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Organopalladium approaches to oxygen heterocycles

Dean E. Stinn
Iowa State University

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Organopalladium approaches to oxygen heterocycles

by

Dean E. Stinn

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Iowa State University
Ames, Iowa

1989

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ABBREVIATIONS

Bz	benzyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DMA	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
HMPA	hexamethylphosphoramide
IR	infrared
LDA	lithium diisopropyl amide
Mp	melting point
NMR	nuclear magnetic resonance
PTSA	para-tolulenesulfonic acid
RT	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

GENERAL INTRODUCTION

In recent years, organometallic chemistry has played an increasingly important role in organic synthesis. Organopalladium chemistry in particular has emerged as an extremely versatile and powerful tool for the synthetic organic chemist.[1,2] The synthesis of organopalladium compounds can be readily accomplished by a variety of methods: transmetallation of organomercurials with palladium(II) salts, oxidative addition of palladium(0) reagents to organic halides and oxypalladation of olefins in the presence of palladium(II) salts to mention just a few methods.

Recent work by Larock et al.[3] and by Fugami et al.[4] has shown that intramolecular olefin addition of organopalladium compounds can be used to produce oxygen heterocycles. A variety of oxygen heterocycles, including bicyclic lactones, bicyclic acetals, butenolides and benzofurans, have been prepared using this methodology.

The synthesis of these oxygen heterocycles is the subject of this thesis. The contents of this thesis are presented in four parts. The first part is a literature survey covering organopalladium approaches used towards the synthesis of oxygen heterocycles. The second part will discuss the synthesis of butenolides and their organomercurial precursors. The third part will present the

synthesis of bicyclic lactones and their organomercurial precursors, and the synthesis of protected bicyclic acetals. Finally, the fourth part will include the synthesis of benzofurans via the palladium-catalyzed cyclization of o-iodophenyl allyl ethers or via the palladium-assisted cyclization of o-chloromecurio-phenyl allyl ethers.

PART I. LITERATURE SURVEY OF ORGANOPALLADIUM APPROACHES TO OXYGEN HETEROCYCLES

INTRODUCTION

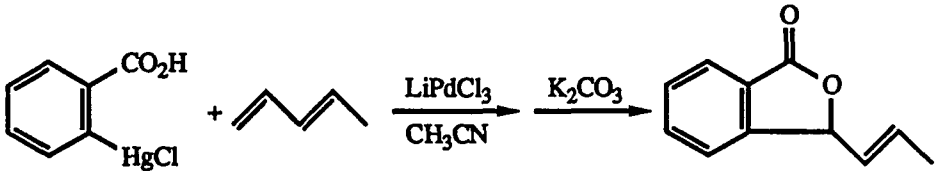
In the last two decades, the application of organopalladium chemistry to the synthesis of oxygen heterocycles has seen significant utilization. A variety of approaches has been used in the synthesis of oxygen heterocycles. The majority of these approaches involve the synthesis of a carbon heteroatom bond via either π-allylpalladium formation, followed by intramolecular nucleophilic displacement of the palladium moiety, or by intramolecular oxypalladation, followed by elimination of HPdX. Palladium-assisted carbon-carbon bond formation has also been used to prepare oxygen heterocycles.

The first part of this chapter will cover oxygen heterocycle formation via intramolecular nucleophilic displacement of the palladium moiety of π-allylpalladium compounds. Included in this section will be the use of oxygen and carbon nucleophiles. The second part will cover oxypalladation routes to oxygen heterocycles. The third part of this chapter will cover carbon-carbon bond formations used in the synthesis of oxygen heterocycles, followed by some miscellaneous methods used.

USE OF π-ALLYLPALLADIUM COMPOUNDS

The use of π-allylpalladium compounds is one of the most elegant methods employed for the formation of oxygen heterocycles. A variety of oxygen heterocycles can be prepared by intramolecular nucleophilic attack on the π-allylpalladium intermediate. Both carbon and oxygen nucleophiles have been used.

Larock et al.[1] have reported that conjugated or non-conjugated dienes or vinylcyclopropanes react with $LiPdCl_3$ and organomercurials bearing carboxylic acid, phenol, or alcohol functionality to generate π-allylpalladium compounds. Upon the addition of an appropriate base, these intermediates readily undergo intramolecular nucleophilic displacement of palladium by oxygen to give a wide variety of oxygen heterocycles (eq. 1).

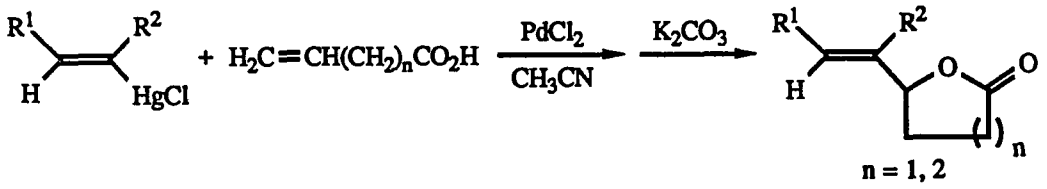


(1)

Thallated compounds have also been used in the synthesis of heterocyclic products.[2] With organothallium compounds only catalytic amounts of palladium(II) salts are required. The palladium(0) formed in the displacement step is reoxidized to palladium(II) by the thallium(III) salt

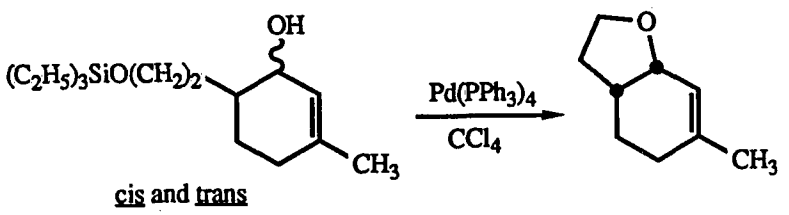
present in the reaction mixture after the transmetallation step.

Larock et al. also used a similar approach for the synthesis of vinylic five- and six-membered ring lactones (eq. 2).[3] Here, vinylmercuric chlorides, $PdCl_2$ and alkenoic acids afford π-allylpalladium compounds. Intramolecular nucleophilic displacement, facilitated by base, produces the anticipated five- and six-membered ring lactones in high yields.



(2)

Stanton et al.[4] have developed a method for the preparation of oxygen-containing heterocycles based on intramolecular alkoxide attack of π-allylpalladium compounds (eq. 3). The authors state that alkoxides exhibit a small



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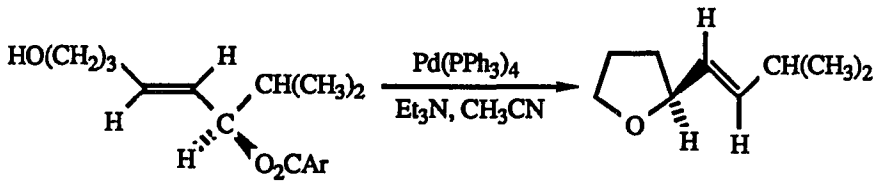
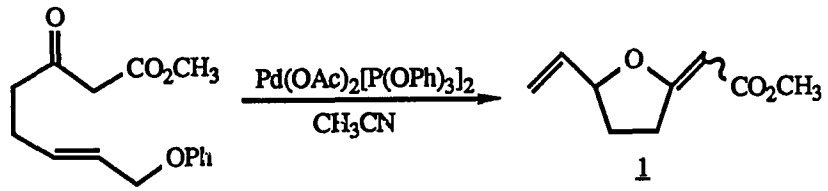
energy difference between backside attack on the π-allyl ligand and attack at the metal center, followed by reductive elimination. Stork and Poirer[5] have also used an intramolecular attack in their method for the preparation of

2-substituted tetrahydrofurans of known absolute stereochemistry (eq. 4).



(4)

Tsuji et al.[6] and Trost and Runge[7] have also reported the use of oxygen nucleophiles for displacements on π-allyl-palladium compounds generated from allylic phenoxides and acetates respectively (eqs. 5, 6). Cyclization of the



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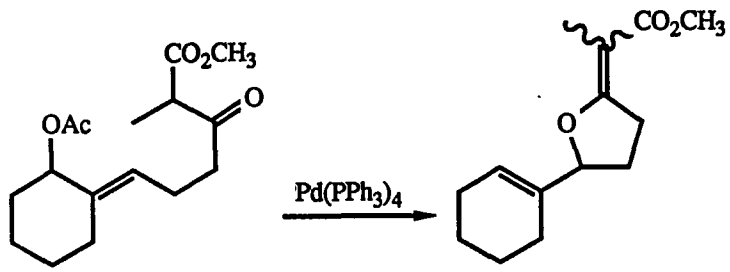
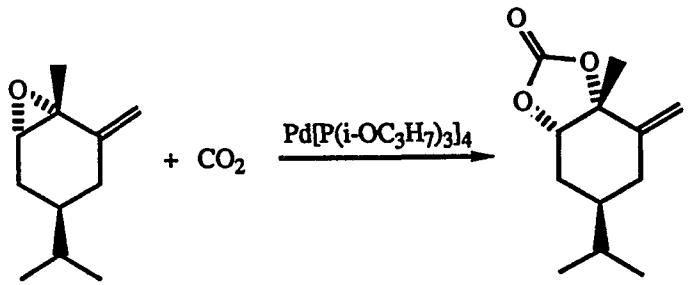


(6)

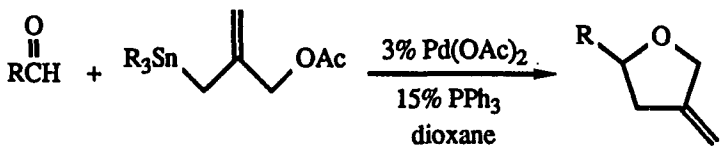
β-keto ester anions can lead to formation of either carbocycles or heterocycles. Only compound 1 was obtained when triphenylphosphite was used as the ligand. With other phosphine ligands, compound 1 rearranges under the reaction conditions to a mixture of the five- and seven-membered carbocycles.

Trost and Angle[8] have also recently reported a very novel synthesis of an oxygen heterocycle via a palladium intermediate. By reacting a vinylic epoxide with a palladium(0) catalyst in the presence of carbon dioxide, a vinylic carbonate is synthesized. The initially formed π-allylpalladium alkoxide reacts with the carbon dioxide to produce a carbonate anion. This carbonate anion attacts the π-allylpalladium intermediate to displace the palladium and yield a cyclic vinylic carbonate (eq. 7).



(7)

Trost and Bonk[9] recently reported another novel route to cyclic ethers in which they used a trimethylenemethane palladium intermediate (eq. 8). The intermediate species

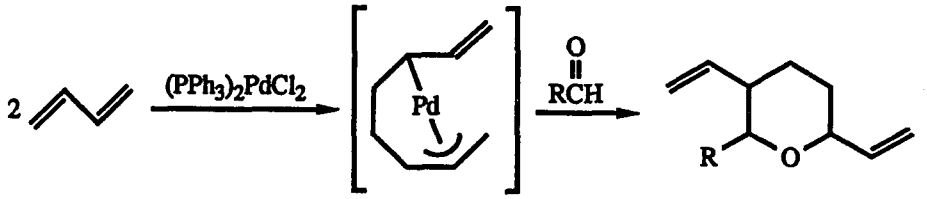


(8)

generated from an allylic tri-n-butyltin acetate precursor readily added to aldehydes yielding tetrahydro β-methylene furans.

Ohno et al.[10,11] also used aldehydes for the formation of oxygen heterocycles. He observed that a σ-allyl π-allyl-

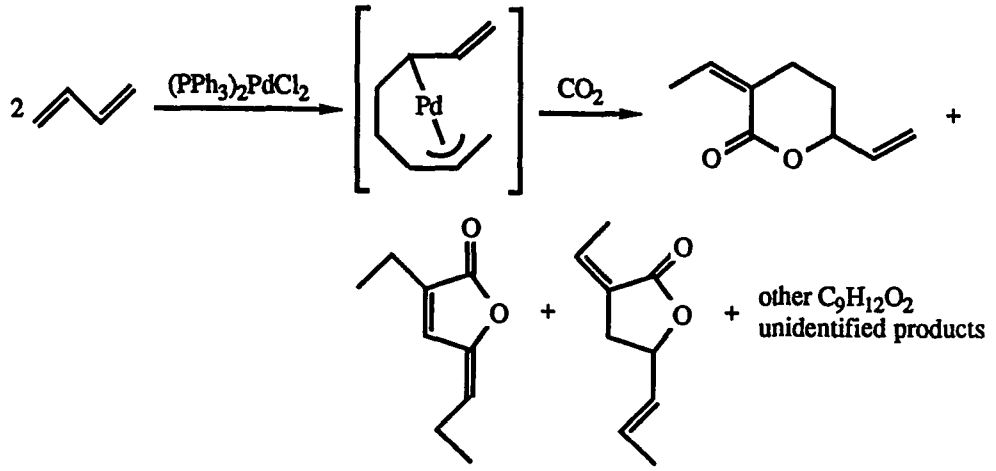
palladium complex resulted from the reaction of two equivalents of butadiene with a palladium(II) salt (eq. 9).



(9)

This intermediate then reacted with an aldehyde to give an alkoxide which intramolecularly displaced the palladium giving rise to a variety of divinyl substituted cyclic ethers.

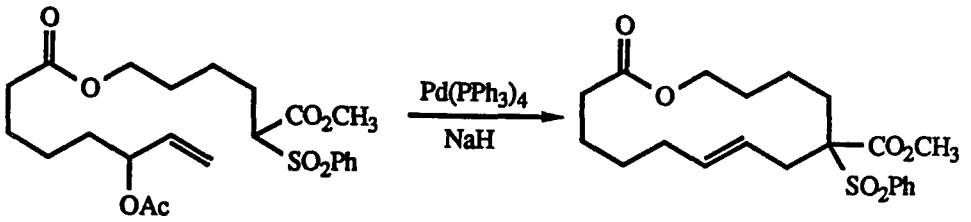
Another very similar reaction is the telomerization of butadiene and carbon dioxide (eq. 10).[12] This reaction does not give one product, but several.



(10)

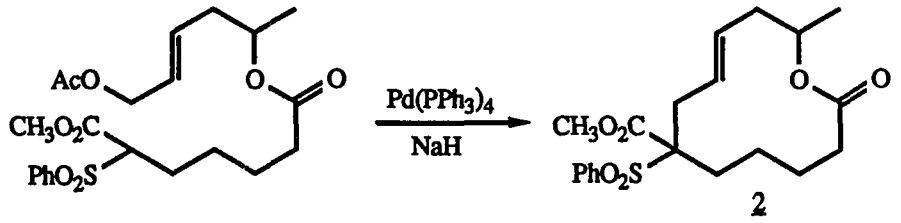
Trost and Verhoeven[13] have examined the attack of stabilized carbon nucleophiles on π-allylpalladium compounds to form new carbon-carbon bonds. In the course of their studies, they looked at the formation of oxygen heterocycles. Macrolide skeletons have been constructed by

the intramolecular reaction of carbanions, and allylic acetates in the presence of catalytic amounts of $Pd(PPh_3)_4$ (eq. 11).



(11)

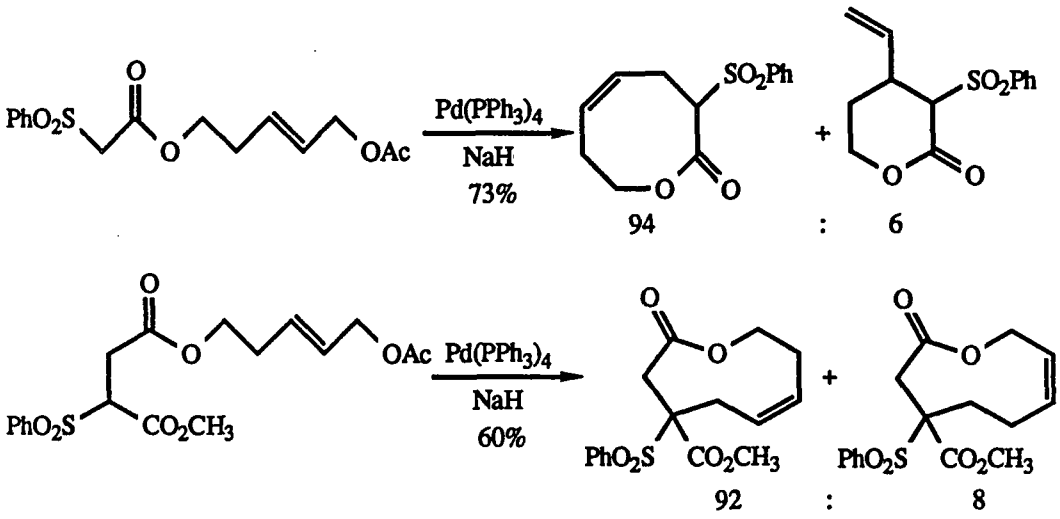
This cyclization method has been applied to the synthesis of reciferolide 2 (eq. 12). Lactone 2 is obtained



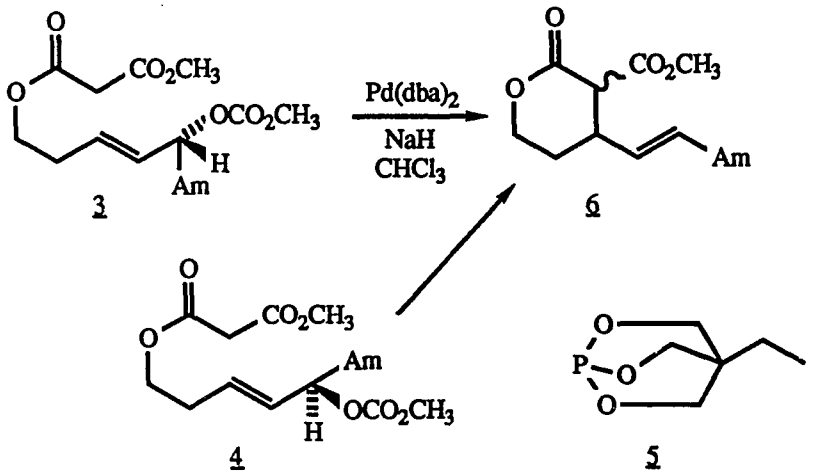
(12)

in 78% yield with the E isomer being produced stereo- and regioselectively without ten-membered ring lactone formation.[14]

This cyclization method, based on the intramolecular reaction of alkyl phenylsulphonyl acetates with allylic acetates, has been applied to the synthesis of the ten-membered ring lactones phoracantholide I and J.[15] Trost and Verhoeven[15] found that eight-membered ring lactones can be obtained with little formation of six-membered ring lactones, and nine-membered ring lactones can be obtained with no formation of seven-membered ring lactones (eqs. 13, 14).



An efficient carbon-oxygen to carbon-carbon intramolecular chirality transfer reaction has been achieved in reactions of E- and Z-allylic carbonates 3 and 4 by using palladium(0) and the bicyclic phosphite 5 as the catalyst (eq. 15).[16] Reaction of compound 3 in the presence of



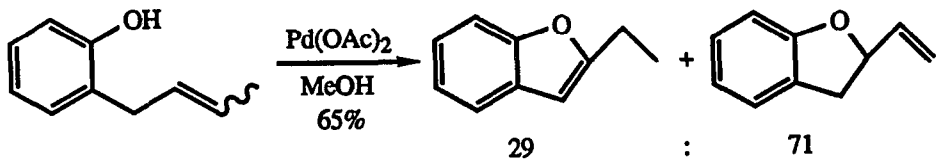
phosphite 5 and NaH gave the lactone (3R)-6 with 96% chirality transfer. Reaction of 4 under the same conditions gave (3S)-6 with 94% chirality transfer.

OXYPALLADATION ROUTES TO OXYGEN HETEROCYCLES

By far, the most widely used organopalladium approach for the synthesis of oxygen heterocycles is that of oxypalladation. Even though the mechanism of oxypalladation is basically the same as that for oxymercuration, oxypalladation is quite different from oxymercuration. For instance, the initially formed organopalladium species is unisolable whereas the products of oxymercuration are generally stable and isolable. The fact that the initial oxypalladation product is capable of undergoing further reaction makes oxypalladation attractive as a synthetic tool. The effectiveness of oxypalladation as a route to oxygen heterocycles is demonstrated by the enormous variety of oxygen heterocycles formed via oxypalladation processes. Included in this list of oxygen heterocycles are benzofurans, lactones, butenolides, cyclic ethers, acetals, ketals and isoxazoles.

Hosokawa et al.[17-20] have extensively studied the synthesis of benzofurans via oxypalladation. They have cyclized a variety of 2-allylic phenols giving rise to numerous 2-substituted benzofurans. When they treated 2-(2'-butenyl)phenol with $Pd(OAc)_2$ in MeOH, they obtained a 29:71 mixture of 2-ethyl benzofuran and 2-vinyl-2,3-dihydrobenzofuran in a 65% yield (eq. 16). When they reacted the same phenol with $PdCl_2$ in MeOH a 50:11:18:21 mixture of

2-methyl chromene, 2-methyl-4-methoxychroman, 2-methyl-2-methoxychroman and 2-ethyl benzofuran was obtained in 34% yield (eq. 17).



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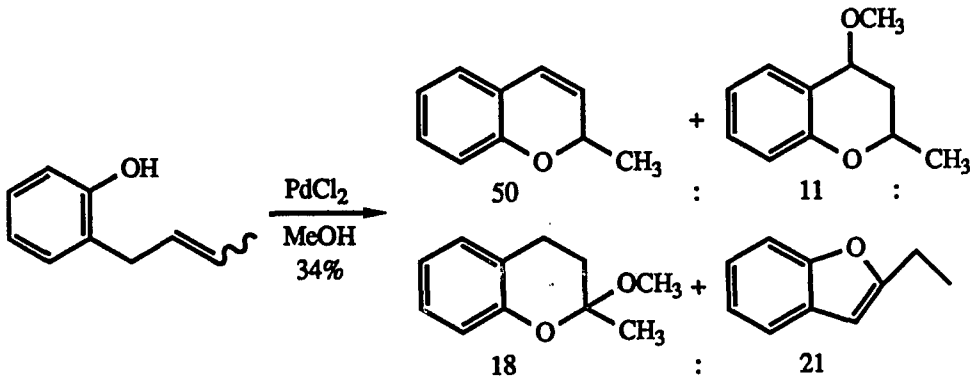
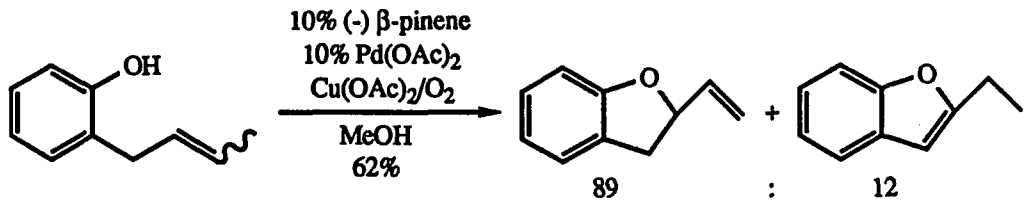


(17)

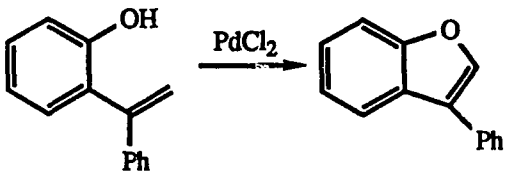
Hosokawa et al.[21] demonstrated the feasibility of making the reaction catalytic with respect to the palladium(II) salt. He also examined whether stereochemical inductions could be accomplished. When he reacted 2-(2'-butenyl)phenol with 10% $Pd(OAc)_2$ in the presence of (-) β-pinene with $Cu(OAc)_2$ present as a reoxidant, he obtained a 62% yield of



(18)

an 89:12 mixture of 2-vinyl-2,3-dihydrobenzofuran and 2-ethyl benzofuran. The vinyl compound was obtained in 12% optical yield (eq. 18).

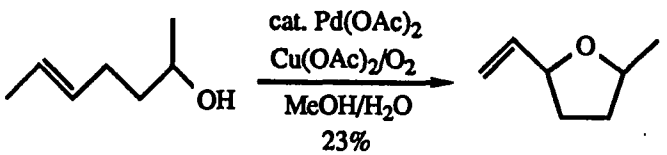
Benzofurans substituted in the 3-position have also been prepared by oxypalladation.[22,23] Casiraghi et al.[22] have published several examples of which the following is one (eq. 19).



(19)

Flavones and isocoumarins have been prepared in a similar fashion.[24-26]

The synthesis of butenolides,[25,27,28] cyclic ethers,[25,27,28] lactones[28,29] and pyrones[30] have been accomplished via oxypalladation by Kasahara et al. (eqs. 20-23).



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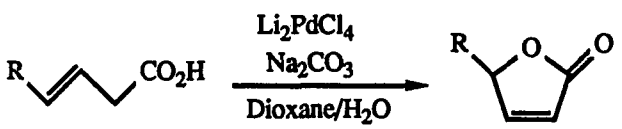

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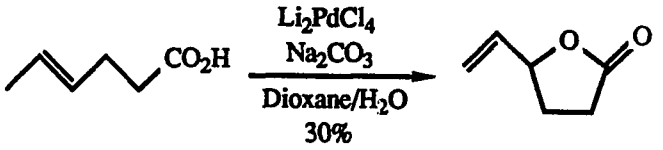

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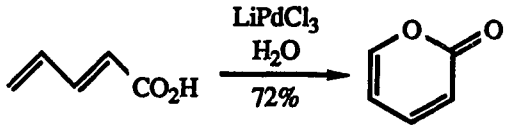
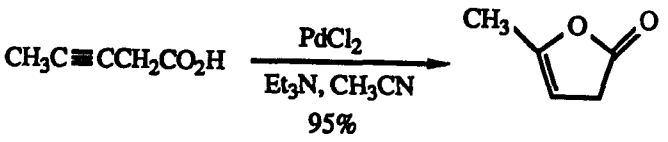


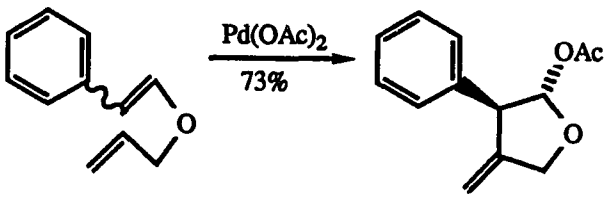
(23)

The oxypalladation of alkynes has also been reported.[31,32] Utimoto published palladium(II)-catalyzed cyclizations of various alkynoic acids (eq. 24).



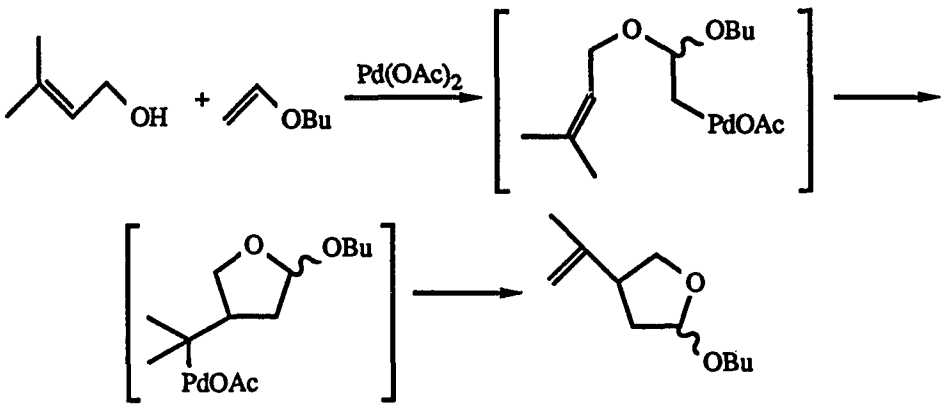
(24)

Oxypalladation has also been used in the synthesis of acetals or protected lactols. Kende and Wustrow[33] have published an intermolecular version of the formation of an acetal from an allyl vinyl ether (eq. 25). The ether linkage present in the starting material ultimately becomes the oxygen in the oxygen heterocycle.



(25)

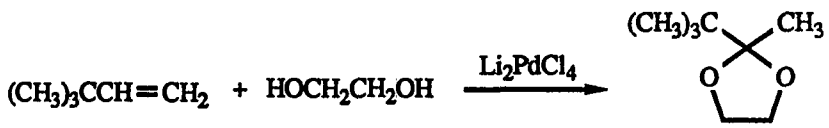
Fugami et al.[34] found that they could accomplish the same type of transformation in a slightly different fashion (eq. 26). They used an intermolecular oxypalladation



(26)

reaction in which an allylic alcohol was added to a vinyl ether. The initially formed organopalladium species then added back across the olefin of the allylic alcohol giving rise to an alkyl-protected lactol. Acetals and ketals have also been prepared from inter- and intramolecular oxypalladation of olefins with diols.[35,36]

Lloyd and Luberoff[35] have published representative examples of the synthesis of both acetals and ketals (eqs. 27, 28).



