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New organometallic approaches to heterocycles

by

Leslie Wayne Harrison

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1984

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GENERAL INTRODUCTION

Organomercurials have been known for many years and there exist a large number of procedures available for their preparation (1). They possess a wide variety of characteristic features which make organomercurials suitable intermediates for many synthetic transformations.

Organomercurials are generally not very reactive towards organic substrates. Therefore, methods have been devised to enhance their reactivity. One widely used method takes advantage of the fact that organomercurials can be readily transmetallated by various transition metals. This metal exchange reaction transforms the organomercurial into a more highly reactive transition metal organometallic compound. These compounds which can also often accommodate a wide range of functionality can then be used to perform a variety of synthetic transformations. The transition metal that is most commonly used for the transmetallation of organomercurials is palladium. Through the use of transmetallation with palladium salts, organomercurials can now be used as precursors for many synthetic transformations.

The work that is described in this thesis is divided into two parts. The first part deals with the synthesis of heterocyclic and carbocyclic compounds via the mercuration of various aryl acetylenes. The second part involves the synthesis of heterocyclic compounds using the transmetallation of an organomercurial by a palladium salt followed by cyclization via an intramolecular nucleophilic displacement on the intermediate palladium compound.

SYNTHESIS OF HETEROCYCLES BY AN INTRAMOLECULAR MERCURATION OF ARYL ACETYLENES

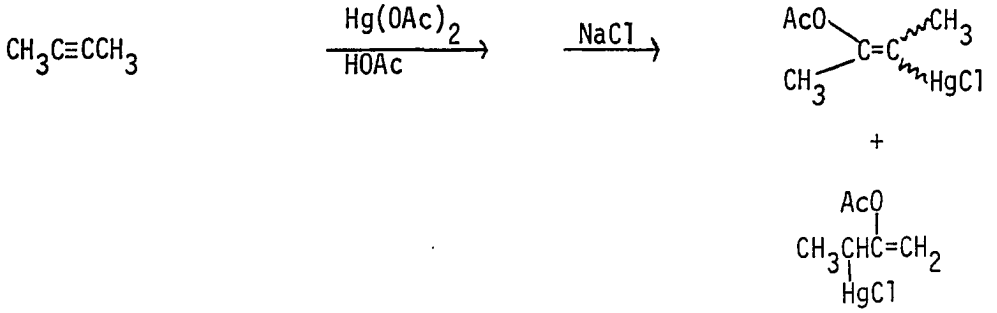
Introduction

Mercury(II) salts are known to add to a variety of acetylenes to afford vinyl mercurials (eq. 1). Thus, mercuric halides are reported to

(1)

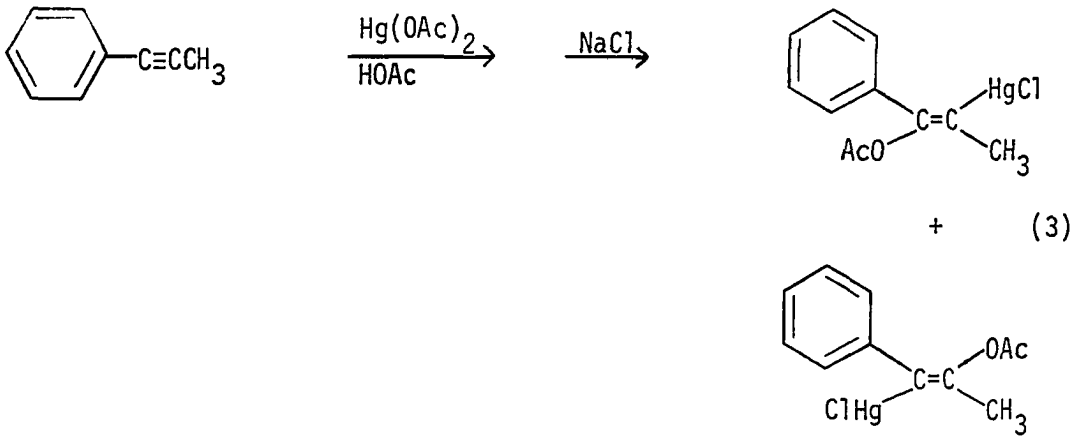
add to acetylene (anti) (2-7), propyne (anti) (8), cyclooctyne (9), vinylacetylene (anti ?) (8, 10-12), alkynyl ethers (13-15), propargylic alcohols (anti) (16-18), ethers (19), halides (anti) (16, 20) and α, β-unsaturated ketones (21), acids (anti) (22-24), and esters (anti ?) (22, 25, 26) with the stereochemistry indicated.

The reaction of acetylenes with mercuric acetate in acetic acid is reported to generate several different types of addition compounds. Terminal alkynes generally give dialkynylmercurials (27-29). Simple internal aliphatic acetylenes appear to afford both regio- and stereochemical mixtures of vinylmercurials with the anti adduct predominating (30-33), as illustrated by the reaction of 2-butyne (eq. 2) (34-36).



(2)

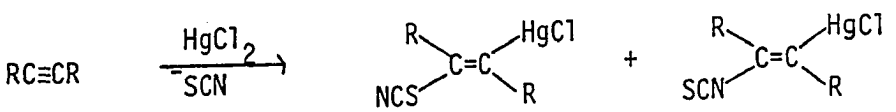
The reaction of aryl alkyl acetylenes with mercuric salts provides a regiochemical mixture of exclusively anti adducts (37), as shown by the reaction of 1-phenyl-1-propyne with mercuric acetate (eq. 3) (28, 38).



(3)

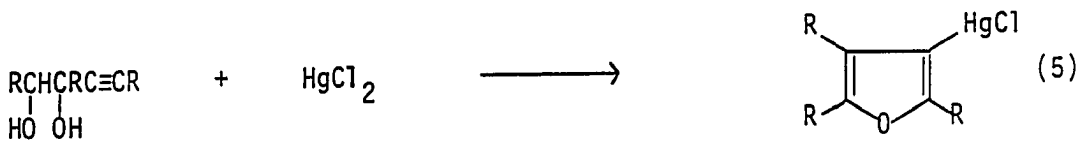
Diphenylacetylene affords both the syn and anti addition adducts, but in this case the syn adduct predominates (28, 34, 36, 37, 39).

It has been recently shown that mercuric chloride and thiocyanide anion add to internal acetylenes to give either nitrogen- or sulfur-bonded anti adducts (eq. 4) (40).



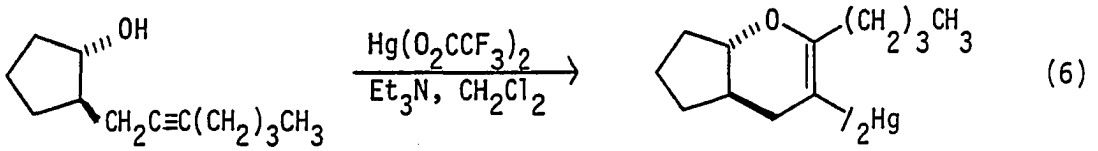
(4)

There are very few examples in the literature of alkoxymercuration and aminomercuration of acetylenes. Mercuric chloride has been added to acetylenic diols to prepare furylmercurials (eq. 5) (41-48). Riediker



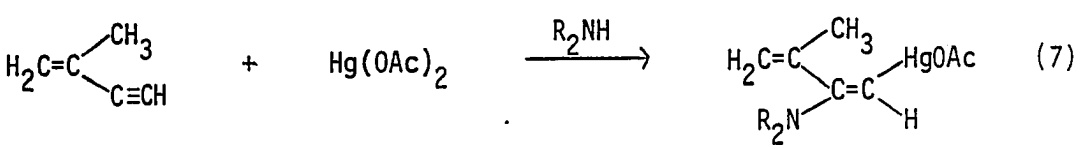
(5)

and Schwartz (49) have cyclized certain acetylenic alcohols by reacting them with a mercuric salt. The organomercury intermediate was usually intercepted by N-halosuccinimides to give the β-halo substituted enol ethers. In only one example did they actually isolate the intermediate organomercurial in a yield of 15% (eq. 6). Hudrlik and Hudrlik (50) have



(6)

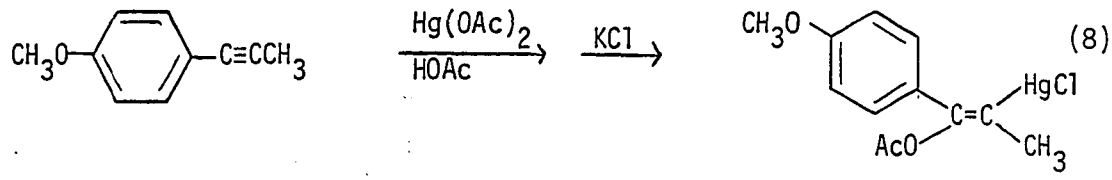
reacted terminal acetylenes with mercury(II) salts in the presence of acetic anhydride, alcohols, pyrrolidine, and aziridine. The mercuration reaction was followed immediately by reduction with sodium borohydride to produce enol acetates, enol ethers, amines, and aziridine enamines, respectively. Isopropenyl acetylene has been reacted with mercuric acetate in the presence of various amines to yield the aminomercuration product (eq. 7) (51).



(7)

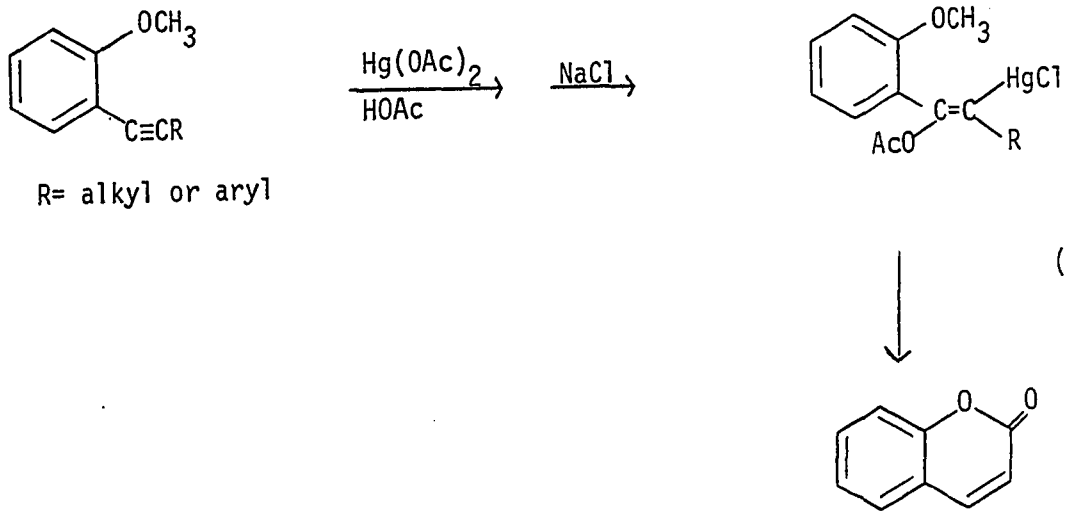
It has been shown by Spear and Jensen (37) that the reaction of 1-p-

anisyl-1-propyne and other related aryl alkyl acetylenes with mercuric acetate in acetic acid produces the β-acetoxy vinyl mercury compound (eq. 8). It was believed that the reaction of the ortho substituted compound



(8)

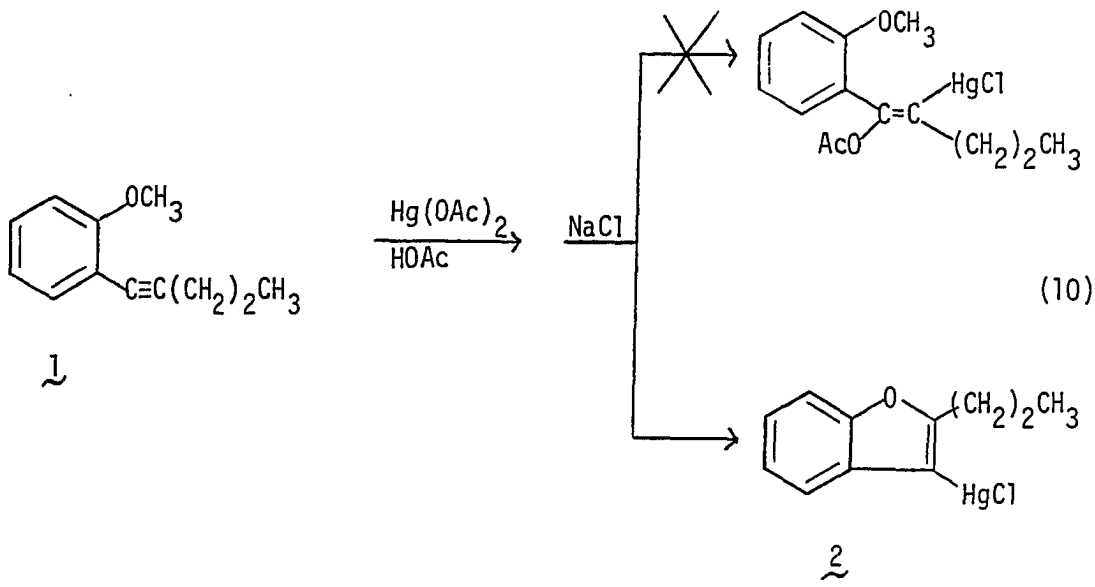
should behave in a similar manner and produce the corresponding β-acetoxy vinyl mercury compound. Subsequent palladium catalyzed carbonylation followed by cyclization would provide an easy entry into the important coumarin ring system (eq. 9).



R= alkyl or aryl

(9)

In examining the reaction of 2-(1-pentynyl)anisole 1 with mercuric acetate, it was observed that, unlike the para isomer, 1 does not undergo mercuric acetate addition to the carbon-carbon triple bond, but instead undergoes intramolecular alkoxymercuration to produce 3-chloromercuri-2-propylbenzofuran (2) upon aqueous sodium chloride work-up (eq. 10).



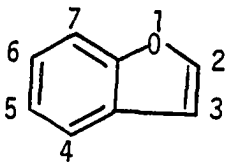
1 2 (10)

This type of intramolecular cyclization proved to be fairly general, thus, allowing several other mercurated heterocyclic ring systems to be prepared. Since the mercury moiety in these compounds can be readily substituted by a variety of other functional groups, this intramolecular cyclization provides a unique method for the synthesis of disubstituted heterocyclic compounds.

Results and Discussion

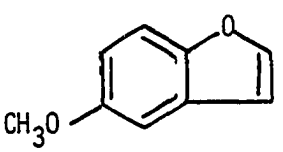
Benzofurans The benzofuran nucleus (3) occurs widely in nature and the synthesis of the ring system and its derivatives have been the subject of much research. There are several important reviews (52, 53) and a book (54) devoted to various aspects of both synthetic and naturally occurring benzofurans. This introduction will present only a brief overview of some of the biological activity of benzofuran

derivatives and the major methods used in the synthesis of the benzofuran nucleus.



3

The simplest naturally occurring benzofuran is 5-methoxybenzofuran (4). It was discovered as a result of fungal contamination of oak beer barrels which gave the beer a strong, persistent, distasteful scent (55). Among the other natural benzofurans are the Moracins (5a-c) which show antifungal activity (56, 57) and the quettamines which are a new class of isoquinoline alkaloids that possess a benzofuran nucleus (58). Coumestrol (59, 60) (6) is a benzofuran derivative isolated from alfalfa and it is one of the phytoestrogenic substances that stimulates animal growth.



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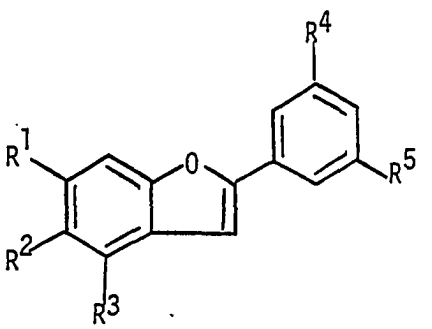
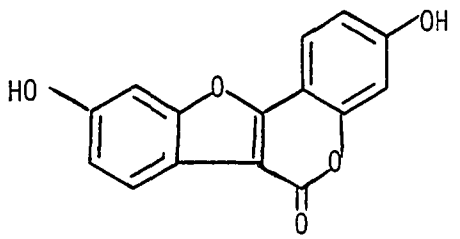


5a: A-R^1=R^3=OCH_3, R^2=H, R^4=R^5=OH

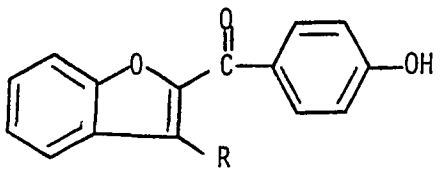
b: B-R^1=R^4=OCH_3, R^2=R^5=OH, R^3=H

c: F-R^1=R^2=OCH_3, R^4=R^5=OH, R^3=H



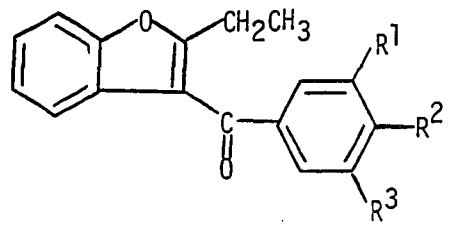
6

Among the synthetic benzofurans, 2-(4-hydroxybenzoyl)benzofuran (7a) and its 3-ethyl derivative (7b) both exhibit estrogenic activity (61); 2-ethyl-3-(4-hydroxybenzoyl)benzofuran (8), or Benzarone, is an angitropic, antiinflammatory and fibronolytic agent (62) (used clinically under the name of Fragivix L); 2-ethyl-3-(3,5-diiodo-4-hydroxybenzoyl) benzofuran (9), or Benziodarone (clinically used as Amplivix), is a coronary vasodilator (63).



