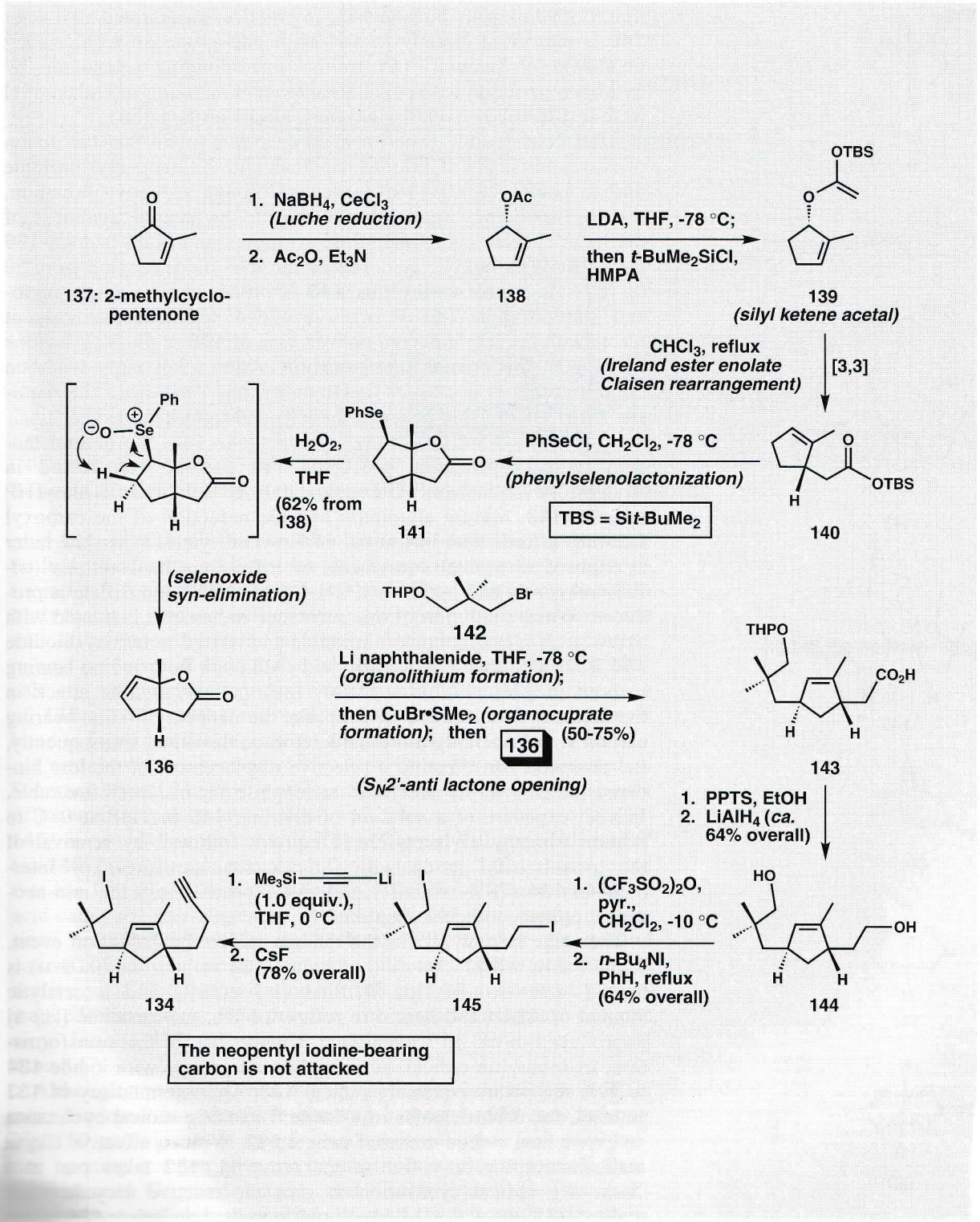


Scheme 27. Retrosynthetic analysis of hirsutene (**1**).