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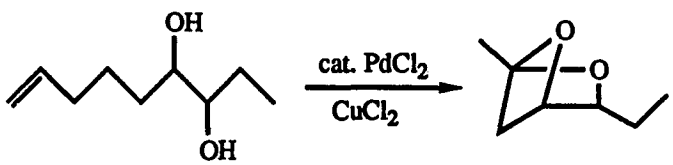
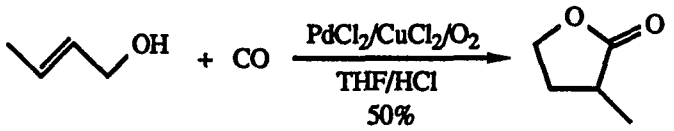


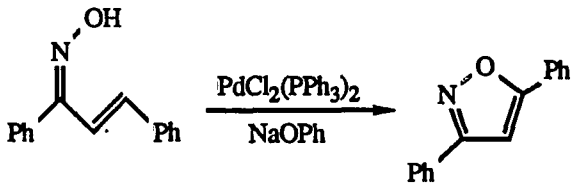
(28)

Reactions in which allylic alcohols are carbonylated and cyclized catalytically with palladium(II) salts have been reported by Alper and Leonard (eq. 29)[37,39] and Tamaru et al.[38]



(29)

Hosokawa et al.[40,41] have synthesized isoxazoles from oximes via oxypalladation (eq. 30). They obtained decent yields for a variety of substitution patterns.



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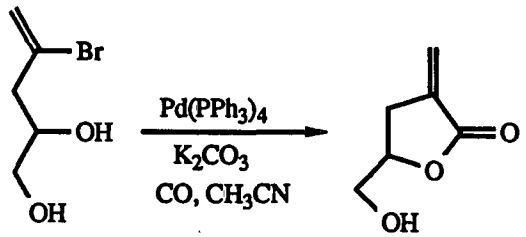
ACYLPALLADIUM SPECIES AS INTERMEDIATES FOR THE SYNTHESIS OF OXYGEN HETEROCYCLES

One widely used method for the formation of carbon-carbon bonds involves formation of an organopalladium intermediate via oxidative addition of a palladium(0) catalyst to a carbon halide or carbon triflate bond.[42-46] Carbonylation of this intermediate gives an acylpalladium species which can be trapped intramolecularly with an alcohol to yield an oxygen heterocycle. Cowell and Stille[43,44], Echavarren and Stille[45], and Martin and Stille[46] among others,[42] have reported the formation of oxygen heterocycles from acylpalladium intermediates (eqs. 31, 32). The first example is unique in that the



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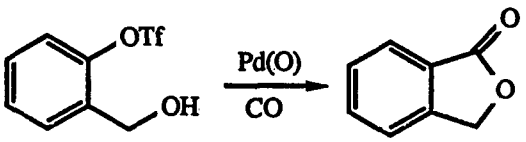
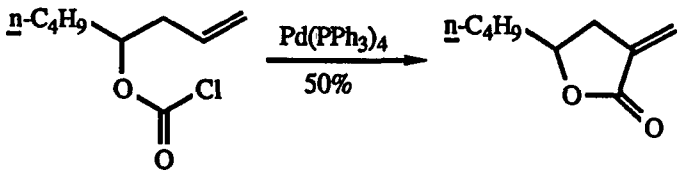


(32)

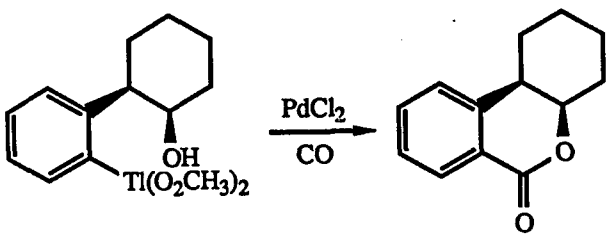
acylpalladium species may be trapped to form either a five- or a six-membered ring lactone. Only the five-membered ring product is found. The second example shows the use of an aryl triflate as the starting material for the formation of the organopalladium intermediate. Henin and Pete[47] have

synthesized unsaturated butyrolactones using palladium(0)-catalyzed intramolecular carboalkoxylation of homoallylic chloroformates (eq. 33).



(33)

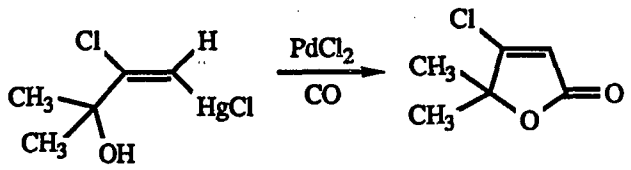
Transmetallation of organometallic compounds with palladium(II) salts is another method of forming reactive organopalladium compounds. Among the organometallic compounds that can undergo transmetallation by palladium are organothallium, -mercury, and -tellurium compounds. Larock and Fellows[2] reported the synthesis of lactones via organothallium compounds (eq. 34). After transmetallation, the



(34)

intermediate organopalladium species is carbonylated and the acylpalladium species is then trapped intramolecularly by the alcohol functionality resulting in the formation of the lactone.

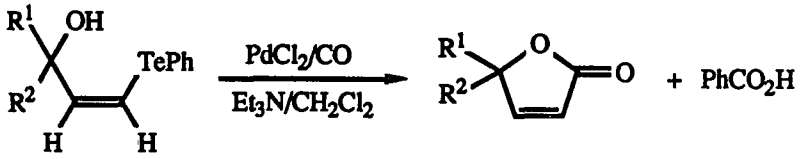
Larock et al.[48] have also reported the synthesis of butenolides via organomercurials (eq. 35). Transmetallation



(35)

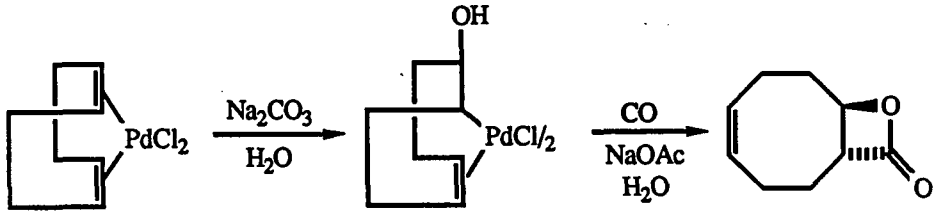
of the vinylic mercurial with a palladium(II) salt forms an organopalladium species that is carbonylated and then trapped intramolecularly to give a butenolide.

Ohe et al.[49] have reported a very similar synthesis of butenolides, but via organotellurium compounds (eq. 36).



(36)

Another acylpalladium approach reported by Stille and James[50] that does not require oxidative addition or transmetallation is shown below (eq. 37). In this example,

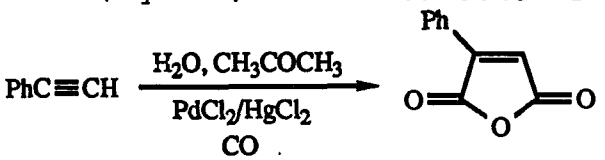


(37)

a stable σ-palladium species is generated by oxypalladation of cyclooctadiene palladium dichloride. This σ-palladium compound is then carbonylated and the acylpalladium species trapped to give a four-membered ring lactone.

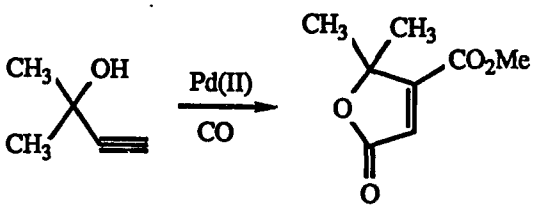
MISCELLANEOUS APPROACHES TO OXYGEN HETEROCYCLES

Of the miscellaneous organopalladium approaches to oxygen heterocycles, carboalkoxylation of acetylenes is one method widely employed. Heck[51] found that under the proper conditions he could convert phenyl acetylene into phenyl maleic anhydride (eq. 38). This reaction is an example of



(38)

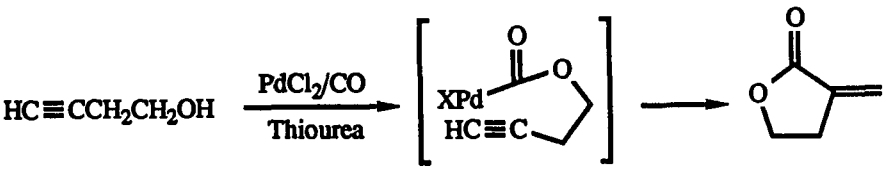
dicarboalkoxylation of an acetylene. Nogi and Tsuji[52-54] have carried out similar reactions in which butenolides were obtained (eq. 39). Under the reaction conditions,



(39)

lactonization followed the dicarboalkoxylation of the propargyl alcohol.

Chiusoli et al.[55] reported a very similar reaction where they obtained α-methylene lactones from acetylenic alcohols (eq. 40).

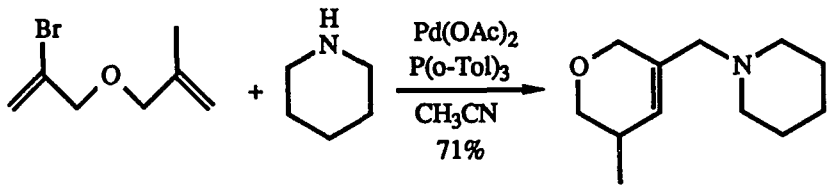


(40)

The carboalkoxylpalladium intermediate adds to the acetylene to give a five-membered ring lactone-vinyl palladium species. The palladium is then removed by protonolysis. Murray et al.[56] reported the same reaction and obtained the same product under slightly different conditions. Samsel and Norton[57] examined the mechanism of the carboalkoxylation of acetylenes. Yanagihara et al.[58] extended the intramolecular carboalkoxylation of acetylenes by allylating the intermediate vinylpalladium species with allylic halides. Chavdaria et al.[59] employed acetylene carboalkoxylation in their synthesis of vernolepin.

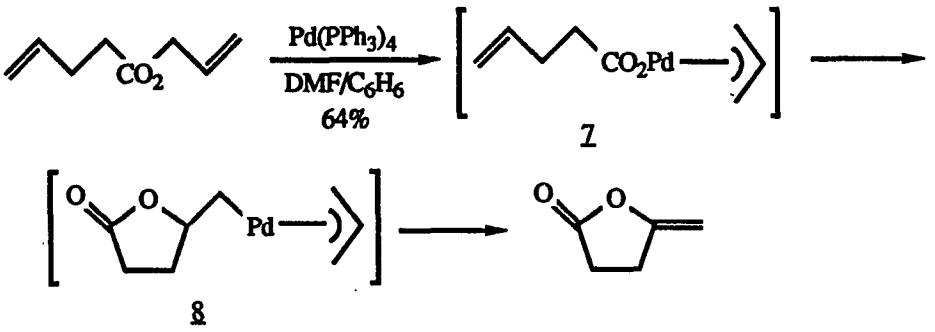
Another method of generating oxygen heterocycles involves intramolecular cyclization of organopalladium intermediates containing oxygen functionality. Some of the organopalladium intermediates are formed via oxidative addition and others are formed via transmetallation.

Shi et al.[60] studied the palladium-catalyzed cyclizations of bromo dialkenyl ethers and amines (eq. 41).



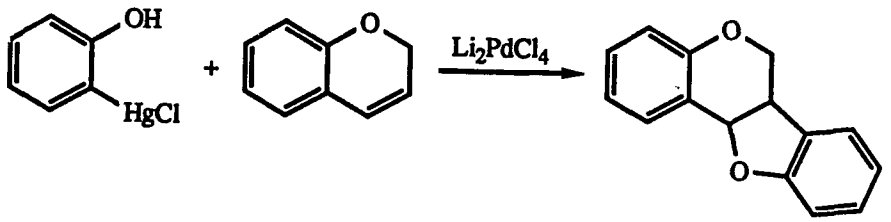
(41)

Tsuda and co-workers[61] form lactones in a different manner (eq. 42). This reaction is thought to proceed through intermediates 7 and 8.



7 8 (42)

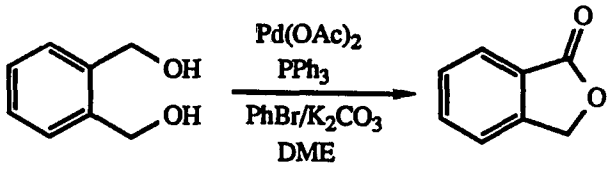
Horino and Inoue[62] reported the synthesis of a complex cyclic ether (eq. 43). The o-(chloromercurio)phenol is



(43)

reacted with Li_2PdCl_4 to form the organopalladium species which adds across the olefin. The resulting palladium species undergoes palladium displacement by oxygen, resulting in ether formation.

Oxidation of diols by palladium(II) salts followed by lactonization has been reported by Tamaru et al. (eq. 44).[63]

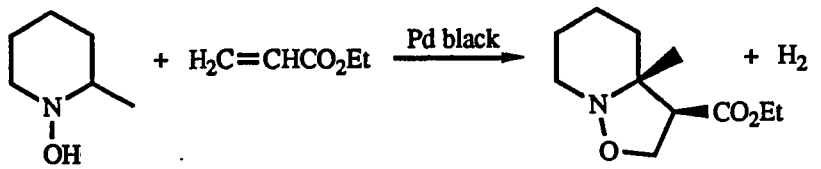


(44)

Bromobenzene acts as the oxidant in these reactions. It reacts by oxidative addition with a palladium(0) catalyst generated in situ to give an arylpalladium species. This

arylpalladium species reacts with the alcohol functionality to give an aldehyde and benzene. Further oxidation yields an hydroxy acid which then forms the lactone. They also used aliphatic diols to afford aliphatic lactones. Camus et al.[64] have used similar reaction conditions to obtain furans. Itahara,[65] and Ames and Opalka[66] have also oxidized diaryl ethers to furans using palladium(II) salts.

One other novel approach towards the synthesis of oxygen heterocycles is shown below (eq. 45). Murahashi et al.[67] found that amine oxides could be dehydrogenated and that the dehydrogenated product would react with ethyl acrylate to give the heterocycle shown.



(45)

CONCLUSION

An enormous variety of oxygen heterocycles can be prepared using organopalladium chemistry. Lactones, cyclic ethers and cyclic carbonates have been prepared from π-allylpalladium compounds. Benzofurans, chromones, cyclic ethers, lactones, butenolides, pyrones, acetals and ketals have been synthesized using oxypalladation. Acylpalladium intermediates have been used in the synthesis of lactones, butenolides and anhydrides.

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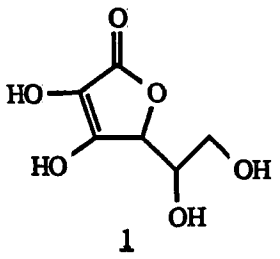
PART II. SYNTHESIS OF BUTENOLIDES VIA PALLADIUM-ASSISTED CYCLIZATION

INTRODUCTION

The $\Delta^{\alpha,\beta}$-butenolide ring is present in many natural products and physiologically active substances.[1-4] For example, it is a constituent of vitamin C 1, α- and β-angelica lactones 2,[5] protoanemonie 3,[6] digetoxigenin 4,[7] and many other compounds.



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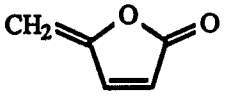

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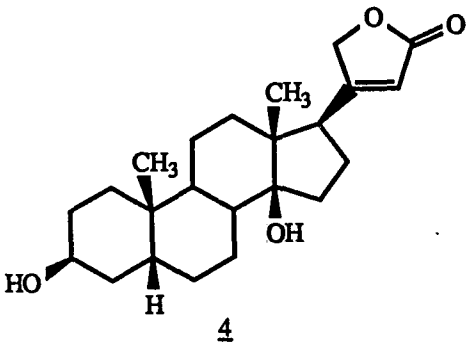


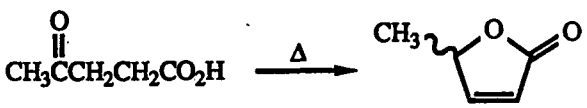
4

It has been established that the activity of vitamin C is due to the presence of the butenolide system.[8] Both α- and β-angelica lactones exhibit bactericidal properties and hydrolysis of the lactone as well as hydrogenation of the double bond entails loss of activity of these compounds.[5] Protoanemonie is an effective antibacterial substance.[6] Cardenolides, of which digitoxigenin is an example, promote the normal activity of the cardiac muscle in man and

animals.[7] The butenolide ring is a major structural feature necessary for the activity of all of these compounds.

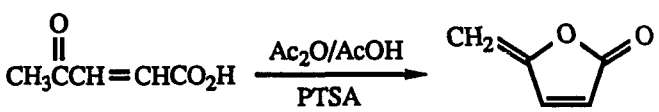
The fact that the butenolide ring is present in so many different natural products explains why there are so many methods available for the synthesis of this class of compounds.[9] However, many of these do not qualify as general, because they are only useful for specific cases. Therefore, the following discussion of the synthesis of butenolides concerns some of the more general methods only.

One of the common methods for the synthesis of butenolides involves the intramolecular cyclization of various keto- and diketo-acids and their derivatives. One of the first butenolides obtained was angelica lactone, synthesized as early as 1885 from levulinic acid (eq. 1).[10]



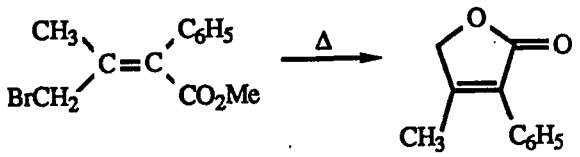
(1)

When β-acetylacrylic acid is heated with a mixture of acetic anhydride and acetic acid, protoanemie is obtained (eq. 2).[11] Substituted protoanemines have been obtained in a similar fashion.[12]



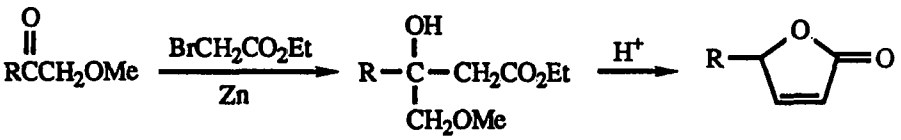
(2)

Another synthesis of butenolides involves the thermal cyclization of γ-bromo-α,β-unsaturated acids. Several groups of researchers have reported that these acids and their methyl esters will thermally lactonize to afford substituted butenolides.[13-15] One such example is shown below (eq. 3).



(3)

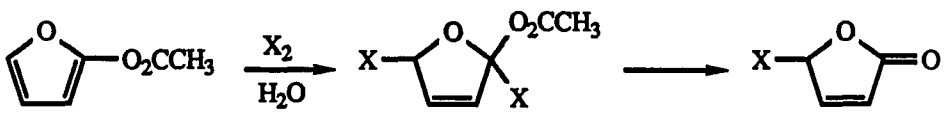
Another widely used method for the synthesis of butenolides and steroidal lactones is the Reformatsky reaction (eq. 4). This reaction, first used in 1912, has



(4)

been used by numerous investigators in different applications while being modified extensively.[16-18]

Butenolides have also been synthesized from furans. The reaction of 2-acetoxyfuran with chlorine or bromine in the presence of water or lead tetraacetate results in the synthesis of γ-halo or γ-acetoxybutenolides (eqs. 5, 6).[19]



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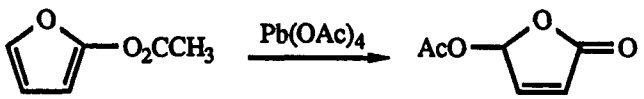
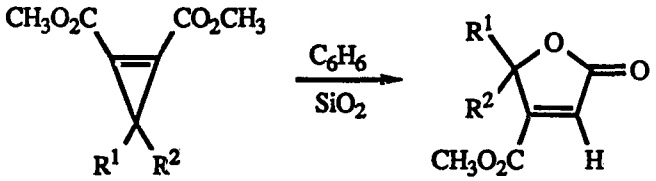


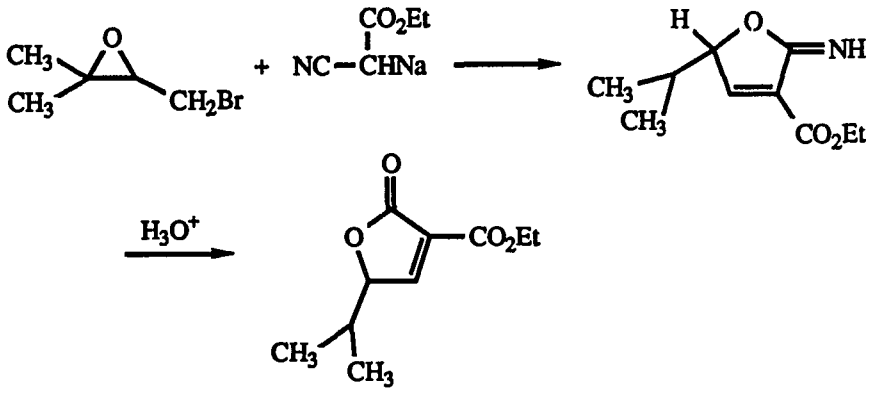
(6)

There are several methods available for the synthesis of butenolides from cyclopropanes[20-23] and cyclobutanes.[24] One method in which cyclopropanedicarboxylic esters rearrange in benzene in the presence of silica gel is shown below (eq. 7).[23]



(7)

Epoxides have also been used for the synthesis of butenolides.[25,26] One such example is shown in equation 8.[25] Another synthesis involving epoxides is shown in equation 9.[26] Here epoxidation of α,β-unsatutated acids followed by heating with a catalytic amount of acid produces β-hydroxy-γ-lactones. Subsequent dehydration of the lactones results in the formation of butenolides.



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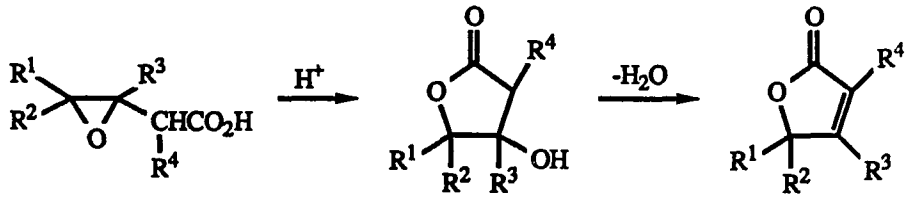
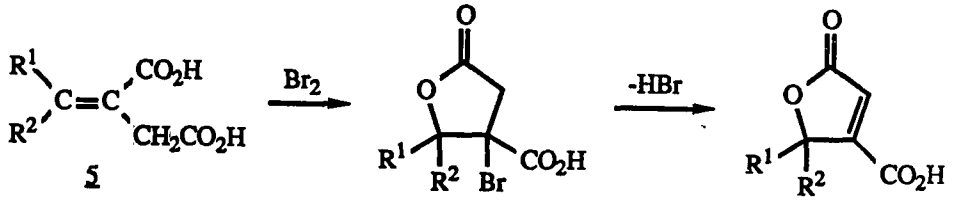


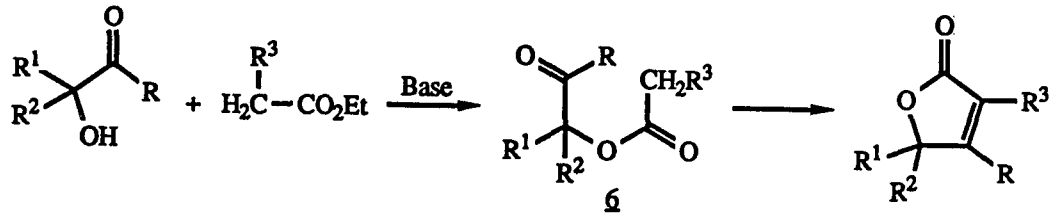
(9)

Stobbe has shown that itaconic acid derivatives similar to 5 add bromine to give bromolactones which on dehydrobromination yield butenolides (eq. 10).[27]



(10)

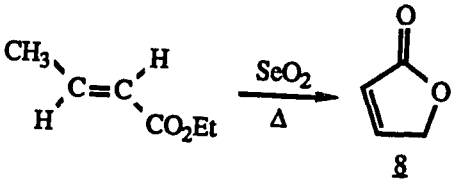
An important disadvantage of the above methods is the difficulty of introducing functionality into the butenolide ring. Because of this, the condensation of α-hydroxyketones with esters containing active methylene groups may be regarded as a general method for the synthesis of butenolides containing functional groups.[18] Condensation of the α-hydroxyketone with the ester leads to compounds such as 6. Compound 6, in the presence of alkaline catalysts such as sodium ethoxide cyclizes to the butenolide 7. The group R^3 must be an electron-withdrawing group that facilitates formation of the anion of compound 6 (eq. 11).



(11)

6

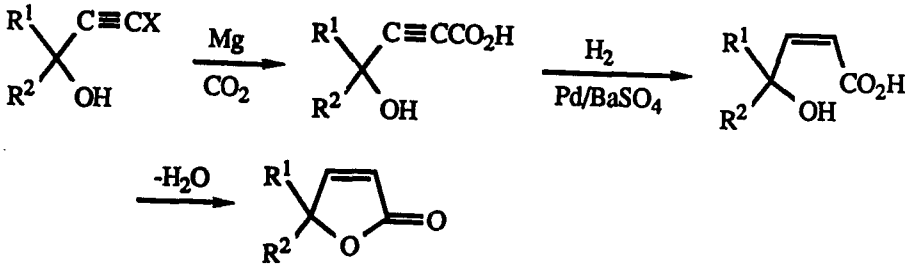
There are also several organometallic approaches used for the synthesis of butenolides in addition to the methods using organopalladium chemistry mentioned in Part I of this thesis. When ethyl crotonate is heated with selenium dioxide, the simplest butenolide 8 is obtained (eq. 12).[28] Presumably allylic oxidation occurs followed by lactonization.



(12)

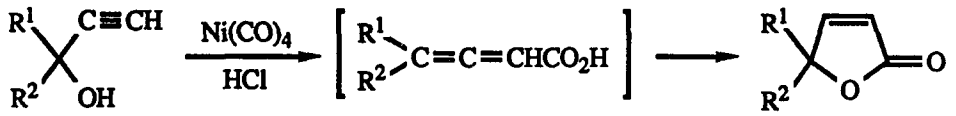
8

Acetylenecarboxylic acids, when reduced to olefinic acids, can cyclize to butenolides upon heating (eq. 13).[29] The requisite acetylenic compounds can be readily prepared via the Grignard reagent as shown.



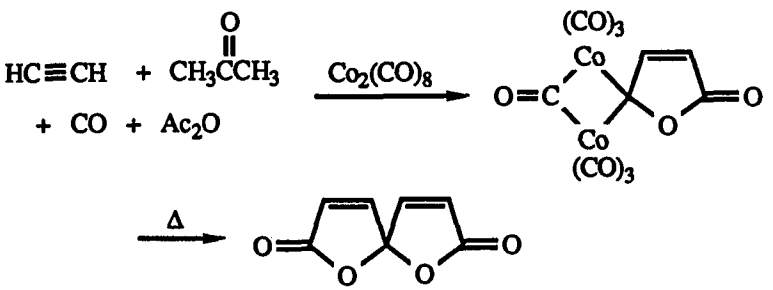
(13)

A variation of this reaction is the conversion of a propargylic alcohol into a butenolide upon heating with nickel carbonyl in a butanol-hydrochloric acid mixture (eq. 14).[30] It is suggested that the reaction proceeds via an allene carboxylic acid.



(14)

Sternberg et al.[31] reported the synthesis of a butenolide when acetylene was heated with acetone and acetic anhydride in an autoclave at 100°C and a pressure of 250 atmospheres in the presence of dicobalt octacarbonyl (eq. 15).

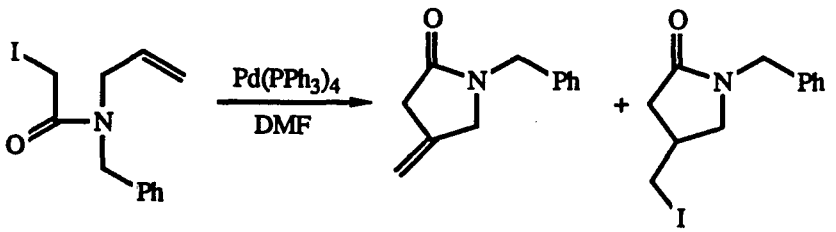


(15)

Although the methods discussed above for the synthesis of butenolides are not a complete list, they are some of the more general methods available, accompanied by some of the organometallic methods which have been employed previously.

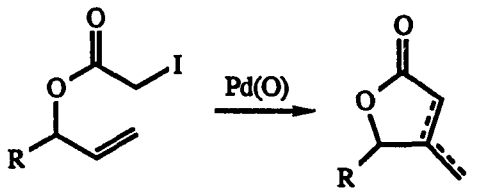
RESULTS AND DISCUSSION

Transition metal reagents have proven highly valuable for the cyclization of α-haloamides and α-haloketones having internal double bonds. Nickel,[32] copper,[33] ruthenium,[33] antimony[34] and palladium[35,36] have all been used for such cyclizations. Mori et al.[35] have reported that α-haloamides having internal olefins react with catalytic amounts of $Pd(PPh_3)_4$ in the presence of proton sponge to produce pyrrolidines (eq. 16).

