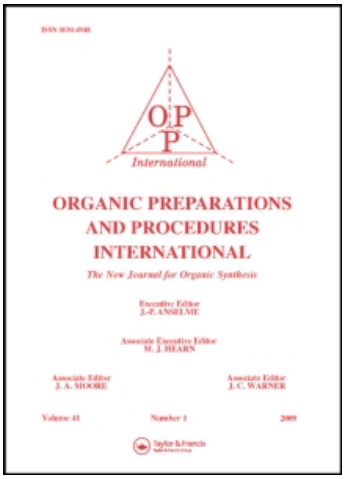

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RECENT DEVELOPMENTS IN THE AREA OF ANNDLATED FURANS. A REVIEW

Albert Padwa[a]; S. Shaun Murphree[ab]
[a] Department of Chemistry, Emory University, Atlanta, GA [b] Department of Chemistry, Wesleyan University, Middletown, CT

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*Albert Padwa**

Department of Chemistry
Emory University, Atlanta, GA 30322

S. Shaun Murphree

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INTRODUCTION

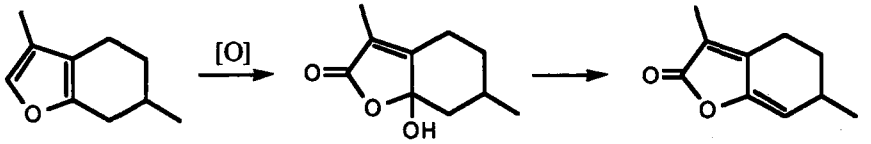
Fused polycyclic furans have continued to hold a fascination for the synthetic organic chemist for many decades. The furan nucleus occurs in a variety of natural products from both land and marine sources[1], with 2,3- and 3,4-substitution being most commonly found in nature. Furans are also useful synthetic intermediates, as they participate in inter- and intramolecular Diels-Alder reactions and may be converted by oxidation to a variety of products.[2] A well-studied class of compounds, the annulated furans can boast a daunting number of biologically significant members, some known since antiquity.[3] Various types of sesqui- and diterpenes contain an annulated furan ring as a common structural feature. Some prominent members of this class of compounds are the paniculides[4], the cytotoxic furanonaphthoquinones[5], as well as furodysin and furodysinin.[6] In most of the synthetic routes to annulated furans, the furan ring is assembled onto an existing cyclic backbone.[7] Other methods start with a functionalized furan as a template for the attachment of additional rings. Certainly, there is no paucity in the variety or quantity of approaches by which these compounds have been prepared. Indeed, this area of organic synthesis has been consistently well-documented by ample review articles.[8] However, during the past five years a sufficient body of interesting and novel chemistry has been reported in relation to this topic that a brief compilation is in order.

Annulated furans define a broad category encompassing a variety of structural features (i.e., benzofurans, naphthofurans, etc.) containing any number of degrees of unsaturation. However, for the purposes of this work, discussion will be limited to substrates containing a fully oxidized furan nucleus which is fused to a more or less saturated ring. Inasmuch as these compounds are most often encountered as synthetic targets, emphasis will be placed upon their preparation, with further reactions being discussed when appropriate.

I. NATURAL PRODUCTS SYNTHESIS

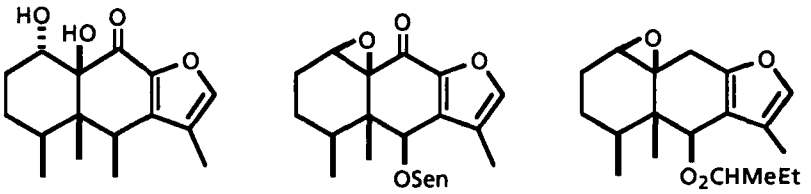
The antibiotic, antifeedant, and antitumor activity long associated with the furano-eremophi-

lanes[9] is believed to derive from their biogenetic oxidation to the corresponding sesquiterpene lactones, or eremophilides[10]. This oxidation is known to occur readily *in vitro*, as illustrated by the autoxidation of tetrahydrobenzofuran (**1**) to the butenolide (**2**).[11]



1 **2**

Despite the large body of naturally occurring furan compounds which have already been catalogued[12], new entries continue to be added, as exemplified by recent reports of the isolation of novel furanoeremophilanes from the leaves of *S. andreuxii* (**3** and **4**)[13] and *S. doria* (**5**)[14]. Crews and coworkers have recently demonstrated that some *Dysidea* extracts have quite significant anti-helminthic properties attributable to furanoid compounds[15], an observation which has caused renewed interest in the synthesis of naturally occurring furans.



3 **4** **5**

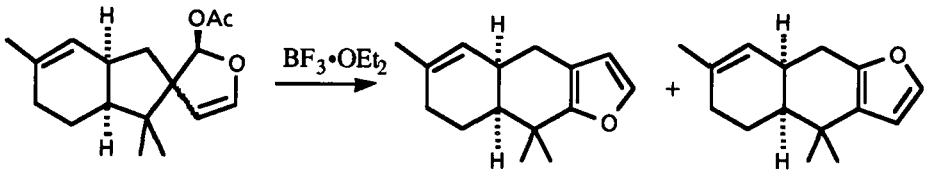
The furanosesquiterpenes can be classified into two major divisions: (a) 2,3-fused systems, as in **6** (to which the eremophilanes belong), and (b) 3,4-fused systems, as in **7** (to which the drimanes belong). The synthetic approaches toward these two classes are, in general, distinct, and therefore will be discussed separately.

6 **7**

a) 2,3-Fused Systems

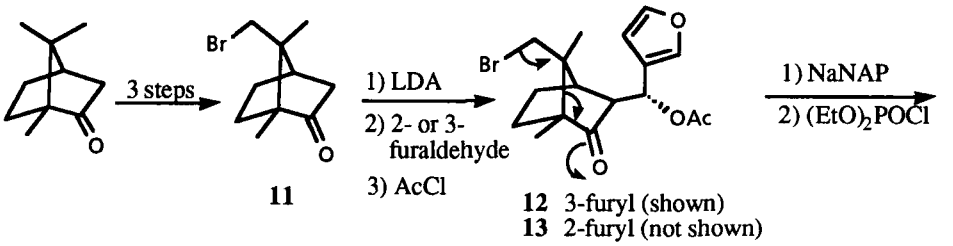
One synthetic approach toward the 2,3-fused furan moiety echoes biosynthetic mechanisms, namely cationic processes. For example, the two natural products furodysin (**9**) and furodysinin (**10**) are believed to arise from the same biogenetic precursor, spirodysin (**8**), through a 1,2-carbon-bond migration.[16] The conversion of **8** to an equimolar mixture of **9** and **10** upon treatment with boron

trifluoride etherate demonstrates the viability of this process.[17]

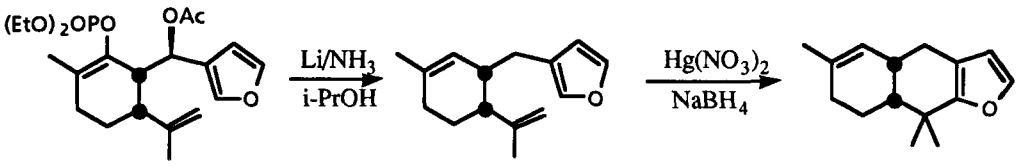


8 **9** **10**

Albizati and coworkers[18] have developed a synthesis of **9** and **10** based upon a related process, wherein the ultimate step is a mercuric ion assisted cationic cyclization, the course of which is dictated by the position of the tether on the furan nucleus. The two isomeric precursors (**16** and **17**) are derived from a common precursor, 9-bromocamphor (**11**). Aldol condensation onto 3-furaldehyde (in the synthesis of furodysin) or 2-furaldehyde (in the synthesis of furodysinin) gives rise to a substituted camphor derivative (**12** or **13**), which suffers a novel Grob fragmentation to provide a suitably arranged intermediate (**14** or **15**). In this way camphor was used as an effective chiral pool element for six-membered rings annulated onto the furan nucleus.