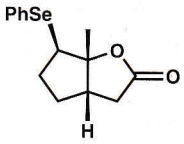
introduction of the left-hand side chain **135** by S_N2'-*anti* opening of vinyl lactone **136**, followed by standard manipulations, could furnish the penultimate intermediate **134**. The left-hand side chain in **134** possesses the initiating terminus for the tandem radical cyclization, while the terminal alkyne in the right-hand side chain constitutes the cascade terminator. The execution of Curran's total synthesis of (±)-hirsutene [(±)-**1**] and (±)-$\Delta^{9(12)}$-capnellene [(±)-**2**] based on this strategy is described below.

23.3 *Total Synthesis*

Schemes 28 and 29 illustrate Curran's synthesis of (±)-hirsutene [(±)-**1**]. Luche reduction[58] of 2-methylcyclopentenone (**137**), followed by acetylation of the resulting allylic alcohol, furnishes allylic acetate **138**. Although only one allylic acetate stereoisomer is illustrated in Scheme 28, compound **138** is, of course, produced in racemic form. By way of the powerful Ireland ester enolate Claisen rearrangement,[59] compound **138** can be transformed to γ,δ-unsaturated *tert*-butyldimethylsilyl ester **140** via the silyl ketene acetal intermediate **139**. In **140**, the silyl ester function and the methyl-substituted ring double bond occupy neighboring regions of space, a circumstance that favors a phenylselenolactonization reac-



Scheme 23. Curran's synthesis of (±)-hirsutene [(±)-**1**]: construction of intermediate **134**.



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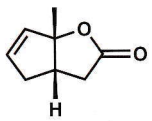

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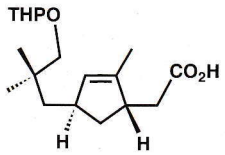

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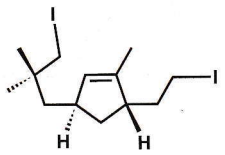