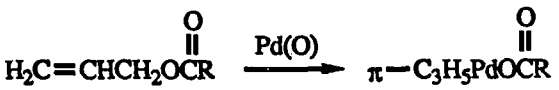


(16)

Applying this same methodology to the cyclization of α-haloesters of allylic alcohols to afford unsaturated lactones or butenolides (eq. 17) is much more problematical as a route to butenolides in view of the known ability of palladium(0) to react with allylic acetates to form π-allylpalladium compounds (eq. 18).[37]

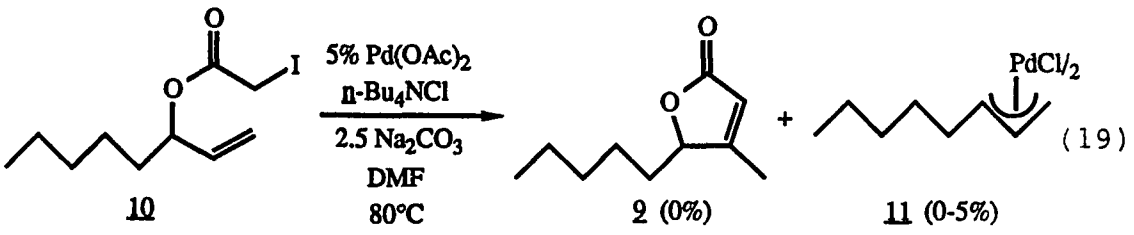


(17)



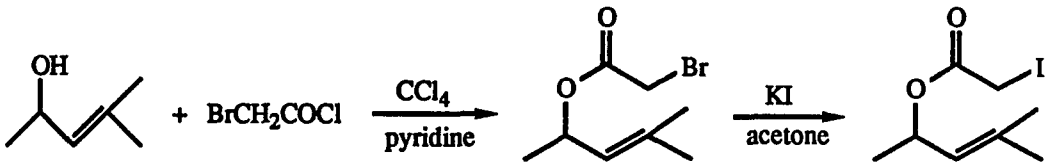
(18)

When the conditions employed by Larock and Babu for the synthesis of nitrogen heterocycles were applied to the synthesis of the butenolide 9 using the α-iodoacetate ester 10 as the substrate, only the π-allylpalladium compound 11 was obtained (eq. 19).[38] With the appearance of the π-allylpalladium compound 11 and the obvious lack of formation of the butenolide 9, oxidative addition of the palladium(0) to the carbon-oxygen bond must be more facile than is oxidative-addition to the carbon-iodide bond.



(19)

Osakada et al.[39] have reported that substitution at the remote end of the allyl group slows or prevents π-allyl-palladium formation. With this in mind, the preparation of the substrate 12 was undertaken (eq. 20). Upon removal of the solvent during isolation, the α-iodo ester 12 was found to decompose into an intractable solid within 5 minutes. This was somewhat surprising because compound 10 appeared to be a quite stable oil.



(20)

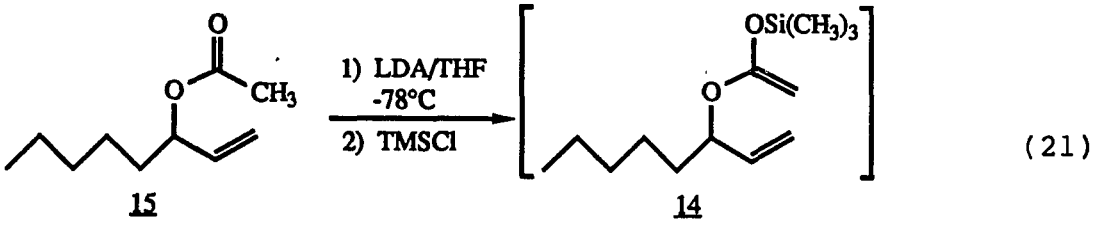
12

With the appearance of reports by Ito et al.[40] and Kende et al.[41] of the palladium(II)-promoted cyclization of olefinic silyl enol ethers, we examined a slightly different approach for the synthesis of the butenolide 9 (eq. 21). Compound 13 arises from the Claisen rearrangement of the enol silyl ether 14. Ireland et al.[42] reported that the t-butyldimethylsilyl enol ether corresponding to 14 rearranges with a half life of 6 minutes at 32°C. He states that the lithium enolates rearrange more slowly or only upon heating. Knowing this, we were encouraged to examine the reaction shown in equation 22. The reaction in equation 22 is the same as that shown in equation 21 except for the absence of trimethylsilyl chloride. The results of several different reaction conditions employed to effect this transformation are shown in Table 1.

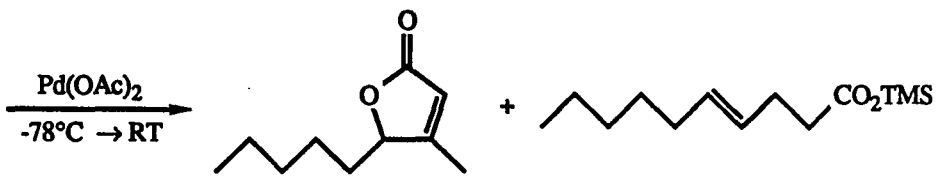
As seen in Table 1, significant amounts of the π-allyl-palladium compound 11 were formed in addition to the butenolide 9. Ultimately, the results shown in Table 1 discouraged any further examination of this pathway for the preparation of butenolides.

Table 1. Preparation of the butenolide 9 via palladium(II)-assisted cyclization of the lithium enolate 16

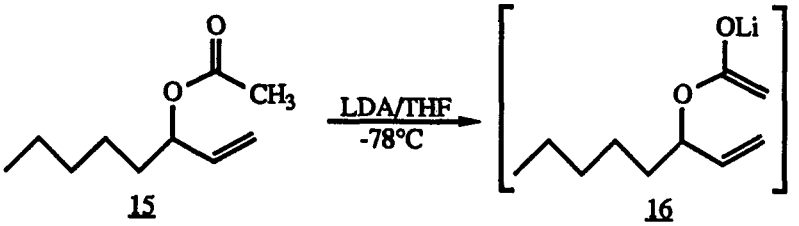
Entry	Equiv. LDA	Pd(II) salt	Temp. (°C)	Product(s) (% yield) 9	11
1	1.1	$Pd(OAc)_2$	0	38	40
2	1.1	$Pd(OAc)_2$	-78	34	33
3	1.1	$PdCl_2 \cdot (CH_3CN)_2$	-78	---	
4	2.3	$Pd(OAc)_2$	-78	21	7



15 14 (21)



9 (36%) 13 (20%)

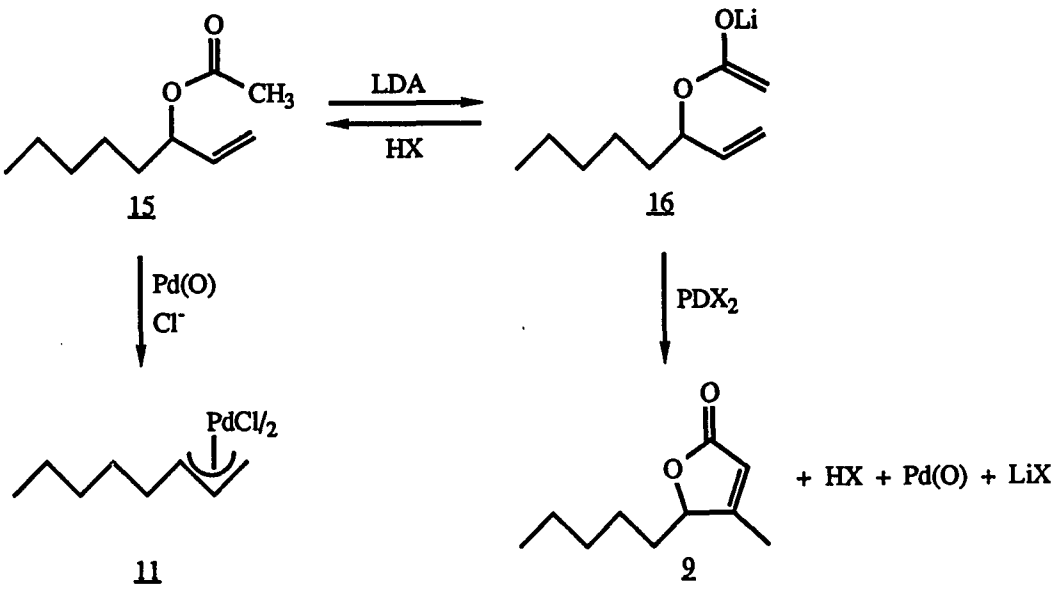


15 16 (22)

Pd(II)
Temp → RT
15 h
9 + 11

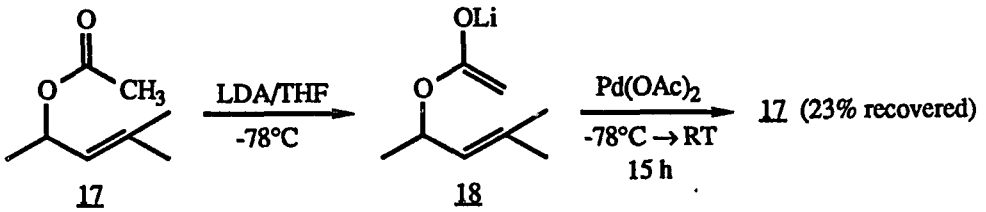
The π-allylpalladium compound 11 must arise from palladium(0) reacting with the ester 15. The ester 15 must be regenerated from the enolate 11 by the reaction of it with the one equivalent of acid that is generated upon formation of the butenolide 9. This process is shown in Scheme 1. The use of $PdCl_2 \cdot (CH_3CN)_2$ as the palladium(II) reagent resulted in no identifiable products being formed (Table 1, entry 3). The use of 2.3 equivalents of LDA did not improve the yield of the butenolide 9. It was hoped that the excess LDA would be efficient as a base for the removal of the acid generated upon butenolide formation.

Scheme 1

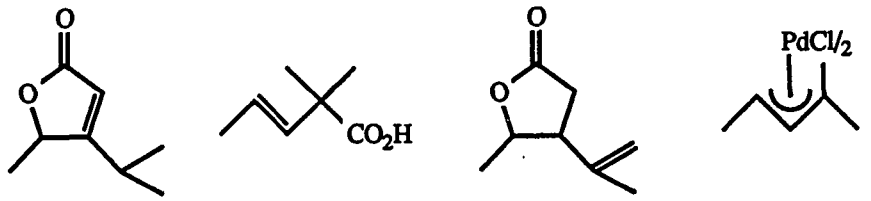


Knowing that the use of a more highly substituted allylic moiety might reduce or possibly eliminate π-allyl-palladium formation prompted the preparation of the allylic

acetate 17. Subjecting 17 to the above conditions (Table 1, entry 2) produced none of the desired product 19 (eq. 23). Other possible products that were expected from this reaction were compounds 20, 21, and 22. However, only compound 17 was detected in the reaction mixture.



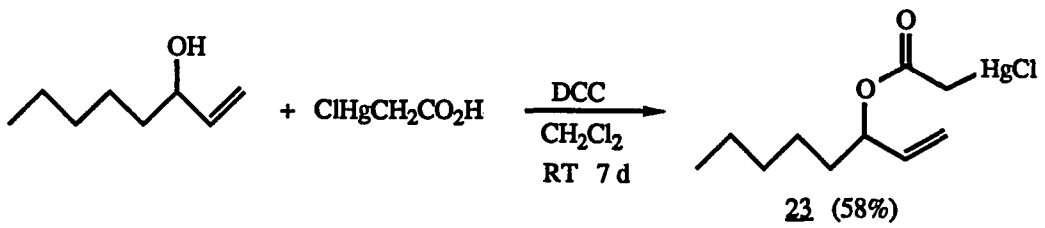
17 18 (23)



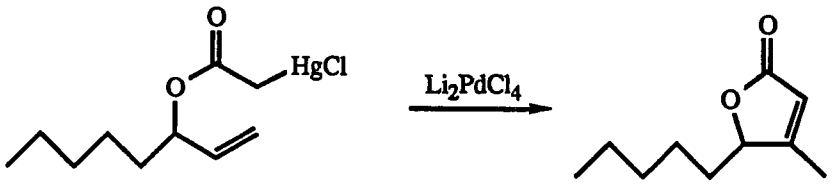
19 21 21 22

In order to effectively carry out the synthesis of butenolides, a slightly different approach towards the preparation of the desired organopalladium intermediates was undertaken. It is known that palladium(II) salts will effectively transmetallate with organomercurials to give the corresponding organopalladium species. Subsequently, the organomercurial 23 was prepared by the DCC assisted condensation of the readily available α-chloromercurioacetic acid with 1-octen-3-ol (58% yield, eq. 24). Cyclization of the organomercurial 23 using one equivalent of Li_2PdCl_4 in a suitable solvent was found to occur in a matter of hours to yield the butenolide 9 (eq. 25). Several sets of reaction

conditions were examined. The results are presented in Table 2.



23 (58%) (24)



23 9 (25)

As seen from the results presented in Table 2, the synthesis of the butenolide 9 can be effected by the reaction of the organomercurial 23 with Li_2PdCl_4. Entries 1 and 2, Table 2, indicate that the use of a mixed solvent system such as 5:1 THF/HMPA or 5:1 THF/DMF and employing 2 equivalents of a base such as triethylamine resulted in the highest isolated yield of the butenolide 9. Entry 3, Table 2, indicates that potassium carbonate will also function reasonably well as the base, whereas entries 4 and 5 illustrate that a base is necessary to obtain decent yields of butenolide. Entries 6-9, show the effects of different solvents on the reaction outcome.

Since it appears that butenolides can be prepared via the palladium(II)-assisted cyclization of organomercurials,

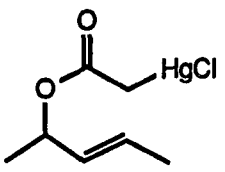
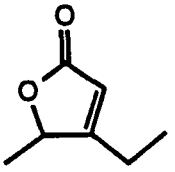
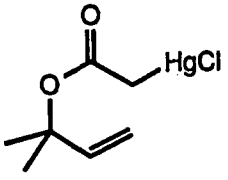
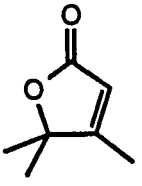
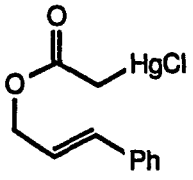
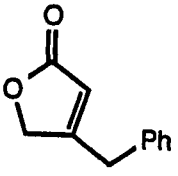
Table 2. Cyclization of organomercurial 23 to butenolide 9

Entry	Base	Solvent	Time (h)	Yield of 9 (% isolated)
1	Et_3N	5:1 THF/DMF	11	86
2	Et_3N	5:1 THF/HMPA	26	85
3	K_2CO_3	5:1 THF/DMF	7	73
4	--	5:1 THF/DMF	6	55
5	--	5:1 THF/HMPA	28	45
6	Et_3N	CH_3CN	19	61
7	Et_3N	THF	26	43
8	Et_3N	CH_2Cl_2	30	39
9	Et_3N	DMF	12	72

as presented in equation 25, several other organomercurials were prepared and cyclized. The results are presented in Table 3.

The cyclization of organomercurial 24 proceeded without incident. The isolated yield of the butenolide 25 using 5:1 THF/HMPA as the solvent was 63% (entry 1, Table 3). The reaction took 4 d at room temperature for the complete disappearance of the starting material 24 as determined by TLC analysis. Running the reaction with 5:1 THF/DMF as the solvent gave a 38% isolated yield of the butenolide 25 in 4

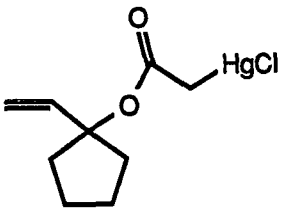
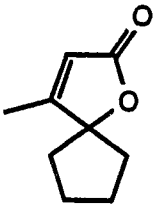
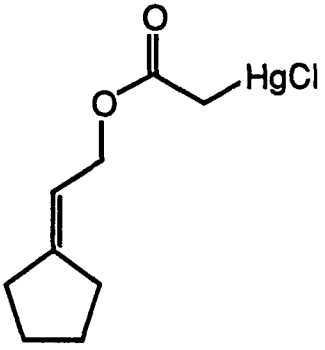
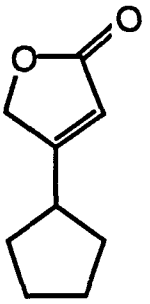
Table 3. Preparation of butenolides via Li_2PdCl_4 assisted cyclization of organomercurials

Entry	Substrate (% isolated yield)	Product (% isolated yield)	Conditions[a]
1	 <u>24</u> (55)[b]	 <u>25</u> (63)	5:1 THF/HMPA; Et_3N; RT, 4 d
2	<u>24</u>	<u>25</u> (38)	5:1 THF/DMF; Et_3N; RT, 4 d
3	<u>24</u>	<u>25</u> (51)	5:1 THF/DMF; Et_3N; RT, 4 d; then reflux, 1 h
4	 <u>26</u> (28)[b]	 <u>27</u> (65)	5:1 THF/DMF; Et_3N; RT, 2 h
5	 <u>28</u> (81)[b]	 <u>29</u> (29)	5:1 THF/DMF; Et_3N; RT, 24 h

[a]The reaction was run at room temperature (RT) until no starting substrate was seen by TLC.

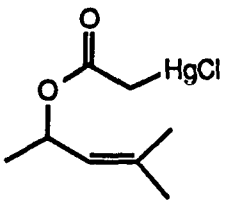
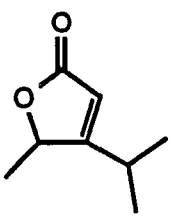
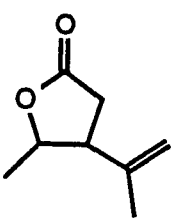
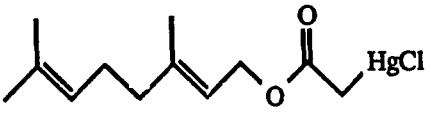
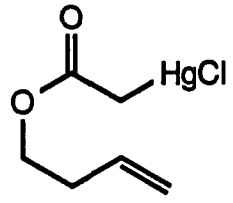
[b]The number in parentheses is the % isolated yield of the organomercurial via the DCC-assisted condensation of the allylic alcohol and α-chloromercurioacetic acid.

Table 3. Continued

Entry	Substrate (% isolated yield)	Product (% isolated yield)	Conditions[a]
6	<u>28</u>	<u>29</u> (71)	5:1 THF/DMF; Et_3N; RT, 23 h; then reflux, 1 h
7			5:1 THF/DMF; Et_3N; RT, 6 h
	<u>31</u> (75)[c]	<u>32</u> (56)	
8			5:1 THF/DMF; Et_3N; RT, 3 d
	<u>33</u> (72)[c]	<u>34</u> (19)	
9	<u>33</u>	<u>34</u> (30)	5:1 THF/DMF; Et_3N; RT, 3 d; then reflux 1 h

[c]The number in parentheses is the % isolated yield of the organomercurial prepared by trapping the lithium enolate of the corresponding ester with mercuric chloride.

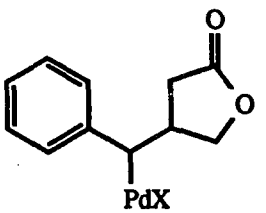
Table 3. Continued

Entry	Substrate (% isolated yield)	Product (% isolated yield)	Conditions[a]
10	  		5:1 THF/DMF; Et_3N; RT, 5 d
	36 (60)[b]	37 (49) 38 (16)	
11	36	37 (47) 38 (42)	5:1 THF/DMF; Et_3N; RT, 3 d
12	36	37 (69) 38 (26)	5:1 THF/HMPA; Et_3N; RT, 3 d
13	36	37 (62) 38 (14)	HMPA; Et_3N; RT, 3 d
14	36	37 (38) 38 (6)	DMF; Et_3N; RT, 3 d
15		----	5:1 THF/HMPA; Et_3N; RT, 3 d
	39 (36)[b]		
16		----	5:1 THF/HMPA; Et_3N; RT, 4 d
	42 (61)[b]		

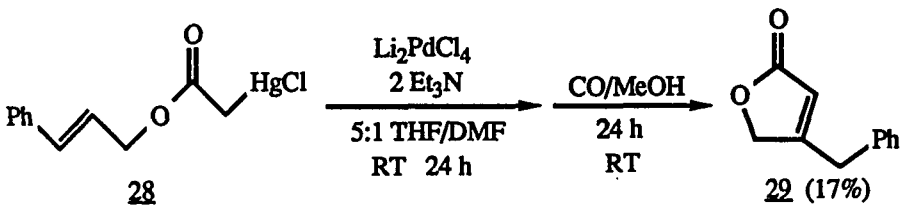
d at room temperature. This yield could be increased to 51% by refluxing the reaction for 1 h prior to workup.

Cyclization of the organomercurial 26 provided the butenolide 27 in 65% yield and in only 2 h. Apparently the geminal dimethyl groups sterically encourage reaction between the organopalladium intermediate and the olefin.

The cinnamyl-substituted organomercurial 28 would only cyclize in 29% isolated yield when carried out at room temperature, but the yield of the butenolide 29 increased to 71% when the reaction was refluxed for 1 h after the disappearance of 28 as determined by TLC analysis. Apparently, the intermediate benzylic palladium species 30, or some other intermediate, is stable enough to require heating in order to drive the reaction to completion. In order to see if there was some intermediate palladium species that was trappable, such as 30, the reaction was run under a carbon monoxide atmosphere as shown in equation 26. The only product isolated from the reaction mixture was the butenolide 29 in 17% yield.



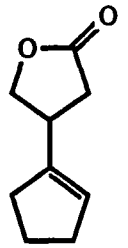
30



(26)

As seen in Table 3, entry 7, the organomercurial 31 cyclized forming the butenolide 32 in 56% yield in 6 h using 5:1 THF/DMF as the solvent.

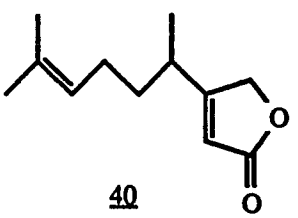
The organomercurial 33 was cyclized using the conditions shown in Table 3, entries 8 and 9. The maximum yield of compound 34 obtained was 30% (Table 3, entry 9). It was somewhat surprising that none of the lactone 35 was formed considering the results obtained below for the cyclization of organomercurial 36.



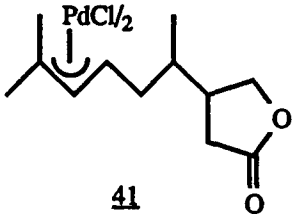
35

The organomercurial 36 was cyclized under several sets of reaction conditions (Table 3, entries 10-14). Under all of the conditions employed, some amount of the undesired lactone 38 was formed. The best yield obtained of the butenolide 37 was 69% using the conditions shown in Table 3, entry 12.

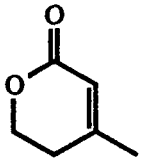
The organomercurial 39, when subjected to the cyclization conditions shown in Table 3, entry 15, resulted in no identifiable products being obtained. Possible products expected from this reaction were compounds 40 and 41. The π-allylpalladium product 41 was expected if the palladium migrated towards the olefin. Recent work by Larock indicates that this could be possible.[43]



40



41

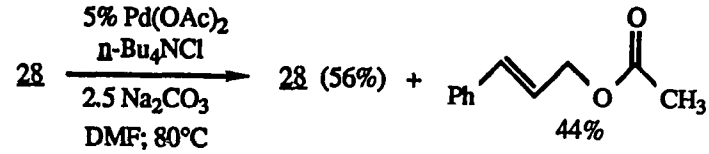


43

The homoallylic mercurial 42 was subjected to the conditions shown in Table 3, entry 16. No identifiable products were obtained from this reaction. The expected product was compound 43.

Since the use of a full equivalent of palladium becomes expensive when one does large scale reactions, the organomercurial 28 was subjected to the catalytic palladium conditions shown in equation 19 (eq. 27). As can be seen from the results, no cyclization occurred and a significant quantity of the protonolysis product was obtained. The proton source needed for the formation of the product probably was water in the tetra-n-butylammonium chloride. The reaction was repeated with extra precautions being taken

to exclude all water from the system, but only unreacted starting material was recovered.

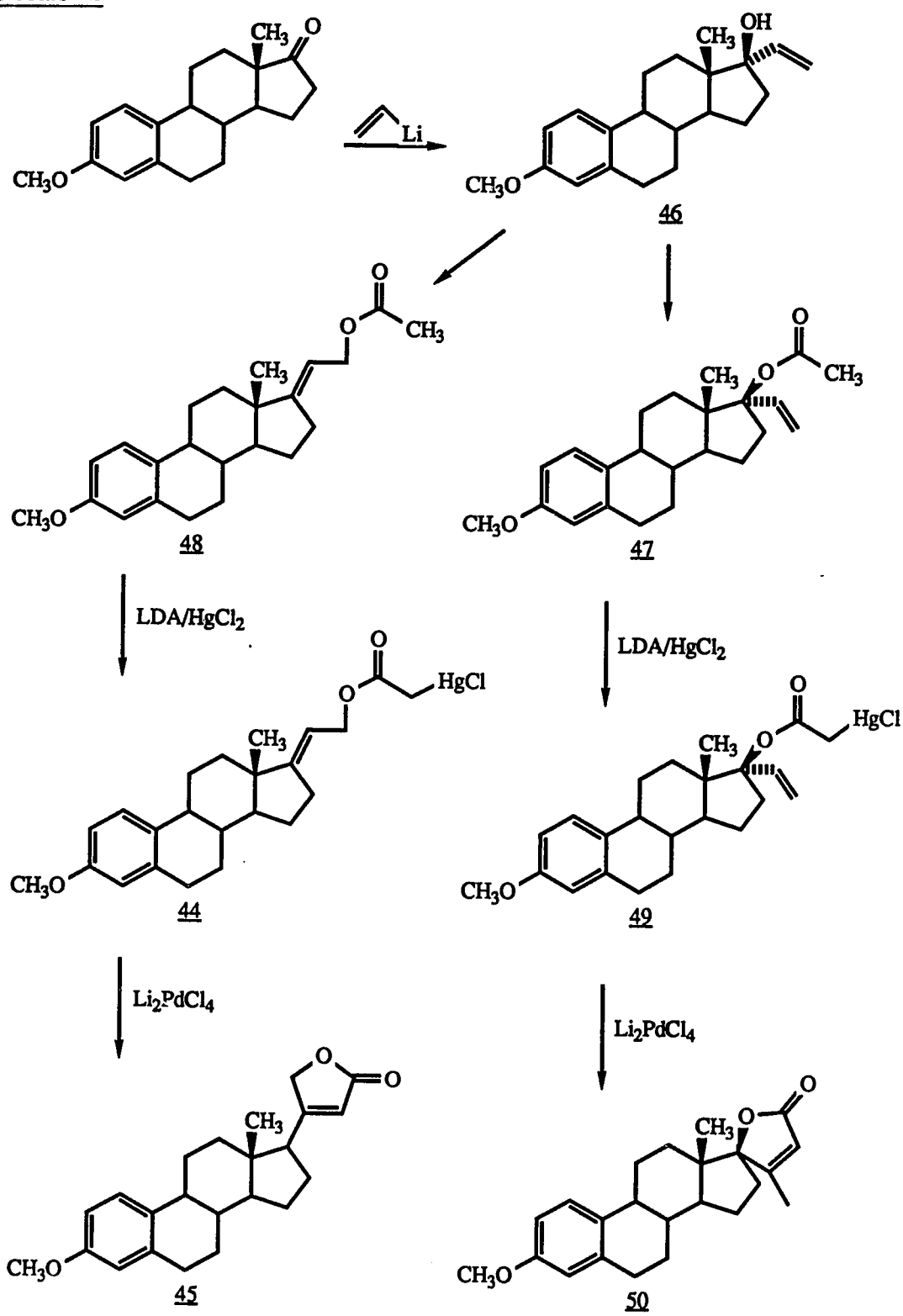


(27)

Since the successful synthesis of a variety of butenolides containing various substitution patterns was achieved, a slightly more complex system was examined. It was proposed that the palladium(II)-assisted cyclization of the organomercurial 44 would provide product 45. The conversion of compound 44 to 45 would be a good model system for the synthesis of cardenolides.

In order to synthesize the organomercurial 44, either the allylic alcohol 46 or the allylic acetate 47 was required. Scheme 2 shows the proposed synthesis of both. Synthesis of the allylic alcohol 46 proceeded as reported in the literature.[44] Synthesis of 48 following the literature procedure worked well.[44] Use of Overman's procedure[45] for the synthesis of 48 from 47 could not be done due to the fact that all attempts at acetylating 46 to form ester 47 proved futile. Attempted conversion of the allylic acetate 48 into the organomercurial 44 via the lithium enolate resulted in extensive decomposition of compound 48. Kanojia states that excess vinyl lithium, when employed for the synthesis of 46 will decompose the steroid via deprotection

Scheme 2


CH3 O
CH3O
Li
CH3 OH
CH3O
46
O
O
CH3
CH3
CH3O
48
CH3 O
O
CH3
CH3O
47
LDA/HgCl2
LDA/HgCl2
O
O
HgCl
CH3
CH3O
44
CH3 O
O
HgCl
CH3O
49
Li2PdCl4
Li2PdCl4
O
O
O
CH3
CH3O
45
CH3 O
O
O
CH3O
50

of the 3-methoxy group.[46] This could account for the decomposition seen when the enolate of 48 was prepared.

It should also be stated that if the allylic acetate 47 could have been prepared, synthesis of the organomercurial 49 may have been possible. The palladium(II)-assisted cyclization of 49 should provide 50. The conversion of compound 49 to 50 could be a model system for the synthesis of γ-steroidal lactones which are important biological regulators.