12 3-furyl (shown)
13 2-furyl (not shown)



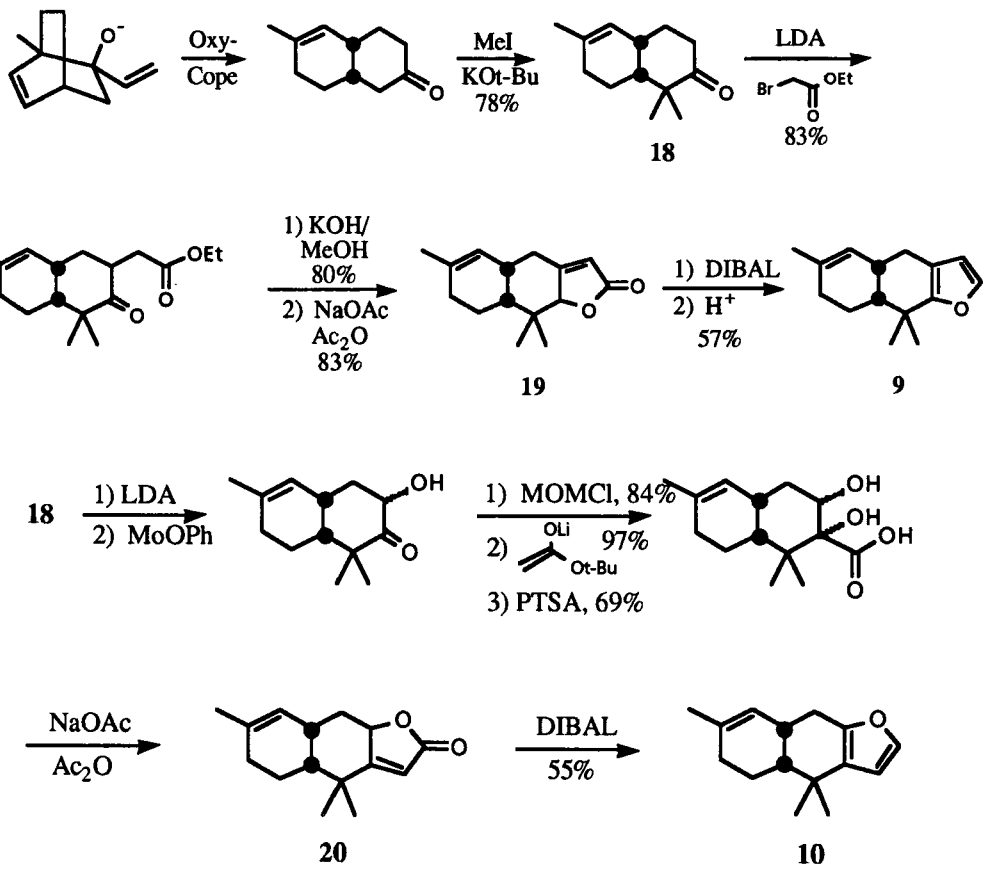
14 3-furyl (shown)
15 2-furyl (not shown)

16 3-furyl (shown)
17 2-furyl (not shown)

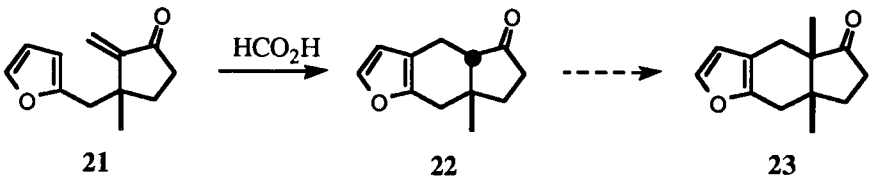
9

Hirota and coworkers[19] also published a synthesis of furodysin and furodysinin using the bicyclic ketone **18** as a common precursor. In this case the furan nucleus is annulated onto the ketone functionality *via* the butenolides **19** and **20**, which are reduced using DIBAL to give furodysin (**9**) and furodysinin (**10**), respectively.

Sesquiterpenes of the pinguisane class have recently attracted interest because of their biological activity and rare carbon skeleton.[20] A simple synthesis of norpinguisone (**23**) from 2,3-



dimethylcyclopentenone was recently described.[21] The key step involves an uncommon furan β-terminated cationic cyclization employing an enone system as the initiator. The resultant *cis*-indane system of **22** exhibits less torsional strain and is therefore more stable than the alternative *trans* isomer. Furan **22** was converted to norpinguisone **23** in four additional steps in 47% overall yield.

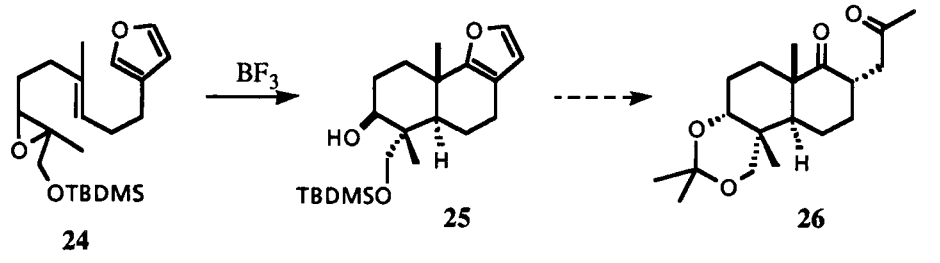


21 **22** **23**

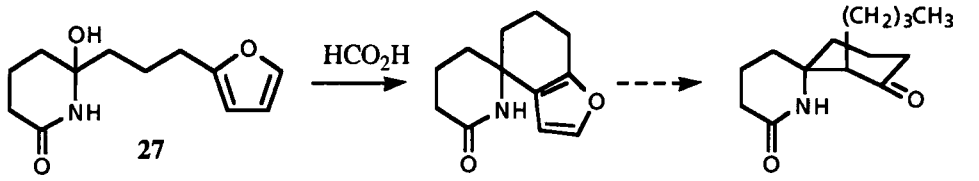
Tanis and co-workers have taken advantage of a cationic cyclization in the formal synthesis of the natural products (+)-aphidocolin[22] and perhydrohistrionicotoxin[23]. In these cases, the furan ring is not present in the final target, but rather serves as a template with which to conveniently capture an electrophilic center. In the aphidocolin synthesis, the epoxide intermediate **24** is induced to undergo a polyolefin-type cyclization to produce the tricyclic furan **25**, which is converted into the target inter-

mediate **26**, in which the latent functionality of the furan nucleus has been unmasked. In the case of the perhydrohistrionicotoxin precursor **29**, ring formation is accomplished by attack of the furan at the 3-position onto an incipient iminium species (which is generated by treatment of hydroxyamide **27** with formic acid) to form the spirotricyclic intermediate **28**.

Bicyclo[5.3.0]decane subunits occur in nature as integral parts of complex bioactive natural products such as guaianolides and pseudoguaianolides.[24] These compounds, with their often daedal

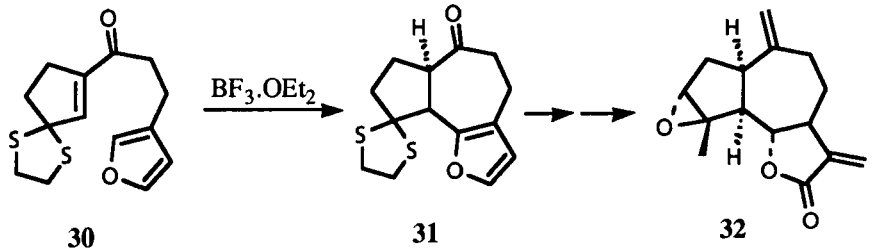


24 **25** **26**



27 **28** **29**

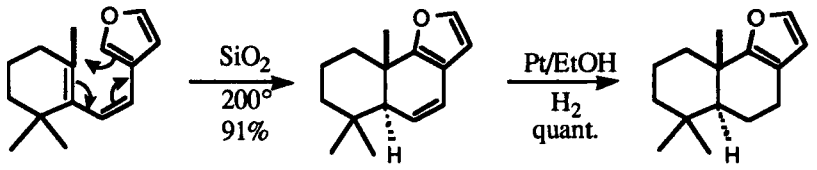
array of functional groups and stereocenters, have attracted considerable attention from the chemical community, due in large part to potent and diverse biological activities which have been associated with various members of these classes. One interesting approach toward the synthesis of these molecules makes use of a furan as a terminator function in cationic cyclization sequences[25]. The furan ring supplies the requisite double bond equivalent, enabling the β-ring to adopt a stable chair conformation, insuring the correct stereochemistry, and yielding the desired butyrolactone after