7a: R=H

b: R=CH_2CH_3

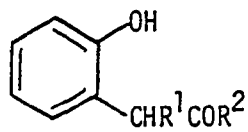


8: $R^1=R^3=H$; $R^2=OH$

9: $R^1=R^3=I$; $R^2=OH$

There are numerous synthetic procedures available for the synthesis

of the benzofuran nucleus. One of the major methods involves the cyclodehydration of compounds such as 10 and 11 with sulfuric acid or polyphosphoric acid (54). The cyclodehydration reaction was employed by



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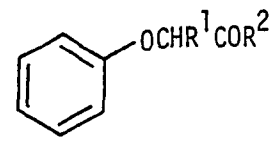
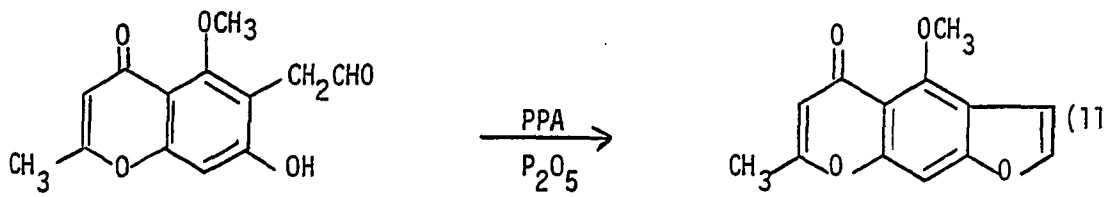


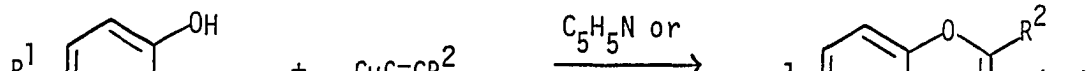
11

Aneja and co-workers (64) in the synthesis of visnagin (12) which is the major component of the seeds of Ammi Visnaga, an important plant drug (eq. 11).



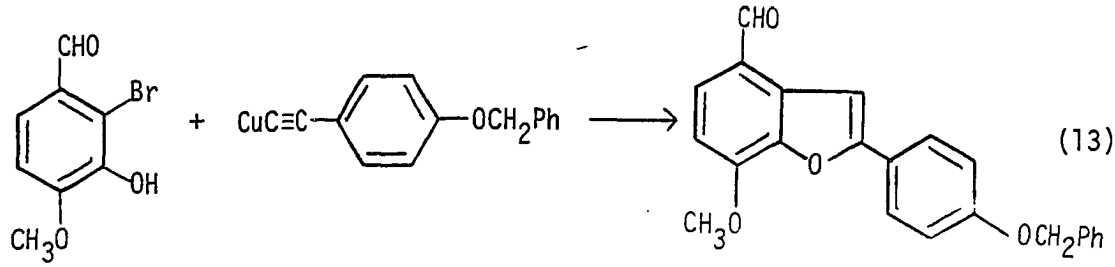
12

The reaction of cuprous acetylides with aryl bromides or aryl iodides has proven to be a very effective pathway for the preparation of a wide variety of aromatic acetylenes. Moreover, when the aryl bromide or aryl iodide bear an ortho hydroxy group, the reaction with a cuprous acetylide provides a very nice entry into 2-substituted benzofurans (65) (eq. 12). In their synthesis of secoquettamine, Biftu, Schneiders and Stevenson (66) used the cuprous acetylide cyclization to prepare the requisite benzofuran skeleton 13 (eq. 13).



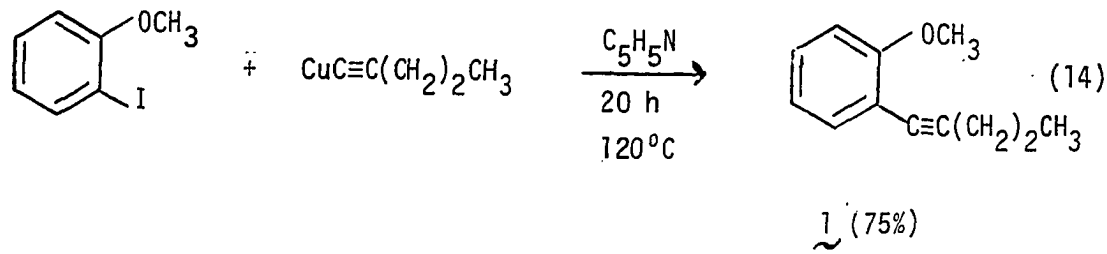
X=Br, I

(12)



(13)

Since it was thought that the acetoxymercuration of a 2-methoxy substituted aryl acetylene might be used to prepare the coumarin ring system, the mercuration of 2-(1-pentynyl)anisole (1) was examined. The preparation of 2-(1-pentynyl)anisole (1) was effected by the reaction of cuprous n-propylacetylide with 2-iodoanisole in refluxing pyridine using the procedure of Castro and coworkers (65) (eq. 14). As discussed in the



(14)

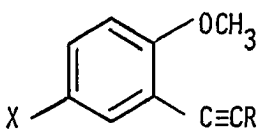
1 (75%)

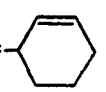
introduction, compound 1 was found by us to undergo an intramolecular cyclization to produce 3-chloromercuri-2-propylbenzofuran 2 when treated with mercuric acetate in glacial acetic acid.

The initial cyclization of the acetylene compound involved the

reaction of 1 with one equivalent of mercuric acetate in glacial acetic acid at 0°C for twenty hours followed by treatment with aqueous sodium chloride. These reaction conditions produced the mercurated benzofuran as the only isolated producted in a yield of 45%. Since the initial reaction conditions produced the mercurated benzofuran in somewhat low yield, many variations in the reaction conditions were examined. The results are summarized in Table I. Best results were obtained using one equivalent of mercuric acetate in acetic acid for 30 minutes at room temperature.

Several other acetylenes (14-18) were examined to determine how general a route to mercurated benzofurans this reaction is.



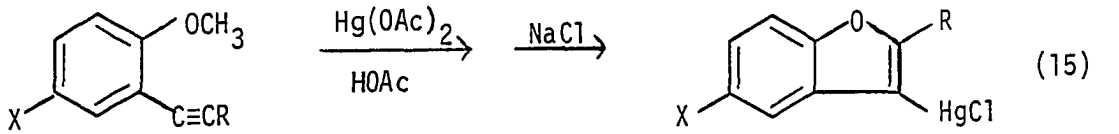
14: X=OCH_3, R=$(CH_2)_2CH_3$
15: X=NO_2, R=$(CH_2)_2CH_3$
16: X=H, R=C_6H_5
17: X=H, R= 
18: X=H, R=o-$CH_3OC_6H_4$

The acetylenes 14-16 were all prepared by the reaction of the corresponding aryl iodide with the desired cuprous acetylide. The reaction of these acetylenes with mercuric acetate resulted in cyclization to the mercurated benzofurans (19-21) in the yields indicated (eq. 15).

Table I. Reaction Conditions for the Mercuration of 1

mercuric salt (equiv)	solvent	time (h)	temp (°C)	yield of 2 (%)[a]
$Hg(OAc)_2$ (1)	CH_3CO_2H	4	0	31
		20		44
		0.25	25	64
		0.5		65-70
		4		52
$Hg(OAc)_2$ (2)		0.5		51
$Hg(OAc)_2$ (1)	CH_3OH	0.5		0
	CH_3NO_2	0.5		15
$Hg(O_2CCF_3)_2$ (1)	THF	10	0	37
		20		35
		0.25	25	51
(2)				54
(1)		20		48
	CH_3CO_2H	0.33		48
	CF_3CO_2H	0.5		0
		20		0

[a]Isolated, recrystallized yield.

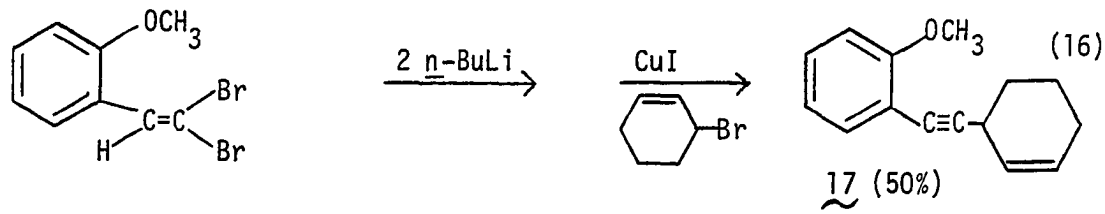


(15)

14-16

19: X=OCH_3, R=$(CH_2)_2CH_3$ (60%)
20: X=NO_2, R=$(CH_2)_2CH_3$ (45%)
21: X=H, R=C_6H_5 (59%)

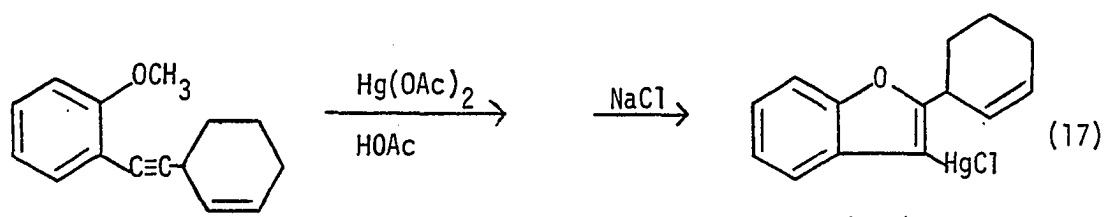
The acetylenic compound 17 was prepared by alkylation of the requisite lithium acetylide with 3-bromocyclohexene in the presence of cuprous iodide (eq. 16). If the reaction is performed without the added



(16)

17 (50%)

cuprous iodide, the yield of alkylated product is very low. Cyclization of acetylene 17 by mercuric acetate produced the desired mercurated benzofuran (22) in a yield of 30% (eq. 17). This reaction shows that



(17)

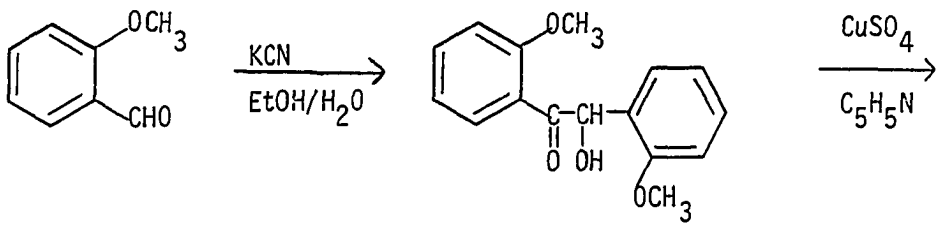
17

22 (30%)

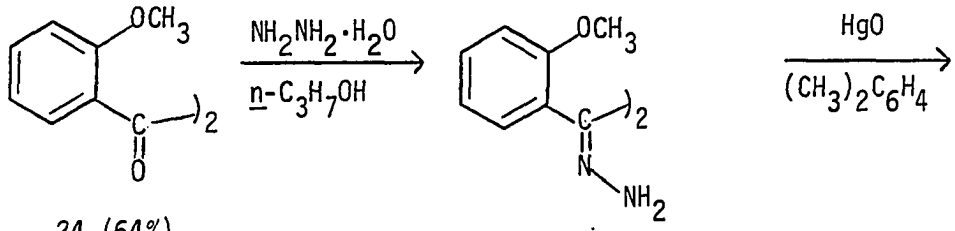
additional carbon-carbon double bonds can be accommodated.

The preparation of 2,2'-dimethoxydiphenylacetylene (18) was accomplished in a series of steps starting from 2-anisaldehyde (Scheme I). The benzoin condensation of 2-anisaldehyde using potassium cyanide

Scheme I

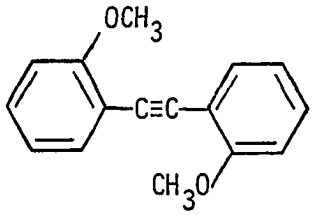


23 (42%)



24 (64%)

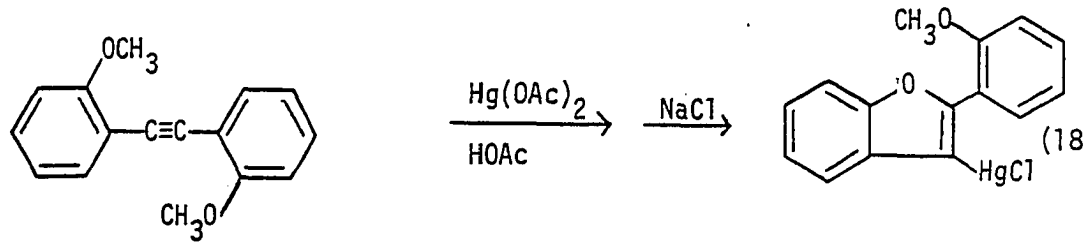
25 (50%)



18 (17%)

(67) produced 2,2'-dimethoxybenzoin (23) which was then oxidized with copper(II) sulfate-pyridine (68) to yield 2,2'-dimethoxybenzil (24). The benzil derivative was converted to the corresponding dihydrazone 25 which was subsequently eliminated using mercuric oxide in refluxing xylenes to produce the desired acetylene (69). The acetylene was then cyclized by the reaction with mercuric acetate to produce 2-(2-anisyl)-3-

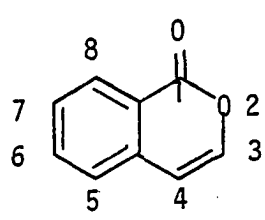
chloromercuribenzofuran (26) in 58% yield (eq. 18).



(18)

18 26 (58%)

Isocoumarins and chromones Isocoumarins (1H-2-benzopyran-1-one, 27) (70) are a class of naturally occurring lactones. Among the isocoumarins that have been isolated are: 3-(2-butynyl)isocoumarin (28), or capillarin, which is one of the acetylenic components of Chrysanthemum frutescens L. (71); 3,4-dimethyl-8-hydroxyisocoumarin (29), or oosporalactone, which is reported to be produced by the mycelium and cell filtrate of Oospara, a microorganism obtained from air (72); artemidin (30) which is isolated from the above ground portion of the tarragon plant (73); 3-n-propylisocoumarin (31) which has been isolated from the roots of Felicia wrightii (74); and 3-phenylisocoumarin (32) which has been found in the leaves of Homalium laurifolium Jaco (75).



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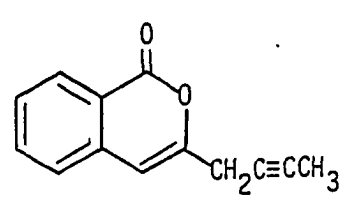

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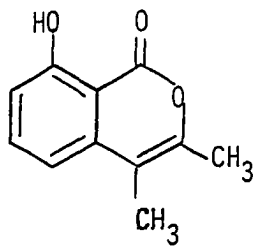

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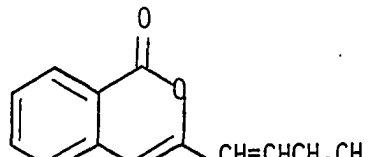

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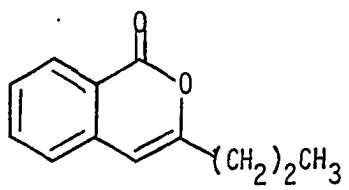

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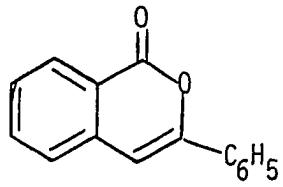
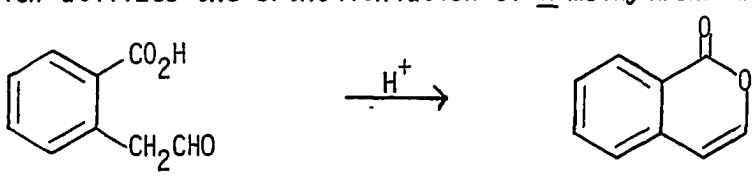


32

Isocoumarins have been prepared in many ways. The cyclization of homophthalic acid derivatives provides an entry into the isocoumarin ring system (70) (eqs. 19, 20). The cyclization of 2-carboxybenzyl ketones is a method that has been used to prepare substituted isocoumarins (eq. 21) (76). Narasimhan and Bhide (77) have developed an isocoumarin synthesis which utilizes the ortholithiation of N-methylbenzamides (eq. 22).