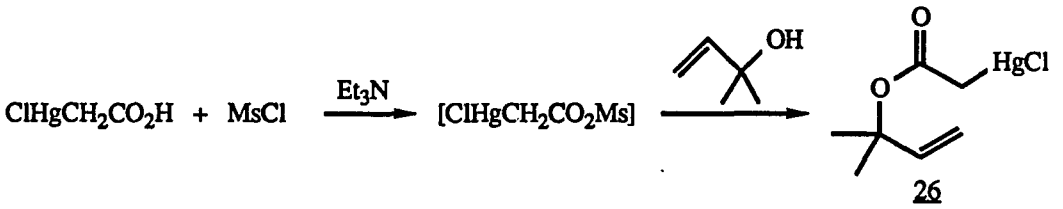
As seen in equation 24 and Table 3, the yields for the synthesis of the organomercurials via the DCC-assisted condensation of the allylic alcohol and α-chloromercurio-acetic acid have room for improvement. Generally the more highly substituted the allylic alcohol, the lower the yield. Even the addition of 4-N,N-dimethylaminopyridine, which has been reported in the literature to improve the yields of such reactions, failed to improve the yield or shorten the reaction time.[47]

Use of the acid chloride of α-chloromercurioacetic acid for the synthesis of the esters is not possible. Although it is known that mercuric chloride will add to ketene at low temperature to form the acid chloride 51, the reaction is reversible and at the temperatures required for reaction with the alcohol, the acid chloride is not stable.[48] There

is also no report in the literature of the formation of the anhydride 52 of α-chloromercurioacetic acid.

51 52

Preparation of mixed anhydrides has been reported as a method of activating acids for esterification reactions.[49] The use of mesyl chloride as the reagent for the formation of the mixed anhydride with α-chloromercurioacetic acid was examined (eq. 28). The alcohol that was reacted with this mixed anhydride was the highly hindered 3-methyl-2-buten-3-ol. The results of these reactions are shown in Table 4.



(28)

The results indicate that neither temperature nor solvent has much effect on this reaction. None of the conditions employed resulted in a significant yield of the organomercurial 26.

Another related reaction involves activation of acids by phenyldichlorophosphate.[50] When this reagent was employed using α-chloromercurioacetic acid and 3-methyl-2-buten-3-ol, a bright yellow unidentifiable precipitate formed. None of

Table 4. Preparation of the organomercurial 26 via the mixed anhydride

Entry	Conditions	Isolated yield of 26 (%)
1	CH_2Cl_2; -20°C, 0.5 h; then -20°C -> RT, 5 h	16
2	THF; -20°C, 0.5 h; then -20°C -> RT, 5 h	< 5
3	CH_2Cl_2; 0°C, 1.0 h; then 0°C -> RT, 5 h	< 5
4	CH_2Cl_2; -78°C, 1.0 h; then -78°C -> RT, 6 h	< 5
5	CH_2Cl_2; -20°C, 1.0 h; then -20°C -> RT, 6 h	< 5
6	THF; -20°C, 1.0 h then -20°C -> RT, 6 h	< 5

the desired product 26 was formed. Apparently, this phosphate reagent does not tolerate mercurial functionality.

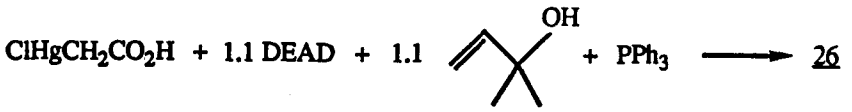
Another convenient and mild synthesis of esters involves the use of DEAD and triphenylphosphine to couple acids and alcohols.[51] Subsequently, the following reactions were performed (eq. 29, Table 5). As can be seen in Table 5,

Table 5. Preparation of the organomercurial 26 using triphenylphosphine and DEAD

Entry	Solvent	Temperature	Time	Isolated Yield of 26 (%)
1[a]	THF	RT	5 h	17
2	THF	RT	5 h	18
3	THF	0°C -> RT	5 h	22
4	CH_2Cl_2	0°C -> RT	5 h	14
5	diethyl ether	0°C -> RT	5 h	5
6	DMF	0°C -> RT	5 h	4
7	acetone	0°C -> RT	5 h	16

[a]This reaction was run at 1/10 the concentration of the others.

entries 1 and 2, the reaction concentration affects the yield of 26 very little. Due to the low solubility of α-chloromercurioacetic acid, it was thought that more dilute conditions might be advantageous. Entry 3 indicated that starting the reaction at a lower temperature did improve the yield of 26 somewhat. Again due to the low solubility of

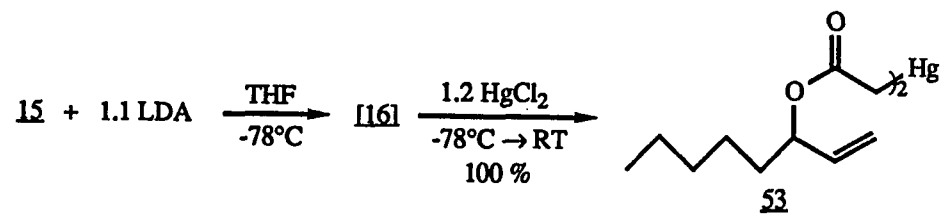


(29)

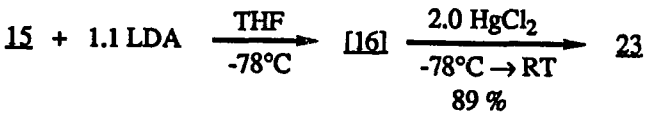
the acid, it was hoped that changing the solvent might improve the yield of 26. However, the yield obtained in

entries 3 to 7 indicated little correspondence between the solubility of the acid and the yield obtained. Under the reaction conditions, the acid was completely soluble in DMF and acetone. However, the yields obtained using these two solvents were not the highest.

Another route towards the synthesis of these esters involves the trapping of the lithium enolates with mercuric chloride at low temperatures. When the ester 15 was treated with 1.2 equivalents of LDA in THF at -78°C, the enolate 16 was formed. Upon addition of 16 to 1.2 equivalents of mercuric chloride at -78°C, the dialkylmercurial 53 was formed in quantitative yield (eq. 30). When the same reaction was carried out using 2 equivalents of mercuric chloride were used, the organomercurial 23 was formed in 89% isolated yield (eq. 31). This method has proved to be the most reliable method for the synthesis of the α-chloromercurio-acetate esters thus far.



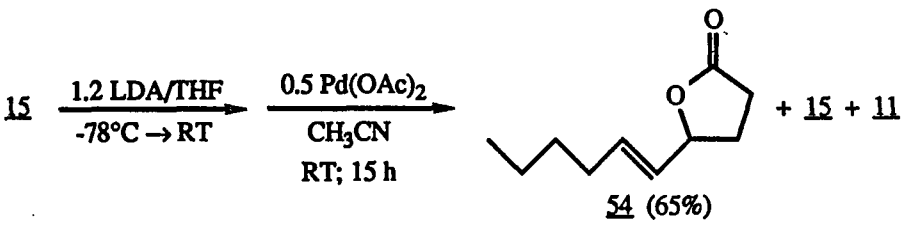
(30)



(31)

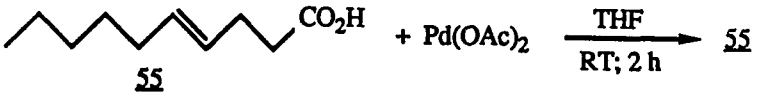
Another interesting observation relating to the synthesis of butenolides via the method shown earlier in

equation 22 is shown in equation 32. It was observed that the product arising from the Claisen rearrangement of the enolate would cyclize to form the lactone 54 in the presence of a palladium(II) species. The isolated yield of lactone 54 for this reaction (eq. 32) was 65% based on the amount of palladium acetate used. Also obtained from this reaction was an undetermined amount of the starting ester 15 and a small quantity of a yellow solid tentatively identified as the π-allylpalladium compound 11.



(32)

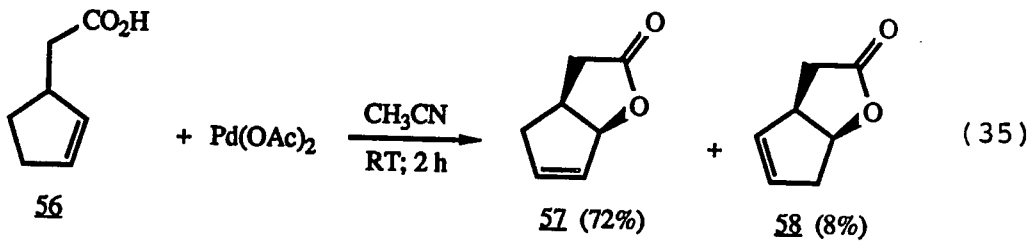
At this point, the carboxylic acid 55 was prepared and subjected to the palladium cyclization conditions shown in equations 33 and 34.



(33)

(34)

Another unsaturated acid, 56, was also subjected to the conditions shown in equation 34 (eq. 35). The bicyclic lactones 57 and 58 were obtained in yields of 72% and 8%, respectively.



56 57 (72%) 58 (8%) (35)

CONCLUSION

A variety of substituted butenolides were synthesized via the palladium(II)-assisted cyclization of organomercurials. Limitations of other approaches towards the preparation of butenolides were also determined.

EXPERIMENTAL SECTION

Equipment

Proton NMR spectra were recorded on a Nicolet NT-300 spectrometer. ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer operating at 75 MHz for carbon nuclei. Infrared spectra were recorded on either a Beckman Acculab 2 or an IBM IR-98 spectrometer. Exact mass spectral data were obtained on a Kratos MS-50 high resolution spectrometer. Gas chromatographic-mass spectral analysis were performed on a Finnigan 4000 spectrometer. Gas chromatographic analyses were done on a Varian 3700 gas chromatograph. Melting points were done with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc.

Reagents

All compounds were used directly as obtained commercially unless otherwise noted. All starting materials were purchased from Aldrich (2-methyl-3-penten-2-ol, cinnamyl alcohol, 3-buten-1-ol, cyclopentanone, 2-cyclopentene-1-acetic acid, geraniol, n-butyl lithium, diisopropylamine, mesityl oxide, acetyl chloride, dicyclohexylcarbodiimide, sodium borohydride, mercuric chloride, mercuric acetate), J. T. Baker (3-penten-2-ol, lithium chloride), PCR Research Chemicals (1,1-difluoro-

ethylene), Alpha (vinylmagnesium bromide, 3-methoxy estrone, 1-octen-3-ol). Tetrahydrofuran was distilled from benzophenone-sodium ketyl; N,N-dimethylformamide was distilled from calcium hydride; diisopropylamine was distilled from sodium hydroxide; acetyl chloride was distilled from calcium hydride; trimethylsilyl chloride was distilled from calcium hydride. Lithium chloride was dried at 120°C at 0.5 mm Hg prior to use. Palladium chloride and palladium acetate were generously supplied by Johnson-Matthey, Inc. 4-Methyl-3-penten-2-ol was prepared by a literature procedure.[52] 1-Ethenyl-1-cyclopentanol acetate was prepared following the procedure of Song.[53] The allylic acetate required for the synthesis of the organomercurial 33 was prepared following the procedure of Overman.[45] 3-Acetoxy-1-octene was prepared following a literature procedure.[42] α-Chloromercurioacetic acid was prepared following a literature procedure.[54] Compounds 10,[42] 17,[42] 46,[44] 48,[44] and 55[42] were prepared following literature procedures.

All α-chloromercurioacetate ester syntheses were done using the following general procedures.

Preparation of 23 via procedure A: DCC-assisted condensation. A solution of 1.000 g (3.53 mmol) of α-chloromercurioacetic acid, 1.000 g (5.0 mmol) of dicyclohexylcarbodiimide, and 0.53 ml (3.53 mmol) of

1-octen-3-ol in 20 ml of methylene chloride was stirred at room temperature for 7 d. The reaction was then diluted with 25 ml of methylene chloride and filtered to remove the urea. The solvent was then removed by rotary evaporation and the crude product purified by column chromatography on silica gel with 2:1 hexanes/ethyl acetate as eluent to yield a 2:1 mixture of the product 23 and 1-octen-3-ol (R_f = 0.71). This mixture was placed under vacuum at 0.5 mm Hg for 12 h at which time the 1-octen-3-ol was found to be removed to yield 0.83 g (58% yield) of the organomercurial 23. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 7.0 Hz, CH_3), 1.29 (m, 5 H, CH_2's), 1.58 (m, 3 H, CH_2's), 2.71 (s, 2 H, CH_2Hg), 5.21 (m, 2 H, OCH, =CH-), 5.76 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.81, 25.89, 32.06, 32.86, 35.66, 62.90, 123.33, 143.89, 170.88; IR ($CDCl_3$) 3010, 2960, 1690, 1440, 1210, 1040, 940 cm^{-1}; Anal. calcd for $C_{10}H_{17}O_2HgCl$: C, 29.63; H, 4.24; Hg, 49.49. Found: C, 29.41; H, 3.96; Hg, 49.13.

Compound 36 via procedure A: 60% yield; R_f = 0.57, 2:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 1.71 (d, 3 H, J = 3.9 Hz, $=C(CH_3)_2$), 1.72 (d, 3 H, J = 3.9 Hz, $=C(CH_3)_2$), 2.69 (s, 2 H, CH_2Hg), 5.14 (dq, 1 H, J = 1.2 Hz, J = 7.8 Hz, OCH), 5.56 (dq, 1 H, J = 6.3 Hz, J = 9.0 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 14.33, 28.43, 29.76, 29.95, 68.37, 121.92, 134.37, 173.68; IR ($CDCl_3$)

2970, 2930, 2870, 1685, 1445, 1410, 1375, 1250, 1150, 1080, 1060, 1030, 960, 860 cm^{-1}; Anal. calcd for $C_8H_{13}O_2HgCl$: C, 25.47; H, 3.48; Hg, 53.17. Found: C, 25.15; H, 3.41; Hg, 53.01.

Compound 26 via procedure A: 28% yield; R_f = 0.70, 2:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.52 (s, 6 H, $C(CH_3)_2$), 2.68 (s, 2 H, CH_2Hg), 5.12 (d, 1 H, J = 18.3 Hz, cis $=CH_2$), 5.17 (d, 1 H, J = 24.9 Hz, trans $=CH_2$), 6.08 (dd, 1 H, J = 18.3 Hz, J = 24.9 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 28.91, 32.88, 50.60, 120.97, 142.63, 172.05; IR ($CDCl_3$) 2995, 2940, 1710, 1465, 1415, 1380, 1265, 1140, 1085 cm^{-1}; Anal. calcd for $C_7H_{11}O_2HgCl$: C, 23.15; H, 3.06; Hg, 55.23. Found: C, 23.41; H, 3.21; Hg, 54.97.

Compound 28 via procedure A: 81% yield; Mp = 114.5-115.5°C; R_f = 0.36, 2:1 hexanes/diethyl ether; ^1H NMR ($CDCl_3$) δ 2.73 (s, 2 H, CH_2Hg), 4.74 (dd, 2 H, J = 1.2 Hz, J = 6.3 Hz, CH_2O), 6.27 (dt, 1 H, J = 6.6 Hz, J = 15.9 Hz, $CH_2\underline{CH}=$), 6.67 (d, 1 H, J = 15.6 Hz, PhCH=), 7.33 (m, 5 H, Ar); ^{13}C NMR unable to obtain due to low solubility; IR ($CDCl_3$) 3160, 2875, 1720, 1250, 1085 cm^{-1}; Anal. calcd for $C_{11}H_{11}O_2HgCl$: C, 32.13; H, 2.70; Hg, 48.77. Found: C, 32.20; H, 2.83; Hg, 48.53.

Compound 24 via procedure A: 55% yield; R_f = 0.48, 4:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 10.0 Hz, $OCHC\underline{H}_3$), 1.71 (dd, 3 H, J = 3.0 Hz, J = 10.2 Hz,

=CHC$\underline{H}_3$), 2.68 (s, 2 H, CH_2Hg), 5.30 (m, 1 H, OCH), 5.46 (m, 1 H, $CH_3C\underline{H}$=), 5.72 (m, 1 H, OCHCH=); ^{13}C NMR ($CDCl_3$) δ 30.12, 38.38, 40.50, 70.32, 138.76, 140.39, 170.54; IR ($CHCl_3$) 3020, 2960, 2920, 2850, 1680, 1445, 1410, 1250, 1080, 1035, 910, 750 cm^{-1}; mass spectrum m/e 363.20801 (calcd for $C_7H_{11}O_2HgCl$, 363.20752).

Compound 42 via procedure A: 61% yield; R_f = 0.65, 2:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 2.40 (qt, 2 H, J = 1.2 Hz, J = 6.6 Hz, =CH-C$\underline{H}_2$), 2.68 (s, 2 H, CH_2Hg), 4.16 (t, 2 H, J = 6.6 Hz, CH_2O), 5.12 (m, 2 H, $=CH_2$), 5.79 (m, 1 H, =CH-); IR ($CDCl_3$) 3100, 2980, 1720, 1650, 1420, 1380, 1250, 1090, 990 cm^{-1}. Complete characterization was not done because this substate failed to cyclize in the the desired manner.

Preparation of 23 via procedure B: quenching of the lithium enolate with mercuric chloride.

To a stirred solution of 0.726 mmol of lithium diisopropylamide in 4 ml of THF at -78°C under nitrogen was added a solution of 0.1030 g (0.605 mmol) of the ester 15 in 2 ml of THF. The resulting solution was stirred at -78°C for 15 min at which time it was transferred via cannula to a stirred suspension of 0.3285 g (1.21 mmol) of mercuric chloride in 4 ml of THF at -78°C. The resulting mixture was allowed to warm to room temperature and then stirred for an additional 15 h. The solution was then quenched with 1 ml

of saturated aqueous ammonium chloride, diluted with 20 ml of diethyl ether and then washed with 3 times 15 ml of saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The crude product was purified by column chromatography on silica gel with 2:1 hexanes/ethyl acetate to yield 0.2182 g (89% yield) of an oil. The spectral data for this compound were identical with that reported above for 23.

Compound 33 via procedure B: 72% yield; R_f = 0.33, 3:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.66 (m, 4 H, $CH_2(C\underline{H}_2)_2CH_2$), 2.30 (t, 4 H, J = 6.0 Hz, $C\underline{H}_2(CH_2)_2C\underline{H}_2$), 2.68 (s, 2 H, CH_2Hg), 4.56 (dd, 2 H, J = 0.9 Hz, J = 6.3 Hz, CH_2O), 5.46 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 25.96, 26.12, 28.83, 31.35, 33.78, 63.47, 113.74, 150.91, 172.38; IR ($CDCl_3$) 3030, 2960, 1680, 1610, 1440, 1210, 1090, 990 cm^{-1}; Anal. calcd for $C_9H_{13}O_2HgCl$: C, 27.77; H, 3.37. Found: C, 27.34; H, 3.27.

Compound 31 via procedure B: 75% yield; R_f = 0.33, 4:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.69 (m, 4 H, $CH_2(C\underline{H}_2)_2CH_2$), 1.89 (m, 2 H, cis or trans $C\underline{H}_2(CH_2)_2C\underline{H}_2$), 2.12 (m, 2 H, cis or trans $C\underline{H}_2(CH_2)_2C\underline{H}_2$), 2.63 (s, 2 H, CH_2Hg), 5.10 (d, 1 H, J = 7.5 Hz, cis $=CH_2$), 5.14 (d, 1 H, J = 14.1 Hz, trans $=CH_2$), 6.16 (dd, 1 H, J = 7.5 Hz, J = 14.1 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 23.20, 32.84, 37.53, 90.95,

113.20, 140.51, 171.37; IR ($CDCl_3$) 3020, 2980, 2940, 1690, 1600, 1450, 1220, 1100, 940 cm^{-1}; Anal. calcd for $C_9H_{13}O_2HgCl$: C, 27.77; H, 3.37, Hg, 51.53. Found: C, 27.60; H, 3.24; Hg, 51.60.

The butenolide synthesis from the organomercurials follows the general procedure below for the preparation of the butenolide 9 from organomercurial 23. To a stirred, homogenous solution of 0.0887 g (0.5 mmol) of palladium chloride, 0.0425 g (1.0 mmol) of lithium chloride, and 0.14 ml (1.0 mmol) of triethylamine in 9 ml of tetrahydrofuran and 2 ml of hexamethylphosphoramide was added 0.2027 g (0.5 mmol) of the organomercurial 23 in 1 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 26 h and then diluted with 20 ml of diethyl ether. The solution was then filtered through Celite to remove the palladium metal, washed with 3 times 50 ml of saturated aqueous ammonium chloride and dried over magnesium sulfate. The solvent was then removed by rotary evaporation and the crude product purified by column chromatography on silica gel with 2:1 hexanes/ethyl acetate as eluent to yield 0.0712 g (85% yield) of the butenolide 9. ^1H NMR ($CDCl_3$) δ 0.81 (t, 3 H, J = 6.6 Hz, $CH_2\underline{CH_3}$), 1.30 (m, 6 H, CH_2's), 1.81 (m, 2 H, CH_2), 1.98 (d, 3 H, J = 0.9 Hz, $=CCH_3$), 4.75 (t, 1 H, J = 3.6 Hz, OCH), 5.71 (t, 1 H, J = 1.5 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 14.14, 15.76, 17.27, 17.48, 27.89, 27.99, 78.35,

114.44, 169.69, 180.30; IR (neat) 2990, 2850, 1745, 1640, 1390, 1110, 940 cm^{-1}; mass spectrum m/e 168.23747 (calcd. for $C_{10}H_{16}O_2$, 168.23782.

Compound 27: reaction ran at room temperature for 2 h using (5:1) THF/DMF as the solvent; 65% yield; R_f = 0.40, 2:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.46 (s, 6 H, $C(CH_3)_2$), 2.05 (d, 3 H, J = 1.5 Hz, $=CCH_3$), 5.68 (s, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 19.19, 28.43, 78.81, 111.14, 143.23, 184.40; IR (neat) 2990, 2920, 1735, 1640, 1430, 1265, 900, 740 cm^{-1}; mass spectrum m/e 126.15690 (calcd. for $C_7H_{10}O_2$, 126.15655.

Compound 29: reaction ran at room temperature for 23 h, then at reflux for 1 h using 5:1 THF/DMF as the solvent; 71% yield; ^1H NMR and IR were identical with that reported in the literature.[55]

Compound 37: reaction ran at room temperature for 3 d using 5:1 THF/HMPA as solvent; 69% yield; R_f = 0.45, 2:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 7.2 Hz, CH_3), 1.25 (d, 3 H, J = 6.6 Hz, CH_3), 1.45 (d, 3 H, J = 6.9 Hz, $OCHC\underline{H}_3$), 2.58 (d septets, 1 H, J = 1.2 Hz, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 5.04 (dq, 1 H, J = 1.5 Hz, J = 6.9 Hz, OCH), 5.75, (t, 1 H, J = 1.3 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 19.50, 27.17, 27.27, 79.35, 112.97, 172.90, 179.99; IR (neat) 2985, 1750, 1640, 1450, 1360, 1090, 960 cm^{-1}; mass spectrum m/e 140.18341 (calcd. for $C_8H_{12}O_2$, 140.18364).

Compound 38: reaction ran at room temperature for 3 d using 5:1 THF/HMPA as solvent; 26% yield; R_f = 0.57, 2:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.41 (d, 3 H, J = 6.3 Hz, $CHC\underline{H}_3$), 1.76 (s, 3 H, $=CCH_3$), 2.63 (m, 3 H, $CHCH_2CO_2$), 4.44 (dq, 1 H, J = 6.3 Hz, J = 7.5 Hz, OCH), 4.87 (s, 1 H, Z C=CH_2), 4.91 (p, 1 H, J = 1.4 Hz, E C=CH_2); ^{13}C NMR ($CDCl_3$) δ 19.60, 19.73, 50.53, 58.35, 79.70, 113.36, 141.36, 175.51; IR (neat) 2920, 2870, 1770, 1530, 1430, 1280, 1085, 950 cm^{-1}; mass spectrum m/e 140.18333 (calcd. for $C_8H_{12}O_2$, 140.18364).

Compound 32: reaction ran at room temperature for 6 h using 5:1 THF/HMPA as solvent; 56% yield; R_f = 0.33, 3:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4 H, $CH_2(C\underline{H}_2)_2CH_2$), 1.95 (m, 4 H, $C\underline{H}_2(CH_2)_2C\underline{H}_2$), 2.05 (d, 3 H, J = 1.2 Hz, CH_3), 5.74 (d, 1 H, J = 1.2 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 24.98, 36.05, 97.61, 108.83, 116.35, 170.07, 172.19; this compound decomposed within 1 h of isolation.

Compound 34: reaction ran at room temperature for 3 d, then at reflux for 1 h using 5:1 THF/HMPA as solvent; 30% yield; R_f = 0.33, 7:2 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.91 (p, 2 H, J = 7.5 Hz, CH_2's), 2.31 (m, 4 H, CH_2's), 2.45 (dd, 1 H, J = 8.7 Hz, J = 17.4 Hz, CH_2's), 2.65 (dd, 1 H, J = 8.7 Hz, J = 17.4 Hz, CH_2's), 3.30 (p, 1 H, J = 7.5 Hz, =CCH), 4.11 (t, 1 H, J = 8.7 Hz, OCH), 4.43 (t, 1 H, J = 8.7 Hz, OCH), 5.52 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 32.22,

32.80, 37.27, 71.81, 126.24, 141.19, 176.83; IR (neat) 3020, 2960, 2860, 1765, 1210, 940 cm^{-1}; mass spectrum m/e 152.19459 (calcd. for $C_9H_{12}O_2$, 152.19479).

Compound 54: ^1H NMR and IR were identical to that reported by Harrison.[56]

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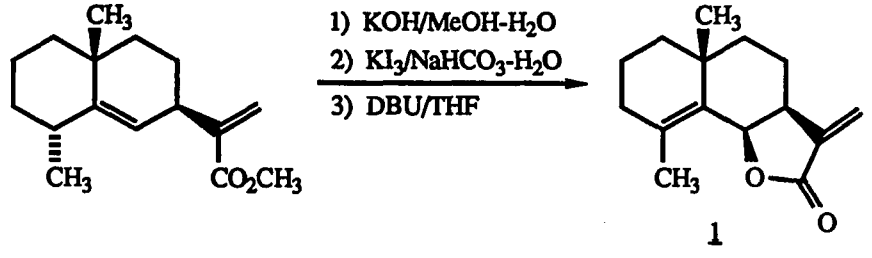
PART III. SYNTHESIS OF BICYCLIC LACTONES AND ACETALS VIA PALLADIUM-ASSISTED CYCLIZATIONS

INTRODUCTION

Lactone rings and their derivatives are present in numerous natural products and biologically active molecules. In turn, examples of the synthesis of lactones are widespread. There are several books and reviews that deal with lactones solely or in part.[1] This introduction will present only a brief discussion of some common methods used in their synthesis.

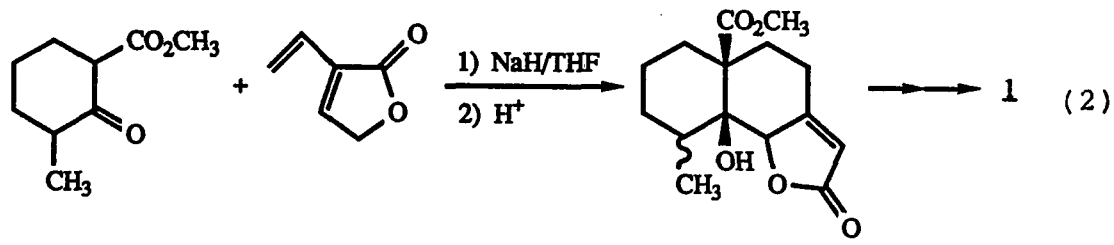
Some common methods used for the synthesis of lactones include iodolactonization, annulation reactions, dehydration, Baeyer-Villager oxidation, and various organometallic approaches.

Still and Schneider[2] used iodolactonization in their synthesis of the allergenic sesquiterpene frullanolide 1 (eq. 1). It is interesting to note that the α-methylene lactone present in the product is stable to the iodolactonization conditions.



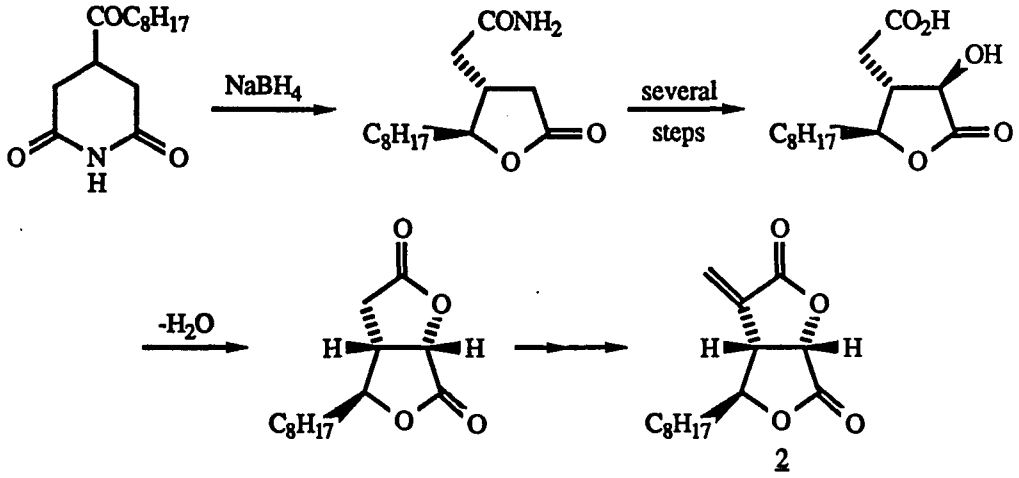
1 (1)

Kido et al.[3] synthesized frullanolide 1 using a novel lactone annulation reaction in the formation of the lactone ring (eq. 2).