30 **31** **32**

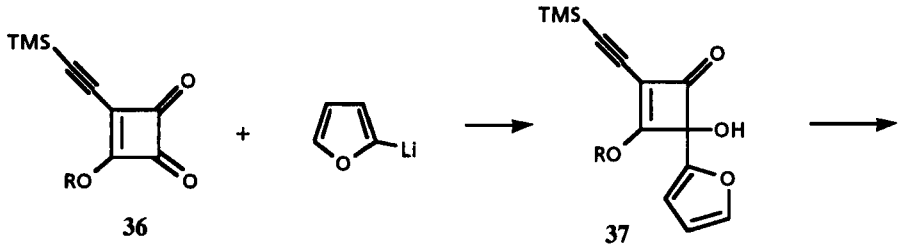
chemical manipulation. Enone **30** was smoothly cyclized with $BF_3.OEt_2$ to provide the *trans* fused furan **31**, which contains the necessary architecture for conversion to the functionally and stereochemically more complex pseudoguaianolide ring system **32**.

The synthesis of furan-containing natural products is by no means limited to the use of such cationic cyclizations. Indeed, many other novel approaches to this structural unit have been brought to light in the immediate past. For example, Liotta and Ott have carried out furannulation by a 6π-electrocyclization reaction (i.e **33**→**34**) in their synthesis of pallescensin A (**35**).[26]

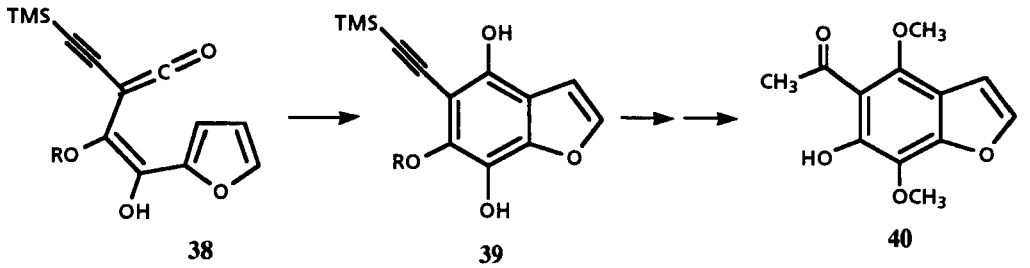


33 **34** **32** **35**

Natural products in the furocoumarin series have been isolated from a variety of plant sources and classified as phytoalexins.[27] A novel and efficient synthesis of furochromone natural products has recently been described by Moore and Reed and involves the thermal rearrangement of



36 **37**

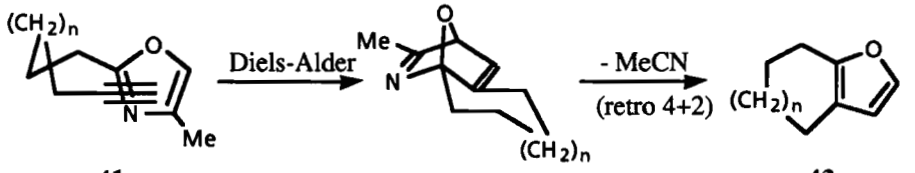


38 **39** **40**

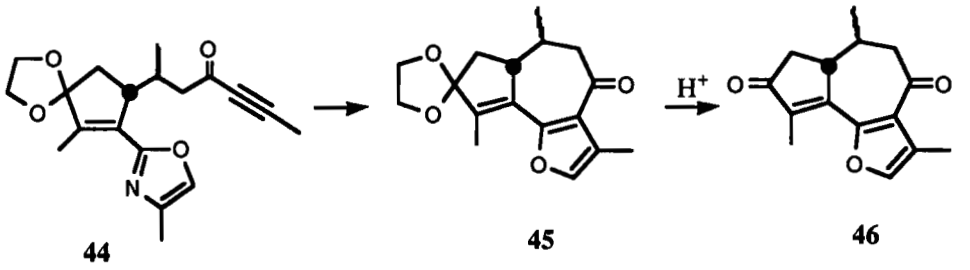
a 4-furyl-4-hydroxycyclobutenone.[28] Cyclobutenedione **36** was converted to the highly functionalized benzofuran **39**, which served as an intermediate in a high yielding synthesis of khellinone (**40**), a versatile precursor to a variety of linear furochromones, including the natural product khellin.

Jacobi and co-workers have published a series of concise natural product syntheses utilizing 2-substituted oxazoles (e.g., **41**) as key intermediates. Engaging such substrates in intramolecular Diels-Alder reactions with tethered alkynes as dienophiles produces aza-bicyclo[2.2.2]octenes (e.g.,

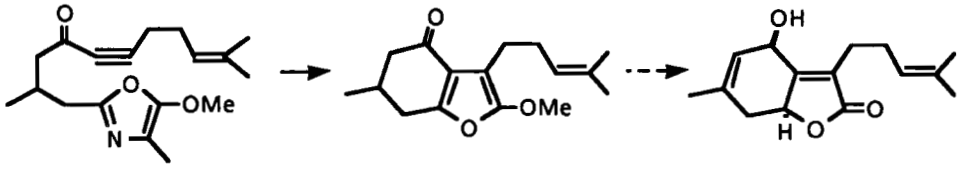
42), which undergo subsequent retro Diels-Alder reaction and expulsion of acetonitrile to give annulated furans (e.g., 43). In this fashion the B and C rings of gnididione (46) were formed in one step



41 42 43



44 45 46



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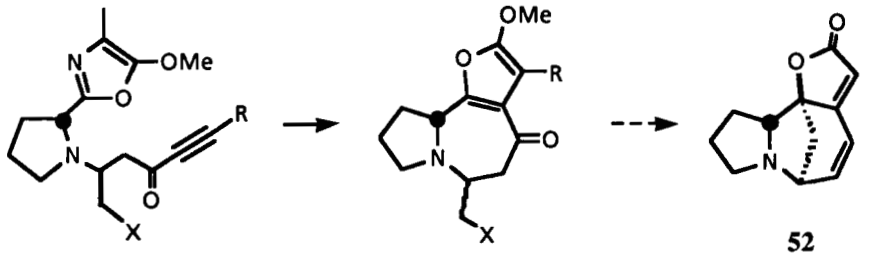
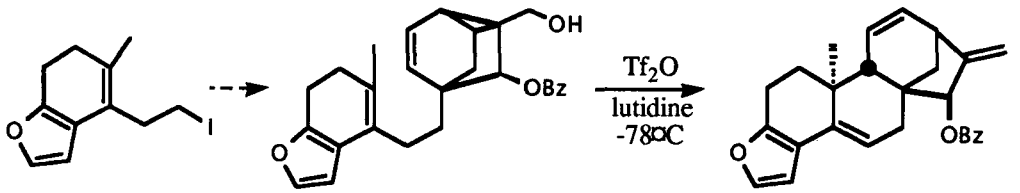


50 51 52

upon thermolysis of oxazole 44.[29] This methodology has also been used in the synthesis of a paniculide *A* precursor (49)(*via* 47 and 48)[30] and in the stereospecific synthesis of both enantiomers of norsecurinine (52) (*via* 50 and 51)[31].