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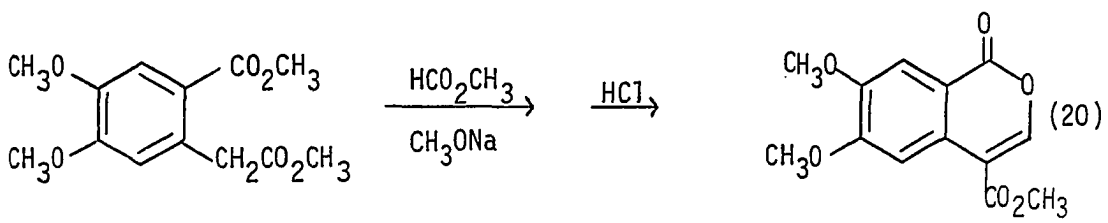

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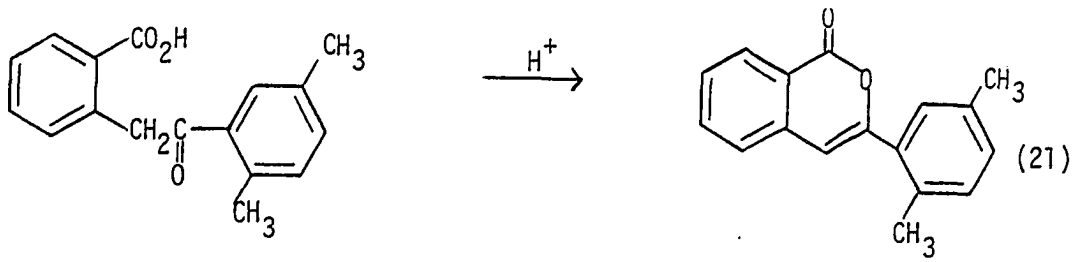

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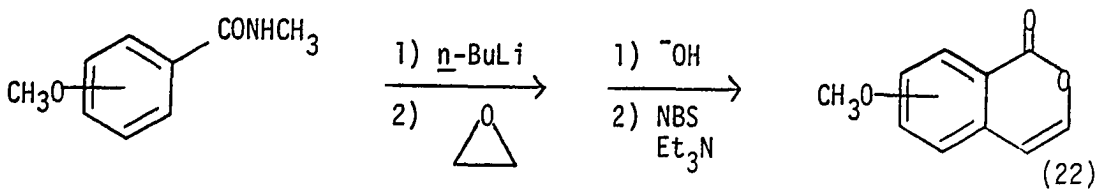
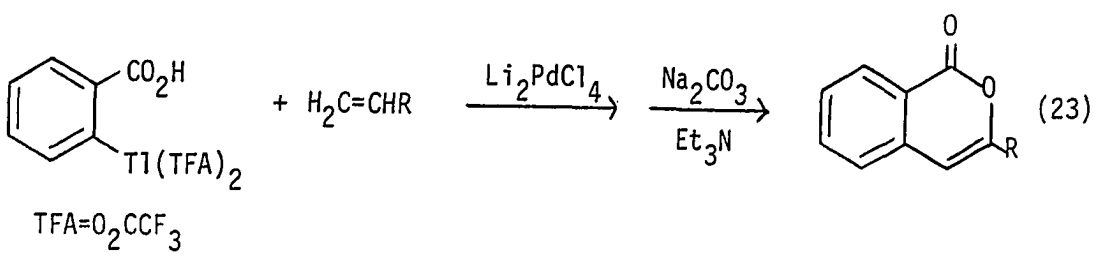


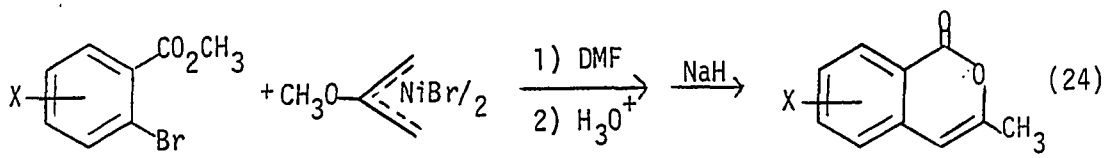
(22)

Recently, two novel approaches for the synthesis of isocoumarins have been developed. Both of these methods involve the use of organotransition metal chemistry. The method developed by Larock and coworkers (78) uses the reaction of an ortho thallated benzoic acid with an olefin in the presence of lithium tetrachloropalladate (eq. 23). A



(23)

variety of substituted isocoumarins have been prepared by this method. Korte, Hegedus, and Wirth (79) have prepared isocoumarins by the reaction of a π-allylnickel complex with a 2-bromobenzoate followed by cyclization of the resulting intermediate (eqs. 24, 25).



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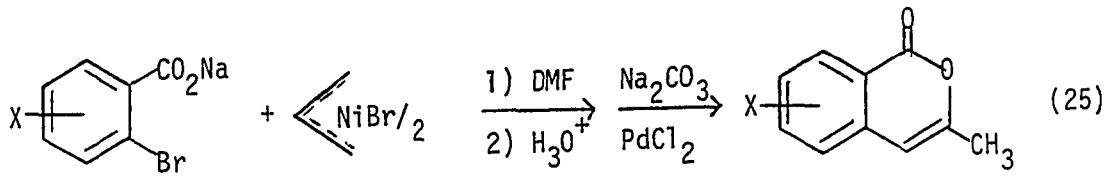
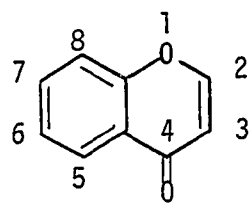


(25)

Chromones (4H-1-benzopyran-4-one, 33) (80) are found much more widely in nature than are isocoumarins. Many of the naturally occurring chromones are substituted in the 2-position with a phenyl derivative. These compounds are classified as flavones. Flavones are found in all parts of plants, but they are most obvious as pigments in flower petals. One of the chief flavones of the flowers and seeds of the hawthorn, Crataegus oxyacantha, is quercetin (34) (81). Flavone (35), primuletin (36a) and primetin (36b) are all found in the powdery coating that develops on the outside of the leaves and stalks of some species of Primula (82, 83).



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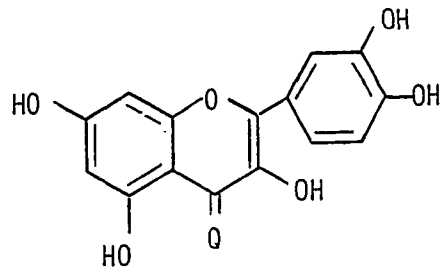

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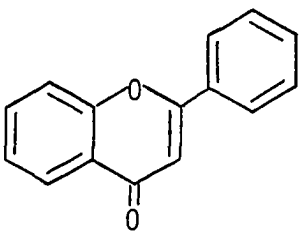

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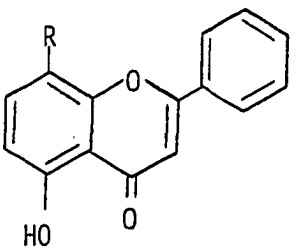
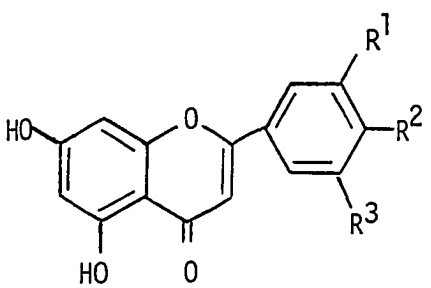
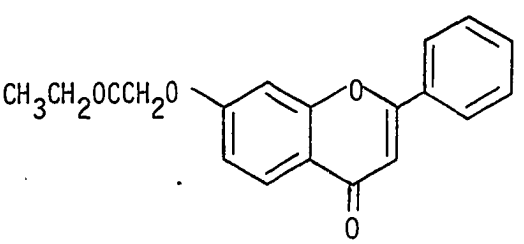


36a: R=H

b: R=OH

Several flavones are reported to possess some biological activity. It has been reported that flavone itself has coronary dilating activity (84). Tricin (37) is held responsible for the disease bloat in cattle eating lucerne (85) by inhibiting smooth muscle movement. Acacetin (38) has been reported to possess antiinflammatory activity and it also causes a reduction in capillary fragility (84). The synthetic flavone (39) has been used clinically in Italy as a coronary vasodilator (84).





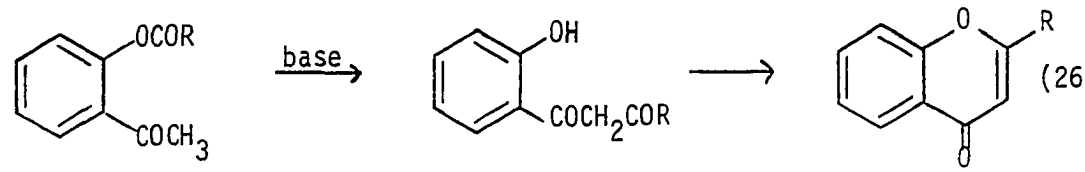
39

37: $R^1=R^3=OCH_3$, $R^2=OH$

38: $R^1=R^3=H$, $R^2=OCH_3$

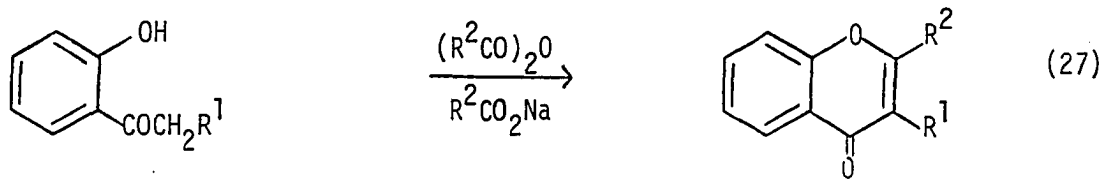
These are two major methods that have been used for the synthesis of chromones. The Baker-Venkataraman rearrangement (80) involves the

isomerization of an o-benzoyloxyacetophenone to an o-hydroxy-β-diketone via an internal Claisen condensation. In some cases, the diketone that is produced will spontaneously cyclize to the chromone while in others an acid catalyst is necessary (eq. 26). The other method is the Allan-



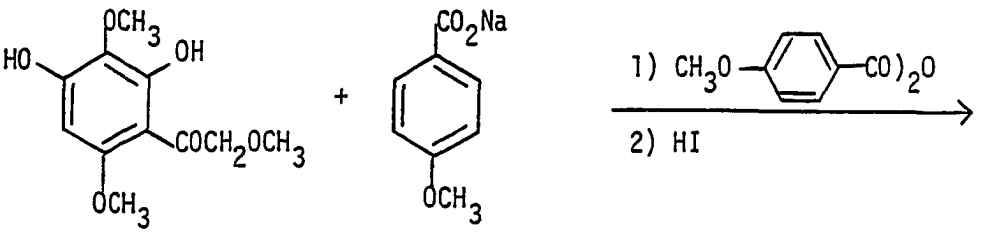
(26)

Robinson condensation (80). This method is a condensed form of the Baker-Venkataraman rearrangement. An o-hydroxyacetophenone intended to provide ring A is heated with a mixture of the sodium salt and the anhydride of an acid intended to provide ring B. This sets up conditions suitable for the successive formation of the o-acyloxyketone, the Baker-Venkataraman rearrangement, and the final cyclization to produce the chromone (eq. 27). If one lets $R^1=OCH_3$; this reaction can be used for



(27)

the synthesis of 3-hydroxychromones. This was employed by Goldsworthy and Robinson (86) in their synthesis of the flavonol herbacetin (40) (eq. 28).



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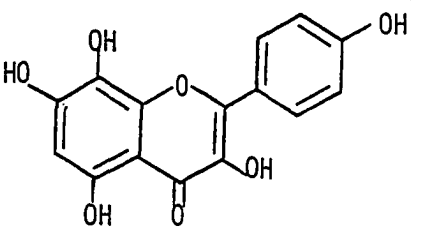
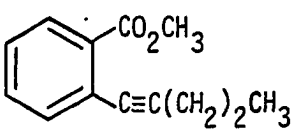
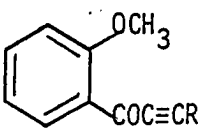


40

In an attempt to extend the mercury-assisted intramolecular cyclization to other naturally occurring ring systems, such as isocoumarins and chromones, the reaction of acetylenes 41-43 was examined.



41

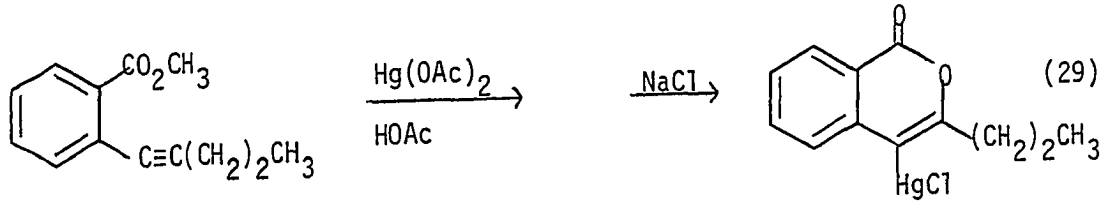


42: R=$(CH_2)_2CH_3$

43: R=C_6H_5

The acetylene 41 was prepared by the reaction of methyl 2-iodobenzoate with cuprous n-propylacetylide in refluxing N,N-dimethylformamide. The reaction of this acetylene with mercuric acetate produced the desired 4-chloromercuri-3-propylisocoumarin (44) in a yield

of 65% (eq. 29).

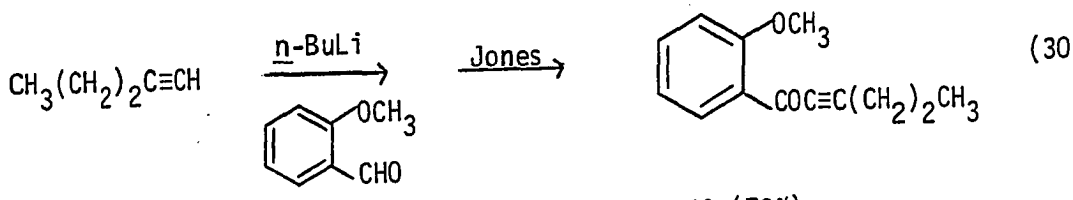


(29)

41

44 (65%)

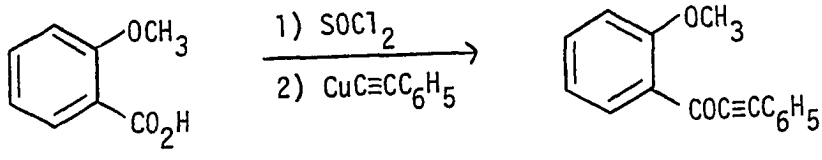
The acetylenes necessary for the synthesis of the chromone ring system were prepared in two different ways. The acetylenic ketone 42 was prepared in 70% yield by the reaction of 2-anisaldehyde with 1-lithio-1-pentyne in tetrahydrofuran followed by oxidation of the intermediate alcohol with Jones reagent (87) (eq. 30). Compound 43 was synthesized by



(30)

42 (70%)

reacting the acid chloride of 2-anisic acid with cuprous phenylacetylide using the procedure of Bourgain and Normant (88) (eq. 31).

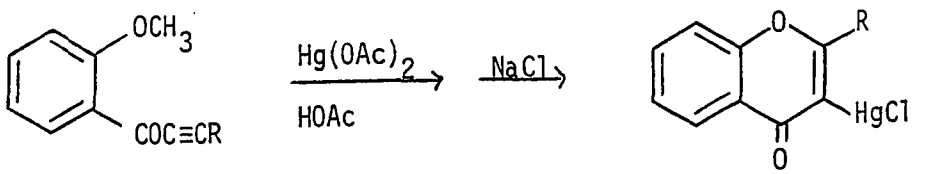


(31)

43 (47%)

The treatment of acetylene 42 with mercuric acetate resulted in the

formation of the 3-mercurated chromone derivative (45) in a yield of 60%. The 3-chloromercuriflavone (46) can be prepared in 58% yield by the cyclization of acetylene 43 (eq. 32).



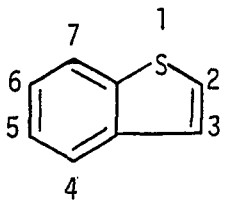
(32)

42, 43

45: R=$(CH_2)_2CH_3$ (60%)

46: R=C_6H_5 (58%)

Benzothiophenes Benzothiophenes (47) are the sulfur-containing analogs of benzofurans. The benzothiophene nucleus is not a common one in natural products, but many synthetic benzothiophene derivatives have found a variety of uses. Benzothiophene has been isolated as a minor component of coffee (89) and it has been reported that benzothiophene possesses some insecticidal properties (90, 91). The disubstituted benzothiophene derivates 48a-b show very good antianginal and antiadrenergic activity (92, 93). Metizoline or Benazoline (49) which contains the benzothiophene nucleus is commercially available as a nasal decongestant (94). The benzothiophene derivative 50 is reported to be useful as a laxative (95) and benzothiophene 51 has been shown to be useful as a contraceptive (96). The acetic acid substituted benzothiophene 52 has shown some antiinflammatory and antiarthritic activity (97).