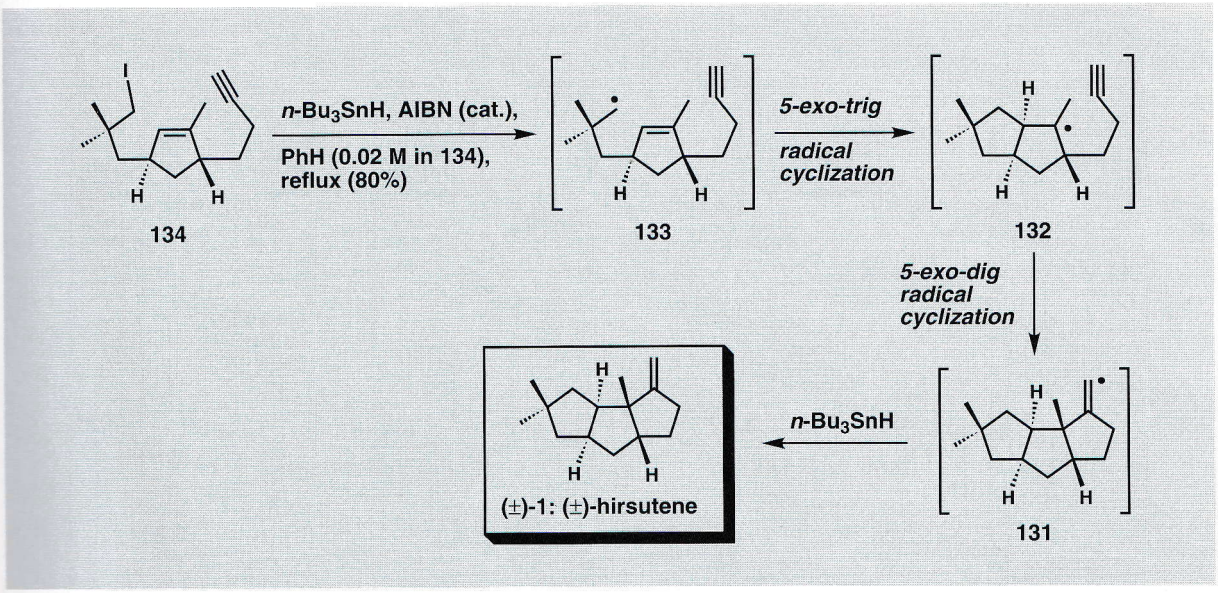
145

tion to give bicyclic lactone **141**. In practice, unsaturated silyl ester **140** is converted directly to **141** with phenylselenenyl chloride.[36] Oxidation of selenide **141** to the corresponding selenoxide by hydrogen peroxide with concomitant *syn* elimination provides vinyl lactone **136** (62 % overall yield from allylic acetate **138**).

After considerable experimentation, it was found that the action of two equivalents of lithium naphthalenide on neopentyl bromide **142** in cold (–78 °C) THF produces, through reductive lithiation, the corresponding organolithium reagent. Sequential treatment of the latter species with $CuBr{\bullet}SMe_2$ complex and vinyl lactone **136** then affords carboxylic acid **143** in variable yields ranging from 50 to 75 %. It is noteworthy that **143** is produced as a single regio- and stereoisomer. The *in situ* generated organocuprate reagent reacts with the less hindered convex face of **136** in the S_N2' lactone opening.[60] This crucial transformation creates a key carbon–carbon bond, introduces necessary functionality, and establishes the requisite *trans* relationship between the left- and right-hand side chains.

From *trans*-3,5-disubstituted cyclopentene **143**, the pivotal tandem radical cyclization precursor **134** can be constructed in straightforward fashion. After acid-catalyzed solvolysis of the THP ether in **143**, lithium aluminum hydride reduction of the carboxyl terminus affords diol **144** in ca. 64 % overall yield. When the latter is exposed to several equivalents of trifluoromethanesulfonic (triflic) anhydride and pyridine in CH_2Cl_2 at –10 °C, a ditriflate is produced. When a solution of this substance in benzene is treated with excess tetra-*n*-butylammonium iodide and heated to reflux, diiodide **145** is formed in 64 % overall yield. Although both iodine-bearing carbons in **145** could conceivably undergo nucleophilic attack in the presence of a reactive nucleophile, the neopentyl iodine-bearing carbon is considerably more hindered than the other. Consequently, the prospects for effecting a selective displacement of the less hindered iodide with an acetylide nucleophile seemed very favorable. Indeed, exposure of a solution of diiodide **145** in THF at 0 °C to lithium trimethylsilylacetylide (1 equiv.), followed by removal of the trimethylsilyl group with fluoride ion, furnishes key intermediate **134** (78 % overall yield). As expected, only the non-neopentyl primary iodide is displaced.

The stage is now set for the tandem radical bicyclization event. Remarkably, when a solution of iodide **134** in benzene (0.02 M) is treated with tri-*n*-butyltin hydride (1.3 equiv.) and a catalytic amount of AIBN and heated to reflux for 1 h, (±)-hirsutene [(±)-**1**] is produced in ca. 80 % yield (see Scheme 29). In this transformation, tri-*n*-butyltin radical, generated *in situ*, reacts with iodide **134** to give the putative primary radical **133**. The intermediacy of **133** is brief, for it participates in a facile 5-*exo*-*trig* radical cyclization to give a new carbon-centered radical **132**. With an effective alkyne radical acceptor only five atoms removed, **132** takes part in a 5-*exo*-*dig* radical cyclization to give the reactive tricyclic vinyl radical **131**; the action of tri-*n*-butyltin radical on iodide **134** brings about successive chain-to-ring and ring-to-chain cyclizations to



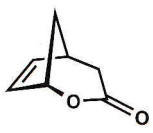
Scheme 29. Synthesis of (±)-hirsutene [(±)-**1**] by tandem radical cyclizations.

give **131**. Finally, abstraction of a hydrogen atom from tri-*n*-butyltin hydride affords (±)-hirsutene [(±)-**1**] and regenerates tri-*n*-butyltin radical. As expected, both 5-*exo* radical cyclizations proceed in a *cis* fashion. The *cis-anti-cis*-stereochemistry present in hirsutene thus arises naturally from the *trans*-3,5-disubstituted cyclopentene radical precursor. It should also be noted that although tertiary radicals are more stable than vinyl radicals, the 5-*exo-dig* cyclization of **132** is still exothermic and fast, because a carbon–carbon σ bond is formed at the expense of a weaker carbon–carbon π bond.