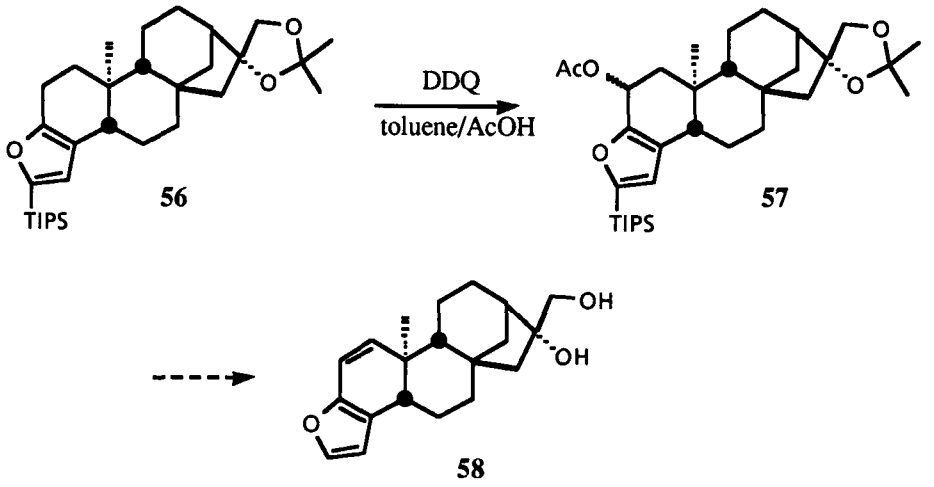
Corey and co-workers[32] have recently published a stereospecific total synthesis of (±)-cafestol, representing the first synthesis of one of the "coffee" diterpenoids. This approach relies upon the stereospecific cyclization of the fused vinyl furan 54 (available by the alkylation of the iodo

derivative **53**) to the pentacycle **55**. The cyclization proceeds with ease, even at low temperatures, owing to the reactivity of the vinyl furan functionality.



53 **54** **55**

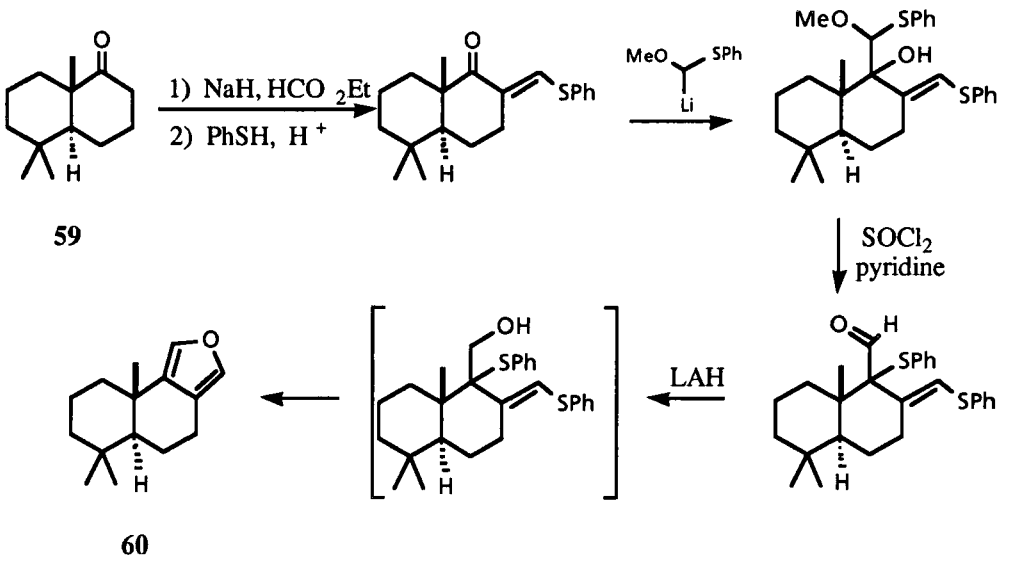
In a subsequent publication,[33] this same group described a novel "*off-ring*" functionalization of annulated furans in their synthesis of kahweol from the aforementioned cafestol. With the furan 5-position protected as the silyl derivative (as in **56**), the methylene position adjacent to the furan ring is smoothly oxidized using DDQ to produce acetate **57**, which was subsequently converted to kahweol (**58**) in two additional steps.



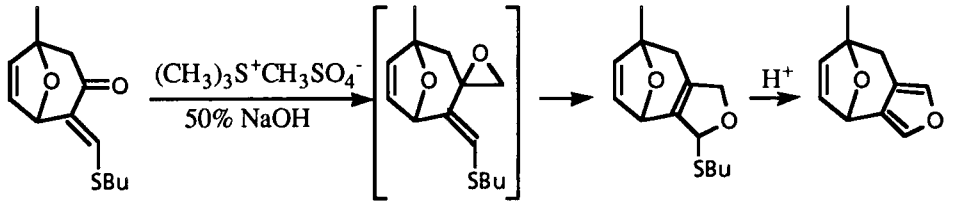
56 **57** **58**

b) 3,4-Fused Systems

Somewhat eclipsed by the activity surrounding the 2,3-fused systems, the 3,4-annulated furans are also of synthetic interest. Occupying one of the highest ranks among this class are the drimanes, of merit because of their potent insect antifeedant activity.[34] A recent synthetic entry into the drimanes has been described by de Groot and co-workers[35] using a furannulation strategy. Substituted and/or fused cyclic ketones were modified by a sequential one-carbon addition, followed by heterocyclization, to afford the 3,4-annulated furan ring system. This methodology has been applied to the total synthesis of euryfuran (**60**), starting from the bicyclic ketone **59**.

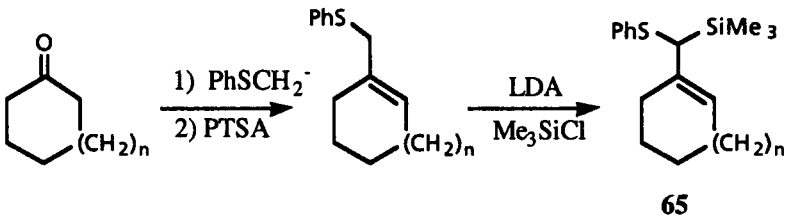


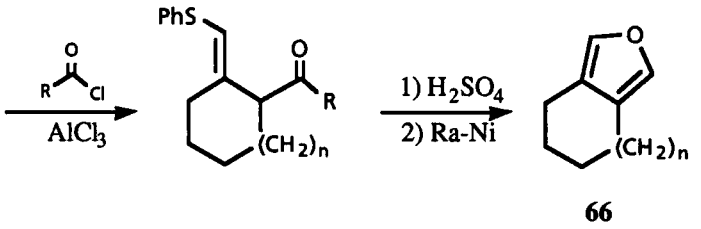
Treatment of cyclic thiomethylene ketones (e.g. **61**) with trimethylsulfonium methylsulfate under phase-transfer conditions leads to the formation of spirooxiranes (e.g. **62**)[36]. These compounds spontaneously isomerize to dihydrofurans (e.g. **63**) at room temperature. Elimination of the alkyl sulfide provides the annulated furans (e.g. **64**).

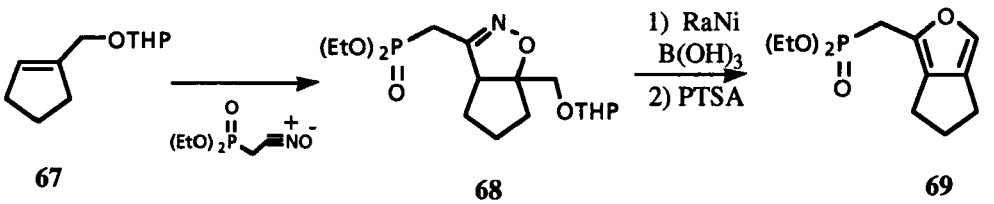


Hiroi and Sato[37] have reported a related approach, similar in concept but distinct in detail. This methodology hinges upon the introduction of a furanogenic carbon *via* the regioselective acylation of phenylthioallylsilanes **65**. Cyclization followed by desulfurization yields annulated furans **66**. Inasmuch as acyl chlorides of various composition are readily available, this method has the advantage of allowing facile introduction of substitution at the furan 2-position.