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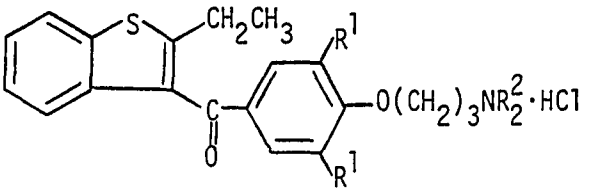
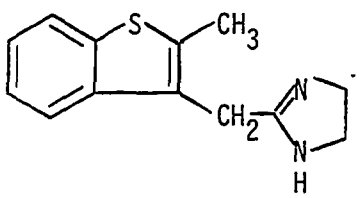


48a: R^1=Br, R^2=$(CH_2)_2CH_3$
b: R^1=CH_3, R^2=$(CH_2)_3CH_3$



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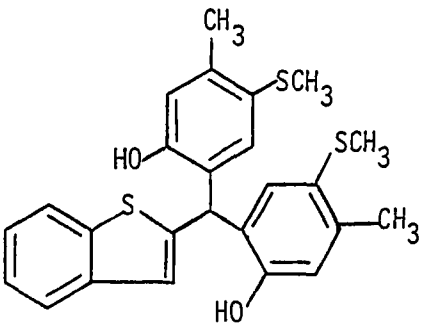

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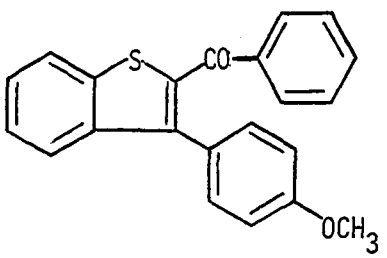

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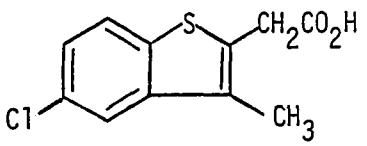
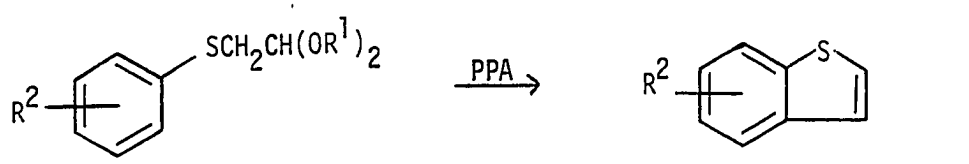


52

The benzothiophene nucleus is prepared in much the same way as is the benzofuran nucleus. The polyphosphoric acid promoted cyclization of (arylthio)acetaldehyde dialkyl acetals and (arylthio)-acetones (94) provides the most useful entry into various substituted benzothiophenes (eqs. 33, 34).



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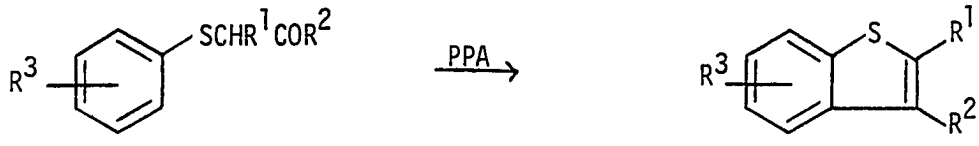


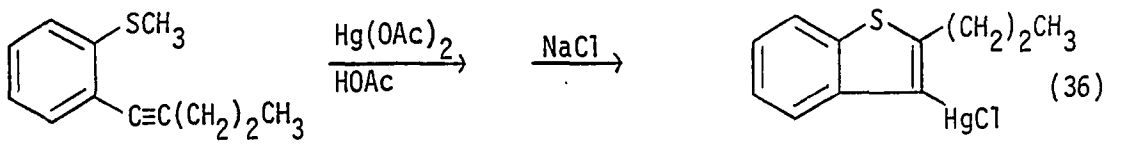
(34)

The reaction of 2-bromothiophenol with a cuprous acetylide under carefully controlled reaction conditions provides a route to 2-substituted benzothiophenes (98) (eq. 35).

(35)

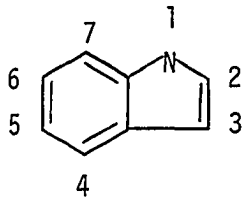
Since benzothiophenes are such an interesting class of heterocyclic compounds, their preparation by the mercury-assisted cyclization was examined. The required acetylene 53 was prepared by the reaction of 2-iodothioanisole with cuprous n-propylacetylide. The reaction of this

acetylene with mercuric acetate led to the formation of the cyclized compound, 3-chloromercuri-2-propylbenzothiophene (54), in a yield of 66% (eq. 36).



53 54 (66%) (36)

Indoles The indoles (55) are one of the most widely studied classes of naturally occurring heterocyclic compounds. Indole derivatives are essential in both plants and animals. There have been many uses discovered for indoles. Trytophan (56) is one of the essential amino acids and it has been reported that tryptophan inhibits the growth of tuberculosis (99, 100). Skatole, 3-methylindole (57), which has been isolated from various sources, is reported to show both antidiuretic (101) and tuberculostatic activity (102). The corresponding 2-methyl derivative has been used as a growth stimulant for farm animals (103). The major plant growth hormone is indoleacetic acid (58) (104). Indomethacin (59) is an enzyme inhibitor (105) and has been reported to have antiinflammatory, antipyretic, and analgesic activity (106). The 2,3-dipenyl indole derivative has found use as an optical bleaching agent for nylon (107).



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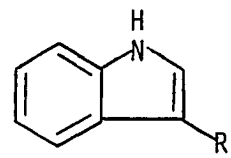
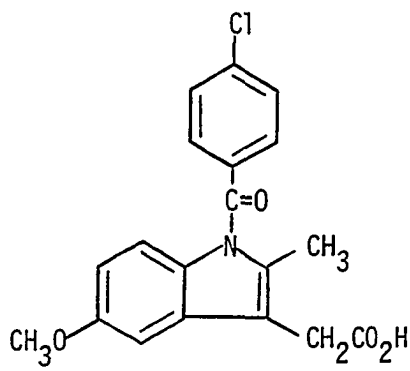


56: R=$CH_2CH(NH_2)CO_2H$

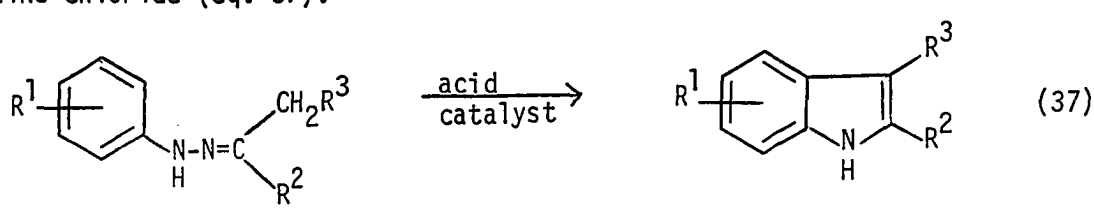
57: R=CH_3

58: R=CH_2CO_2H



59

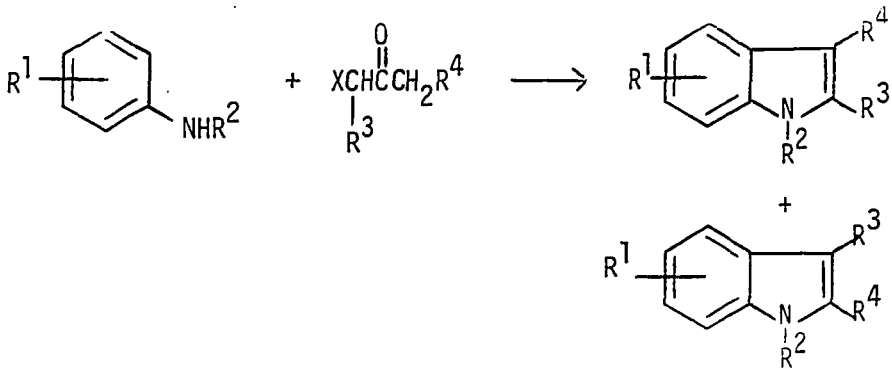
Since its discovery in 1883 (108), the Fischer indole synthesis has remained the most versatile method for the preparation of indoles. The Fischer indole synthesis involves the cyclization of an arylhydrazone by treatment with an acid such as polyphosphoric acid or by treatment with zinc chloride (eq. 37).



(37)

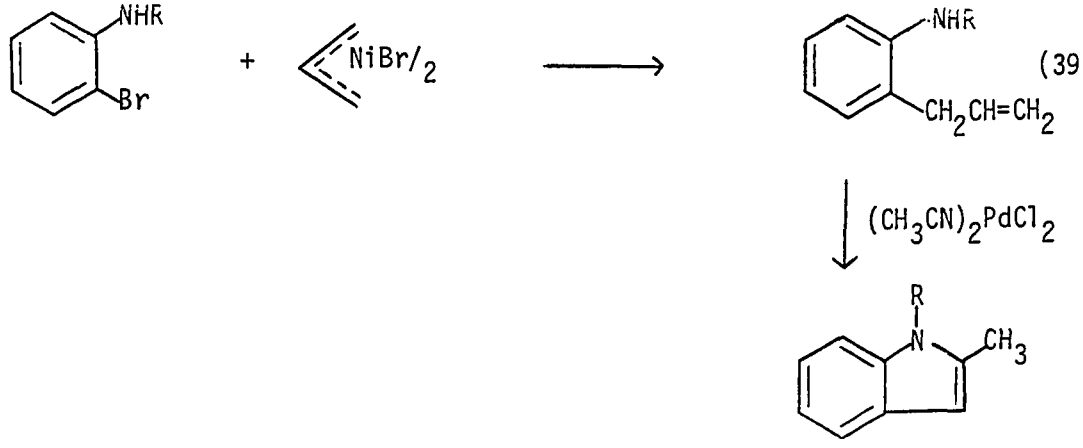
The Bischler indole synthesis (109) is another general method for

the synthesis of indoles. This method involves the reaction of arylamines with α-halogenated ketones, α-hydroxyketones, or α-anilinoketones (eq. 38). This reaction has been used for the synthesis of a variety of substituted tetrahydrocarbazoles (110).



(38)

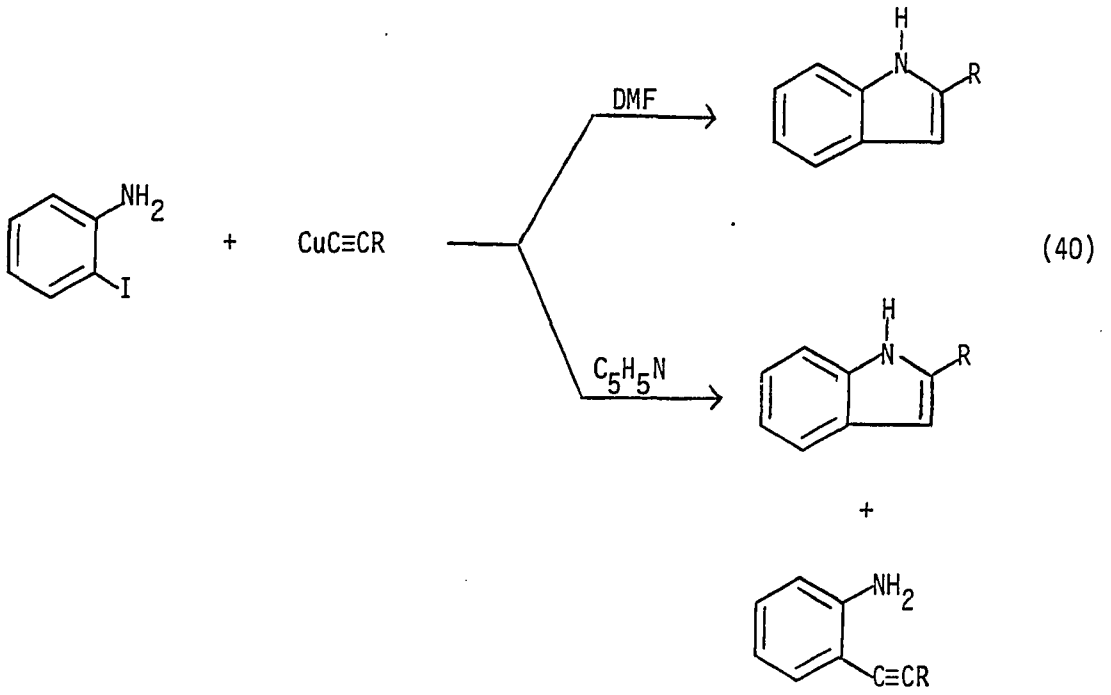
There are also approaches to indoles which utilize organotransition metal chemistry. Hegedus et al. (111) have cyclized 2-allylanilines with a palladium(II) salt to prepare indoles (eq. 39). Castro and coworkers



(39)

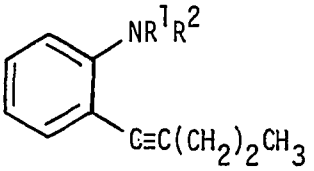
(65) have reported that the addition of a cuprous acetylide to 2-iodoaniline produces indoles if the reaction is performed in N,N-dimethylformamide, but if pyridine is used as the solvent, a mixture of

the acetylene substitution product and the indole are obtained (eq. 40).



(40)

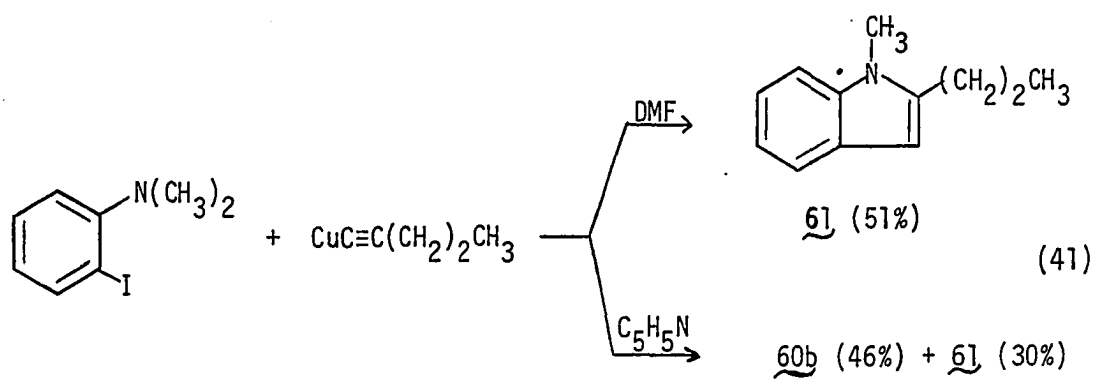
The cyclization of various acetylenic substituted aniline derivatives (60a-d) were examined in an effort to extend the intramolecular cyclization to the preparation of mercurated indoles.



60a: R^1=H, R^2=$COCH_3$
b: R^1=R^2=CH_3
c: R^1=R^2=H
d: R^1=CH_3, R^2=$COCH_3$

The acetylene 60a was prepared by the reaction of N-acetyl-2-iodoaniline with cuprous n-propylacetylide. The reaction of this acetylene with mercuric acetate failed to produce any mercurated indole and resulted only in the recovery of the starting acetylene.

The preparation of acetylene 60b presented some difficulty. If the reaction of the corresponding ortho iodo derivative and cuprous n-propylacetylide was performed in N,N-dimethylformamide, N-methyl-2-propylindole (61) was the sole product isolated in a yield of 51%. When the substitution reaction was done in pyridine, the desired acetylene could be isolated in a yield of 46% along with 30% of the indole (eq. 41). The reaction of the acetylenic compound with either mercuric



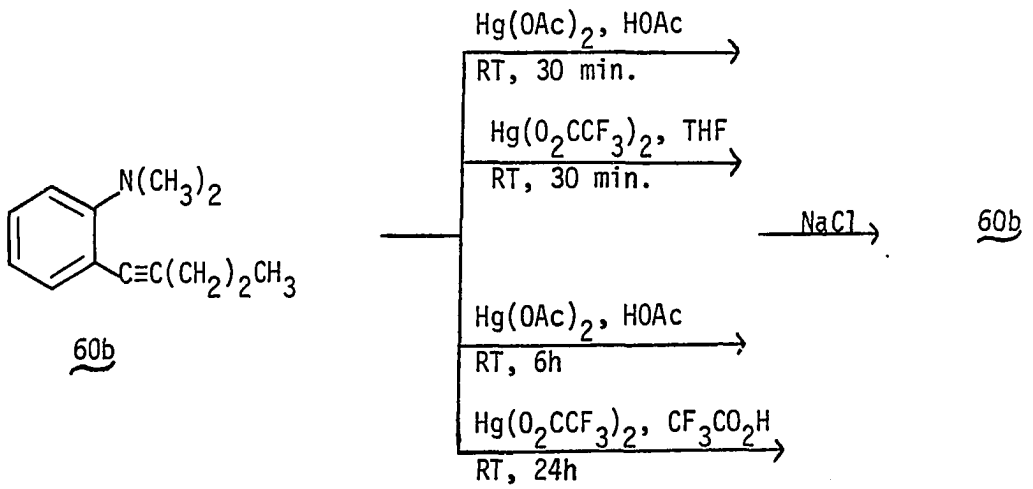
(41)

acetate or mercuric trifluoroacetate also failed to produce the desired mercurated indole (Scheme II).