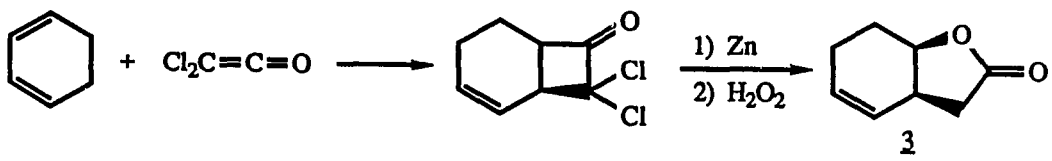
(2)

Parker and Johnson[4] synthesized the mold product avenaciolide 2[5] by a very circuitous route where one lactone ring was formed by a reduction-rearrangement procedure and the other lactone ring was formed by dehydration (eq. 3).



(3)

Corey and Ravindranathan[6] prepared the lactone 3 by the addition of dichloroketene to 1,3-cyclohexadiene, followed by dehalogenation and Baeyer-Villager oxidation (eq. 4). Lactone 3 was then carried on to 11-deoxyprostaglandin and prostaglandin $F_{2\alpha}$.



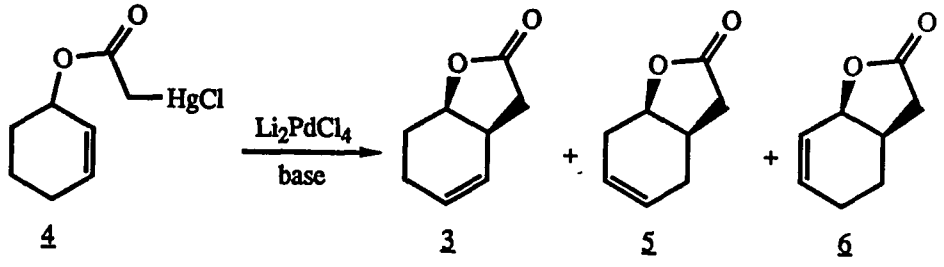
(4)

Transition metal reagents have proven highly valuable for the synthesis of lactones and lactone equivalents. The use of cobalt[7-9] and tin[9-11] catalysts for the cyclization of alkenes containing α-haloesters to afford lactones has been recently studied. The use of palladium catalysts as discussed in Part I of this thesis is also a useful approach for the synthesis of lactones.

The transition metal-assisted methods along with the more common methods of iodolactonization, Baeyer-Villager oxidation, and condensation-dehydration constitute the majority of the published lactone syntheses. However, the inability of these methods to build more complex carbon frameworks and accommodate other functionality somewhat limits their usefulness. It is these limitations that have encouraged us to examine alternative methods for the synthesis of lactones and their derivatives.

RESULTS AND DISCUSSION

The palladium-assisted intermolecular addition of organomercurials to cyclic alkenes has been reported by Heck.[12] This observation coupled with the fact that we were able to synthesize butenolides by the addition of organomercurials to acyclic alkenes encouraged us to try the following reaction (eq. 5).



4 3 5 6 (5)

The organomercurial 4, readily prepared by condensation of α-chloromercurioacetic acid and 2-cyclohexen-1-ol in 68% isolated yield, was found to cyclize in the presence of Li_2PdCl_4 to give the bicyclic lactone 3. However, compound 3 was contaminated by small amounts of the olefin isomers 5 and 6. Compounds 5 and 6 must arise from the palladium-catalyzed olefin isomerization of compound 3 (Scheme 1).

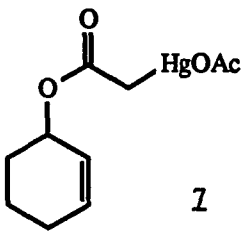
In an attempt to reduce or eliminate this olefin isomerization, several sets of reaction conditions were examined for the reaction shown in equation 5 (Table 1). As seen in Table 1, the isomerization was never completely eliminated. The use of different bases did affect the outcome of the reaction in terms of isomer ratios and yields

Table 1. Synthesis of lactones 3, 5 and 6

Entry	Base (2 equiv.)	Solvent	Isolated Yield (%)	Isomer Ratio[a] 3:5:6
1	none	THF	49	77:4:19
2	K_2CO_3	THF	68	81:13:6
3	MgO	THF	44	62:3:35
4	Et_3N	THF	87	67:22:11
5	NaOAc	THF	80	82:9:9
6	$CaCO_3$	THF	67	72:7:21
7	BaO	THF	37	77:6:17
8	Et_3N	CH_2Cl_2	80	67:22:11
9	Et_3N	CH_3CN	0	---
10	Et_3N	CH_3OH	0	---
11	Et_3N	HMPA	75	90:5:5
12	Et_3N	5:1 THF/DMSO	15	55:27:18
13	Et_3N	5:1 THF/HMPA	90	89:7:4
14	Et_3N	5:1 THF/DMF	90	88:7:5
15[b]	Et_3N	5:1 THF/HMPA	0	---

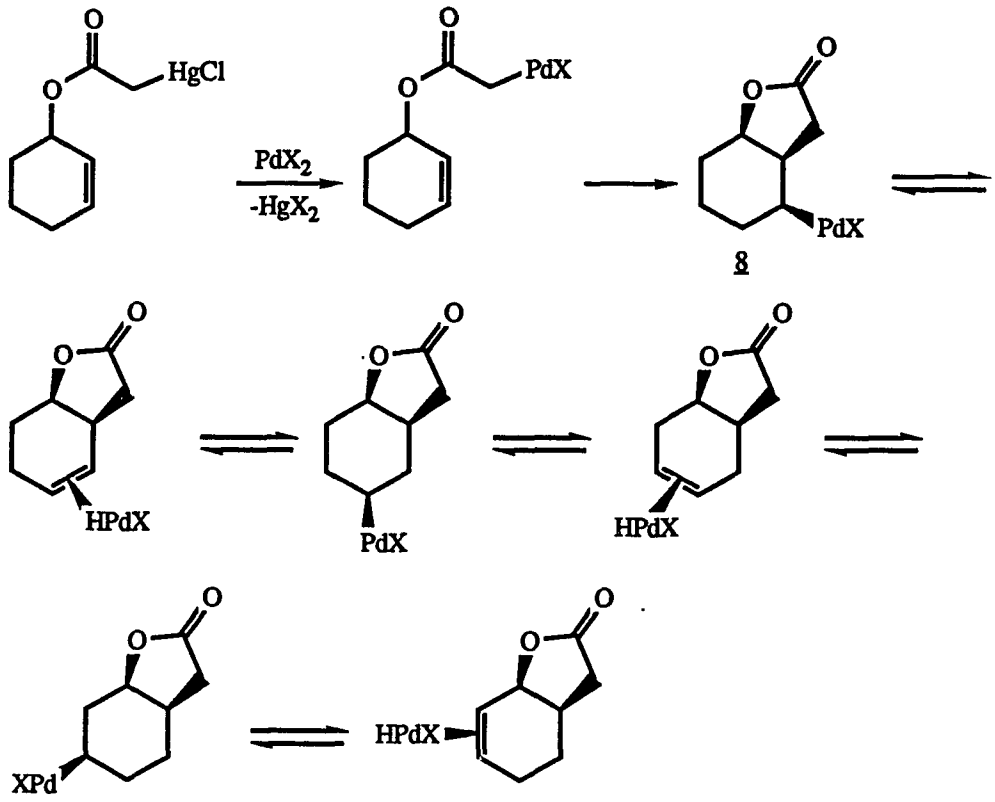
[a]Isomer ratios were determined by capillary gas chromatography.

[b]This reaction was carried out using organomercurial 7 as the substrate and $Pd(OAc)_2$ as the palladium reagent.



7

Scheme 1



(entries 1-7). However, the use of different solvents resulted in the most pronounced effect on the reaction (entries 8-14). Mixed solvent systems such as those shown in entries 13 and 14 proved to be the best in terms of yields and isomer ratios. The use of the organomercuric acetate 7 did not improve the yield or the isomer ratio (entry 15).

Using the reaction conditions described in Table 1, entries 11 and 14, several other ring sizes and substitution patterns were examined (Table 2).

Table 2. Synthesis of bicyclic lactones

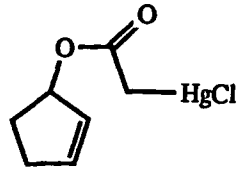
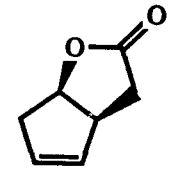
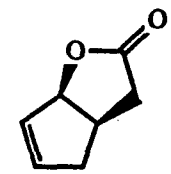
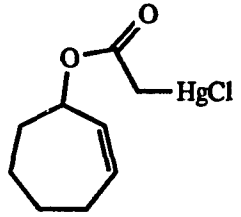
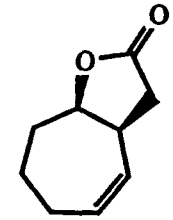
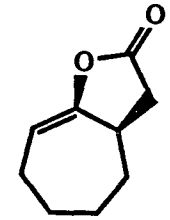
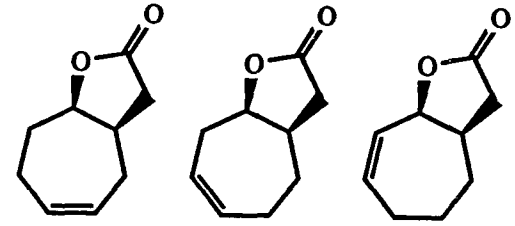
Entry	Substrate	Solvents	Time	Products (% isolated yield)
1	 9	5:1 THF/HMPA	4 d	 10 (57)  11 (13)
2	 12	5:1 THF/HMPA	4 d	 13 (29)  17 (12)  14 15 16 (29)

Table 2. Continued

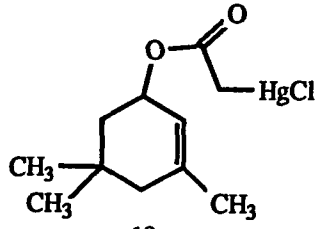
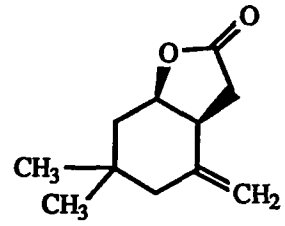
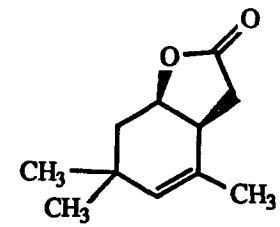
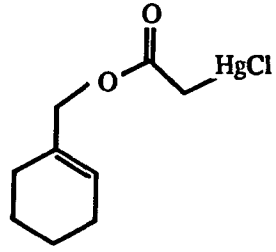
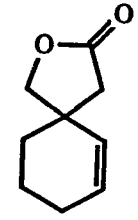
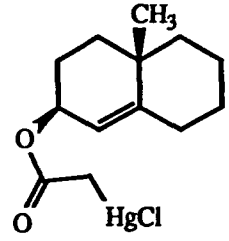
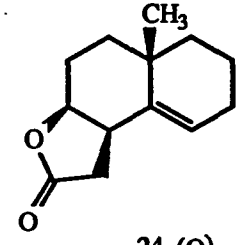
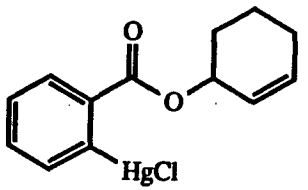
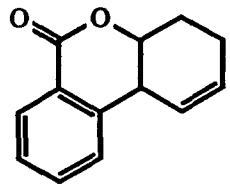
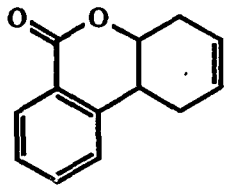
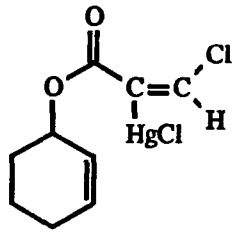
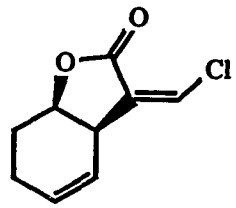
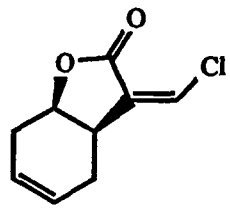
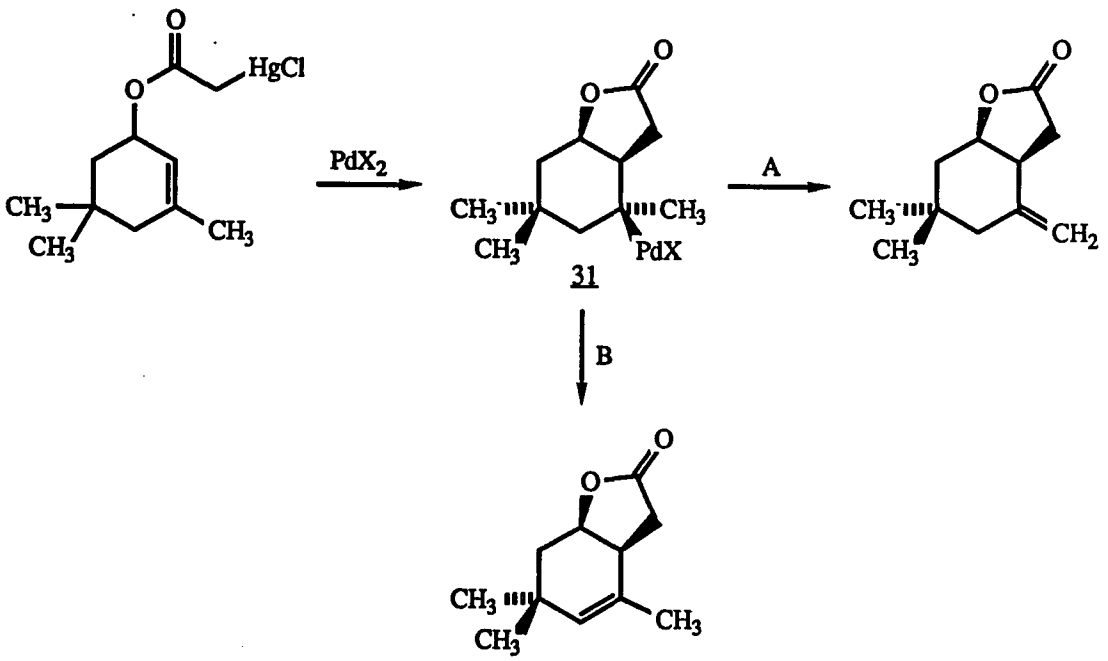
Entry	Substrate	Solvents	Time	Products (% isolated yield)
3	 18	5:1 THF/DMF	30 h	 19 (35)  20 (12)
4	 21	5:1 THF/DMF or 5:1 THF/HMPA	1 d	 22 (0)
5	 23	5:1 THF/DMF	7 d	 24 (0)

Table 2. Continued

Entry	Substrate	Solvents	Time	Products (% isolated yield)
6	 25	5:1 THF/DMF	3.5 h	 26 (29)  27 (5)
7	 28	5:1 THF/HMPA	2.25 h	 29 (4.5)  30 (1.5)

As seen in Table 2, entries 1 and 2, the five- and seven-membered ring examples cyclized in good yields. However, in both cases other olefin isomers accompanied the formation of the desired compound. The seven-membered ring organomercurial 12 yielded five olefin isomers, each being formed in significant amounts. The isophorol organomercurial 18 (Entry 3) produced the two possible olefin isomers 19 and 20 in a 3:1 ratio. This ratio is the same ratio as that expected statistically for the palladium hydride elimination of the intermediate σ-palladium species 31 (Scheme 2).

Scheme 2



As seen in Scheme 2, path A should be the favored pathway 3 to 1 over path B due to the availability of three

hydrogens for elimination compared to path B which has only one cis β-hydrogen available for elimination.

The palladium(II)-assisted intramolecular cyclization of the organomercurial 21 was expected to result in the formation of the spirolactone 22. This transformation was attempted under the two best conditions found for the cyclization of organomercurial 4 (Table 1, entries 13 and 14). Spectroscopic and TLC examination of the crude product mixtures of these reactions showed no evidence for the formation of lactone 22 or any other identifiable product, or the presence of the starting material 21.

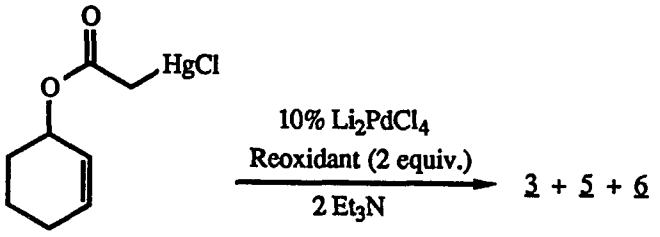
Cyclization of the organomercurial 23 also proved fruitless. Again, spectroscopic and TLC analysis of the crude reaction mixture provided no evidence for the formation of the tricyclic lactone 24. Examination of molecular models of substrate 23 indicated that the bridgehead angular methyl group may sterically hinder addition to the olefin such that intramolecular addition of the intermediate organopalladium species to the olefin is very improbable.

The organomercurial 25, prepared by the DCC-assisted condensation of o-chloromercuriobenzoic acid and 2-cyclohexen-1-ol, was found to cyclize rapidly forming approximately a 5:1 mixture of the tricyclic lactone olefin isomers 26 and 27. As stated earlier, the isomer 27 must

have arisen from the palladium-catalyzed isomerization of product 26.

The final example, entry 7, shows the preparation of an α-methylene bicyclic lactone from the vinylic organomercurial 28. However, only a 6% combined yield of the olefin isomers 29 and 30 was obtained.

The relatively high cost of palladium(II) salts coupled with the known ability of certain reoxidants to reoxidize palladium(0) to palladium(II) encouraged us to make several attempts at cyclizing the organomercurial 4 using a catalytic amount of Li_2PdCl_4 in the presence of a suitable reoxidant (eq. 6). The results of those reactions are presented in Table 3.

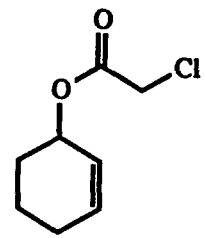


(6)

As seen from the results presented in Table 3, none of the conditions employed proved to be very effective in reoxidizing the palladium(0) to palladium(II) and thus make the synthesis of the bicyclic lactone 3 catalytic with respect to palladium.

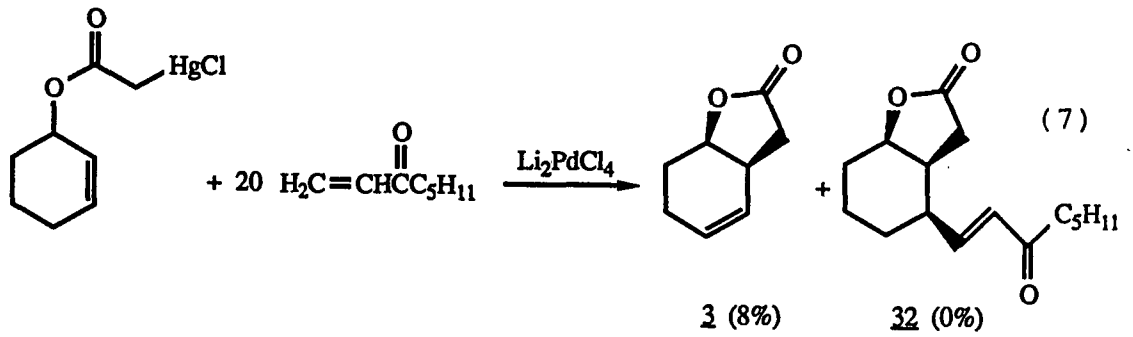
As an extension of this methodology, the trapping reaction shown in equation 7 was performed. It was proposed

Table 3. Catalytic reactions used for the cyclization of organomercurial 4

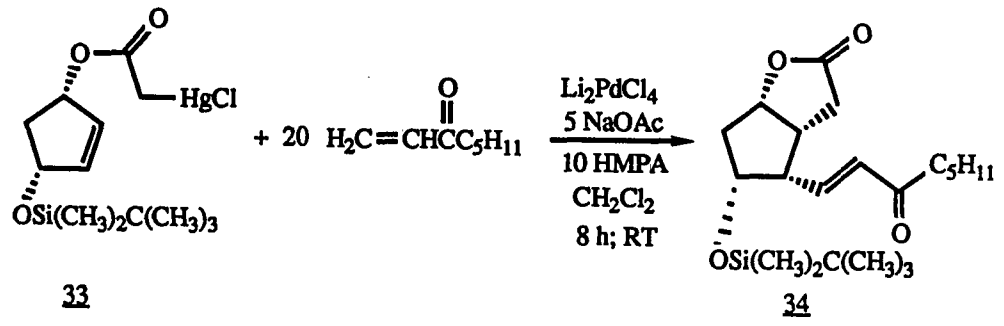
Entry	Reoxidant	Solvents	Time (d)	Temp (°C)	Products (% isolated yield)	Ratio[a]
1	none	5:1 THF/HMPA	4	25	3, 5, 6 (22)	62:21:17
2	benzoquinone	5:1 THF/HMPA	4	25	3, 5, 6 (11)	82:9:9
3	$CuCl_2$	5:1 THF/HMPA	4	25	3, 5, 6 (30)	77:15:8
4	$CuCl_2$	THF	1	Reflux	 (23)	
5	$CuCl_2$	HMPA	10	25	4 (80)	

[a]Where applicable - determined by capillary gas chromatography.

that an external olefin such as 1-octen-3-one could possibly be used to trap the intermediate 8 (Scheme 1) and result in the formation of compound 32. However, only compound 3 was formed in 8% yield. Apparently, elimination of the palladium hydride species into the ring is more facile than intermolecular addition of the intermediate σ-palladium species 8 to an external olefin such as 1-octen-3-one. When β-hydride elimination is blocked, trapping is possible (eq. 8). Thus, Russell[13] found that the organomercurial 33 would cyclize in the presence of excess 1-octen-3-one to give the bicyclic lactone 34. Compound 34 is a possible intermediate for the synthesis of prostaglandin $F_{2\alpha}$ and analogs.[14,15]



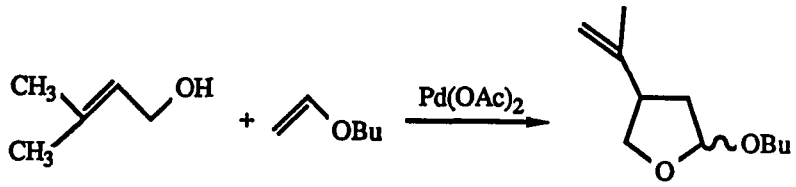
(7)



33 34

(8)

Fugami et al.[16] found that acyclic allylic alcohols reacted with vinyl ethers in the presence of palladium acetate to give dihydrofurans (eq. 9). Due to the fact that unwanted olefin isomers were found to accompany the palladium(II)-assisted cyclization of the above organomercurials, the methodology reported by Fugami et al. for the sythesis of dihydrofurans (eq. 9) was applied to the synthesis of the bicyclic acetal 35 (eq. 10, Table 4).

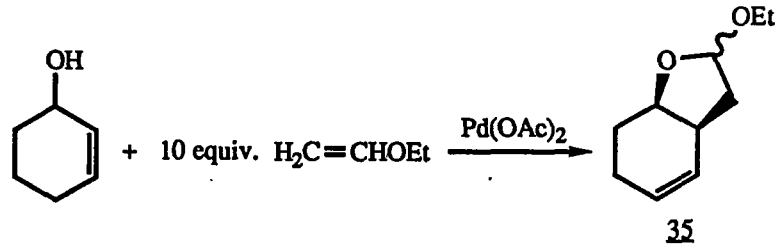


(9)

Using the conditions reported by Fugami et al. (Table 4, entry 1), 2-cyclohexen-1-ol was reacted with 10 equivalents of ethyl vinyl ether in the presence of 1 equivalent of palladium(II) acetate. This reaction formed the bicyclic acetal 35 in 63% isolated yield. Running the same reaction at 0°C for 10 minutes prior to warming to room temperature resulted in a 70% yield of acetal 35 (Table 4, entry 2). Running the reaction with 10 equivalents of diethyl ether as solvent and stirring the reaction at 0°C for 10 minutes prior to warming to room temperature resulted in a 68% yield of acetal 35 (Table 4, entry 3).

Table 4. Synthesis of bicyclic acetal 35 via oxypalladation

Entry	Solvent	Conditions	Isolated Yield of 35 (%)
1	neat	RT, 2 h	63
2	neat	0°C, 10 min; then RT, 2 h	70
3	diethyl ether	0°C, 10 min; then RT, 2 h	68



35 (10)

Several other cyclic allylic alcohols were subjected to the reaction conditions presented in Table 4, entry 2. The results of these are presented in Table 5.

As seen from the results presented in Table 5, entries 1 and 2, the simple disubstituted cyclic allylic alcohols work well. Entries 3, 4 and 5 of Table 5 indicate that 3-substituted-2-cyclopenten-1-ols will also function as substrates for the synthesis of bicyclic acetals. The 6-membered ring allylic alcohols shown in entries 6, 7 and 8, Table 5, result in the formation of the vinyl ethers with no evidence for the formation of the desired bicyclic

Table 5. Synthesis of bicyclic acetals via oxypalladation

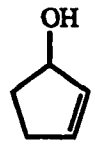
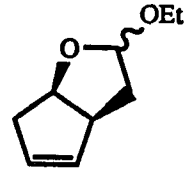
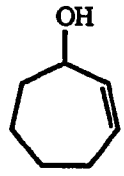
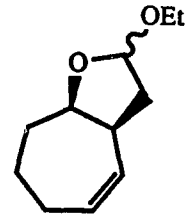
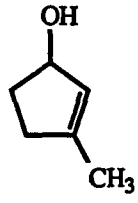
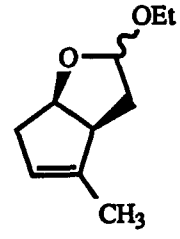
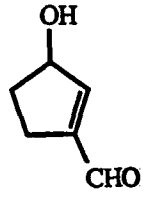
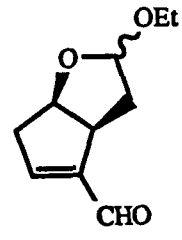
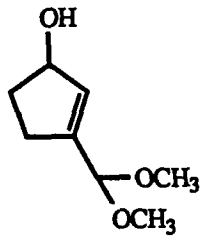
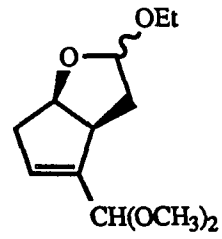
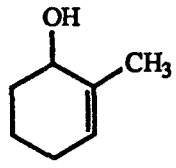
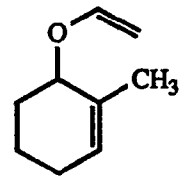
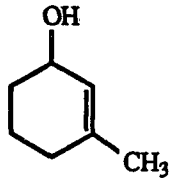
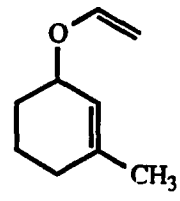
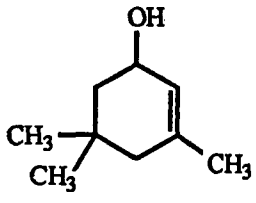
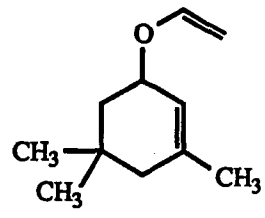
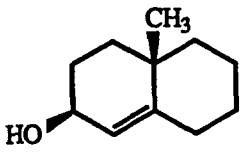
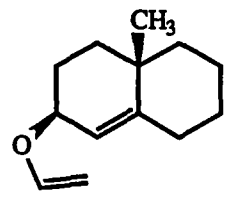
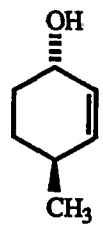
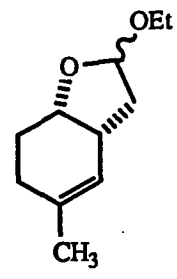
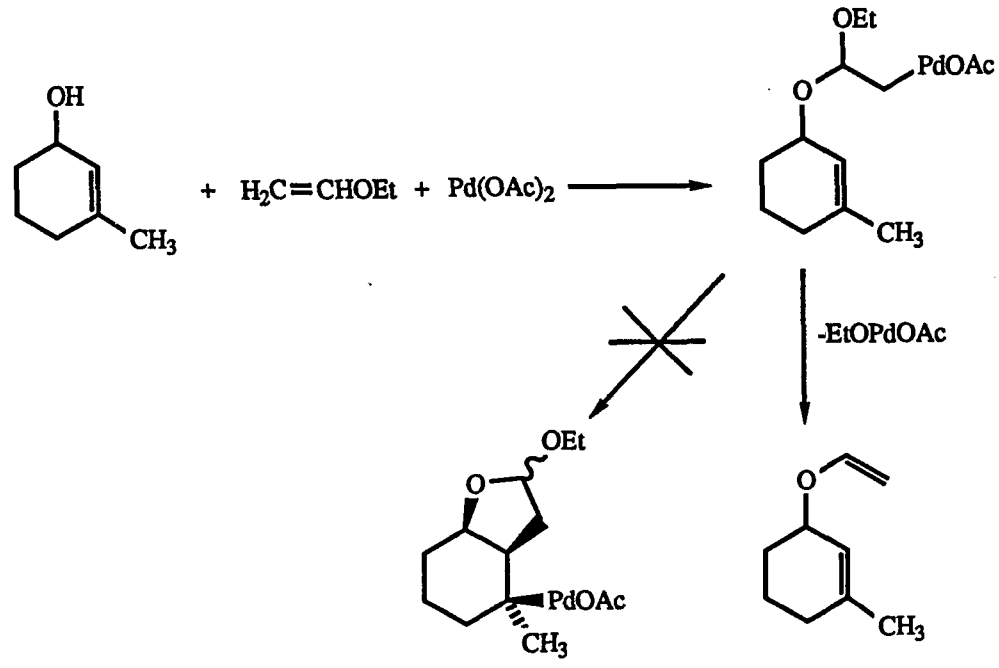
Entry	Substrate	Product	Isolated Yield (%)
1			56
2			60
3			27
4			37
5			52[17]

Table 5. Continued

Entry	Substrate	Product	Isolated Yield (%)
6			5
7			39
8			40
9			47
10			52

acetals. Apparently elimination of the palladium alkoxide proceeds faster than addition of the intermediate oxypalladium species to the olefin of the allylic alcohol (Scheme 3).