A completely different path was explored by Tsuge and co-workers[38], who found that nitrile oxide dipolar-cycloaddition onto alkenes provides an entry into the 3,4-fused systems. Thus, reaction of (diethoxyphosphoryl)acetonitrile oxide with the protected cyclopentenyl-methanol **67** provided dipolar cycloadduct **68**. Reductive cleavage and hydrolysis of **68** yielded the fused furan **69**, containing a phosphoryl appendage which is useful for further elaboration (alkylation, oxidation, olefination, etc.).



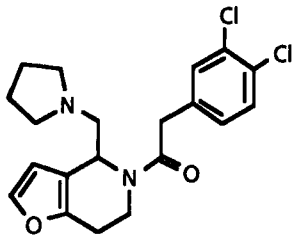




II. OTHER SYNTHETIC METHODOLOGY

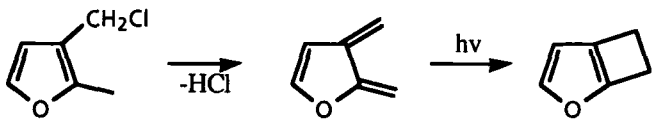
The synthesis of annulated furans is interesting not only because of the importance of the synthetic targets attainable, but also because of the useful methodology that has been elaborated in pursuit of these targets. Furthermore, unnatural annulated furan compounds are often of interest in their own right, whether for medicinal significance or for the synthetic challenge. For example, the furopyridine **70** has been prepared by a patented process[39] and has been found to be useful as a kappa opioid receptor agonist.

As far as methodogy is concerned, much work in all areas of synthetic chemistry has been devoted to the study of strained rings, including fused furans. Recently, the first synthesis of the parent furocyclobutene **73** was reported by Schweig and Münzel.[40] Thermolysis of the chlorofuran



70

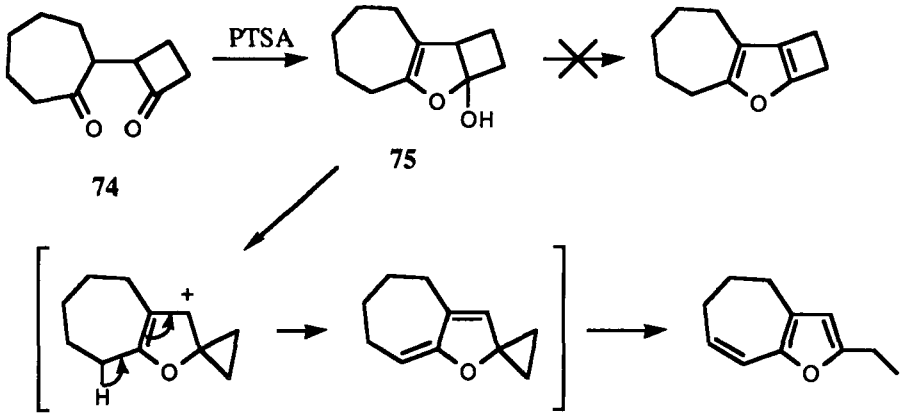
71 led to the formation of the diene **72** by elimination of HCl. Subsequent irradiation induced a photocyclization reaction producing the highly unstable **73**, which could actually be detected by



71 72 73

carrying out the irradiation in an argon matrix.

This observation led Spencer and Kaydos[41] to explore the possibility of preparing substituted furocyclobutenes *via* the Paal-Knorr dehydration of ketocyclobutanones. Even though a variety of ketocyclobutanones (e.g., **74**) were examined, no furocyclobutenes were found to be formed. Instead, the intermediate hemiacetals (e.g., **75**) underwent carbon-carbon bond migration in preference to dehydration to produce unsaturated macrocyclic annulated furans (e.g., **76**).



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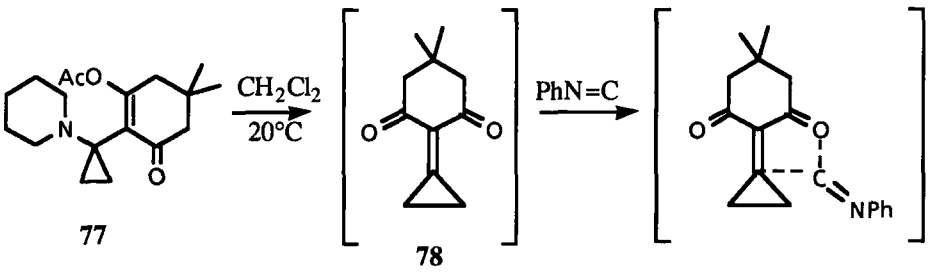

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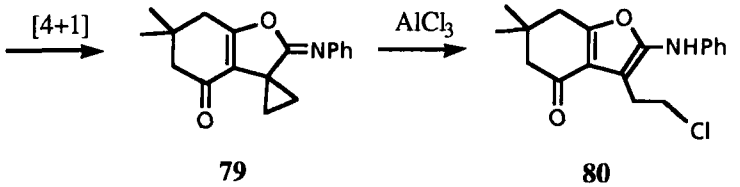
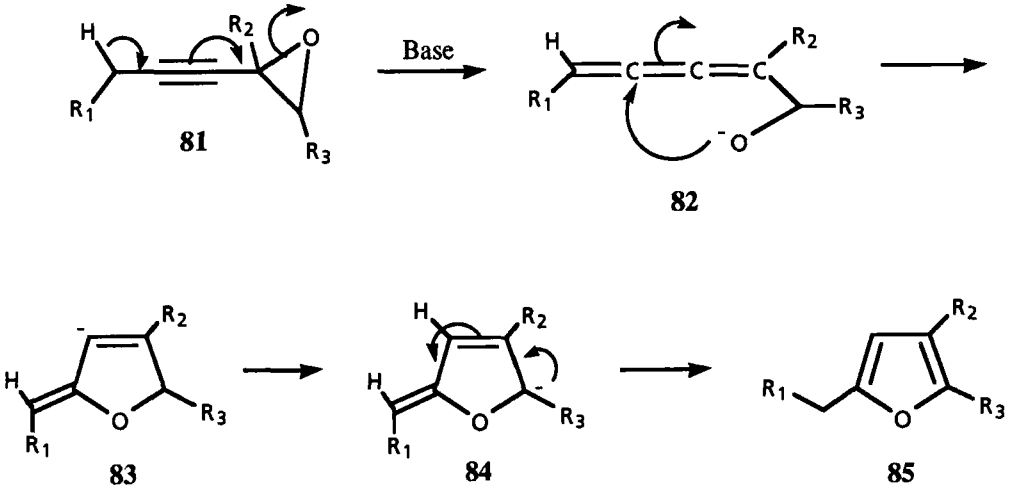


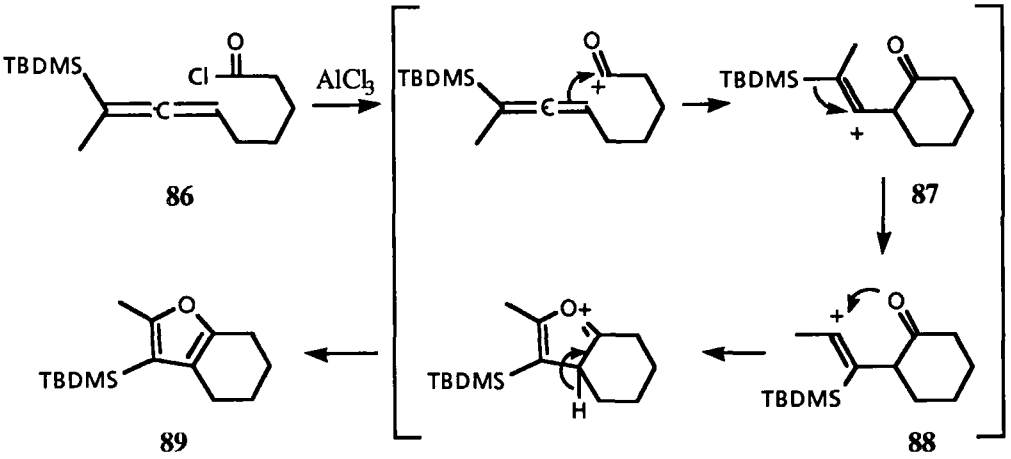
79 80

Some furan syntheses have centered around the use of various reactive intermediates. For example, Vilsmaier and co-workers[42] generate 2-cyclopropylidene-1,3-cycloalkanediones (e.g. **78**) by the novel eliminative fragmentation of acylate dimedone derivatives (e.g. **77**). The reactive species formed can be trapped *in situ* by a [4+1]-cycloaddition using isocyanides to give imino furans **79**. Ring cleavage of the cyclopropane moiety with aluminum trichloride provided 2-aminofurans **80**.