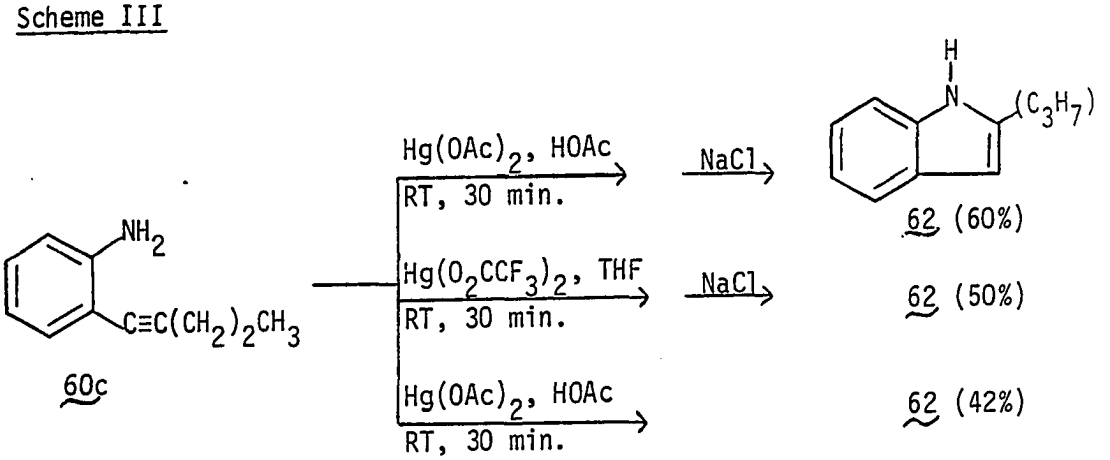
The free amine compound, 2-(1-pentynyl) aniline (60c), had to be prepared by the reaction of 2-iodonitrobenzene with cuprous n-propylacetylide followed by reduction of the nitro group with stannous chloride. Treatment of this acetylene with mercuric acetate did produce the indole in 60% yield, but, the compound did not contain any mercury

group. The NMR spectrum for the compound isolated was identical to that reported for 2-propylindole (62) (112). Several other mercuration reactions of this acetylene were examined in hopes of isolating the mercurated indole. The results of these reactions are shown in Scheme III.

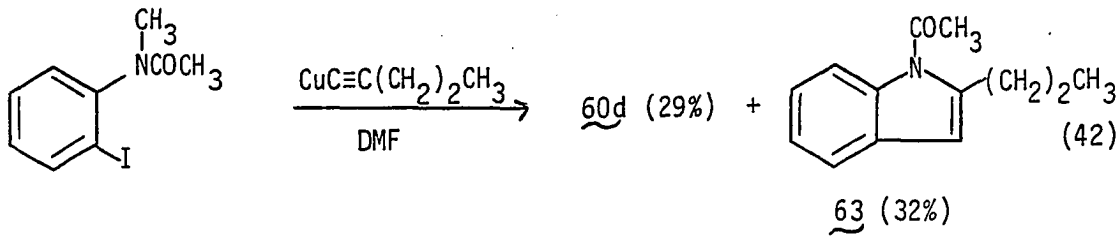
Scheme II



Scheme III



The preparation of compound 60d was also accomplished by the reaction of the 2-iodo derivative with cuprous n-propylacetylide in refluxing N,N-dimethylformamide. The substitution reaction produced the desired acetylene in a yield of 29%, but it also produced N-acetyl-2-propylindole (63) in 32% yield (eq. 42). Treatment of compound 60d with

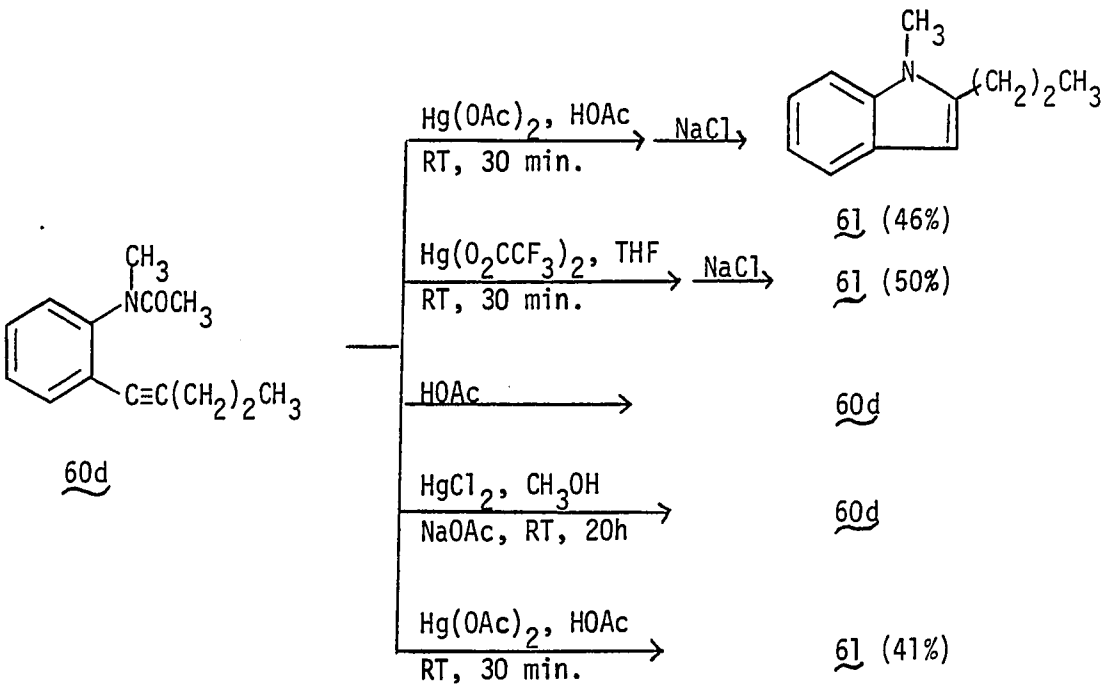


(42)

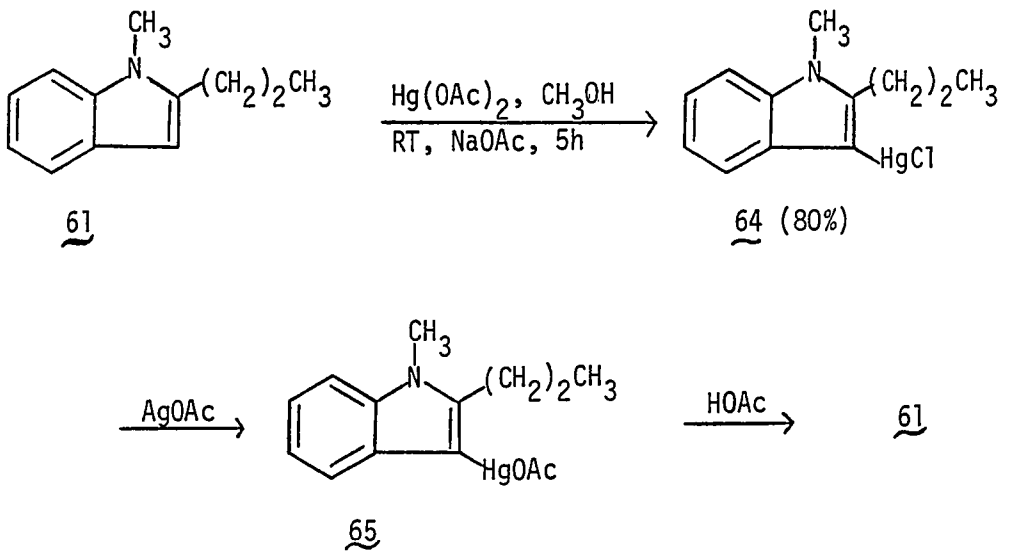
either mercuric acetate in acetic acid or mercuric trifluoroacetate in tetrahydrofuran followed by an aqueous sodium chloride work-up produced N-methyl-2-propylindole (61) in yields of 46% and 50%, respectively. Since the corresponding 3-chloromercuri compound was not isolated, the acetylene was stirred in glacial acetic acid to determine if the cyclization was occurring because of the acid, but this led only to the recovery of the starting acetylene. Various other conditions were examined in an attempt to isolate the desired mercurated indole (Scheme IV).

The indole 61 can be mercurated directly to provide N-methyl-3-chloromercuri-2-propylindole (64) in a yield of 80%. Treatment of the chloromercuri compound with silver acetate to effect ligand exchange gives the intermediate 65 which upon stirring in glacial acetic acid produces the starting indole (Scheme V). This shows that the acetic acid

Scheme IV

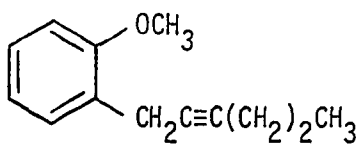


Scheme V

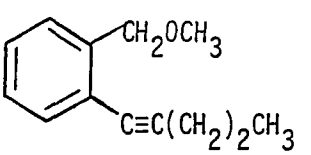


in the reaction is causing protodemercuration of the intermediate mercury compound to produce the indole. In the reaction with mercuric trifluoroacetate in tetrahydrofuran, the proton source could possibly arise from acid generation during the aqueous sodium chloride work-up.

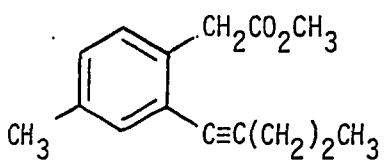
Other cyclizations There are other classes of heterocyclic compounds which could possibly be prepared by the intramolecular cyclization reaction. The preparation of benzopyran derivatives and dihydrobenzoxepin derivatives by this reaction was attempted through the use of acetylenes 66-69.



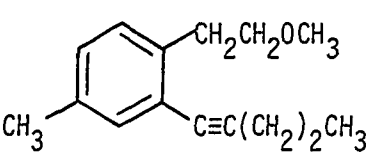
66



67



68

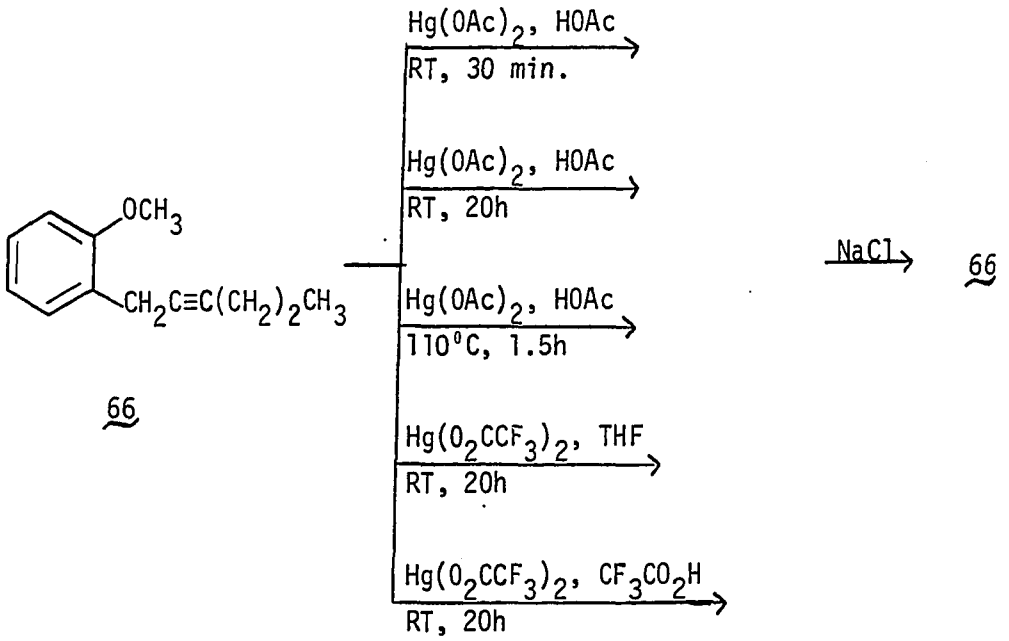


69

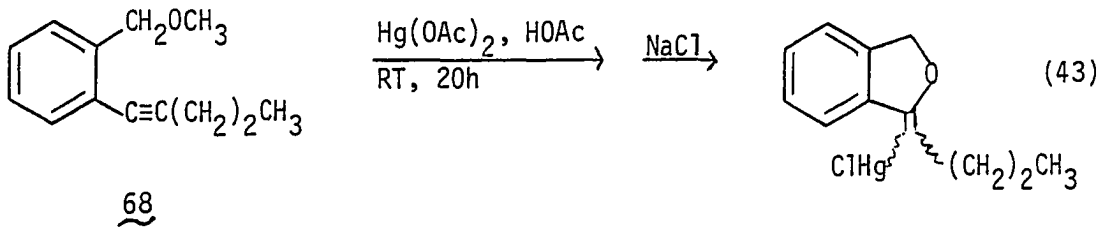
The acetylene 66 was easily prepared by the reaction of o-methoxybenzyl bromide with 1-lithio-1-pentyne. Treatment of this acetylene with either mercuric acetate or mercuric trifluoroacetate under a variety of conditions failed to produce any cyclized compound and the only compound isolated was the starting acetylene (Scheme VI). This is a bit surprising since 2-butyne reacts under similar conditions to provide

the corresponding acyloxymercury addition compound.

Scheme VI



The preparation of methyl 2-(1-pentynyl)benzyl ether (67) was accomplished by the reaction of the 2-iodo compound with cuprous n-propylacetylide. The reaction of compound 67 with mercuric acetate using the usual thirty minute cyclization condition resulted in the recovery of the starting acetylene. If the reaction time was increased to twenty hours, intramolecular cyclization did occur. However, the product that was isolated was not the expected mercurated 2-benzopyran, but instead the corresponding 5-membered ring heterocycle 70 (eq. 43).

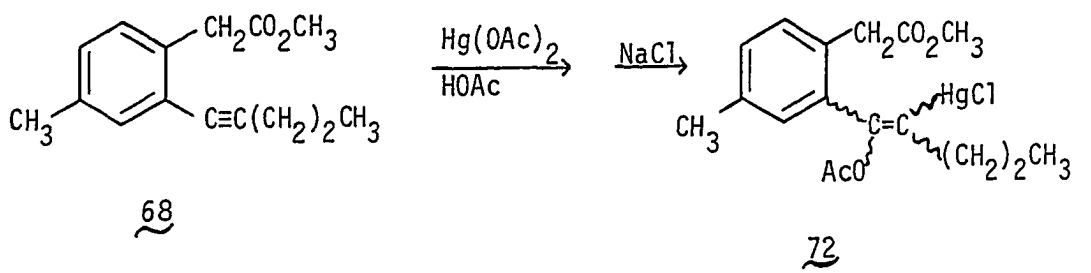


(43)

68

70 (39%)

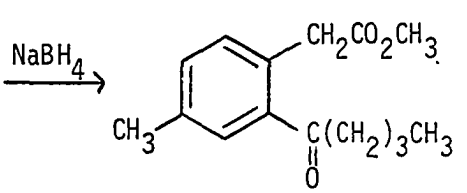
The acetylenes 68 and 69 were both prepared from p-tolylacetic acid by ortho thallation with thallium trifluoroacetate followed by iodination with potassium iodide. The acid was then esterified and reacted with cuprous n-propylacetylide to produce acetylene 68. The acetylene 69 was prepared by reduction of the iodo acid followed by formation of the methyl ether and reaction with cuprous n-propylacetylide. Treatment of compound 68 with mercuric acetate followed by reduction with alkaline sodium borohydride produced the ketone 71 as determined by gas chromatographic-mass spectral analysis. The ketone 71 presumably arises from the β-acetoxy vinylmercury compound 72 (eq. 44). The reaction of



68

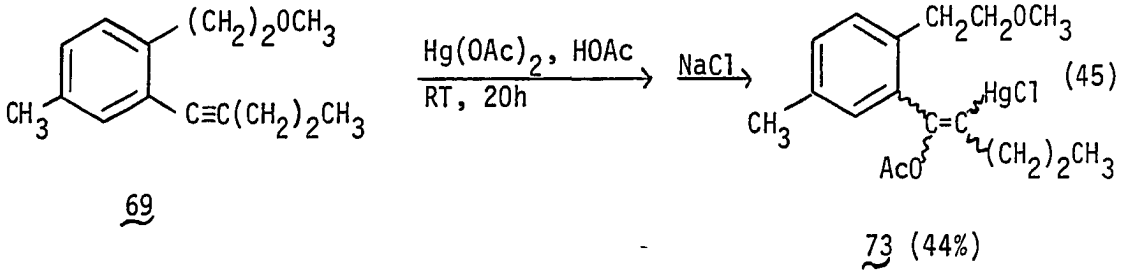
72

(44)



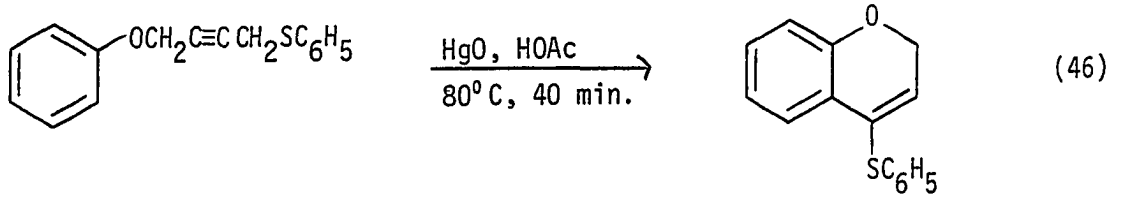
71

acetylene 69 with mercuric acetate for thirty minutes at room temperature led to the recovery of the starting acetylene. When the reaction was carried out for twenty hours at room temperature, the product isolated was the β-acetoxy vinylmercury compound 73 in a yield of 44% after column chromatography (eq. 45).