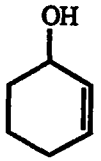
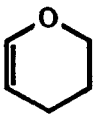
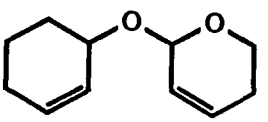
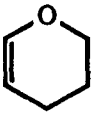
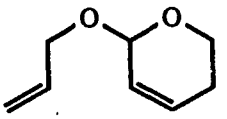
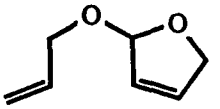
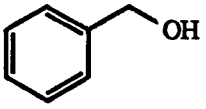
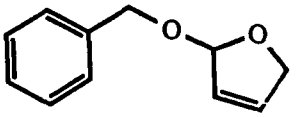
Scheme 3



To further examine the scope and limitations of this oxypalladation reaction, 2,3-dihydrofuran and 2,3-dihydro-2H-pyran were reacted with several alcohols. The results of these reactions are presented in Table 6.

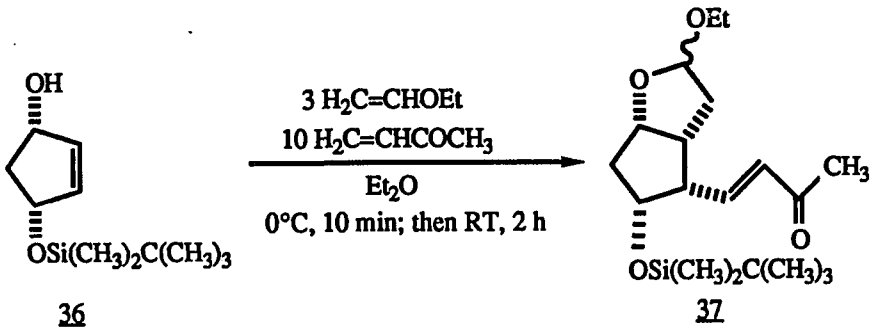
The results in Table 6 indicate that cyclic vinyl ethers will undergo oxypalladation with allylic alcohols, but the major product is that of subsequent palladium hydride elimination rather than further cyclization. Thus, more

Table 6. Miscellaneous oxypalladation reactions

Entry	Allylic Alcohol	Vinyl Ether	Product (% isolated yield)
1			 (60)
2			 (33)
3			 (17)
4			 (60)

complex heterocyclic skeletons cannot be formed using this methodology.

The same reaction conditions reported in Table 4, entry 3, were used for the synthesis of a model system for prostaglandin synthesis. When the readily prepared monoprotected cis-3,5-cyclopentendiol 36 was reacted with ethyl vinyl ether, palladium acetate and methyl vinyl ketone, a 40% yield of the bicyclic acetal 37 was obtained (eq. 11).


OH
OSi(CH3)2C(CH3)3
3 H2C=CHOEt
10 H2C=CHCOCH3
Et2O
0°C, 10 min; then RT, 2 h
OEt
O
CH3
O
OSi(CH3)2C(CH3)3

36 37

(11)

CONCLUSION

A variety of bicyclic lactones and acetals have been conveniently synthesized from cyclic allylic alcohols via palladium(II)-assisted cyclization of organomercurials and via palladium(II)-assisted oxypalladation of vinyl ethers.

EXPERIMENTAL SECTION

Equipment

Proton NMR spectra were recorded on a Nicolet NT-300 spectrometer. ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer operating at 75 MHz for carbon nuclei. Infrared spectra were recorded on either a Beckman Acculab 2 on an IBM-98 spectometer. Exact mass spectral data were recorded on a Kratos MS-50 high resolution mass spectometer. Gas chromatographic-mass spectral analysis were performed on a Finnigan 4000 spectrometer. Gas chromatographic analysis was carried out on a Varian 3700 gas chromatograph. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc.

Reagents

All compounds were used directly as obtained commercially unless otherwise noted. Most starting materials were purchased from Aldrich (2-cyclohexen-1-ol, 3-methyl-2-cyclohexen-1-ol, allyl alcohol, ethyl vinyl ether, methyl vinyl ketone, 2,3-dihydrofuran, 2,3-dihydro-2H-pyran, diisopropylamine, n-butyllithium, 2-cyclopentenone, dicyclohexylcarbodiimide, acetyl chloride, sodium borohydride, propiolic acid, mercuric chloride, mercuric acetate, isophorone, peracetic acid, methyllithium, cuprous

iodide, 1,3-cyclohexadiene), J.T. Baker (lithium chloride), Alfa (1-octen-3-ol), and PCR Research Chemicals (1,1-difluroethylene). Tetrahydrofuran was distilled from benzophenone-sodium ketyl; N,N-dimethylformamide was distilled from calcium hydride; diisopropylamine was distilled from sodium hydroxide; acetyl chloride was distilled from calcium hydroxide; methylene chloride was distilled from phosphorous pentoxide. Lithium chloride was dried at 120°C at 0.5 mm Hg prior to use. Palladium chloride and palladium acetate were generously supplied by Johnson Matthey, Inc. 2-Methyl-2-cyclohexenone was supplied by Bill Gong. 3-Methyl-2-cyclopenten-1-ol was supplied by Dr. G. A. Kraus. 1'-Cyclohexenylmethanol was supplied by K. Oertle. Compound 36 was provided by N. H. Lee. 2-Cyclohepten-1-ol,[18] trans-4-methyl-2-cyclohexen-1-ol,[19] 10-methyl-1(9)-octal-2-ol,[20,21] and 10-methyl-1-(9)-octal-2-acetate[22] were prepared by literature procedures. Isophorol, 2-methyl-2-cyclohexen-1-ol and 2-cyclopenten-1-ol were prepared from the corresponding ketones by a literature procedure.[22] α-Chloromercurioacetic acid,[23] o-chloromercuriobenzoic acid,[24] and E-2-chloromercurio-3-chloro-2-propenoic acid[25] were prepared by literature procedures.

All α-chloromercurioacetate ester syntheses were effected using one of the following general procedures.

Preparation of organomercurial 4 via procedure A: DCC-assisted condensation. A solution of 1.00 g (3.35 mmol) of α-chloromercurioacetic acid, 1.00 g (5.00 mmol) of DCC, and 0.32 ml (3.35 mmol) of 2-cyclohexen-1-ol in 20 ml of methylene chloride was stirred at room temperature for 7 d. The reaction was then diluted with 25 ml of methylene chloride and filtered to remove the by-product urea. The solvent was then removed by rotary evaporation and the crude product purified by column chromatography on silica gel using 2:1 hexanes/ethyl acetate as eluent to yield 0.842 g (68% yield) of the white solid 4: R_f = 0.30, 2:1 hexanes/ethyl acetate; Mp = 69.5-71°C; ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 6 H, CH_2's), 2.60 (s, 2 H, CH_2Hg), 5.20 (m, 1 H, OCH), 5.80 (m, 2 H, =CH-'s); ^{13}C NMR ($CDCl_3$) δ 25.10, 32.35, 69.15, 125.45, 132.73, 172.10 (only signals found); IR ($CDCl_3$) 3070, 1700, 1260, 700 cm^{-1}; Anal. calcd for $C_8H_{11}O_2HgCl$: C, 25.61; H, 2.96; Hg, 53.46. Found: C, 25.47; H, 3.03; Hg, 53.18.

Compound 9 via procedure A: yield 68%; R_f = 0.35, 2:1 hexanes/ethyl acetate; Mp = 84.5-86°C; ^{1}H NMR ($CDCl_3$) δ 2.30 (m, 4 H, CH_2CH_2), 2.75 (s, 2 H, CH_2Hg), 5.90 (m, 2 H, OCH, =CH-), 6.25 (m, 1 H, =CH-); ^{13}C NMR unable to obtain due to low solubility; IR ($CHCl_3$) 3020, 2950, 2860, 1685, 1610, 1250 cm^{-1}; Anal. calcd for $C_7H_9O_2HgCl$: C, 23.89; H, 2.58; Hg, 56.97. Found C, 23.54; H, 2.50; Hg, 57.34.

Compound 12 via procedure A: yield 68%; R_f = 0.13, 2:1 hexanes/ethyl acetate; Mp = 71.5-72.5°C; ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 8 H, $(CH_2)_4$), 2.73 (s, 2 H, CH_2Hg), 5.42 (m, 1 H, OCH), 5.66 (m, 1 H, =CH-), 5.87 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 26.41, 26.61, 28.50, 32.02, 32.83, 75.12, 131.99, 133.32, 171.51; IR ($CDCl_3$) 3020, 2980, 2850, 1690, 1465, 1250, 1040 cm^{-1}; Anal. calcd for $C_9H_{13}O_2HgCl$: C, 27.77; H, 3.37; Hg, 51.53. Found: C, 28.00; H, 3.56; Hg, 51.61.

Compound 18 via procedure A: yield 42%; R_f = 0.55, 3:1 hexanes/ethyl acetate; Mp = 87-88°C; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.40 (dd, J = 7.5 Hz, J = 12.7 Hz, $OCCH_2$) 1.60 (s, 3 H, $=CCH_3$), 1.89 (d, 2 H, J = 18.1 Hz, $=CCH_2$), 2.71 (s, 2 H, CH_2Hg), 5.32 (m, 1 H, OCH), 5.37 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 30.63, 32.02, 71.07, 118.90, 138.77, 171.95 (only signals found); IR ($CDCl_3$) 2990, 2960, 2900, 2860, 1700, 1450, 1350, 1260, 1080, 900, 730 cm^{-1}; Anal. calcd for $C_{11}H_{17}O_2HgCl$: C, 31.66; H, 4.11; Hg, 48.06. Found: C, 31.88; H, 3.90; Hg, 47.76.

Compound 21 via procedure A: yield 55%; R_f = 0.28, 4:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 4 H, CH_2's), 2.02 (d, 4 H, J = 18.0 Hz, CH_2's), 2.71 (s, 2 H, CH_2Hg), 4.45 (s, 2 H, OCH_2), 5.75 (s, 1 H, =CH-); IR (neat) 2960, 2880, 1700, 1250, 1090, 910, 730 cm^{-1}. No elemental analysis was obtained since it failed to cyclize in the desired manner.

Compound 25 via procedure A: yield 43%; R_f = 0.70, 2:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.85 (m, 6 H, $(CH_2)_3$), 5.43 (d, 1 H, J = 2.1 Hz, OCH), 5.74 (dt, 1 H, J = 1.5 Hz, J = 9.9 Hz, =CH-), 5.95 (dt, 1 H, J = 3.3 Hz, J = 9.9 Hz, =CH-), 7.30 (t, 1 H, J = 7.8 Hz, Ar), 7.38 (d, 1 H, J = 6.9 Hz, Ar), 7.50 (t, 1 H, J = 7.5 Hz, Ar), 8.11 (d, 1 H, J = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 18.87, 24.90, 28.31, 70.08, 125.06, 128.60, 130.87, 133.36, 133.40, 134.94, 136.92, 151.12, 168.95; IR ($CDCl_3$) 3010, 2980, 2960, 1780, 1650, 1590, 1400, 1210 cm^{-1}. No elemental analysis was obtained due to the relatively rapid decomposition of this material.

Compound 28 via procedure A: yield 50%; R_f = 0.60, 2:1 hexanes/ethyl acetate; Mp = 159-160°C; ^1H NMR ($CDCl_3$) δ 1.75 (m, 6 H, $(CH_2)_3$), 5.37 (m, 1 H, OCH), 5.75 (m, 1 H, =CH-), 6.01 (m, 1 H, =CH-), 6.52 (s, 1 H, =CHCl); the ^{13}C NMR spectrum could not be obtained due to low solubility; IR ($CHCl_3$) 3080, 3020, 2930, 2860, 1690, 1575, 1240 cm^{-1}. No elemental analysis was obtained due to the relatively rapid decomposition of this material.

Preparation of organomercurial 23 via procedure B: enolate quenching with mercuric chloride. To a stirred solution of 2.457 mmol of LDA in 4 ml of THF at -78°C under nitrogen was added a solution of 0.394 g (1.89 mmol) of 10-methyl-1(9)-octal-2-acetate in 2 ml of THF. The

resulting solution was stirred at -78°C for 15 min at which time it was transferred via cannula to a stirred suspension of 1.0229 g (3.78 mmol) of mercuric chloride in 4 ml of THF at -78°C. The resulting mixture was warmed to room temperature and stirred an additional 15 h. The solution was then quenched with 1 ml of saturated aqueous ammonium chloride, diluted with 20 ml of diethyl ether and washed with 3 times 15 ml of saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The crude product was purified by column chromatography on silica gel with 2:1 hexanes/ethyl acetate as the eluent to yield 0.760 g (91% yield) of the organomercurial 23: R_f = 0.40, 2:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3 H, CH_3), 1.63 (m, 12 H, CH_2's), 2.67 (s, 2 H, CH_2Hg), 5.25 (m, 2 H, OCH, =CH-); ^{13}C NMR could not be obtained due to low solubility; IR ($CDCl_3$) 3030, 2980, 2860, 1705, 1575, 1470, 1300, 1250, 1080 cm^{-1}. No elemental analysis was obtained due to the relatively rapid decomposition of this material.

Preparation of the organomercurial 7 from organomercurial 4. To a stirred solution of 0.200 g (0.52 mmol) of organomercurial in 5 ml of methanol was added 0.089 g (0.52 mmol) of silver acetate in 10 ml of H_2O. The solution was stirred until the precipitation of silver chloride ceased. It was then diluted with 15 ml of methanol and

filtered through Celite. The solvent was removed by rotary evaporation. The resulting solid was taken up in 20 ml of methylene chloride and dried with magnesium sulfate. The solvent was then removed by rotary evaporation leaving 0.1795 g (87% yield) of a solid identified as 7. ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 6 H, CH_2's), 2.60 (s, 2 H, CH_2Hg), 5.22 (m, 1 H, OCH), 5.80 (m, 2 H, -CH=CH-).

The organomercurial cyclizations follow the general procedure below:

Preparation of the lactone 3 from the organomercurial 4. To a stirred, homogenous solution of 0.0887 g (0.5 mmol) of palladium chloride, 0.0425 g (1.0 mmol) of lithium chloride, and 0.14 ml (1.0 mmol) of triethylamine in 10 ml of tetrahydrofuran and 2 ml of hexamethylphosphoramide was added 0.1987 g (0.5 mmol) of organomercurial 4. The mixture was stirred at room temperature for 4 d and then diluted with 20 ml of diethyl ether. The solution was then filtered through Celite to remove the palladium metal, washed with three times 50 ml of saturated aqueous ammonium chloride and dried over magnesium sulfate. The solvent was then removed by rotary evaporation and the crude product purified by column chromatography on silica gel with 2:1 hexanes/ethyl acetate as the eluent to yield 0.0622 g (90% yield) of a 40:3:2 mixture of the lactone isomers 3, 5, and 6, as determined by gas chromatography-mass spectrometry. The

major isomer 3 was identified by its ^{1}H NMR spectrum which was consistent with that reported in the literature.[6] For lactone 3: R_f = 0.35, 2:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 4 H, CH_2's), 2.55 (m, 3 H, $COCH_2CH$), 4.75 (m, 1 H, OCH), 5.70 (m, 2 H, -CH=CH-); IR (neat) 3060, 1785, 1660, 1175, 720, cm^{-1}; mass spectrum obtained as a mixture, m/e 138.06854 (calcd for $C_8H_{10}O_2$, 138.06808). Compounds 5 and 6 were identified by minor peaks in the ^{1}H NMR spectrum of compound 3 and by gas chromatography-mass spectroscopy.

Compound 10 obtained as a mixture with compound 11: R_f = 0.37, 2:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 2.45 (d, 2 H, J = 17.9 Hz, CH_2), 2.73 (m, 2 H, CH_2), 3.52 (m, 1 H, =CCH), 5.13 (m, 1 H, OCH), 5.65 (m, 1 H, =CH-), 5.81 (m, 1 H, =CH-); IR (as a mixture of compounds 10 and 11, neat), 3005, 2960, 2920, 1770, 1210 cm^{-1}. These data are consistent with that reported in the literature.[26]

Compound 11: R_f = 0.37, 2:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 2.27 (dd, 2 H, J = 5.7 Hz, J = 18.3 Hz, CH_2), 2.81 (dt, 2 H, J = 8.1 Hz, J = 18.6 Hz, CH_2), 3.15 (m, 1 H, $CH_2\underline{CH}CH_2$), 5.52 (d, 1 H, J = 7.5 Hz, OCH), 5.87 (dd, 1 H, J = 2.4 Hz, J = 5.4 Hz, =CH-), 6.09 (dd, 1 H, J = 3.0 Hz, J = 3.0 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 35.02, 35.87, 39.61, 89.57, 128.86, 136.85, 177.62; IR (as a mixture of lactones 10 and 11, neat) 3005, 2960, 2920, 1770, 1210 cm^{-1}.

Compounds 26 and 27: obtained as a 5:1 mixture respectively. R_f = 0.37, 4:1 hexanes/ethyl acetate; ^{1}H NMR for compound 26 ($CDCl_3$) δ 2.11 (m, 1 H, CH_2), 2.31 (m, 1 H, CH_2), 2.55 (m, 1 H, CH_2), 2.99 (m, 1 H, CH_2), 3.59 (m, 1 H, =CCH), 4.82 (q, 1 H, J = 2.7 Hz, OCH), 5.71 (m, 1 H, =CH-), 5.82 (m, 1 H =CH-), 7.28 (m, 1.2 H, Ar), 7.41 (m, 1.2 H, Ar), 7.54 (m, 1.2 H, Ar), 8.11 (m, 1.2 H, Ar); ^{1}H NMR for compound 27 ($CDCl_3$) δ 2.11 (m, 1 H, CH_2), 2.31 (m, 2 H, CH_2), 2.55 (m, 1 H, CH_2), 3.59 (m, 1 H, ArCH), 4.97 (m, 1 H, OCH), 5.99 (m, 1 H, =CH-), 6.15 (m, 1 H, =CH-), 7.28 (m, 1 H, Ar), 7.41 (m, 1 H, Ar), 7.54 (m, 1 H, Ar), 8.11 (m, 1 H, Ar); IR (as a mixture of 26 and 27, $CDCl_3$) 3090, 2970, 2895, 1740, 1630, 1480, 1285, 1130, 1100, 1040, 920, 740 cm^{-1}.

Cyclization of the organomercurial 12: purification of the crude residue by column chromatography on silica gel using 3:1 hexanes/ethyl acetate as the eluent provided: fraction 1, 12% yield; R_f = 0.53; ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 9 H, CH_2's), 2.90 (m, 1 H, CH_2), 3.14 (m, 1 H, =CH-), 5.54 (m, 1 H, =CH-); IR (neat) 2980, 2960, 2920, 2850, 1795, 1685, 1435, 1375, 1205, 1100, 740 cm^{-1}; mass spectrum m/e 152 (M+), 137, 124, 98, 97, 96, 95, 83, 82, 81, 80, 79, 70, 69, 68, 67, 55 (base), 54, 53. Fraction 2: 29% yield; R_f = 0.43; ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 8 H, CH_2's), 3.05 (m, 1 H, OCCH), 3.93 (m, 1 H, OCH), 5.64 (m, 1 H, =CH-), 5.99 (m, 1 H, =CH-); IR (neat) 3030, 2935, 2860, 1780, 1445, 1420,

1220, 1200, 1010, 750 cm^{-1}; mass spectrum m/e 152 (M+), 124, 95, 81, 80 (base), 79, 67, 54. Fraction 3: 15% yield; R_f = 0.38; ^1H NMR ($CDCl_3$) δ 2.20 (m, 9 H, CH_2's), 3.95 (m, 1 H, OCH), 5.82 (m, 2 H, =CH-'s); IR (neat) 3040, 2950, 2880, 1785, 1650, 1450, 1220, 1190, 1015, 750 cm^{-1}; gas chromatography-mass spectrum (2 compounds): for A, m/e 152 (M+), 134, 124, 123, 110, 109, 108, 107, 106, 98, 97, 96, 95, 93, 92, 91, 83, 82, 81, 80, 79, 78, 77, 70, 69, 68, 67, 66, 65, 60, 55, 54 (base); for B: 152 (M+), 124, 110, 98 (base), 97, 96, 95, 91, 82, 81, 80, 79, 77, 70, 69, 68, 67, 65, 55, 54, 53, 51. Fraction 4: 24% yield; R_f = 0.32; ^1H NMR ($CDCl_3$) δ 2.27 (m, 9 H, CH_2's), 4.75 (m, 1 H, CH), 5.62 (m, 2 H, =CH-'s); IR (neat) 3040, 2950, 2860, 1775, 1220, 1175, 1015, 750 cm^{-1}; gas chromatography-mass spectrum (2 compounds): for A, m/e 152 (M+), 93, 92 (base), 91, 81, 80, 79, 77, 68, 67, 66, 60, 55, 54, 53; for B: 152 (M+), 134, 124, 123, 110, 109, 108, 107, 106, 98, 97, 96, 95, 93, 92, 91, 83, 82, 81, 80, 79, 78, 77, 70, 69, 68, 67, 65, 60, 57, 56, 55, 54 (base), 53, 51. Fraction 1 was determined to be lactone 17 from its ^1H NMR, IR and mass-spectral fragmentation pattern. Fraction 2 was determined to be lactone 13 from its ^1H NMR, IR and mass-spectral fragmentation pattern and by comparison of its ^1H NMR spectrum with that for lactones 3 and 10. Fractions 3 and 4

were determined to be mixtures of the lactones 14, 15, and 16 as determined by ^{1}H NMR, IR, and mass-spectral data.

Compounds 29 and 30: R_f = 0.61, 4:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 5.2 H, CH_2's), 3.60 (m, 3 H, CH_2's), 4.15 (m, 1 H, =CCHC=), 5.35 (m, 1 H, OCH), 5.55 (m, 0.3 H, OCH), 5.75 (m, 1 H, =CH-), 5.85 (m, 0.3 H, =CH-), 6.05 (m, 1.3 H, =CH-), 6.70 (s, 1 H, =CHCl), 7.00 (s, 0.3 H, =CHCl); gas chromatography-mass spectrum (2 compounds): for A, m/e 186 (M+2), 184 (M+), 149, 148, 132, 130, 95 (base), 91, 77, 54, 51; for B: m/e 186 (M+2), 184 (M+), 168, 166, 158, 156, 149, 148, 145, 143, 142, 141, 140, 138, 131, 130, 128, 121, 112, 106, 105, 103, 95, 93, 92, 91, 89, 79, 78, 77 (base), 75, 74, 73, 71, 67, 65, 63, 62, 55, 54, 53, 52, 51, 50; mass spectrum (as a mixture) 184.62301 (calcd for $C_9H_9O_2Cl$, 184.62388). The ratio of 29:30 was 3:1 by ^{1}H NMR spectroscopy and gas chromatography. The identity of compound 29 was confirmed by comparison of its ^{1}H NMR spectrum to that of compound 3 and from the mass spectral fragmentation pattern.

Compounds 19 and 20: R_f = 0.49, 3:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3 H, CH_3), 1.00 (s, 5 H, CH_3), 1.05 (s, 1 H, CH_3), 1.70 (m, 4.4 H, CH_2,CH_3), 2.65 (m, 2.7 H, CH_2), 3.87 (q, 1 H, J = 8.1 Hz, =CCH), 4.13 (q, 0.33 H, J = 7.5 Hz, =CCH), 4.67 (ddd, 1 H, J = 6.9 Hz, J = 9.6 Hz, J = 9.9 Hz, OCH), 4.83 (m, 0.33 H, OCH), 4.87 (s, 1 H,

$=CH_2$), 4.96 (s, 1 H, $=CH_2$), 5.30 (s, 0.33 H, =CH-); ^{13}C NMR - insufficient material; IR ($CDCl_3$) 3000, 2970, 2905, 1785, 1180, 1010, 905, 730 cm^{-1}; mass spectrum (as a mixture) 180.24990 (calcd for $C_{11}H_{16}O_2$, 180.24897). The ratio of lactones 19 to 20 was determined by ^1H NMR spectroscopy and by gas chromatography to be 3:1.

General procedure for the oxypalladation reactions employing ethyl vinyl ether. To a solution of 0.10 ml (1.0 mmol) of 2-cyclohexen-1-ol in 1.0 ml (10.0 mmol) of ethyl vinyl ether at 0°C in an ice bath was added 0.2244 g (1.0 mmol) of palladium acetate. The ice bath was then removed and the solution stirred at room temperature for 2 h. The mixture was then diluted with 20 ml of hexanes and 0.20 ml (2.5 mmol) of pyridine was added. After stirring at room temperature for an additional 10 min, the solution was filtered through Celite to remove the palladium metal and the filtrate was concentrated by rotary evaporation. Purification of the residual oil by column chromatography on silica gel with 12:1 hexanes/ethyl acetate gave 0.0870 g or a 70% yield of the bicyclic acetal 35, the ^1H NMR and IR spectra of which were consistent with that reported in the literature.[27]

Oxypalladation reaction of 2-cyclopenten-1-ol with ethyl vinyl ether: product was obtained as a 1:1 mixture of epimers in 56% yield; R_f = 0.35, 14:1 hexanes ethyl acetate;

^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 7.2 Hz, CH_3), 1.20 (t, 3 H, J = 7.2 Hz, CH_3), 1.81 (dt, 2 H, J = 13.2 Hz, CH_2), 1.91 (d, 2 H, J = 13.2 Hz, CH_2), 2.09 (m, 2 H, =CHCH), 2.54 (m, 4 H, CH_2's), 3.39 (m, 2 H, $CH_3C\underline{H}_2$), 3.69 (m, 2 H, $CH_3C\underline{H}_2$), 4.73 (m, 1 H, OCH), 4.83 (m, 1 H, OCH), 5.11 (t, 2 H, J = 6.6 Hz, OCHOEt), 5.59 (m, 3 H, =CH-'s), 5.67 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 37.55, 37.67, 38.16, 38.33, 39.12, 41.58, 48.50, 48.78, 62.36, 62.56, 80.76, 82.76, 103.83, 104.21, 127.86, 127.99, 132.89, 133.25; IR (neat) 3010, 2960, 1670, 1215, 1090, 1070, 1030, 930, 900 cm^{-1}; mass spectrum m/e 154.21106 (calcd for $C_9H_{14}O_2$, 154.21073).

Oxypalladation reaction of 2-cyclohepten-1-ol with ethyl vinyl ether: product was obtained as a 1:1 mixture of epimers in 60% yield; R_f = 0.45, 12:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 7.0 Hz, CH_3), 1.75 (m, 5 H, CH_2's), 2.22 (m, 3 H, CH_2's), 2.35 (m, 1 H, =CHCH), 3.45 (m, 1 H, $CH_3C\underline{H}_2$), 3.75 (m, 1 H, $CH_3C\underline{H}_2$), 5.07 (m, 1 H, OCH), 5.55 (m, 1 H, OCHOEt), 5.60 (m, 1 H, =CH-), 5.90 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 25.46, 25.65, 27.03, 28.09, 28.66, 29.05, 33.32, 33.63, 35.29, 36.08, 70.06, 70.81, 122.34, 122.88, 140.57, 142.81, 149.72 (only peaks found); IR (neat) 2990, 2890, 2850, 1670, 1470, 1320, 1200, 940 cm^{-1}; mass spectrum m/e 182.26408 (calcd for $C_{11}H_{18}O_2$, 182.26491).

Oxypalladation reaction of <u>trans</u>-4-methyl-2-cyclohexen-1-ol with ethyl vinyl ether: product was obtained as a 2:1

mixture of epimers in 52% yield; R_f = 0.30, 12:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.12 (m, 9 H, $C\underline{H}_3CH_2$), 1.58 (s, 9 H, $=CCH_3$), 1.90 (m, 18 H, CH_2's), 2.59 (m, 1 H, =CCH), 2.70 (m, 2 H, =CHCH), 3.35 (m, 3 H, $CH_3C\underline{H}_2$), 3.68 (m, 3 H, $CH_3C\underline{H}_2$), 4.15 (m, 2 H, OCH), 4.58 (m, 1 H, OCH), 5.01 (m, 3 H, OCHOEt), 5.13 (m, 2 H, =CH-), 5.19 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ 25.27, 25.96, 36.71, 37.21, 62.79, 62.94, 74.47, 75.14, 77.42, 77.74, 102.83, 103.25, 103.99, 104.47, 107.75, 107.95, 117.78, 118.01, 122.08, 122.78, 133.90, 134.13; IR (neat) 2940, 2860, 1660, 1200, 1110, 940 cm^{-1}; mass spectrum m/e 182.26438 (calcd for $C_{11}H_{18}O_2$, 182.26491).