Curran's synthesis of (±)-$\Delta^{9(12)}$-capnellene [(±)-**2**] is detailed in Schemes 30 and 31. This synthesis commences with the preparation of racemic bicyclic vinyl lactone **147** from (±)-norbornenone [(±)-**145**] by a well-known route.[61] Thus, Baeyer–Villiger oxidation of (±)-**145** provides unsaturated bicyclic lactone **146**, a compound that can be converted to the isomeric fused bicyclic lactone **147** by acid-catalyzed rearrangement. Reaction of **147** with methylmagnesium bromide/CuBr•SMe_2 in THF at –20 °C takes the desired course and affords unsaturated carboxylic acid **148** in nearly quantitative yield. Iodolactonization of **148** to **149**, followed by base-induced elimination, then provides the methyl-substituted bicyclic vinyl lactone **150** as a single regioisomer in 66% overall yield from **147**.

Although the methyl-bearing sp^2-hybridized carbon in **150** is more hindered than the corresponding carbon in **136** (see Scheme 28), **150** participates in a regio- and stereoselective S_N2'-*anti* lactone opening reaction with the organocuprate reagent formed from the indicated Grignard reagent and CuBr•SMe_2.[62,63] This S_N2' addition accomplishes the introduction of the left-hand side chain and the requisite quaternary stereocenter. The desired unsaturated

(±)-145: (±)-norbornenone



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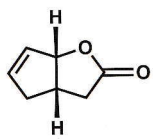

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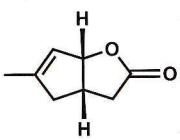