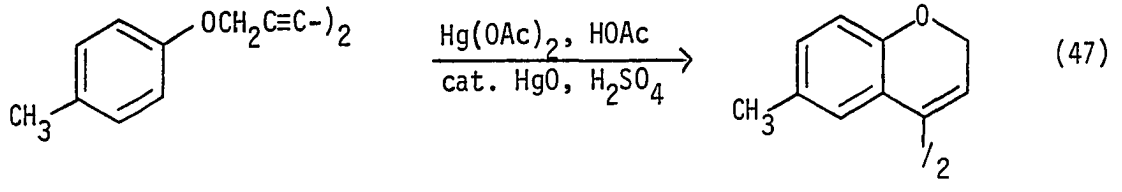


69 73 (44%) (45)

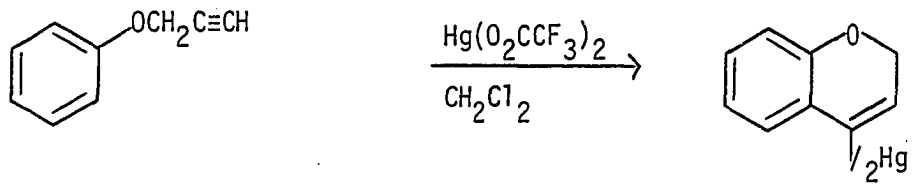
It has been reported by several workers that various aryl propargylic ethers will undergo cyclization when treated with a mercuric salt (eq. 46-48) (113-115). Most of these cyclizations have been carried out under acidic conditions, and the organomercurials were not isolated. The only case where the organomercurial was isolated was the reaction performed by Bates and Jones (eq. 48) (115).



(46)



(47)



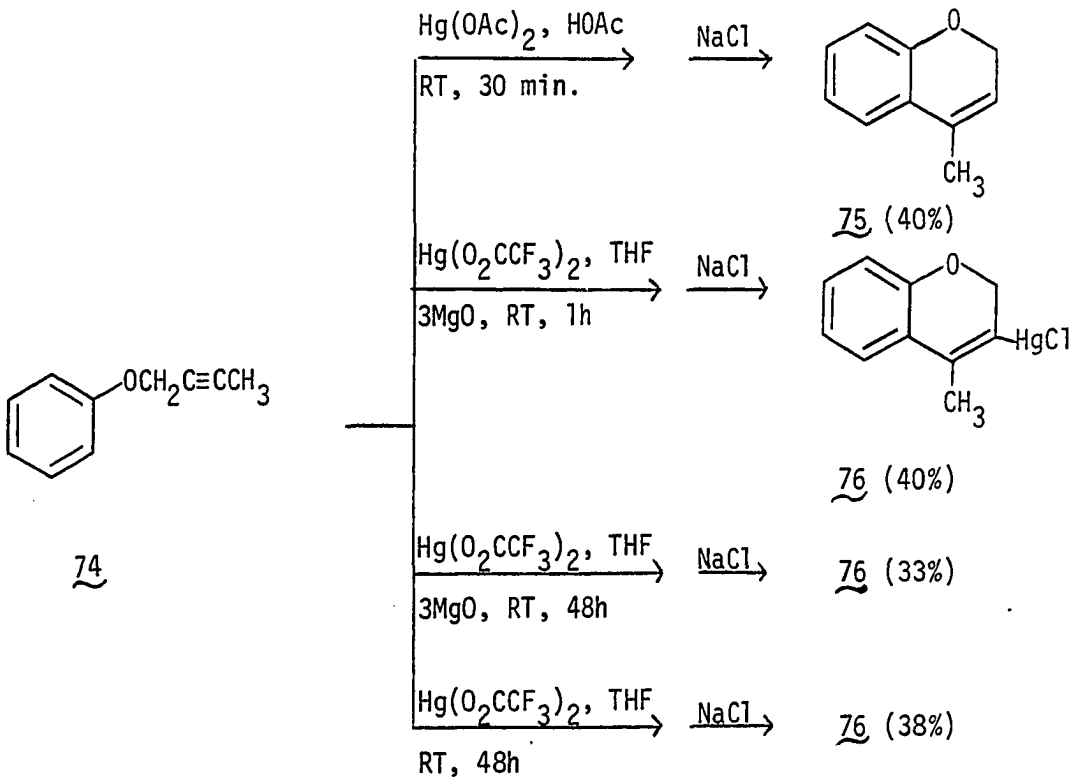
(48)

In an attempt to prepare the mercurated benzopyran ring system, the cyclization of the aryl propargylic ether 74 was examined. The ether was prepared by the reaction of sodium phenoxide with 1-iodo-2-butyne. The reaction of 2-butynyl phenyl ether (74) with mercuric acetate in acetic acid produced the cyclized compound 75 in which protodemercuration had occurred. When the reaction was performed using mercuric trifluoroacetate in tetrahydrofuran with or without added base, the desired 3-chloromercuri-4-methyl-2H-1-benzopyran (76) could be isolated in 33-40% yield (Scheme VII).

Based on the results of the cyclization of 2-butynyl phenyl ether, it was believed that if the ring was kept about the same electronically as in the above case, then this reaction could possibly be used for the preparation of mercurated carbocycles. This possibility was examined by using acetylenes 77a-c.

Acetylene 77a was prepared by the reaction of 3-methoxybenzyl bromide with 1-lithio-1-pentyne. All attempts at cyclization of this compound failed and resulted in the recovery of starting material.

Scheme VII



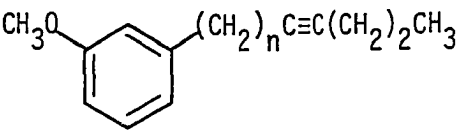
74

75 (40%)

76 (40%)

76 (33%)

76 (38%)

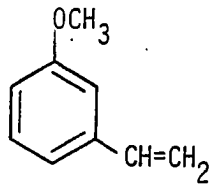


77a: n=1

b: n=2

c: n=3

The synthesis of 77b was accomplished by the procedure of Suzuki et al. starting with 3-methoxystyrene 78 (eq. 49) (116). The reaction

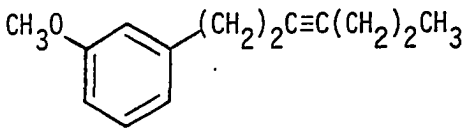


78

1) $BH_3 \cdot THF$
2) $LiC{\equiv}C(CH_2)_2CH_3$
3) I_2

77b (49)

of 77b with mercuric trifluoroacetate in tetrahydrofuran in the presence of three equivalents of magnesium oxide for ten hours produced the desired 3-chloromercuri-7-methoxy-4-propyl-1,2-dihydronaphthalene (79) in a yield of 30%. The same yield was obtained if the reaction time was increased to twenty hours (eq. 50).

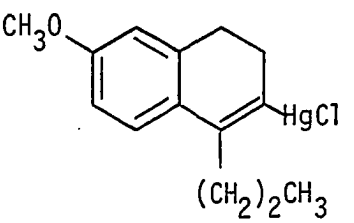


77b

$Hg(O_2CCF_3)_2$, THF
3MgO, RT, 10h

NaCl

(50)

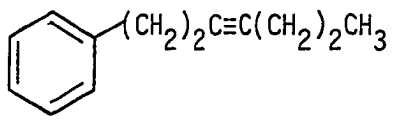


79 (30%)

Compound 77c was prepared in the same manner as 77b starting with 3-allylanisole. The reaction of 77c under the conditions used for the cyclization of 77b led mainly to recovery of starting material with no

cyclized product being observed.

The acetylene 80 was also examined to determine if the methoxy substituent is necessary for cyclization. Treatment of 1-phenyl-3-heptyne (80) with mercuric trifluoroacetate followed by alkaline sodium borohydride reduction produced a mixture of two ketones, 81 and 82, as determined by gas chromatographic-mass spectral analysis and infra-red analysis (eq. 51). These two ketones presumably arise from a mixture of



80 (51)

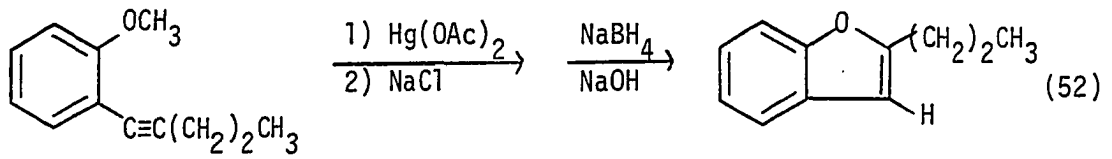
81 82

β-trifluoroacetoxy vinyl mercury compounds which result from mercuric trifluoroacetate addition across the carbon-carbon triple bond.

Functionalization of the organomercurials There are a variety of reactions which organomercurials are known to undergo (i). These reactions have been used in this work both as a tool for determining the product of the mercuration reaction and as a method for the preparation of the disubstituted ring system.

Removal of the mercury moiety by reduction with alkaline sodium borohydride (117) was the most common method used for structure identification. This reaction was especially useful in those cases where

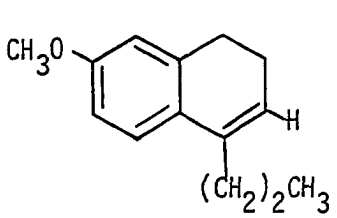
the cyclization reaction could produce either of two ring sizes. The reduction of the product from the cyclization of 2-(1-pentynyl)anisole (1) provided 2-propylbenzofuran (83) in 90% yield (eq. 52). Reduction of



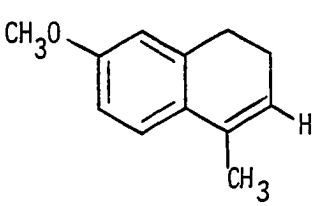
(52)

1 83 (90%)

the mercurial formed from the cyclization of methyl 2-(1-pentynyl) benzoate (41) proved that the cyclized compound was the isocoumarin (44) and not the corresponding five-membered phthalide on the basis of the chemical shift and multiplicity of the vinyl hydrogen. The reduction of compound 76 also provided evidence for cyclization to the six-membered ring. The chemical shift and multiplicity of the vinyl hydrogen in compound 84 obtained by the sodium borohydride reduction of compound 79 provided evidence for formation of the six-membered ring product. The ring size and regiochemistry of compound 84 were most easily determined by comparison of its spectral data with that reported for compound 85 (118).

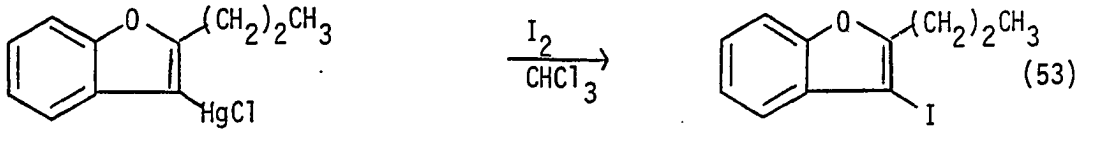


84



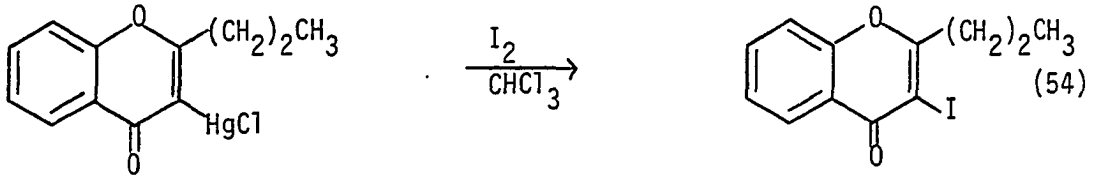
85

The halogenation of an organomercurial provides another useful method for determination of the position of the mercury atom in the molecule. The iodination was performed using two different substrates to produce the corresponding halogenated heterocyclic compounds (eqs. 53, 54).



(53)

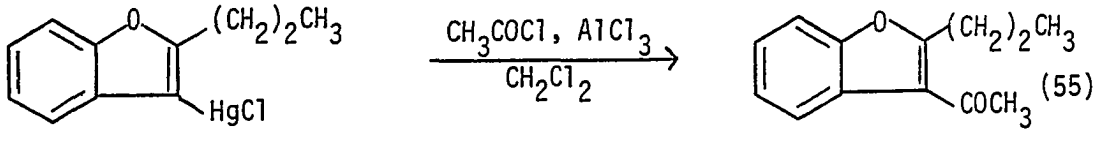
2 86 (75%)



(54)

45 87 (93%)

Recently, Larock and Bernhardt (119) have developed a procedure for the acylation of organomercurials using an acid halide in the presence of aluminum trichloride. This acylation reaction was carried out using 3-chloromercuri-2-propylbenzofuran (2) and acetyl chloride to provide the 2,3-disubstituted compound, 3-acetyl-2-propylbenzofuran (88), in a yield of 75% (eq. 55).

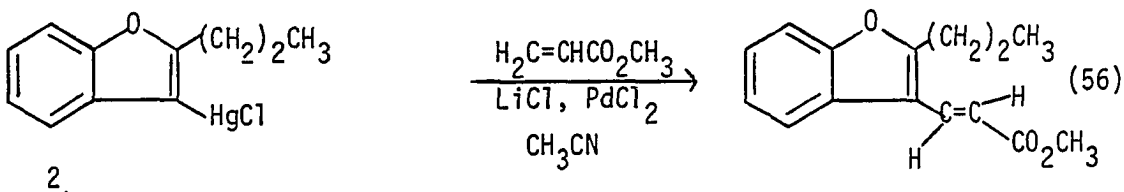


(55)

2 88 (75%)

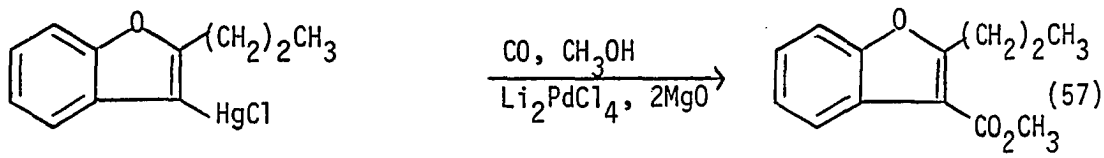
There are several useful methods which utilize the transmetallation

of organomercurials by palladium (II) salts to transform the mercury moiety into other functional groups. Heck (120) has reacted organomercurials with olefins in the presence of palladium salts to provide products where the olefin has replaced the mercury group. The reaction of 3-chloromercuri-2-propyl-benzofuran (2) with methyl acrylate under the conditions used by Heck did produce the desired olefin 89 in a yield of 65% (eq. 56). Larock (121) has developed a procedure for the



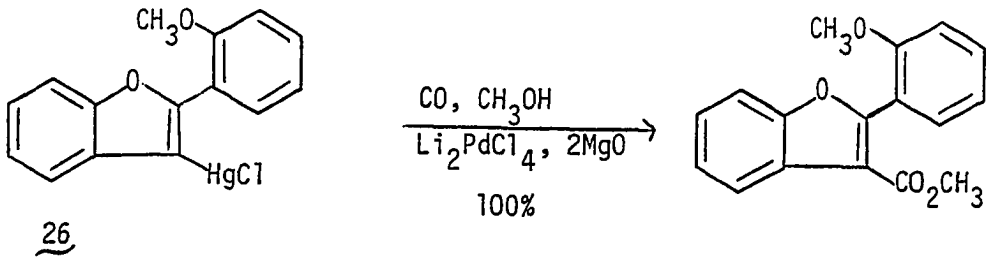
2 89 (65%) (56)

preparation of esters and acids using the reaction of an organomercurial with carbon monoxide in the presence of lithium tetrachloropalladate. This reaction was performed using 3-chloromercuri-2-propylbenzofuran (2) to provide 3-carbomethoxy-2-propylbenzofuran (90) in 89% yield (eq. 57).