The base promoted isomerization of alkynyloxiranes has recently emerged as a viable new route to furans.[43] Treatment of alkynyloxiranes of type **81** with KOtBu in t-BuOH causes isomerization to the furans **85**. The reaction involves a base initiated 1,4-elimination of the alkynyloxirane **81** to give the cumulene alkoxide **82**. Cyclization of the alkoxide ion *via* the vinylic anion **83** followed



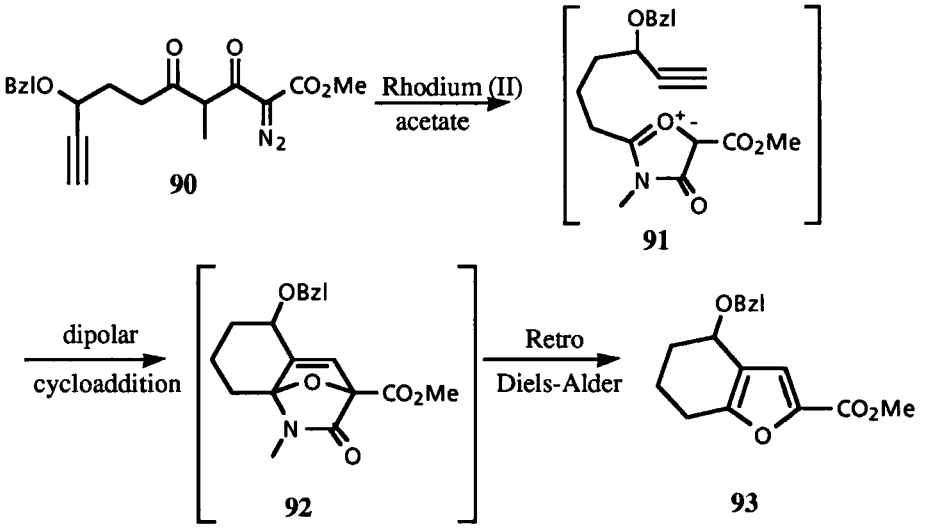
by proton transfer leads to the furanoid system. The method is noteworthy as most existing furan syntheses employ strong acid.[44]



Danheiser and coworkers[44] have developed a clever strategy toward the synthesis of furans using allenylsilanes as three-carbon [3+2] annulation units. The reaction of allenyl-silanes with acylium species (generated *in situ* from acyl chlorides) resulted in a regiocontrolled cyclization, directed by the silyl functionality, to provide furans in a single step. Thus, treatment of the bifunctional allene **86** with aluminum trichloride gave the annulated furan **89** in good yield. Integral to the facility of this reaction is the high migratory aptitude of silicon, resulting in a rapid transfer of electrophilic character between two adjacent carbon centers *via* a 1,2-silyl group migration (i.e. **87**→**88**).

Bicyclic furans have been prepared from linear precursors in one step by the intramole-cular cycloaddition of isomünchnones onto tethered acetylenes[45]. The reactive intermediate is generated by the rhodium-catalyzed decomposition of a diazoimide. The isomünchnone so formed (**91**) undergoes intramolecular dipolar cycloaddition with the acetylenic moiety. The resulting cycloadduct **92** is unstable and readily undergoes a retro-Diels-Alder reaction. In an illustrative example, diazoimide **90** was heated in a toluene solution containing a catalytic amount of rhodium (II) acetate to provide the annulated furan **93** in fair yield.

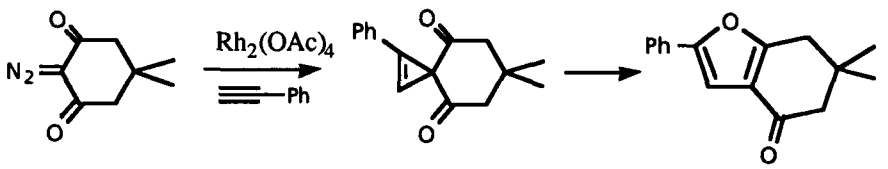
Davies and co-workers[46] have found that the intermolecular reaction of cyclic diazoketones (e.g. **94**) and electron-rich alkynes in the presence of rhodium (II) acetate results in the formation of bicyclic furans (e.g. **96**). This transformation has been shown to proceed through the intermediacy of



90 **91** **92** **93**

a cyclopropene (e.g. **95**), which arises from the direct addition of a rhodium carbenoid across the carbon-carbon triple bond. Spirocycle **95** undergoes cleavage of the phenyl substituted ß-bond to produce a vinylcarbene which subsequently cyclizes onto the adjacent carbonyl group to give the observed furan.

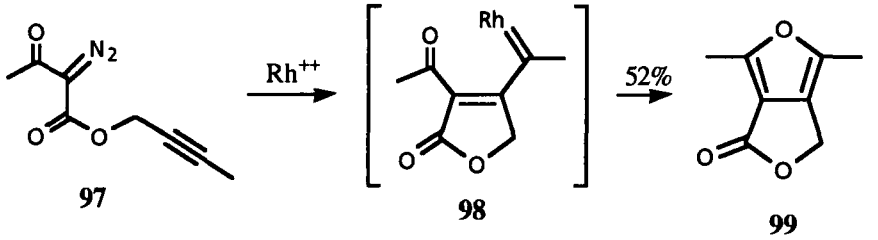
The Padwa group has utilized the corresponding intramolecular process involving a vinyl carbenoid intermediate to construct interesting bi- and tricyclic furans (i.e. **99** and **102**) from the



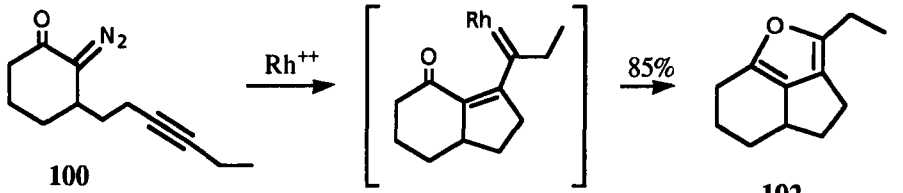
94 95 96

appropriately functionalized diazo precursors (**97**, **100**)[47]. The reaction is believed to proceed by addition of a rhodium-stabilized carbenoid onto the acetylenic π-bond to give the vinyl carbenoid which undergoes further cyclization onto the neighboring carbonyl. The potential for many diverse chemical pathways exists through the generation and further reactions of these rhodium carbenoids.