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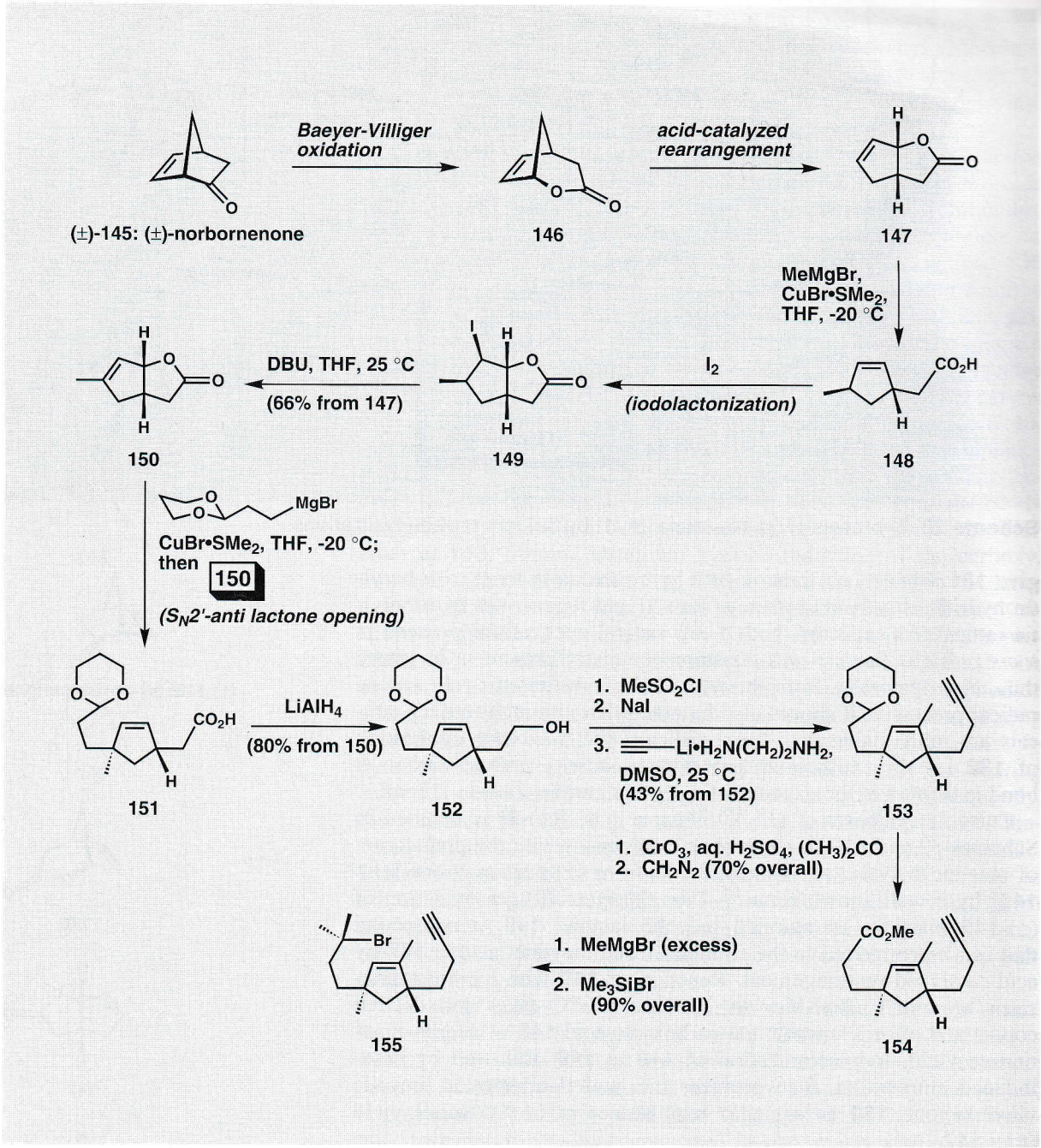
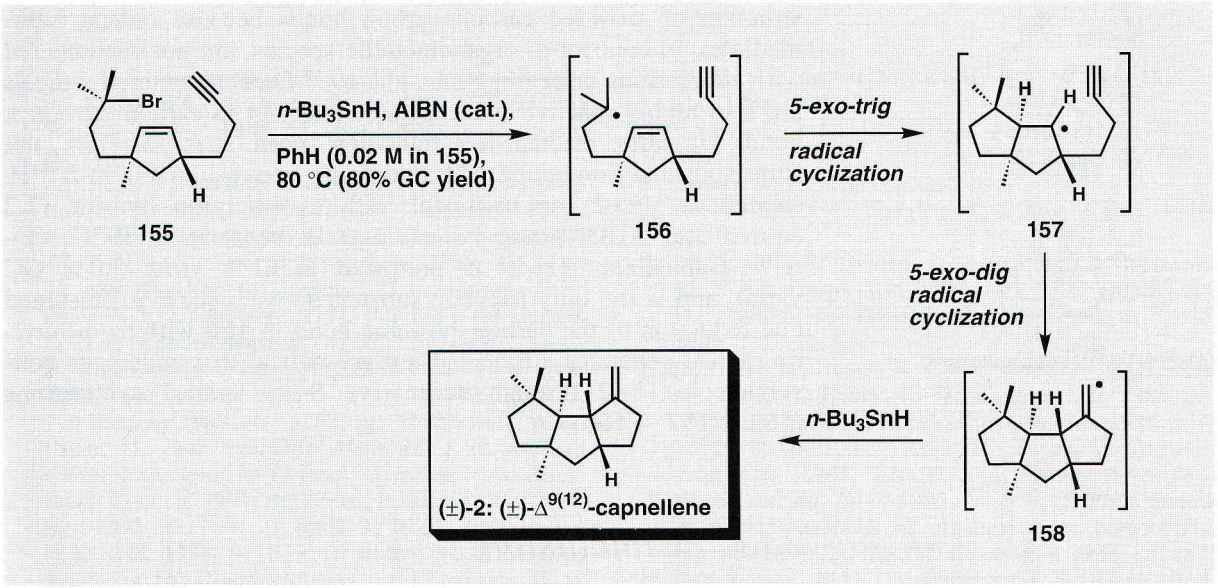


Scheme 30. Curran's synthesis of (±)-$\Delta^{9(12)}$-capnellene [(±)-**2**]: construction of intermediate **155**.