Oxypalladation reaction of 3-methyl-2-cyclopenten-1-ol with ethyl vinyl ether; 2 products were obtained; epimer 1 was obtained in 14% yield; R_f = 0.23, 20:1 pentanes/diethyl ether; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 6.9 Hz, $C\underline{H}_3CH_2$), 1.67 (d, 3 H, J = 0.6 Hz, $=CCH_3$), 1.79 (ddd, 1 H, J = 5.4 Hz, J = 5.4 Hz, J = 12.9 Hz, CH), 2.06 (ddd, 1 H, J = 1.2 Hz, J = 9.6 Hz, J = 12.9 Hz, CH), 2.37 (d, 1 H, J = 17.4 Hz, =CCH), 2.57 (ddd, 1 H, J = 5.4 Hz, J = 5.4 Hz, J = 17.4 Hz, =CCH), 3.18 (ddd, 1 H, J = 5.4 Hz, J = 5.4 Hz, J = 9.6 Hz, =CCH), 3.44 (m, 1 H, $CH_3C\underline{H}_2$), 3.73 (m, 1 H, $CH_3C\underline{H}_2$), 4.72 (t, 1 H, J = 6.3 Hz, OCH), 5.14 (d, 1 H, J = 5.4 Hz, OCHOEt), 5.16 (d, 1 H, J = 5.4 Hz, =CH-); IR (neat) 2990, 1630, 1440, 1220, 1000, 930 cm^{-1}; mass spectrum m/e 168.23766 (calcd for $C_{10}H_{16}O_2$, 168.23782); epimer 2 was

obtained in 13% yield; R_f = 0.16, 20:1 pentanes/diethyl ether; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3 H, J = 6.9 Hz, $C\underline{H}_3CH_2$), 1.72 (s, 3 H, =CCH), 1.93 (d, 1 H, J = 12.0 Hz, CH_2), 2.02 (m, 1 H, CH_2), 2.43 (dt, 1 H, J = 1.5 Hz, J = 17.5 Hz, =CCH), 2.61 (m, 1 H, $=CCH_2$), 3.04 (m, 1 H, $=CCH_2$), 3.52 (m, 2 H, OCH_2), 4.79 (m, 1 H, OCH), 5.11 (dd, 1 H, J = 1.1 Hz, J = 5.4 Hz, OCHOEt), 5.17 (s, 1 H, =CH-); IR (neat) 2985, 1630, 1440, 1210, 1010, 930, 740 cm^{-1}; mass spectrum m/e 168.23771 (calcd for $C_{10}H_{16}O_2$, 168.23782).

Oxypalladation reaction of 2-methyl-2-cyclohexen-1-ol with ethyl vinyl ether; product was obtained in 5% yield; R_f = 0.40, 15:1 pentanes/diethyl ether; ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 4 H, CH_2's), 1.90 (m, 2 H, CH_2), 2.07 (s, 3 H, CH_3), 4.00 (dd, 1 H, J = 0.9 Hz, J = 6.1 Hz, <u>cis</u> $=CH_2$), 4.34 (dd, 1 H, J = 0.9 Hz, J = 14.3 Hz, <u>trans</u> $=CH_2$), 5.68 (m, 1 H, OCH=), 6.28 (m, 1 H, OCH); insufficient material for complete analysis.

Oxypalladation reaction of 3-methyl-2-cyclohexen-1-ol with ethyl vinyl ether; product was obtained in 39% yield; R_f = 0.72, 12:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3 H, CH_3), 1.76 (m, 4 H, CH_2's), 1.95 (m, 2 H, CH_2), 4.01 (dd, 1 H, J = 0.9 Hz, J = 6.5 Hz, <u>cis</u> $=CH_2$), 4.31 (m, 1 H, OCH), 4.31 (dd, 1 H, J = 0.9 Hz, J = 14.1 Hz, <u>trans</u> $=CH_2$), 5.53 (m, 1 H, CC=CH), 6.37 (dd, 1 H, J = 6.5 Hz, J =

14.1 Hz, OCH=); IR (neat) 3040, 2980, 2800, 1650, 1590, 1210, 940 cm^{-1}.

Oxypalladation reaction of isophorol with ethyl vinyl ether; product was obtained in 40% yield; R_f = 0.45, 12:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.40 (dd, 2 H, J = 8.7 Hz, J = 12.6 Hz, CH_2), 1.69 (s, 3 H, =CCH), 1.85 (m, 2 H, CH_2), 4.02 (dd, 1 H, J = 1.5 Hz, J = 6.9 Hz, cis $=CH_2$), 4.32 (dd, 1 H, J = 1.5 Hz, J = 14.1 Hz, trans $=CH_2$), 4.39 (m, 1 H, OCH), 5.48 (m, 1 H, CC=CH), 6.37 (dd, 1 H, J = 6.9 Hz, J = 14.1 Hz, OCH=); IR (neat) 3030, 2960, 2920, 1660, 1550, 1290, 930 cm^{-1}.

Oxypalladation reaction of 10-methyl-1(9)-octal-2-ol with ethyl vinyl ether; product was obtained in 47% yield; R_f = 0.89, 6:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H, CH_3), 1.60 (m, 10 H, CH_2's), 4.01 (dd, 1 H, J = 1.5 Hz, J = 6.0 Hz, cis $=CH_2$), 4.30 (dd, 1 H, J = 1.5 Hz, J = 14.1 Hz, trans $=CH_2$), 4.35 (m, 1 H, OCH), 4.35 (d, 1 H, J = 1.2 Hz, CCH=), 6.37 (dd, 1 H, J = 6.0 Hz, J = 14.1 Hz, OCH=); IR (neat) 2980, 2850, 1440, 1200, 1110, 990 cm^{-1}.

General Procedure for Oxypalladation Reaction Employing Cyclic Vinyl Ethers

Oxypalladation reaction of 2-cyclohexen-1-ol and 3,4-dihydro-2H-pyran: to a stirred solution of 0.10 ml (1.0 mmol) of 2-cyclohexen-1-ol in 0.91 ml (10.0 mmol) of 3,4-dihydro-2H-pyran at 0°C in an ice bath was added 0.2244

g (1.0 mmol) of palladium acetate. The ice bath was then removed and the resulting solution was stirred at room temperature for 2 h. The mixture was then diluted with 20 ml of hexanes and 0.2 ml (2.5 mmol) of pyridine was added. After stirring an additional 10 min at room temperature, the solution was filtered through Celite to remove the palladium metal and the filtrate was concentrated by rotary evaporation. The residual oil was purified by column chromatography on silica gel with 9:1 hexanes/ethyl acetate to yield 60% of a yellow oil: R_f = 0.60; ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 6 H, CH_2's), 2.28 (m, 2 H, CH_2), 3.71 (m, 1 H, OCH_2), 3.97 (m, 1 H, OCH_2), 4.24 (m, 1 H, OCH), 5.07 (d, 1 H, J = 11.5 Hz, OCHC=), 5.76 (m, 3 H, =CH-'s), 6.01 (m, 1 H, =CH-).

Oxypalladation reaction of allyl alcohol with 2,3-dihydro-2H-pyran: product was obtained in 33% yield; R_f = 0.60, 12:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.91 (ddt, 1 H, J = 1.2 Hz, J = 3.9 Hz, J = 18.0 Hz, $=CCH_2$), 2.30 (m, 1 H, $=CCH_2$), 3.73 (ddt, 1 H, J = 1.2 Hz, J = 6.0 Hz, J = 11.1 Hz, OCH), 3.94 (dt, 1 H, J = 3.6 Hz, J = 11.4 Hz, OCH), 4.05 (qt, 1 H, J = 1.2 Hz, J = 6.3 Hz, OCH), 4.26 (ddt, 1 H, J = 1.5 Hz, J = 5.1 Hz, J = 12.9 Hz, OCH), 4.95 (d, 1 H, J = 0.9 Hz, =CCH), 5.18 (dq, 1 H, J = 1.2 Hz, J = 10.2 Hz, =CH-), 5.29 (dq, 1 H, J = 1.5 Hz, J = 17.1 Hz, =CH-), 5.74

(ddt, 1 H, J = 1.2 Hz, J = 3.0 Hz, =CH-), 5.94 (m, 1 H, =CH-), 6.04 (m, 1 H, =CH-).

Oxypalladation reaction of allyl alcohol with 2,3-dihydrofuran: product was obtained in 17% yield; R_f = 0.60, 12:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 4.06 (ddd, 1 H, J = 0.9 Hz, J = 5.8 Hz, J = 11.6 Hz, OCH_2), 4.22 (ddd, 1 H, J = 0.9 Hz, J = 5.8 Hz, J = 12.8 Hz, OCH_2), 4.57 (m, 1 H, OCH_2C=), 4.73 (m, 1 H, OCH_2C=), 5.18 (dd, 1 H, J = 3.5 Hz, J = 9.3 Hz, cis =CH_2), 5.79 (dd, 1 H, J = 3.5 Hz, J = 16.8 Hz, trans =CH_2), 5.83 (m, 1 H, OCHO), 5.90 (m, 1 H, =CH-), 5.97 (dd, 1 H, J = 9.3 Hz, J = 16.8 Hz, CH_2=C<u>H</u>), 6.27 (m, 1 H, =CH-). The product is quite volatile. This may account for the low yield obtained.

Oxypalladation reaction of benzyl alcohol with 2,3-dihydrofuran: product was obtained in 60% yield; R_f = 0.45, 6:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 4.58 (d, 1 H, J = 11.5 Hz, ArCH), 4.61 (m, 1 H, OCH), 4.76 (d, 1 H, J = 11.5 Hz, ArCH), 5.78 (m, 1 H, OCH), 5.85 (m, 1 H, OCHO), 5.97 (dd, 1 H, J = 0.6 Hz, J = 1.8 Hz, CHC<u>H</u>=), 6.39 (dd, 1 H, J = 0.6 Hz, J = 3.7 Hz, CH_2C<u>H</u>=), 7.33 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 68.62, 74.38, 107.90, 125.81, 127.41, 127.73, 128.21, 132.00, 138.04; IR (neat) 3040, 3020, 2980, 2960, 1440, 1200, 1160, 940 cm^{-1}.

Compound <u>37</u>: obtained as a 2:1 mixture of epimers; R_f = 0.25, 4:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3

H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 1.18 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.91 (m, 2 H, CH_2), 2.28 (s, 3 H, $COCH_3$), 2.37 (m, 1 H, CH_2), 2.62 (m, 1 H, CH_2), 3.03 (m, 1 H, CH), 3.41 (m, 1 H, $C\underline{H}_2CH_3$), 3.68 (m, 1 H, $C\underline{H}_2CH_3$), 4.12 (q, 1 H, J = 6.6 Hz, =CCH), 4.23 (t, 1 H, J = 2.7 Hz, SiOCH), 4.70 (t, 1 H, J = 6.9 Hz, OCH), 5.14 (d, 1 H, J = 4.8 Hz, OCHOEt), 6.11 (d, 1 H, J = 16.2 Hz, COCH=), 6.95 (dd, 1 H, J = 6.9 Hz, J = 16.2 Hz, COCH=C$\underline{H}$). The ^1H NMR is in good agreement with that reported by Lee and Russell for similar compounds.[28]

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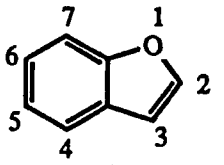
PART IV. SYNTHESIS OF BENZOFURANS VIA PALLADIUM-ASSISTED CYCLIZATION

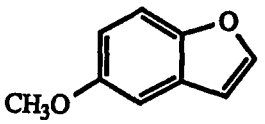
INTRODUCTION

The benzofuran nucleus 1 occurs widely in nature and the synthesis of benzofurans and their derivatives has been extensively researched. There are a book[1] and two reviews[2,3] devoted to various aspects of both naturally-occurring and synthetic benzofurans. This introduction will present a brief overview of the biological activity of benzofuran derivatives and some of the major methods used in the synthesis of the benzofuran nucleus.



1

The simplest, naturally-occurring benzofuran derivative is 5-methoxy benzofuran 2. Discovered as a result of fungal contamination of oak beer barrels, it was found to give the beer a strong, persistent, distasteful scent.[4] Among other natural benzofurans are the Moracins (3a-c) which show antifungal activity[5,6] and the quettamines which are a class of isoquinoline alkaloids possessing a benzofuran nucleus.[7] A benzofuran derivative isolated from alfalfa is coumestrol 4.[8,9] It is one of the phytoestronic substances that stimulates animal growth.



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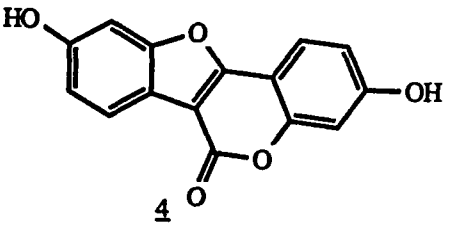

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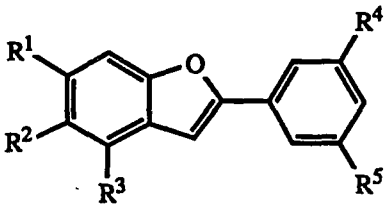
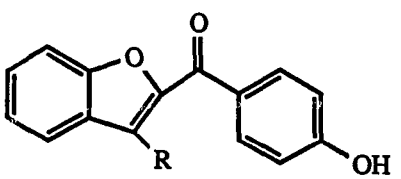


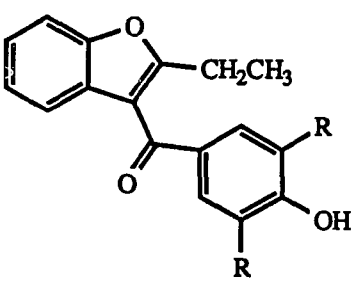
3

3a: $R^1 = R^3 = OCH_3, R^2 = H, R^4 = R^5 = OH$
3b: $R^1 = R^4 = OCH_3, R^2 = R^5 = OH, R^3 = H$
3c: $R^1 = R^2 = OCH_3, R^3 = H, R^4 = R^5 = OH$

Among the synthetic benzofurans, 2-(4-hydroxybenzoyl)-benzofuran 5a and its 3-ethyl derivative 5b both exhibit estrogenic activity;[10] 2-ethyl-3-(4-hydroxybenzoyl)-benzofuran 6, or benzarone, is an angitropic, antiinflammatory and fibronolytic agent[11] (used clinically under the name Flargivix L); 2-ethyl-3-(3,5-diiodo-4-hydroxybenzoyl)-benzofuran 7, or benziodarone (clinically used as Amplivix), is a coronary vasodilator.[12]

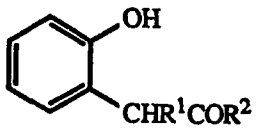


5a: R = H
5b: R = CH_2CH_3



6: R = H
7: R = I

There are several synthetic procedures available for the synthesis of benzofurans. One of the major methods involves the cyclodehydration of compounds such as 8 or 9 with sulfuric acid or polyphosphoric acid.[1] The cyclodehydration



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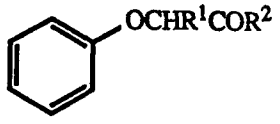
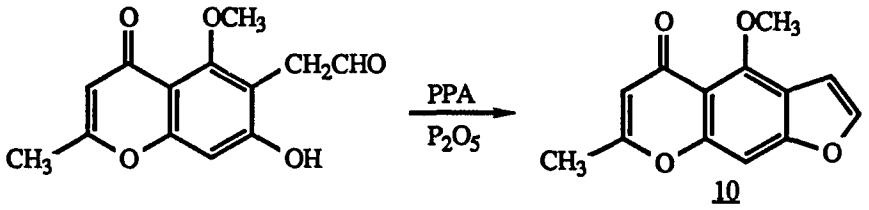


9

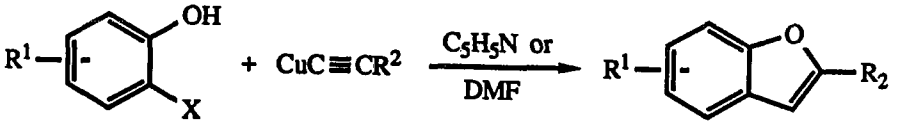
reaction was employed by Aneja and co-workers[13] in the synthesis of visnagin 10 which is the major component of the seeds of Ammi Visnaga, an important plant drug (eq. 1).



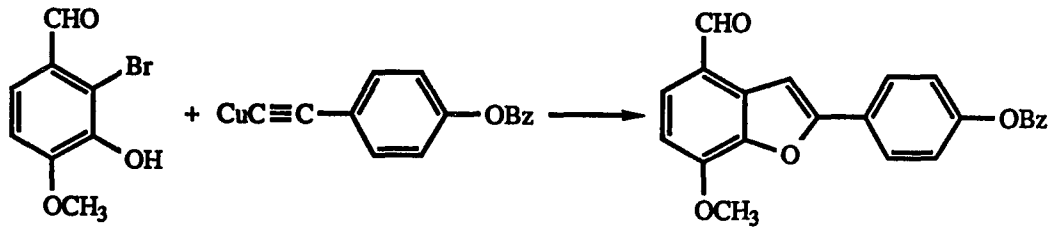
10

(1)

The reaction of cuprous acetylides with aryl bromides or aryl iodides bearing an ortho hydroxyl group provides an entry into 2-substituted benzofurans (eq. 2).[14] In their synthesis of secoquettamines, Biftu, Schneiders and Stevenson[15] used the cuprous acetylide cyclization to prepare the required benzofuran skeleton (eq. 3).



(2)

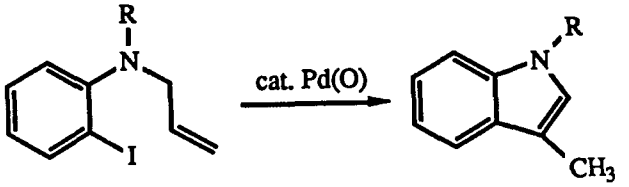


(3)

Another general procedure for the synthesis of 2- and 3-substituted benzofurans involves the cyclization of ortho-allyl phenols and ortho-vinyl phenols respectively via oxypalladation. This approach was discussed in Part 2 of this thesis.

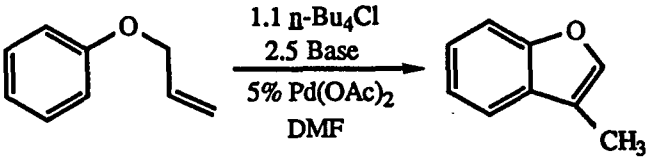
RESULTS AND DISCUSSION

Transition metal reagents have proven highly valuable for the cyclization of nitrogen containing ortho-haloaryl alkenes to heterocycles. Nickel[16-23] and palladium[24-29] catalysts are the most useful for such cyclizations. Larock and Babu[30] recently reported that variations of Jeffery's[31-33] palladium catalyst system cyclize such o-iodoaryl alkenes to indoles, indolines, oxindoles, quinolines, isoquinolines and isoquinolones under mild reaction temperatures, in short reaction times, and in high yield (eq. 4).

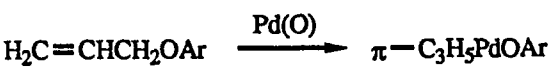


(4)

Applying this same methodology to the cyclization of o-iodoaryl allyl ethers to afford benzofurans (eq. 5) is much more problematical as a route to benzofurans in view of the known ability of palladium(0) to react with aryl allyl ethers to form π-allylpalladium compounds (eq. 6).[34]



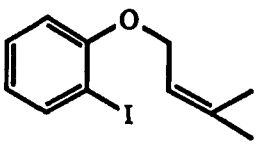
(5)



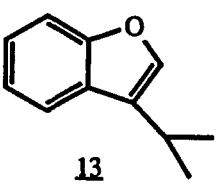
(6)

When the same conditions employed by Jeffery were applied to the synthesis of 3-methyl benzofuran using o-iodophenyl allyl phenyl ether as the substrate, some interesting results were obtained (Table 1). As seen from the results in Table 1, it was obvious that the reaction would not proceed under the same conditions employed in the indole synthesis reported above. With the appearance of o-iodophenol as well as the coupled product 11, some oxidative addition to the carbon-oxygen bond was apparently occurring with the concomitant formation of π-C_3H_5PdOAr. As seen in entry 7, the use of a preformed palladium(0) catalyst did not help the reaction, since no identifiable products were obtained.

Observing that the reaction did proceed to a certain extent and with the precedent that substitution at the remote end of the allyl group slows or prevents π-allylpalladium formation,[35] the substrate 12 was prepared and subjected to various palladium-catalyzed cyclization conditions (Table 2).



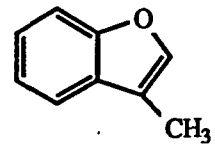
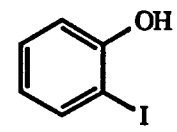
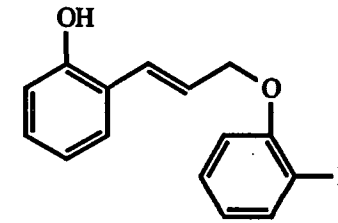
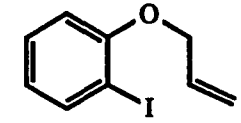
12



13

The desired product and the observed product were 3-isopropylbenzofuran 13. The reaction proceeded with

Table 1. Synthesis of 3-methylbenzofuran

Entry	Base	Temp[b] (°C)	Time (d)	Yield (%)[c]	Product Ratio[a]			
							 11	
1	Na_2CO_3	RT	7	70	3	2	4	56
2	NaOAc	RT	7	86	11	16	6	17
3	Et_3N	RT	7	80	1	1	1	20
4	Na_2CO_3	80	1	42	2	0	5	0
5	$NaHCO_3$	80	1	55	7	2	6	2
6	K_2CO_3	80	1	79	15	26	8	29
7[d]	Na_2CO_3	80	1	0	--	--	--	--

[a]Gas chromatography products were identified by retention times and gas chromatography - mass spectroscopy.

[b]RT is 23-25°C.

[c]Mass recovery.

[d]$Pd(dba)_2$ was used. No identifiable products were obtained.

Table 2. Synthesis of 3-isopropylbenzofuran (13)

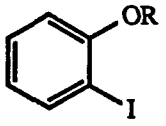
Entry[a]	Base (2.5 eq.)	Temp (°C)	Time (d)	Pd reagent (%)	Yield of 13 (%)
1	Na_2CO_3	80	2	$Pd(OAc)_2$ (5)	50
2	$NaHCO_3$	80	2	$Pd(OAc)_2$ (5)	44
3	Na_2CO_3	25	7	$Pd(OAc)_2$ (5)	< 5
4	Na_2CO_3	45	8	$Pd(OAc)_2$ (5)	< 10
5	Na_2CO_3	80	1	$Pd(OAc)_2$ (10)	65
6	Na_2CO_3	80	2	$Pd(OAc)_2$ (10)	50
7	Na_2CO_3	80	2	$Pd(dba)_2$ (10)	54
8	Na_2CO_3	80	2	$Pd(PPh_3)_4$ (10)	< 5
9	Na_2CO_3	80	2	$Pd(OAc)_2$ (20)	47
10	Na_2CO_3	80	3	$Pd(OAc)_2$ (20)[b]	74
11	Na_2CO_3	80	2	$Pd(OAc)_2$ (5)	76[c]

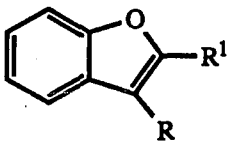
[a]Entries 1-9 contained undetermined amounts of the starting material 12 after the reaction was stopped.

[b]The catalyst was added in 5% portions at 0, 12, 24, and 48 h.

[c]The reaction contained 1 equivalent of NaO_2CH.

complete disappearance of the starting material by adding one equivalent of sodium formate to the reaction as shown in entry 11. With this observation in hand, several other substrates 14-19 were prepared and subjected to the same cyclization conditions. The expected products were the benzofurans 20-25. The results are presented in Table 3.



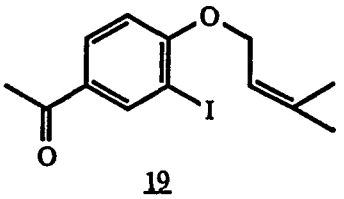


14: R = CH_2CH=

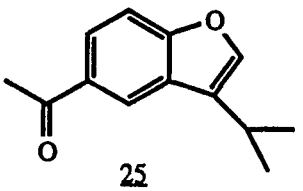
15: R = E-CH_2CH=CHPh
16: R = E-CH_2CH=$CHCH_3$
17: R = CH_2CH=$CHCH_2CH_2CH_2CH_2CH_3$
18: R = $CH(CH_3)CH$=$CHCH_3$

20: R = CH_2 , R^1 = H

21: R = CH_2Ph, R^1 = H
22: R = CH_2CH_3, R^1 = H
23: R = n-C_6H_{13}, R^1 = H
24: R = CH_2CH_3, R^1 = CH_3



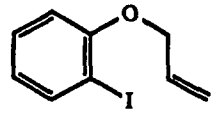
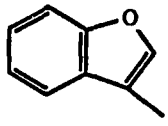
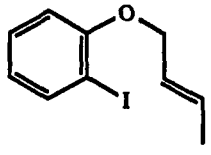
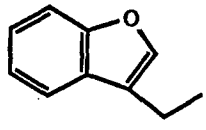
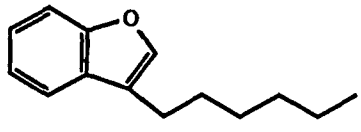
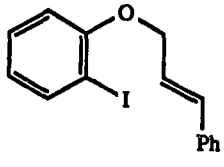
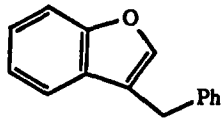
19



25

As seen in Table 3, most of the entries proceeded quite well under these conditions. Apparently the formate reduces any π-allylpalladium intermediates formed by insertion of the palladium into the carbon-oxygen bond of the substrate and, therefore, keeps the palladium(0) catalyst active. Consistent with the idea that palladium(0) insertion into the carbon-oxygen bond is the major side reaction is the observation that the less hindered the double bond (Table 3,

Table 3. Synthesis of benzofurans via o-iodoaryl allyl ethers[a]

Entry	Substrate	Benzofuran[b]	Isolated Yield (%)
1			47
2			83
3			83[c]
4			45[d],81[e]

[a]All reactions were stirred in a 1-dram vial at 80°C for 2 days using 5% $Pd(OAc)_2$ (0.015 mmol), Na_2CO_3 (0.75 mmol), NaO_2CH (0.3 mmol), the substrate (0.3 mmol), DMF (0.6 ml), and n-Bu_4NCl (0.33 mmol).

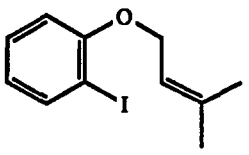
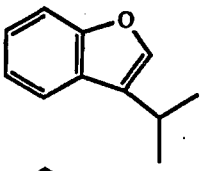
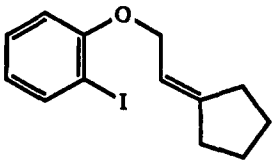
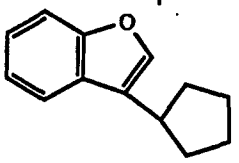
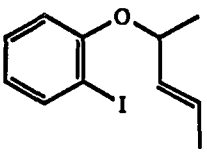
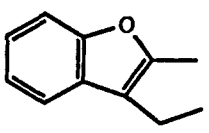
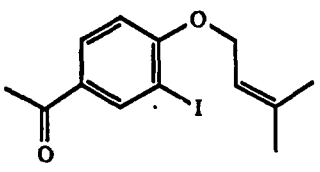
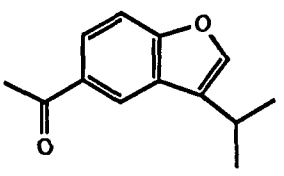
[b]All products gave appropriate ^1H and ^{13}C NMR, IR, and mass spectral data.

[c]Substrate was a 60:40 E/Z mixture.

[d]Contained 45% unreacted substrate.

[e]With 10% $PdCl_2(MeCN)_2$, 81% of the benzofuran product and 9% of the substrate were obtained.

Table 3. Continued

Entry	Substrate	Benzofuran[b]	Isolated Yield (%)
5			76
6			52
7			40[f]
8			42[g]

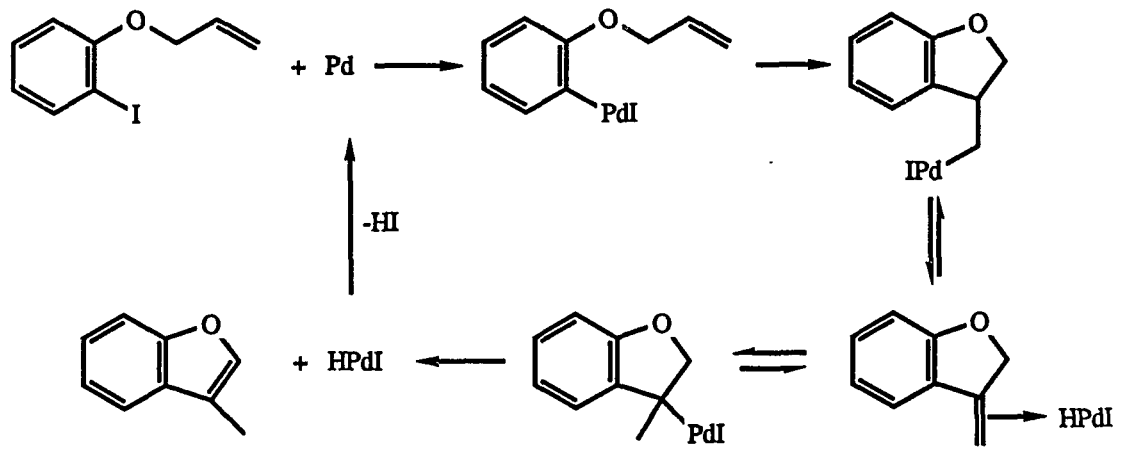
[f]This result has proven to be irreproducible.