Skattebol and coworkers have reported a novel route to 2,3-disubstituted furans starting from α-keto acetals. The reaction of 2,2-dimethoxycyclohexanone with diethyl diazomethylphosphonate and KOtBu in THF at -40°C gave the bicyclic dihydrofuran derivative **105**.[48] Distillation of **105**

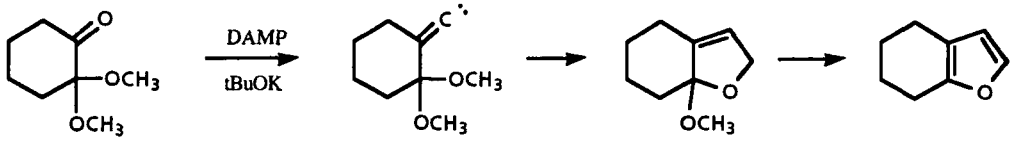


97 98 99



100 101 102

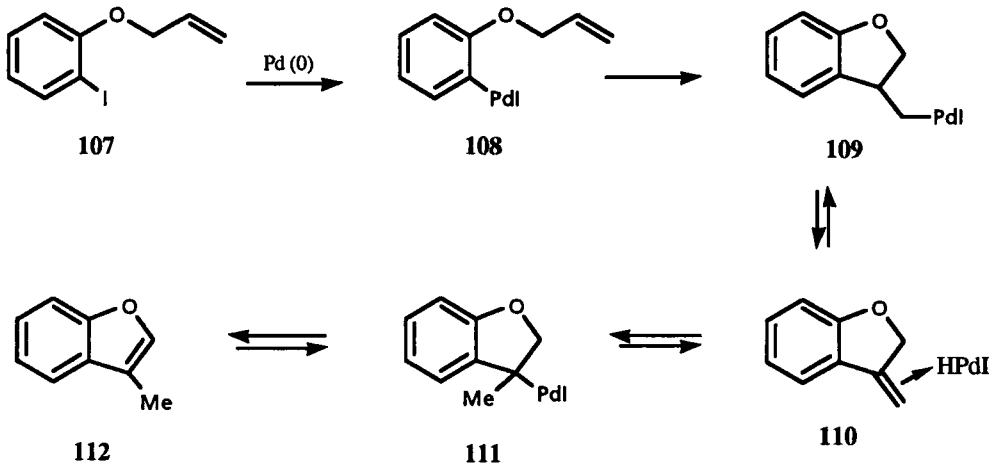
induced elimination of methanol resulting in a 72% yield of furan **106**. The key step in this sequence involves the generation of an alkylidene carbene intermediate **104** which undergoes insertion into a C-H bond of the neighboring methoxy group.



103 104 105 106

Transition metal reagents have also proven to be highly valuable for the cyclization of *ortho*-

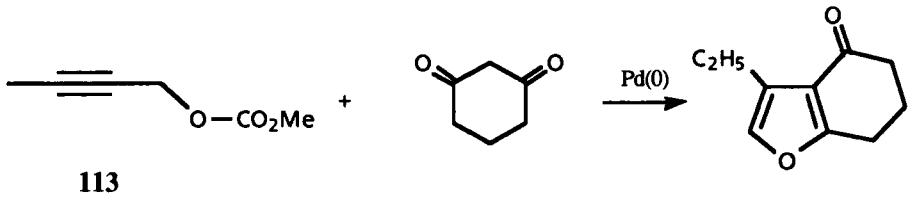
substituted aryl allyl ethers to benzofurans. Larock and Stinn reported that catalytic amounts of $Pd(OAc)_2$ in the presence of n-Bu_4NCl, DMF and an appropriate base cyclize such *o*-iodo aryl allyl



107 108 109 110 111 112

ethers in short reaction times, under mild temperatures and in good yield.[49] The mechanism for cyclization is illustrated by the conversion of **107** to **112**.

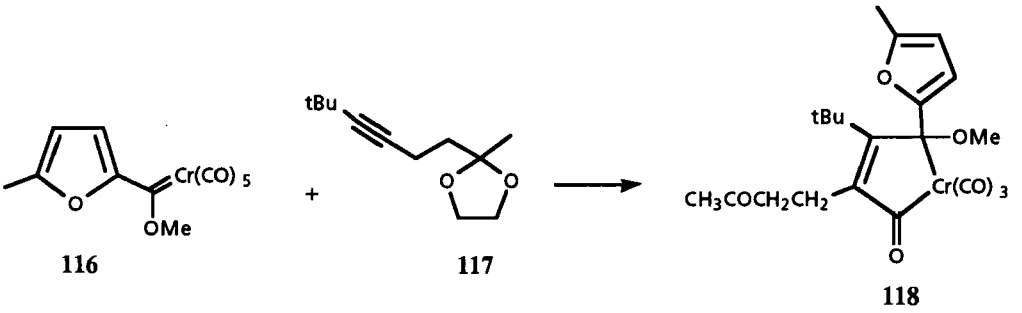
Another interesting annulation approach involves the palladium-catalyzed reaction of 2-alkynyl carbonates or 2-(1-alkynyl)oxiranes with ketoesters[50]. Thus, treatment of 1,3-cyclohexanedione (**114**) with alkynyl carbonate **113** in the presence of a palladium catalyst leads to the formation of furanone **115**. This sequence has the advantage of operating under essentially neutral conditions.



113 114 115

Cyclopenta[b]furans are valuable as synthetic intermediates since they can be hydrolytically converted to highly substituted cyclopentanones. Yamashita and coworkers have reported on the reactions of furyl-methoxy chromium carbenoid complexes with alkynes as a method of providing cyclopentafurans, which serve as useful precursors for cyclopentanones and other ring systems.[51] Treatment of the methoxy furan complex **116** with alkyne **117** gave **119** in 60% yield, which could be further converted to **120** in 62% yield. The mechanism of the process probably involves [2+2]-cycloaddition between the alkyne and the metal ligand followed by a series of electrocyclization reactions then a reductive elimination to give **118**, which is subsequently converted to **119**.

Insertion of carbon monoxide or isonitrile into metal-carbon bonds is a typical method for introducing one carbon units into organometallic compounds. Recently, Takai and coworkers



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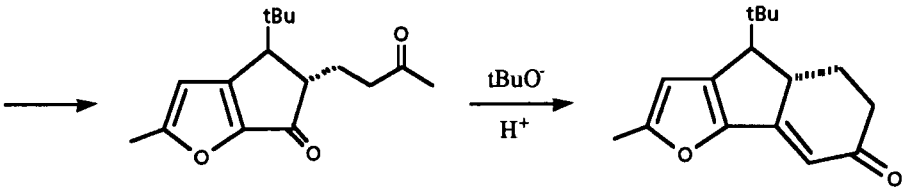
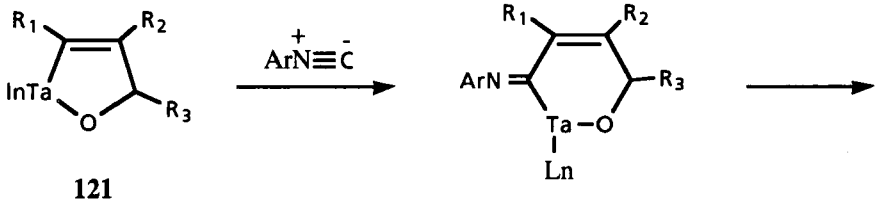
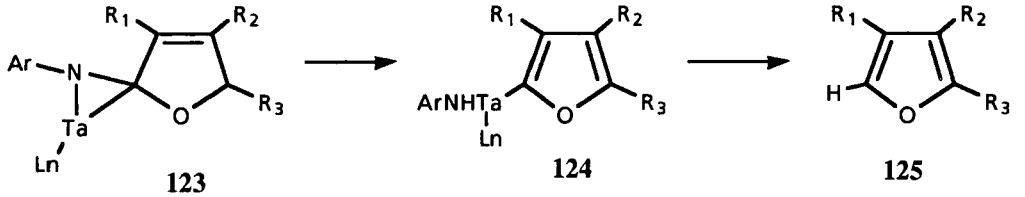


119 120

reported on a novel regioselective synthesis of highly substituted furans by treatment of tantalum-alkyne complexes with aldehydes, followed by addition of an isocyanide.[52] Insertion of the isonitrile into the carbon-tantalum bond of **121** produced the tantalacycle **122**. Migration of oxygen from tantalum to the imino carbon gives an η^2-acylimidoyl complex **123** which ultimately affords the tantalofuran **124** *via* oxygen assisted elimination of the aniline moiety. The affinity of tantalum for heteroatoms provides the driving force for the migration process.