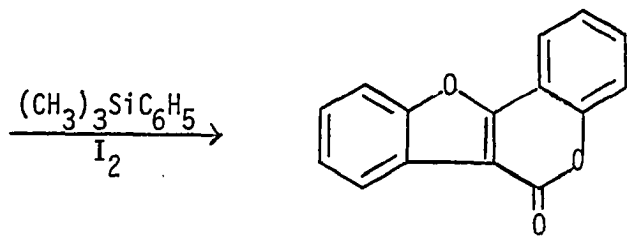
2 90 (89%) (57)

The carbonylation reaction was also used in the synthesis of the biologically important coumestan ring system (91) starting from 2-(2-anisyl)-3-chloromercuri-benzofuran (26) (eq. 58).



26

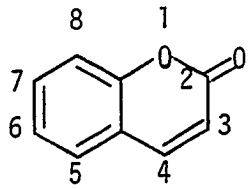
(58)



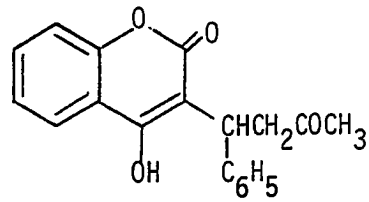
91 (90%)

Coumarins The coumarins (122, 123) (2H-1-benzopyran-2-one, (92)) are a large class of important naturally occurring compounds. They are commonly found in grasses, orchids, and citrus fruits. Many coumarins have been reported to have a variety of physiological activities such as antibacterial, anticarcinogenic, and anticoagulant activity. Some of the most important physiological activity is observed in coumarin derivatives which possess a hydroxyl substituent in the 4-position. One of the widely used rodenticides is the 4-hydroxycoumarin derivative, wayfarin (93) (124). Potent antibacterial activity has also been seen in compounds 94 and 95 (125, 126). The simple 4-hydroxycoumarin 96 exhibits both anticarcinogenic and anticoagulant activity (127, 128). Dicoumarol (97) has found widespread clinical use as a blood anticoagulant (122). Strong anticoagulant activity has also been observed for 3-hexyl-4-

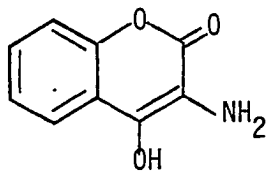
hydroxycoumarin (98a) (129). On the other hand, 3-methyl-4-hydroxycoumarin (98b) has been reported to behave very similar to vitamin K (130).



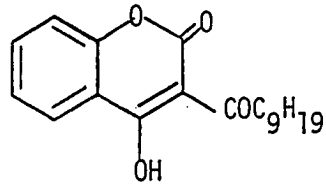
92



93



94



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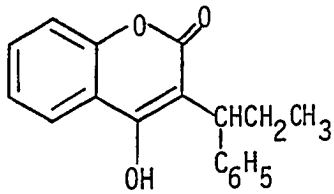
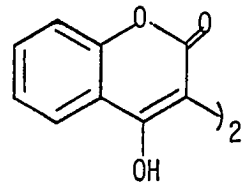
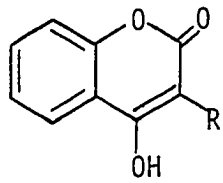


96



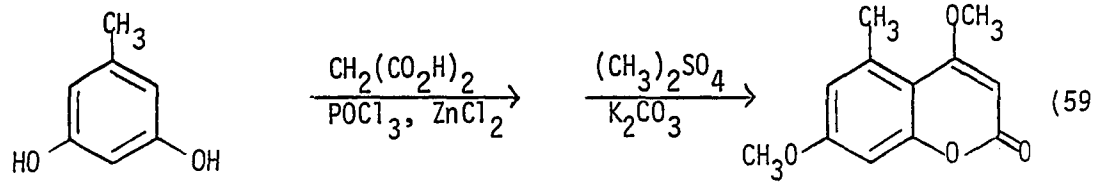
97



98a: R=C_6H_{13}

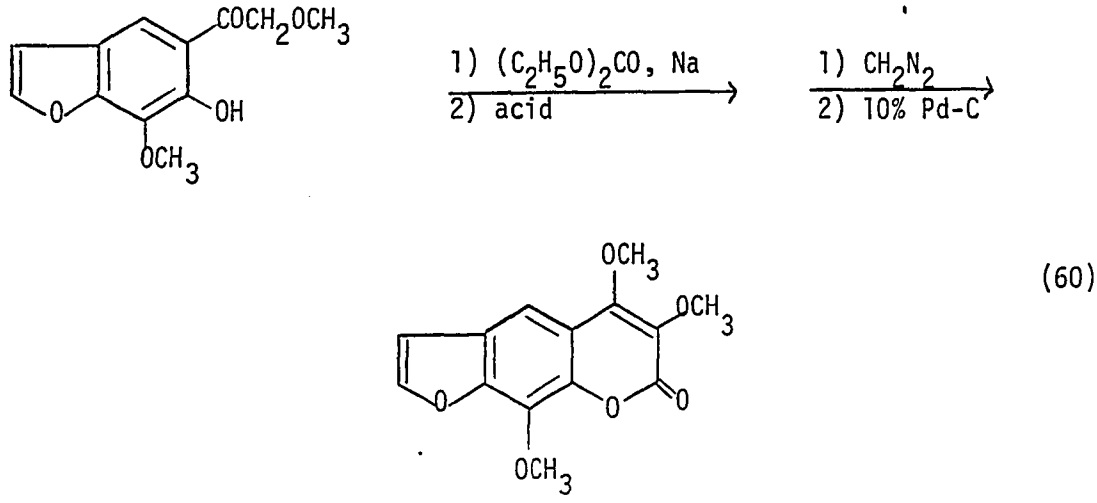
b: R=CH_3

A number of methods are available for the synthesis of 4-hydroxycoumarins. In the simplest method, a phenol is treated with an equimolar amount of malonic acid in the presence of two to three equivalents each of anhydrous zinc chloride and phosphoryl chloride at 60-75°C (131). This method was used by Venturella and co-workers (132) in their synthesis of siderin (eq. 59).



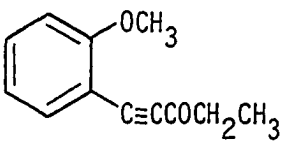
(59)

Boyd and Robertson (133) obtained 4-hydroxycoumarins by condensation of o-hydroxyacetophenones with diethyl carbonate and sodium. Fukui and co-workers (134) used this coumarin preparation in their synthesis of isohalfordin (eq. 60).

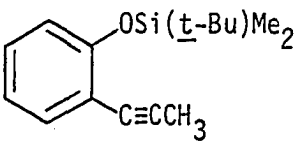


(60)

In an effort to prevent cyclization to the benzofuran nucleus either by a steric or an electronic effect, the mercuration of acetylenes 99 and 100 was examined. It was hoped that these acetylenes might provide the originally desired β-acetoxy vinylmercury compounds. It was anticipated that the β-acetoxy vinylmercury compounds should be easily converted to the biologically active coumarin ring system.

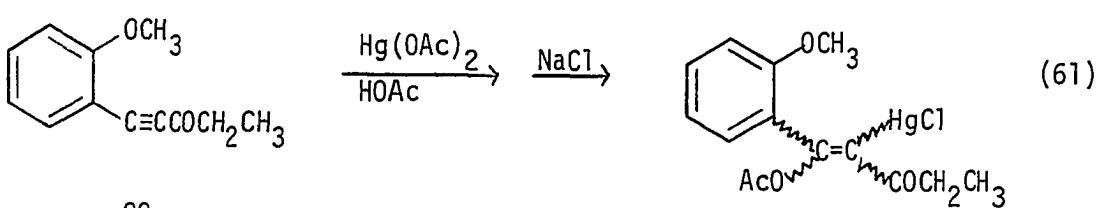


99



100

The acetylenic ketone 99 was prepared by alkylation of lithium 2-methoxyphenylacetylide with propionaldehyde. The resulting alcohol was then oxidized with Jones' reagent to provide the desired acetylene. The reaction of this acetylene with mercuric acetate for thirty minutes at room temperature resulted in recovery of the starting acetylene. When the reaction was carried out for twenty hours, the desired β-acetoxy vinylmercury compound 101 was isolated but in a yield of only 12% (eq. 61). Because of the low yield, no further work was carried out on this system.

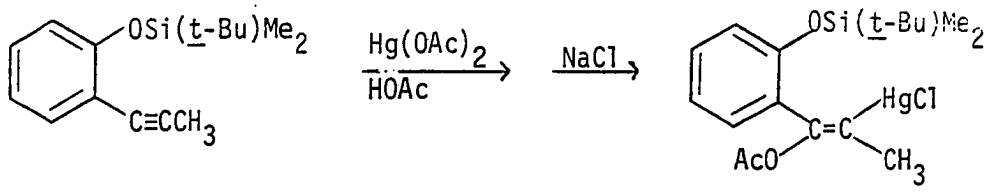


99 → 101 (12%) (61)

The preparation of acetylene 100 involved the alkylation of the lithium acetylide of 2-t-butyldimethylsilyloxyphenylacetylene with dimethyl sulfate. The lithium acetylide was prepared by treating the corresponding gem-dibromoolefin with two equivalents of n-butyllithium. The addition of mercuric acetate to this acetylene produced two isomeric mercurials 102 and 103, as determined by NMR spectral analysis (eq. 62). After thirty minutes, the ratio of 102 to 103 was 5:1, but the total yield was only 27%. After twenty hours, the ratio was the same, but the yield had doubled. Finally, at forty-eight hours, the ratio was 12:1 and the mercurials could be isolated in 66% yield. The structures of 102 and 103 were assigned by comparing the chemical shifts of the acetate and the methyl resonances in the proton NMR with those given by Uemura and coworkers (28) for the adducts of mercuric acetate addition to 1-phenyl-1-propyne. The isomeric ratio was determined by NMR integration of the acetoxy methyl protons. The desired, major isomer (102) could be isolated in pure form by column chromatography.

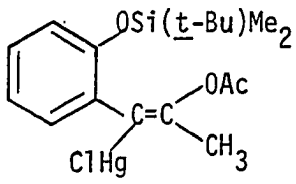
The vinylmercury compound 102 was carbonylated in methanol in the presence of lithium tetrachloropalladate to give the unsaturated ester 104 in a yield of 70% (eq. 63). The carbonylation conditions also led to the formation of the starting acetylene 100 in approximately 20% yield.

Desilylation and cyclization of 104 was then examined to see if this ester could be converted into the coumarin ring system. Attempted desilylation using an acetic acid/tetrahydrofuran/water (3:1:1) mixture (135) at room temperature for twenty hours yielded no silyl ether

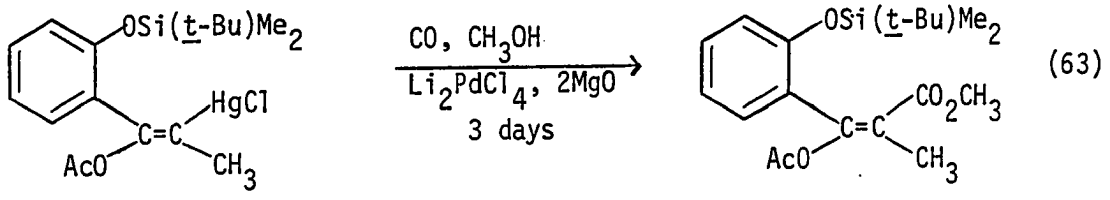


100 102

+ (62)



103

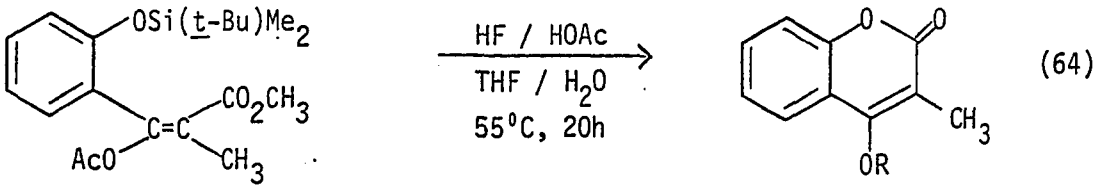


(63)

102 104 (70%)

cleavage and 104 was the only isolated product. The desilylation conditions of Newton et al. (136) (aq. HF/CH_3CN) also proved unsuccessful leading to recovery of 104. The use of tetrabutylammonium fluoride (135) did generate the coumarin ring system as seen by NMR, but the yield was low and the compound could not be isolated cleanly. The desilylation and cyclization of the ester was finally accomplished by heating the ester in a mixture of hydrofluoric acid/acetic acid/tetrahydrofuran/water

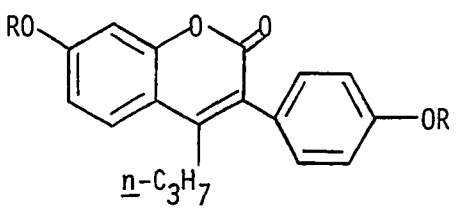
(1:3:1:1) at 55°C for twenty hours followed by quenching the reaction mixture with aqueous potassium carbonate. This method produced the desired 4-acetoxy-3-methylcoumarin (105) in a yield of 65-70%. When the reaction was performed on a larger scale (7 mmoles), the corresponding 4-hydroxy compound 106 was also obtained (eq. 64).



104 (64)

105: R=$COCH_3$
106: R=H

Since the 3,4-disubstituted coumarins such as 107 (137) also show a variety of physiological activity, the substitution of the acetoxy group in 105 by an organocuprate reagent was examined. Under all conditions that were attempted, the major product observed was the starting coumarin. The various conditions examined are given in Table II.



107: R=H or CH_3

Table II. Attempted Alkylation of 105 with Organocuprates

RLi (equiv)	Cu(I) salt (equiv)	solvent	temp (°C); time
CH_3Li (2.2)	CuI (1.1)	Et_2O	-78 ; 30 min
CH_3Li (4)	$(Bu_3P)CuI$ (2)	THF	-78 ; 15 min
CH_3Li (4)	$(Bu_3P)CuI$ (2)	THF	-78 ; 1 h
CH_3Li (4)	$(Bu_3P)CuI$ (2)	THF	-78 ; 30 min
			0 ; 30 min
CH_3Li (4)	CuCN (2)	THF	-78 ; 30 min
			25 ; 5 h
n-C_4H_9Li (4)	CuI (2)	THF	-78 ; 1 h
			0 ; 1 h
			25 ; 15 h

Conclusion

The mercury-assisted intramolecular cyclization of aryl acetylenes presented in this chapter provides a novel approach to a variety of naturally occurring and physiologically active heterocyclic ring systems. Through the use of known reactions of organomercurials, the mercury moiety can be readily substituted by a variety of useful functional groups to generate the disubstituted heterocyclic ring system. The intramolecular cyclization followed by carbonylation of the resulting mercurated benzofuran derivative provides an efficient entry into the biologically important coumestan ring system. By changing the aryl methyl ether to an aryl t-butyldimethylsilyl ether, the intramolecular cyclization can be prevented. The mercuration reaction then furnishes β-acetoxy vinylmercury compounds which can be transformed by carbonylation and cyclization into the naturally occurring coumarin ring system.

Experimental Section

Equipment The infrared spectra were recorded on a Beckman IR-4250 infrared spectrophotometer or a Beckman Acculab 2 spectrophotometer, and the ^{1}H NMR spectra on a Varian Associates A-60 NMR, Hitachi Perkin-Elmer R-20B NMR or a Varian Associates EM-360 NMR spectrometer. The mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer, while the GC/mass spectra were recorded on a Finnegan 4023 GC/MS data system. GLC analyses were performed on a Varian 3700 gas chromatograph

with an attached Varian CDS-111 chromatography data system. Thin-layer chromatography was performed on Merck 60F-254 silica gel plates from MCB Manufacturing Chemists, Inc. Silica gel for column chromatography was purchased from Davison Chemical (60-200 mesh) and MCB Manufacturing Chemists, Inc. (230-400 mesh). 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 unless otherwise indicated. The starting materials were purchased from Aldrich, except for 2-iodoanisole (Columbia Organics) and 1-pentyne (Farchan). Phenyltrimethylsilane was prepared in 67% yield by the reaction of phenylmagnesium bromide with trimethylchlorosilane. 1-Iodo-2-butyne was synthesized by bromination of 2-butyn-1-ol with phosphorus tribromide followed by reaction of the bromide with sodium iodide. Methyllithium was purchased from Alfa and titrated before use by the method of Watson and Eastham (138). *n*-Butyllithium was also obtained from Alfa and titrated using 2,5-dimethoxybenzyl alcohol (139). Mercuric acetate and acetic acid were used directly as obtained from Mallinckrodt and Fischer, respectively. Methanol was distilled from magnesium methoxide; acetonitrile and methylene chloride were distilled from phosphorus pentoxide; diethyl ether and tetrahydrofuran were distilled from calcium hydride; and *N*,*N*-dimethylformamide and pyridine were distilled from barium oxide before using. Magnesium oxide and lithium chloride were purchased from J.T. Baker. Palladium chloride was generously supplied by Johnson Matthey, Inc. and Engelhard Industries. Carbon monoxide was

purchased from Matheson Gas Products.