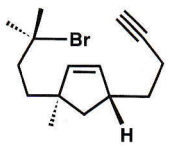


Scheme 31. Synthesis (±)-$\Delta^{9(12)}$-capnellene [(±)-**2**] by tandem radical cyclizations.

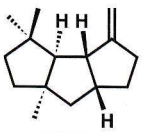
carboxylic acid **151** is obtained in high yield together with a small amount (ca. 10%) of a regioisomeric substance produced by nucleophilic attack at the carbon bearing the lactone ring oxygen (S_N2 opening). To facilitate isolation, the crude mixture of regioisomeric acids was directly reduced with lithium aluminum hydride and the resulting alcohols were separated chromatographically. In this way, the desired alcohol **152** can be obtained in 80% yield from vinyl lactone **150**.

From **152**, the synthesis of the tandem radical cyclization precursor **155** only requires a few manipulations of the two side chains. To this end, treatment of primary alcohol **152** with methanesulfonyl chloride, followed by displacement of the resulting mesylate with iodide ion, provides the corresponding primary iodide. Reaction of the latter substance with lithium acetylide/ethylene diamine complex in DMSO at 25 °C then furnishes alkyne **153** in 43% yield from **152**. Under the conditions of a Jones oxidation, the dioxane acetal is hydrolyzed and the resulting aldehyde is oxidized to the corresponding carboxylic acid. Esterification of the newly formed carboxyl group with diazomethane (CH_2N_2) then gives methyl ester **154** in 70% overall yield. In the presence of excess methylmagnesium bromide, **154** undergoes conversion to a tertiary alcohol that can subsequently be converted to tertiary bromide **155** with trimethylsilyl bromide (90% overall yield). Since compound **155** was difficult to purify by chromatography, it was used in the next step in crude form.

A most attractive feature of radical reactions that recommends their use in the synthesis of complex molecules is that steric crowding, particularly on the radical center, is tolerated in many instances. Indeed, radical reactions are ideally suited for the con-



155



(±)-2: (±)-$\Delta^{9(12)}$-capnellene

struction of crowded carbon–carbon bonds because radical mediates, in contrast to organometallic species, are not encu with counterions or aggregation spheres.[3d] Carbon-centered r are also highly reactive intermediates that add to carbon–ca bonds via early, reactant-like transition states. It is, therefo surprising that compound **155** undergoes conversion to (±)- capnellene [(±)-**2**] on treatment with tri-*n*-butyltin hydrid equiv.) and AIBN (catalytic amount) in benzene at 80 °C $\Delta^{9(12)}$-Capnellene [(±)-**2**] is produced in 61 % yield (80 yield), and is the only tricyclic substance observed. It is pre that reduction of the carbon–bromine bond in **155** with tri-*n* tin radical generates a transient tertiary radical that undergoe version to (±)-**2** through successive 5-*exo* radical cycli (**156** → **157** → **158**).

23.4 Conclusion

Fundamental research in physical organic chemistry unc many of the characteristics of radical reactions and stim impressive advances in organic synthesis in the 1980s. In this ter, an attempt has been made to highlight some of the featu radical reactions that make them ideally suited for applicati organic synthesis. Through the application of radical che valuable functional group transformations and challenging c carbon bond constructions can be achieved under unusuall reaction conditions. The elegant contributions of D. P. Curra others demonstrate that a prudent sequence of elementary reactions can create powerful, one-pot strategies for the sy of complex polycyclic molecules. Indeed, tandem or seq radical cyclizations can offer exceedingly concise solutions t lenging problems in organic synthesis.[64]

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