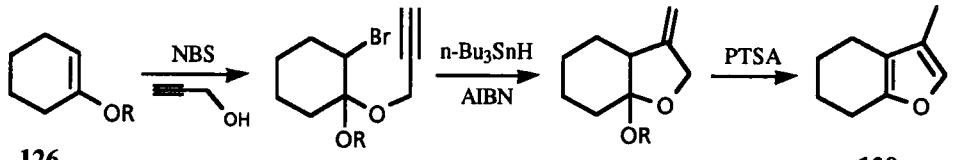
121 122



123 124 125

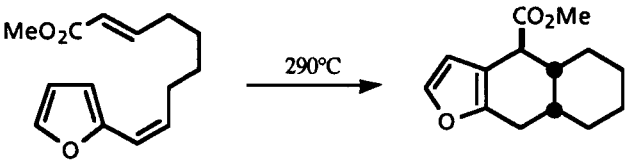
Other more traditional types of cyclization have also been used to construct the fused

bicyclic furan system. Srikrishna and Pullaiah[53] have reported a furannulation technique which relies upon radical cyclization. The radical precursor **127** was prepared by the bromination of cyclic enol ether **126** in the presence of propargyl alcohol. Tributyltin hydride reduction resulted in cyclization to the *exo*-methylene compound **128**, which undergoes a subsequent acid catalyzed elimination and rearrangement to form furan **129** in good yield.

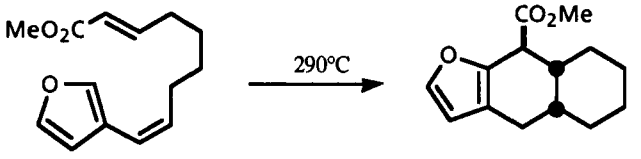


126 **127** **128** **129**

A facile entry into the furanodecalin system has recently been demonstrated by Knight and co-workers.[54] This method entails the intramolecular addition of an electron-deficient alkene across a vinyl furan diene moiety. The Diels-Alder cycloaddition proceeds smoothly in a stereospecific fashion for both 2- and 3-vinyl furans (i.e. **130**→**131** and **132**→**133**).

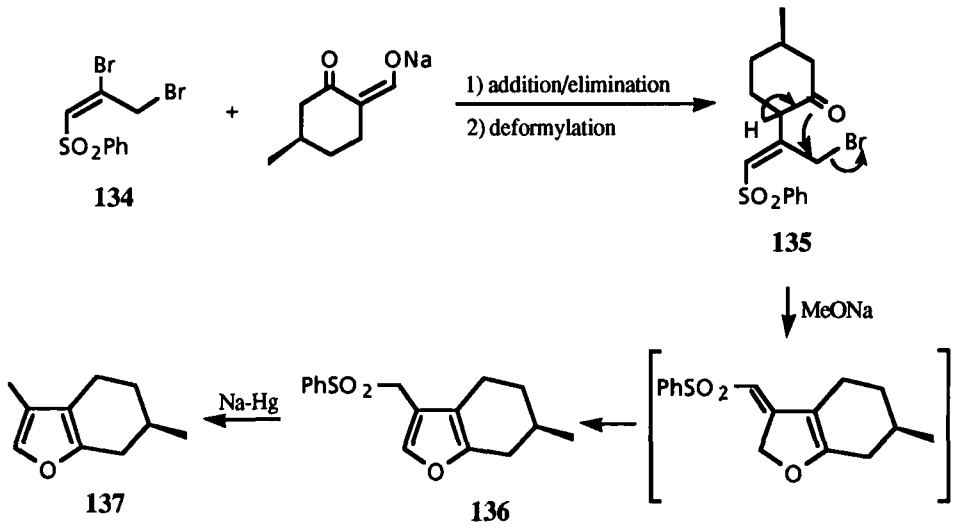


130 **131**

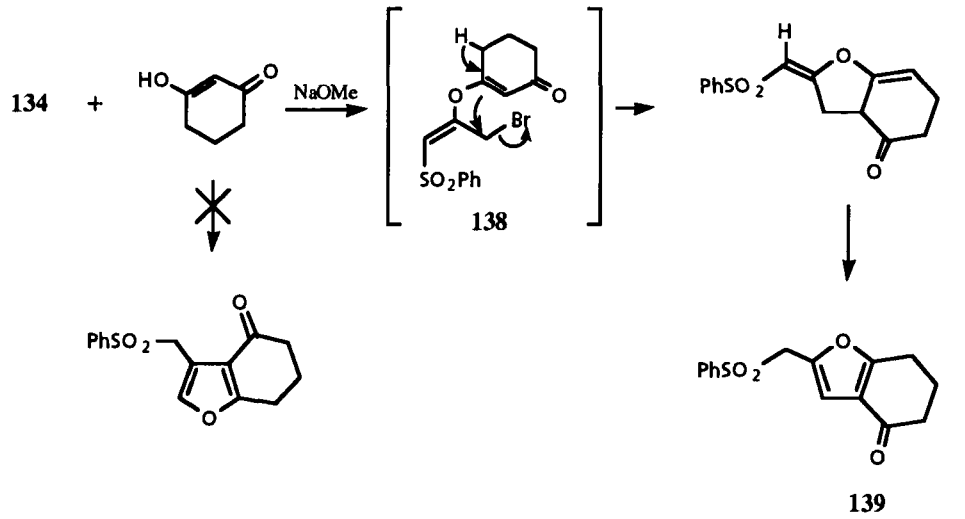


132 **133**

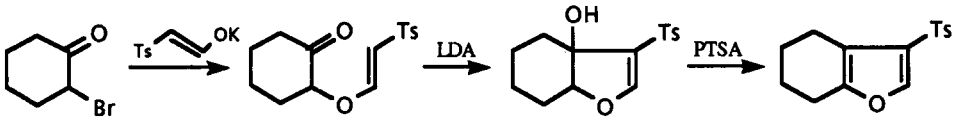
Inasmuch as dicarbonyl compounds are often utilized in condensation reactions by virtue of their active methylene hydrogens, advantage can be taken of these substrates for furannulation. Indeed, Padwa and coworkers[55] have investigated a polyfunctional sulfone which exhibits interesting dielectrophilic behavior toward 1,3-dicarbonyl compounds. 2,3-Dibromo-1-(phenylsulfonyl)-1-propene (**134**) could be induced to engage in C-alkylation with activated cyclic ketones to give isolable intermediates (e.g. **135**) derived from an addition-elimination path. Treatment of **135** with sodium methoxide resulted in a base-catalyzed O-alkylative ring closure to form annulated furans (e.g. **136**). This methodology was used in the synthesis of (*R*)-menthofuran (**137**).



Intriguingly, when cyclic diketones (such as 1,3-cyclohexanedione) were used in the reaction, the products were not 4-(phenylsulfonyl)methyl furans (as in **136**), but rather the corresponding 5-substituted isomers (e.g. **139**). These products presumably arise from initial O-alkylation, inasmuch as cyclic 1,3-diketones are known to preferentially afford O-alkylated products in general. Further reaction of the initially generated bromide with base results in cyclization to **138**, which then undergoes a subsequent aromatization.



McCombie and co-workers also used a sulfone reagent in their furannulation strategy[56]. In this case, bromoketones (e.g. **140**) are treated with the potassium salt of (tolylsulfonyl)-acetaldehyde. The intermediates so formed (e.g. **141**) undergo subsequent base-induced cycliza-tion and acid-catalyzed dehydration to yield annulated furans (e.g. **142**) in good yield.



140 **141** **142**

It is immediately evident upon examination of the literature that the study of annulated furans is a very diverse field. Clearly, a review of this magnitude could not be comprehensive. The aim, therefore, was not to be exhaustive in scope, but rather to convey a flavor of the current activity. Of course, there has yet to be described a single definitive entry into such a varied family as the annulated furans; however, there are enough protocols of sufficient generality to provide a useful base of synthetic strategy, and yet enough challenge to warrant further work in the area.

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