[g]Reaction was run for 1 day.

Entry 1) or the better the aryl leaving group (Table 3, Entry 8), the lower the yield of benzofuran. The cinnamyl aryl ether substrate 15 (Table 3, Entry 4) never reacted completely under these conditions. There is no apparent explanation for this.

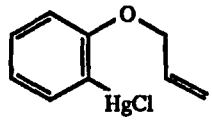
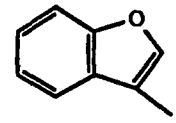
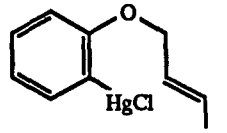
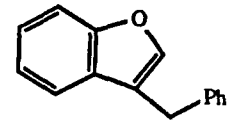
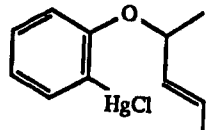
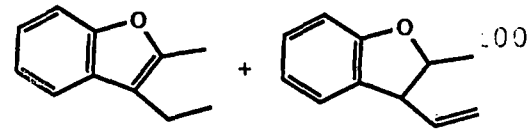
Mechanistically, it is believed that these reactions proceed as indicated in Scheme 1. (Note: additional ligands on palladium have been omitted for clarity.)

Scheme 1



To improve the yields of benzofuran from those systems that do not work well in this palladium(0)-catalyzed process, the palladium(II)-promoted cyclization of the analogous aryl mercurials 26-28 was also examined. Cyclization using one equivalent of Li_2PdCl_4 occurred readily in a matter of minutes at room temperature to afford high yields of the corresponding benzofuran (Table 4). The only

Table 4. Synthesis of benzofurans via organomercurials[a]

Entry	Organomercurial	Time (min)	Benzofuran(s)[b]	Isolated Yield (%)
1	 26	35		65[c]
2	 27	60		98
3	 28	60	 72 : 28	100

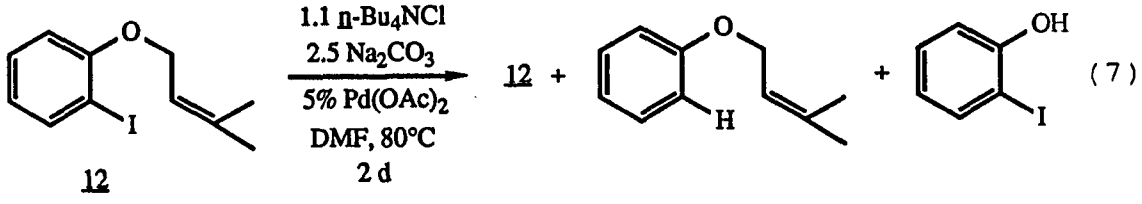
[a]All reactions were stirred at ambient temperature using Li_2PdCl_4 (0.30 mmol), Et_3N (0.6 mmol), the substrate (0.3 mmol), THF (6 ml) and DMF (1.2 ml).

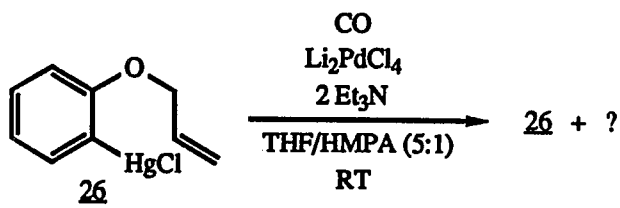
[b]All products gave appropriate ^1H and ^{13}C NMR, IR, and mass spectral data.

[c]HMPA was used instead of DMF.

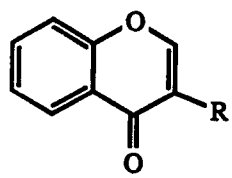
difficulty encountered here is the apparent side chain elimination of palladium hydride noted in Table 4, Entry 3. An attempt to make the process catalytic in $PdCl_2$ (10%) using organomercurial 26 and addition of $CuCl_2$ and O_2 gave back 55% of the starting material and 15% of the benzofuran after 5 days of reaction at room temperature.

Some other work related to these benzofuran systems involved the attempted carbonylation of the intermediate arylpalladium species (Scheme 1) formed prior to cyclization (eq. 7). When the aryl iodide 12 was reacted under CO (1 atmosphere) using the same conditions as those in Table 2, Entry 1, only 12, the dehalogenated analog of 12, and o-iodophenol were obtained in less than 20% yield (eq 7). When the organomercurial 26 was cyclized under CO (1 atmosphere) using conditions identical to those in Table 4, Entry 1, only compound 26 and unidentifiable products were obtained in less than 20% yield (eq. 8). The hoped for products, compounds 29 and 30, are shown below.





(8)



29 R = CH_3
30 R = $CH(CH_3)_2$

CONCLUSION

A variety of 3-substituted benzofurans can be prepared from the palladium(0)-catalyzed cyclization of o-iodoaryl allyl ethers and the palladium(II)-assisted cyclization of o-(chloromercurio)aryl allyl ethers.

EXPERIMENTAL SECTION

Equipment

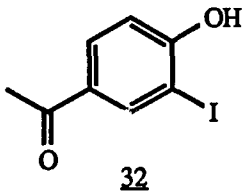
Proton NMR spectra were recorded on a Nicolet NT-300 spectrometer. ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer operating at 75 MHz for carbon nuclei. Infrared spectra were recorded on either a Beckman Acculab 2 or an IBM IR-98 spectrometer. Exact mass spectral data were obtained on a Kratos MS-50 high resolution mass spectrometer. Gas chromatographic-mass spectral analyses were performed on a Finnigan 4000 spectrometer. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc.

Reagents

All compounds were used directly as obtained commercially unless otherwise noted. All starting materials were purchased from Aldrich (allyl alcohol, cyclopentanone, cinnamyl alcohol, acetyl chloride, triethylamine, vinyl magnesium bromide, allyl chloride, potassium carbonate, diethylazodicarboxylate, triphenylphosphine, mercuric chloride, mercuric acetate, 1-bromo-3-methyl-2-butene, 1-bromo-2-butene), Lancaster Synthesis (cinnammyl bromide, o-iodophenol), or J. T. Baker (lithium chloride, 2-penten-4-ol). Tetrahydrofuran was distilled from benzophenone-

sodium ketyl; N,N-dimethylformamide was distilled from calcium hydride; triethylamine from sodium hydroxide; acetyl chloride from calcium hydride. Lithium chloride was dried at 120°C at 0.5 mm Hg prior to use. Palladium chloride was generously supplied by Johnson Matthey, Inc. o-(Chloromercuriophenol,[36] and 2-octen-1-ol[37] were prepared following literature procedures. Compound 31 was prepared following the procedures of Song[38] and Overman.[39] Compound 32 was supplied by N. Berrios-Pena.

31



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All aryl ether syntheses were done using the following general procedures.

Preparation of o-iodoallyl phenyl ether via procedure A: Williamson synthesis. A solution of 1.00 g (4.545 mmol) of o-iodophenol, 0.691 g (5.01 mmol) of potassium carbonate, and 0.8 ml (9.09 mmol) of allyl bromide in 3 ml of acetone was refluxed for 12 h. The reaction mixture was diluted with 40 ml of water and extracted with 3 times 20 ml of ethyl ether. The combined organic layers were washed first with 10 ml of 10% aqueous sodium hydroxide and then with 3 times 15 ml of water and dried over magnesium sulfate. The solvent was then removed by rotary evaporation and the crude

product purified by column chromatography on silica gel with 9:1 hexanes/ethyl acetate to yield 1.18 g (99% yield) of o-iodophenyl allyl ether.

Compound 15: yield 95%; R_f = 0.65, 25 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 4.76 (d, 2 H, J = 1.5 Hz, OCH_2), 6.41 (dt, 1 H, J = 5.4 Hz, J = 16.2 Hz, =CH-), 6.72 (dt, 1 H, J = 1.2 Hz, J = 7.5 Hz, ArCH=), 6.82 (d, 1 H, J = 8.1 Hz, Ar), 6.87 (dd, 1 H, J = 1.2 Hz, J = 8.1 Hz, Ar), 7.73 (m, 6 H, Ar), 7.79 (dd, 1 H, J = 1.5 Hz, J = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 69.54, 85.74, 112.54, 122.63, 123.76, 126.51, 127.80, 128.48, 129.34, 132.70, 136.27, 139.44, 157.00; IR (neat) 3070, 3040, 2900, 1740, 1590, 1480, 1380, 1280, 1240, 1010, 740 cm^{-1}; mass spectrum m/e 336.00127 (calcd for $C_{15}H_{13}OI$, 336.00112).

Compound 16: yield 95%; R_f = 0.75, 9:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.75 (d, 3 H, J = 6.8 Hz, CH_3), 4.52 (d, 2 H, J = 4.9 Hz, CH_2), 5.75 (m, 1 H, =C<u>H</u>-CH_3), 5.88 (m, 1 H, =C<u>H</u>-CH_2-), 6.70 (t, 1 H, J = 6.8 Hz, Ar), 6.82 (d, 1 H, J = 7.4 Hz, Ar), 7.28 (t, 1 H, J = 7.4 Hz), 7.96 (d, 1 H, J = 6.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 64.96, 69.56, 86.68, 112.41, 122.34, 125.40, 129.20, 129.87, 139.35, 157.08; IR (neat) 3030, 2910, 2870, 1585, 1475, 1440, 1380, 1280, 1245, 1020, 1000, 965 cm^{-1}; mass spectrum m/e 273.98567 (calcd for $C_{10}H_{11}OI$, 273.98547).

o-Iodoallyl phenyl ether: yield 99%; R_f = 0.69, 9:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 4.61 (dd, 2 H, J = 1.8 Hz, J = 4.8 Hz, $-CH_2-$), 5.31 (dd, 1 H, J = 1.8 Hz, J = 10.8 Hz, cis $=CH_2$), 5.52 (dd, 1 H, J = 1.8 Hz, J = 17.4 Hz, trans $=CH_2$), 6.06 (m, 1 H, =CH-), 6.71 (dt, 1 H, J = 1.2 Hz, J = 7.5 Hz, Ar), 6.81 (d, 1 H, J = 8.1 Hz, Ar), 7.27 (dt, 1 H, J = 1.5 Hz, J = 8.4 Hz, Ar), 7.78 (dd, 1 H, J = 1.2 Hz, J = 7.5 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 69.51, 88.58, 112.37, 117.47, 122.55, 129.29, 132.44, 139.38, 156.91; IR (neat) 3030, 1575, 1460, 1270, 1235, 990 cm^{-1}; mass spectrum m/e 259.97003 (calcd for C_9H_9OI, 259.96982).

Compound 12: yield 95%; R_f = 0.78, 9:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.74 (s, 3 H, $-CH_3$), 1.79 (s, 3 H, CH_3), 4.55 (d, 2 H, J = 6.4 Hz, CH_2), 5.49 (t, 1 H, J = 6.4 Hz, =CH-), 6.69 (dt, 1 H, J = 1.2 Hz, J = 7.65 Hz, Ar), 6.82 (d, 1 H, J = 8.1 Hz, Ar), 7.27 (dt, 1 H, J = 1.5 Hz, J = 7.8 Hz, Ar), 7.76 (dd, 1 H, J = 1.2 Hz, J = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 18.28, 25.75, 66.06, 86.78, 112.44, 119.36, 122.23, 129.21, 137.63, 139.20, 157.20; IR (neat) 3040, 2950, 2900, 1565, 1450, 1420, 1260, 1220, 980 cm^{-1}; mass spectrum m/e 288.00145 (calcd for $C_{11}H_{13}OI$, 288.00112).

Compound 19: yield 90%; R_f = 0.50, 25:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.76 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 4.66 (d, 2 H, J = 6.5 Hz, CH_2O), 5.50 (m, 1 H, -CH=), 6.82 (d, 1 H, J = 7.8 Hz, Ar), 7.91 (dd, 1 H, J = 1.2 Hz, J

= 7.8 Hz, Ar), 8.38 (d, 1 H, J = 1.2 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 25.69, 26.37, 66.36, 86.48, 111.13, 118.51, 130.38, 131.39, 138.73, 140.18, 159.50, 160.99, 195.51; IR (neat) 3030, 2940, 2890, 1750, 1565, 1450, 1260, 1220, 980 cm^{-1}; mass spectrum m/e 330.01186 (calcd for $C_{13}H_{15}O_2I$, 330.01168).

Preparation of organomercurial 26 via procedure B: Mitsunobu coupling.[40] To a stirred solution of 0.2 ml (3.0 mmol) of allyl alcohol, 0.60 g (2.3 mmol) of triphenylphosphine, and 0.6583 g (2.0 mmol) of o-(chloromercurio)-phenol in 40 ml of tetrahydrofuran, a solution of 0.5 ml diethylazodicarboxylate in 10 ml of tetrahydrofuran was added dropwise over 15 min. The resulting solution was stirred at room temperature for 24 h. The solvent was then removed by rotary evaporation and the crude product purified by column chromatography on silica gel with 2:1 hexanes as eluent to yield 0.3118 g (44% yield) of a white crystalline solid.

Compound 14: yield 90%; R_f = 0.60, 25 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.68 (m, 4 H, $-CH_2(C\underline{H}_2)_2CH_2-$), 2.31 (m, 4 H, $-C\underline{H}_2(CH_2)_2CH_2-$), 4.56 (dt, 1 H, J = 1.2 Hz, J = 6.3 Hz, $-CH_2O-$), 5.62 (m, 1 H, =CH-), 6.69 (dt, 1 H, J = 1.2 Hz, J = 7.5 Hz, Ar), 6.82 (dd, 1 H, J = 1.2 Hz, J = 8.1 Hz, Ar), 7.27 (dt, 1 H, J = 1.5 Hz, J = 7.8 Hz, Ar), 7.63 (dd, 1 H, J = 1.5 Hz, J = 7.8 Hz, Ar); ^{13}C

NMR ($CDCl_3$) δ 26.01, 26.32, 29.08, 33.78, 67.55, 80.90, 112.65, 114.88, 122.33, 129.23, 139.36, 149.15, 157.42; IR (neat) 3030, 2960, 2870, 1585, 1470, 1435, 1275, 1235, 1000, 745, cm^{-1}; mass spectrum m/e 314.01700 (calcd for $C_{13}H_{15}OI$, 314.01677).

Compound 17: yield 80%; R_f = 0.36, hexanes; obtained as a 1.0:0.4 cis/trans mixture; ^1H NMR ($CDCl_3$) δ 0.89 (m, 2t, 4.2 H, CH_3's), 1.20 - 1.45 (m, 8.4 H, $-CH_2-$'s), 2.01 - 2.65 (m, 2.8 H, $=CH-C\underline{H}_2-$), 4.00 (dt, 0.8 H, J = 1.2 Hz, J = 6.6 Hz, trans $-CH_2-O$), 4.54 (dd, 1 H, J = 0.9 Hz, J = 6.0 Hz, cis $-CH_2-O$), 4.64 (d, 1 H, J = 4.8 Hz, cis $-CH_2O$), 5.50 - 5.94 (m, 2.8 H, cis and trans -CH=CH-), 6.69 (m, 1.4 H, Ar), 6.82 (m, 1.4 H, Ar), 7.27 (m, 1.4 H, Ar), 7.76 (m, 1.4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 22.53, 27.89, 28.64, 29.06, 31.44, 31.53, 32.35, 65.31, 69.85, 86.84, 112.08, 112.55, 112.69, 122.30, 122.44, 124.15, 125.24, 125.15, 129.28, 129.38, 133.58, 134.63, 135.43, 139.37, 139.44, 157.23; IR (neat) 3080, 3020, 2970, 2940, 2870, 1590, 1480, 1280, 1250, 1010, 750 cm^{-1}; mass spectrum m/e 330.04822 (calcd for $C_{14}H_{19}OI$, 330.04807).

Compound 18: yield 78%; R_f = 0.55, hexanes; ^1H NMR ($CDCl_3$) δ 1.47 (d, 3 H, J = 6.3 Hz, $=CH-C\underline{H}_3$), 1.69 (dd, 3 H, J = 0.9 Hz, J = 6.0 Hz, $OCH-C\underline{H}_3$), 4.76 (dq, 1 H, J = 6.3 Hz, J = 6.3 Hz, OCH), 5.56 (m, 1 H, $=C\underline{H}CH_3$), 5.70 (m, 1 H, $=C\underline{H}CH$), 6.67 (dt, 1 H, J = 1.5 Hz, J = 7.5 Hz, Ar), 6.82

(dd, J = 1.2 Hz, J = 8.4 Hz, Ar), 7.22 (dd, 1 H, J = 1.5 Hz, J = 7.5 Hz, Ar), 7.75 (dd, 1 H, J = 1.5 Hz, J = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 76.33, 88.26, 108.84, 114.86, 122.40, 127.51, 128.89, 129.01, 131.66, 139.20, 156.71; IR (neat) 3050, 2980, 2910, 1575, 1465, 1430, 1265, 1235, 1035, 1010, 955, 735, cm^{-1}; mass spectrum m/e 288.00115 (calcd for $C_{11}H_{13}OI$, 288.00112).

Compound 26: yield 44%; R_f = 0.73, 2:1 hexanes/ethyl acetate; Mp = 89.5 - 91°C; ^1H NMR ($CDCl_3$) δ 4.56 (d, 2 H, J = 5.4 Hz, CH_2), 5.30 (dd, 1 H, J = 1.5 Hz, J = 9.5 Hz, cis $=CH_2$), 5.39 (dd, 1 H, J = 1.5 Hz, J = 15 Hz, trans $=CH_2$), 6.02 (m, 1 H, =CH-), 6.92 (d, 1 H, J = 8.25 Hz, Ar), 7.02 (t, 1 H, J = 7.5 Hz, Ar), 7.29 (m, 2 H, Ar); IR (neat) 3020, 1575, 1465, 1440, 1215, 1015, 750 cm^{-1}; Anal. calcd for C_9H_9OHgCl: C, 29.27; H, 2.46; Hg, 54.32. Found: C, 29.25; H, 2.45; Hg, 54.60.

Compound 27: yield 25%; R_f = 0.40, 6:1 hexanes/ethyl acetate; Mp = 137.5 - 139°C; ^1H NMR ($CDCl_3$) δ 4.72 (d, 2 H, J = 0.9 Hz, CH_2), 6.37 (dt, 1 H, J = 4.9 Hz, J = 15.4 Hz, $CH_2\underline{CH}=$), 6.72 (d, 1 H, J = 15.4 Hz, PhCH=), 7.02 (m, 2 H, Ar), 7.35 (m, 7 H, Ar); IR (neat) 3030, 3010, 2980, 1600, 1575 1240, 1105, 760 cm^{-1}; Anal. calcd for $C_{15}H_{13}OHgCl$: C, 33.26; H, 3.30. Found: C, 33.57; H, 3.50.

Compound 28: yield 14%; R_f = 0.45, 8:1 hexanes/ethyl acetate; Mp = 70 - 71.5°C; ^1H NMR ($CDCl_3$) δ 1.40 (d, 3 H, J

= 5.9 Hz, =CHC$\underline{H}_3$), 1.70 (d, 3 H, J = 6.3 Hz, OCHC$\underline{H}_3$), 4.76 (dq, 1 H, J = 5.9 Hz, J = 5.9 Hz, OCH), 5.50 (ddd, 1 H, J = 0.9 Hz, J = 5.4 Hz, J = 14.4 Hz, OCHC$\underline{H}$=), 5.67 (dq, 1 H, J = 5.9 Hz, J = 15.6 Hz, =C$\underline{H}$CH$_3$), 6.95 (d, 1 H, J = 8.7 Hz, Ar), 7.01 (d, 1 H, J = 8.7 Hz, Ar), 7.24 (m, 2 H, Ar); IR (neat) 3030, 2985, 2950, 1575, 1460, 1375, 1210, 1040, 750 cm^{-1}; Anal. calcd for $C_{11}H_{13}OHgCl$: C, 40.46; H, 2.94. Found: C, 40.84; H, 3.01.

The preparations of benzofurans from the iodoaryl allyl ethers follow the general procedure below.

Preparation of 3-methylbenzofuran from $\underline{o}$-iodophenyl allyl ether. In a 1-dram vial, a mixture of 0.1125 g (0.4375 mmol) of $\underline{o}$-iodophenyl allyl ether, 0.1322 g (0.480 mmol) of tetra-$\underline{n}$-butylammonium chloride, 0.1146 g (1.084 mmol) of sodium carbonate, 0.0294 g (0.4375 mmol) of sodium formate, and 4.9 mg (0.219 mmol) of palladium acetate, and 0.9 ml of $\underline{N}$,$\underline{N}$-dimethylformamide was stirred at 80°C for 2 days. The reaction mixture was then diluted with 25 ml of diethyl ether. The resulting solution was washed with 2 times 25 ml of saturated aqueous ammonium chloride and dried over magnesium sulfate. The solvent was removed by rotary evaporation and the crude product purified by column chromatography on silica gel using 4:1 hexanes/ethyl acetate as eluent to yield 27 mg (47% yield) of 3-methylbenzofuran:

R_f = 0.74; ^1H NMR and IR were consistent with that reported in the literature.[41]

Compound 24: R_f = 0.60, 50:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.5 Hz, $CH_2\underline{CH_3}$), 2.37 (s, 3 H, $=CCH_3$), 2.61 (q, 2 H, J = 7.5 Hz, CH_2), 7.17 (m, 2 H, Ar), 7.36 (dd, 1 H, J = 1.8 Hz, J = 5.1 Hz, Ar), 7.44 (dd, 1 H, J = 2.0 Hz, J = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 11.82, 14.43, 16.92, 110.49, 117.37, 118.68, 121.85, 122.84, 128.48, 137.27, 159.28; IR (neat) 2990, 2850, 1600, 1450, 1250, 900, 740 cm^{-1}; mass spectrum m/e 160.21801 (calcd for $C_{11}H_{12}O$, 160.21769).

Olefin isomer of compound 24: R_f = 0.60, 50:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.49 (d, 3 H, J = 6.3 Hz, CH_3), 3.62 (dd, 1 H, J = 8.7 Hz, J = 8.7 Hz, $=CHC\underline{H}$), 4.51 (dq, 1 H, J = 2.4 Hz, J = 6.3 Hz, OCH), 5.18 (d, 1 H, J = 9.9 Hz, cis $=CH_2$), 5.22 (d, 1 H, J = 18.9 Hz, trans $=CH_2$), 5.82 (m, 1 H, $=C\underline{H}CH$), 6.76 (d, 1 H, J = 7.8 Hz, Ar), 6.85 (t, 1 H, J = 7.2 Hz, Ar), 7.05 (d, 1 H, J = 6.9 Hz, Ar), 7.26 (t, 1 H, J = 7.5 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 19.67, 54.96, 85.10, 109.45, 115.95, 120.44, 124.73, 129.54, 129.80, 149.92, 153.87; mass spectrum m/e 160.21801 (calcd for $C_{11}H_{12}O$, 160.21769).

Compound 25: R_f = 0.55, 10:1, hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.40 (d, 6 H, J = 6.4 Hz, $CH(C\underline{H_3})_2$), 2.68 (s, 3 H, $COCH_3$), 3.14 (h, 1 H, J = 6.4 Hz, -CH), 7.44 (s, 1 H,

=CH-), 7.49 (d, 1 H, J = 8.3 Hz, Ar), 7.92 (dd, 1 H, J = 0.9 Hz, J = 8.3 Hz, Ar), 8.23 (s, 1 H, Ar); ^{13}C NMR ($CDCl_3$) δ 22.58, 24.50, 26.74, 111.43, 121.21, 124.86, 127.76, 128.05, 131.99, 141.11, 158.21, 197.84; IR (neat) 3000, 2880, 1800, 1580, 1460, 1415, 1320, 1210, 900, 750 cm^{-1}; mass spectrum m/e 202.09967 (calcd for $C_{13}H_{14}O_2$, 202.09938).

Compound 21: R_f = 0.70, 50:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 4.00 (s, 2 H, CH_2), 7.12 - 7.46 (m, 10 H, Ar and =CH-); ^{13}C NMR ($CDCl_3$) δ 29.99, 111.40, 119.65, 119.84, 122.30, 124.17, 126.31, 127.95, 128.46, 128.58, 139.12, 142.07, 155.49; IR (neat) 3010, 2980, 1660, 1400, 1250, 900, 760 cm^{-1}; mass spectrum m/e 208.26280 (calcd for $C_{15}H_{12}O$, 208.26229).

Compound 20: R_f = 0.70, 50:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.76 (m, 4 H, $-CH_2(\underline{CH_2})_2CH_2$), 2.14 (m, 4 H, $-\underline{CH_2}CH\underline{CH_2}$), 3.14 (p, 1 H, J = 8.4 Hz, =CCH), 7.24 (m, 2 H, Ar), 7.37 (d, 1 H, J = 0.9 Hz, =CH), 7.44 (d, 1 H, J = 7.5 Hz, Ar), 7.58 (dd, 1 H, J = 1.5 Hz, J = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 25.20, 32.37, 35.58, 111.40, 120.21, 122.00, 123.92, 124.79, 128.05, 139.80, 155.58 (only signals found); IR (neat) 3040, 2950, 2870, 1580, 1450, 1180, 1090, 740 cm^{-1}; mass spectrum m/e 186.25575 (calcd for $C_{13}H_{14}O$, 186.25593).

Compound 23: R_f = 0.65, hexanes; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 9.8 Hz, CH_3), 1.33 (m, 4 H, $-CH_2$-'s), 1.70 (p,

2 H, J = 7.5 Hz, $-CH_2-$), 2.24 (m, 2 H, $-CH_2-$), 2.65 (t, 2 H, J = 6.9 Hz, $=CCH_2-$), 7.25 (m, 2 H, Ar), 7.38 (s, 1 H, OCH), 7.45 (dd, 1 H, J = 1.2 Hz, J = 7.5 Hz, Ar), 7.54 (dd, 1 H, J = 1.5 Hz, J = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 13.72, 22.62, 23.54, 28.98, 29.17, 31.63, 111.40, 119.56, 120.63, 122.06, 123.99, 128.31, 141.06, 155.29; IR (neat) 2980, 2865, 1610, 1475, 1375, 1250, 890, 750 cm^{-1}; mass spectrum m/e 202.13596 (calcd for $C_{14}H_{18}O$, 202.13577).

Compound 22: R_f = 0.70, hexanes; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H, J = 7.5 Hz, CH_3), 2.69 (q, 2 H, J = 7.5 Hz, CH_2), 7.24 (m, 2 H, Ar), 7.38 (s, 1 H, OCH), 7.45 (dd, 1 H, J = 0.9 Hz, J = 6.9 Hz, Ar), 7.54 (dd, 1 H, J = 1.5 Hz, J = 6.9 Hz, Ar), ^{13}C NMR ($CDCl_3$) δ 16.95, 24.30, 111.41, 118.77, 119.54, 122.23, 123.96, 128.15, 140.35, 155.33; IR (neat) 2990, 2880, 1610, 1450, 1240, 910, 760 cm^{-1}; mass spectrum m/e 146.07332 (calcd for $C_{10}H_{10}O$, 146.07317).

Compound 13: ^1H NMR and IR spectra match those reported in the literature.[42]

3-Methylbenzofuran: ^1H NMR and IR match that reported in the literature.[41]

The organomercurial cyclizations follow the general procedure below.

Preparation of 3-methylbenzofuran from organomercurial 26. To a stirred, homogenous solution of 0.0887 g (0.5 mmol) of palladium chloride, 0.0425 g (1.0 mmol) of lithium

chloride, and 0.14 ml of hexamethylphosphoramide was added 0.1766 g (0.5 mmol) of the organomercurial 26. The reaction mixture was stirred at room temperature for 35 min and then diluted with 20 ml of diethyl ether. The solution was filtered through Celite to remove the palladium metal, washed with 3 times 50 ml of saturated aqueous ammonium chloride and dried over magnesium sulfate. The solvent was then removed by rotary evaporation and the crude residue purified by column chromatography on silica gel using 4:1 hexanes/ethyl acetate as eluent to yield 42.7 mg (65% yield) of 3-methylbenzofuran: R_f = 0.74; ^1H NMR and IR spectra consistent with those reported in the literature.[41]

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GENERAL SUMMARY

In this work, oxygen heterocycles have been prepared from organomercurials, organic halides and allylic alcohols utilizing organopalladium chemistry. The first part of the thesis discusses previous work in which oxygen heterocycles were synthesized via organopalladium chemistry. In the second part of the dissertation, butenolides were prepared by reaction of acyclic, unsaturated esters containing organomercury functionality with palladium(II) reagents. In part three of the dissertation, bicyclic lactones were synthesized from cyclic, unsaturated esters containing organomercury functionality by employing palladium(II) reagents. Acetals were synthesized from cyclic allylic alcohols and vinyl ethers utilizing palladium(II) reagents. In part four, benzofurans were prepared from o-chloromercurio- and o-iodophenyl allyl ethers via palladium-promoted cyclizations.

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