Preparation of aryliodides. The preparation of 2-iodo-4-methoxyanisole, 2-iodo-4-nitroanisole and 2-iodothioanisole were carried out using the procedure of Ullmann (140). The preparation of 2-iodo-4-methoxyanisole is representative. In a 250 mL Erlenmeyer flask was placed 7.66 g (50.0 mmol) of 2,5-dimethoxyaniline in 70 mL of water containing 7 mL of concentrated sulfuric acid. The solution was cooled to 0°C and 3.5 g (50.7 mmol) of sodium nitrite in 15 mL of water was slowly added. The resulting mixture was stirred for 30 min, then added to a cold (~5°C) solution of 15 g (90.4 mmol) of potassium iodide in 60 mL of water and the stirring was continued for 2.5 h. The aqueous solution was extracted with 3 x 100 mL of ether, and the organic extracts were washed with 2 x 50 mL of 10% hydrochloric acid, 2 x 50 mL of saturated sodium bicarbonate, and 2 x 50 mL of a saturated sodium thiosulfate solution, dried ($MgSO_4$) and concentrated. Distillation of the concentrate provided 11.1 g (42 mmol, 84%) of 2-iodo-4-methoxyanisole: bp 98-101°C (0.6 mm Hg) (lit. (141) bp 157°C (10 mm Hg)). The compound distills as a pale yellow liquid, but turns green upon standing. ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.75-7.25 (m, 3H, C_6H_3).

The following two aryl iodides were prepared in identical fashion.

2-Iodo-4-nitroanisole: yield 71%; mp 93°C (lit. (142) mp 96°C); ^1H NMR ($CDCl_3$) δ 4.0 (s, 3H, OCH_3), 6.95 (d, 1H, J=10 Hz, H-6), 8.35 (dd, 1H, J=10 Hz, J=3 Hz, H-5), 8.75 (d, 1H, J=3 Hz, H-3).

2-Iodothioanisole: yield 92%; bp 154-156°C (16 mm Hg) (lit. (143)

bp 173°C (20 mm Hg)); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, SCH_3), 6.61-7.92 (m, 4H, C_6H_4).

Methyl 2-iodobenzoate: In a 100 mL round-bottom flask was placed 12.4 g (50 mmol) of 2-iodobenzoic acid in 20 mL of methanol containing 3 mL of concentrated sulfuric acid. The mixture was refluxed for 2 h, poured into 100 mL of water and extracted with 3 x 50 mL of ether. The ether extracts were washed with 2 x 20 mL of water, 2 x 20 mL of 5% sodium bicarbonate and 2 x 20 mL of brine, dried (Na_2SO_4) and concentrated. Distillation at 146-147°C (16 mm Hg) (lit. (144) bp 145-146°C (16 mm Hg)) provided 10.8 g (41 mmol, 82%) of methyl 2-iodobenzoate: ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.92-8.01 (m, 4H, C_6H_4); IR (neat) 1720 (C=O) cm^{-1}.

N-Methyl-2-iodoaniline. In a flame-dried 100 mL round-bottom flask, 2.25 g (10.3 mmol) of 2-iodoaniline was dissolved in 30 mL of dry tetrahydrofuran. The resulting solution was cooled to -78°C under a nitrogen atmosphere and 6.25 mL of 1.6 M methyllithium (10 mmol) was added dropwise, and the resulting solution was stirred at -78°C for 30 min. To the solution was added 1.90 g (15.1 mmol) of dimethyl sulfate and stirring was continued for 10 min at -78°C. The solution was then warmed to room temperature and stirred for 2 h, followed by acidification with 10% hydrochloric acid. The reaction mixture was diluted with ether and the aqueous layer was removed. The etheral extract was stirred with 30 mL of concentrated ammonium hydroxide for 30 min. The aqueous layer was removed and the organic phase was washed with 20 mL of water and 30 mL of brine, dried ($MgSO_4$) and concentrated. Distillation at 101-105°C

(2.0 mm Hg) (lit. (145) bp 108-110°C (4.5 mm Hg)) yielded 2.03 g (8.7 mmol, 87%) of N-methyl-2-iodoaniline: ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 3H, NCH_3), 4.0 (br s, 1H, NH), 6.2-7.8 (m, 4H, C_6H_4); IR (neat) 3410 (NH), 1590 (C=C) cm^{-1}; mass spectrum m/z 232.97023 (calcd for C_7H_8IN, 232.97015).

N-Acetyl-N-methyl-2-iodoaniline. In a dry 250 ml round-bottom flask, 2.1 g (9.0 mmol) of N-methyl-2-iodoaniline was dissolved in 50 mL of dry ether and the solution was cooled to 0°C. To the solution, 0.931 g (9.2 mmol) of triethylamine was added followed by 0.725 g (9.2 mmol) of acetyl chloride. The reaction mixture was stirred at 0°C for 30 min, then warmed to room temperature and stirred overnight. The amine salts were removed by filtration, and the filtrate was diluted with ether and washed with 2 x 30 mL of water and 1 x 50 mL of brine, dried ($MgSO_4$) and concentrated to yield 2.45 g (8.91 mmol, ~100%) of essentially pure N-acetyl-N-methyl-2-iodoaniline: ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3H, $NCOCH_3$), 3.20 (s, 3H, NCH_3), 6.95-8.07 (m, 4H, C_6H_4); IR (neat) 1665 (C=O), 1590 (C=C) cm^{-1}; mass spectrum (M^+-CH_3) m/z 259.95772 (calcd for C_8H_7INO, 259.95724).

N-Acetyl-2-iodoaniline. This compound was prepared as above starting from 2-iodoaniline: yield 76%; mp 109-110°C (lit. (146) mp 109.5-110°C); ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H, $NCOCH_3$), 6.81-8.40 (m, 5H, C_6H_4 and NH); IR ($CHCl_3$) 3415 (NH), 1690 (C=O) cm^{-1}.

N,N-Dimethyl-2-iodoaniline. In a 100 mL round-bottom flask were placed 8.64 g (39.5 mmol) of o-iodoaniline, 8.47 g (80 mmol) of sodium carbonate and 15.2 g (120.6 mmol) of dimethyl sulfate in 50 mL of a 4:1

ethanol-water mixture. The contents of the flask were refluxed for 48 h. After cooling to room temperature, 30 mL of concentrated ammonium hydroxide was added to the mixture and stirring was continued for an additional 30 min at room temperature. The solution was extracted with 3 x 50 mL of ether, and the ether extracts were combined and washed with 1 x 50 mL of brine and 1 x 50 mL of water, dried ($MgSO_4$) and concentrated. Distillation of the concentrate provided 9.25 g (37.4 mmol, 95%) of the title compound: bp 125-128°C (17 mm Hg) (lit. (147) bp 116°C (11 mm Hg)); ^1H NMR ($CDCl_3$) δ 2.75 (s, 6H, $N(CH_3)_2$), 6.32-7.89 (m, 4H, C_6H_4).

Methyl 2-iodobenzyl ether. In a flame-dried 100 mL round-bottom flask under an atmosphere of nitrogen was placed 1.87 g (7.99 mmol) of 2-iodobenzyl alcohol in 30 mL of dry tetrahydrofuran. The solution was cooled to -78°C and 5.0 mL of 1.6 M methyllithium was added. The solution was stirred for 30 min at -78°C, then treated with 1.5 g (11.9 mmol) of dimethyl sulfate and stirred at -78°C for an additional 30 min. The cooling bath was removed, and the reaction mixture was warmed to room temperature and stirred overnight, followed by acidification with 10% hydrochloric acid. The solution was extracted with ether and the ether was washed with 1 x 30 mL of concentrated ammonium hydroxide, 2 x 30 mL of water and 1 x 50 mL of brine, dried ($MgSO_4$) and concentrated. The concentrate was distilled at 90-94°C (2 mm Hg) (lit. (148) bp 99-103°C (4 mm Hg)) to provide 1.4 g (5.65 mmol, 71%) of methyl 2-iodobenzyl ether: ^1H NMR ($CDCl_3$) δ 3.40 (s, 3H, OCH_3), 4.38 (s, 2H, CH_2O), 6.70-7.80 (m, 4H, C_6H_4).

Methyl 2-iodo-4-methylphenylacetate. The requisite acid was prepared by the thallation-iodination procedure developed by Taylor and coworkers (149). In a dry 100 ml round-bottom flask were placed 10.74 g (19.76 mmol) of thallium trifluoroacetate ($Tl(TFA)_3$ was transferred to the flask in a glove bag) and 2.97g (19.8 mmol) of p-tolylacetic acid in 20 mL of trifluoroacetic acid. The flask was degassed, then stirred under an atmosphere of nitrogen for 48 h at room temperature. The reaction mixture was concentrated under reduced pressure, followed by two co-evaporations with 1,2-dichloroethane to provide 8.4 g (14.5 mmol, 73%) of crude 4-methyl-2-(bis(trifluoroacetoxy)thallium)phenylacetic acid. The crude thallium compound was suspended in 150 mL of water, then 14.9 g (90 mmol) of potassium iodide was added all at once, and the reaction mixture was refluxed for 5 h. After this time, 1.5 g (7.9 mmol) of sodium metabisulfite was added and refluxing was continued for an additional 30 min. The reaction mixture was filtered through Celite while warm, and the Celite was washed with 200 mL of acetone. The aqueous acetone filtrate was extracted with 4 x 60 mL of ether, and the ether extracts were washed with 1 x 40 mL of saturated sodium thiosulfate and 1 x 40 mL of brine, dried ($MgSO_4$) and concentrated. The concentrate was recrystallized from hexanes to produce 3.37 g (12.21 mmol, 84%) of 2-iodo-4-methylphenylacetic acid: mp 137-139°C; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H, $ArCH_3$), 3.81 (s, 2H, $ArCH_2$), 7.01-7.35 (m, 2H, H-5, H-6), 7.72 (br s, 1H, H-3), 11.48 (br s, 1H, CO_2H); IR (nujol) 3000 (broad, CO_2H), 1695 (C=O) cm^{-1}; mass spectrum m/z 275.96553 (calcd for $C_9H_9IO_2$, 275.96473). The ester was prepared as previously described for methyl 2-

iodobenzoate: yield 100%; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, $ArCH_3$), 3.71 (s, 3H, OCH_3), 3.78 (s, 2H, $ArCH_2$), 7.15 (s, 2H, H-5, H-6), 7.70 (br s, 1H, H-3); IR (neat) 1730 (C=O), 1600 (C=C).

Methyl β-(2-iodo-4-methyl)phenethyl ether. The alcohol was prepared by the reduction of 2-iodo-4-methylphenylacetic acid using a modification of the procedure used by Corey and coworkers (150). In a flame-dried 100 mL round-bottom flask, 3.26 g (11.83 mmol) of the acid was dissolved in 50 mL of dry ether, and the solution was cooled to 0°C. To the solution, 6.1 g (47.3 mmol) of diisopropylethylamine was added, followed by 4.47 g (47.3 mmol) of methyl chloroformate, and the reaction mixture was stirred at 0°C for 1 h, filtered and concentrated. The concentrate was placed in a dry 250 mL round-bottom flask with 50 mL of dry tetrahydrofuran, then degassed and cooled to 0°C. To this solution, 0.520 g (23.85 mmol) of lithium borohydride was added (nitrogen backflush) and the reaction was warmed to room temperature and stirred until the intermediate carbonate had disappeared as indicated by TLC analysis (~ 24 h). The reaction mixture was quenched by the addition of water, followed by the dropwise addition of 10% hydrochloric acid, diluted with 50 mL of ether and the aqueous layer was removed. The etheral layer was washed with 2 x 30 ml of brine, dried ($MgSO_4$) and concentrated. The alcohol was isolated by column chromatography using hexanes-ethyl acetate (2:1) as the eluent to yield 2.38 g (9.1 mmol, 77%) of the desired alcohol (R_f 0.33): ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, $ArCH_3$), 2.57 (br s, 1H, OH), 2.92 (t, 2H, J=7 Hz, $ArCH_2$), 3.80 (t, 2H, J=7 Hz, CH_2OH), 7.00-7.15 (m, 2H, H-5, H-6), 7.70 (br s, 1H, H-3); IR (neat) 3150-3550 (OH), 1600 (C=C) cm^{-1}; mass spectrum

m/z 261.98559 (calcd for $C_9H_{11}IO$, 261.98547). The ether was prepared as follows. In a dry 100 ml round-bottom flask was placed 0.330 g (13.75 mmol) of sodium hydride (washed with hexanes and vacuum dried) in 25 mL of dry tetrahydrofuran. The flask was degassed and placed under an atmosphere of nitrogen. Then, 2.38 g (9.1 mmol) of the alcohol in 25 mL of dry tetrahydrofuran was added dropwise and the mixture was stirred for 1.5 h. To the reaction mixture, 2.0 g (15.87 mmol) of dimethyl sulfate was added, and the resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of 10% hydrochloric acid and diluted with ether. After removal of the aqueous layer, the etheral extract was stirred with 30 mL of concentrated ammonium hydroxide for 30 min. The organic phase was washed with 20 mL of water and 30 mL of brine, dried ($MgSO_4$) and concentrated. Column chromatography of the residue using hexanes-ethyl acetate (10:1) as the element provided 1.98 g (7.2 mmol, 79%) of the desired methyl ether (R_f 0.35): ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H, $ArCH_3$), 2.91 (t, 2H, $\underline{J}$=7 Hz, $ArCH_2$), 3.38 (s, 3H, OCH_3), 3.55 (t, 2H, $\underline{J}$=7 Hz, CH_2O), 7.00-7.15 (m, 2H, H-5, H-6), 7.70 (br s, 1H, H-3); IR (neat) 3020 (C=CH), 1600 (C=C) cm^{-1}; mass spectrum m/z 276.00210 (calcd for $C_{10}H_{13}IO$, 276.00112).

Preparation of acetylenes. The majority of the acetylenes were prepared by the reaction of a cuprous acetylide with the appropriate aryl iodide under the conditions described by Castro and coworkers (65). The preparation of 2-(1-pentynyl)anisole (1) is representative. In a 100 mL round-bottom flask under an atmosphere of nitrogen was placed 2.64 g (20.2 mmol) of cuprous n-propylacetylide in 75 mL of dry pyridine. To this

mixture was added 4.66 g (19.9 mmol) of 2-iodoanisole, and the resulting mixture was refluxed for 15-20 h. The reaction mixture was diluted with water and ether, filtered through Celite, and the filter cake was washed several times with ether. The filtrate was separated, and the aqueous phase was extracted with 3 x 50 mL of ether. The combined etheral extracts and washings were washed successively three times each with 50 mL of 1% hydrochloric acid, 50 mL of 5% sodium bicarbonate and 50 mL of water, dried ($MgSO_4$) and concentrated. The concentrate was distilled to provide 2.61 (15 mmol, 75%) of 2-(1-pentynyl)anisole (1): bp 95-100°C (0.7 mm Hg); ^1H NMR ($CDCl_3$) δ 1.0 (t, 3H, J=7 Hz, CH_3), 1.5 (m, 2H, CH_2), 2.3 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 3.8 (s, 3H, OCH_3), 6.4-7.7 (m, 4H, C_6H_4); IR (neat) 2230 (C≡C) cm^{-1}; mass spectrum m/z 174.10449 (calcd for $C_{12}H_{14}O$, 174.10447).

The following acetylenes were prepared in an identical fashion. The acetylenes 14, 15, 53, 60d, 67, 68, and 69 were prepared using dry N,N-dimethylformamide as the solvent, and acetylene 16 was prepared using cuprous phenylacetylide instead of cuprous n-propylacetylide.

4-Methoxy-2-(1-pentynyl)anisole (14): yield 54%; bp 121-124°C (0.6 mm Hg); ^1H NMR ($CDCl_3$) δ 1.01 (t, 3H, J=6 Hz, CH_3), 1.62 (m, 2H, CH_2), 2.45 (t, 2H, J=6 Hz, $C{\equiv}CCH_2$), 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.61-7.20 (m, 3H, C_6H_3); IR (neat) 2210 (C≡C) cm^{-1}; mass spectrum m/z 204.11760 (calcd for $C_{13}H_{16}O_2$, 204.11503).

4-Nitro-2-(1-pentynyl)anisole (15): yield 63%; mp 60-62°C; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3H, J=6 Hz, CH_3), 1.61 (m, 2H, CH_2), 2.45 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 4.00 (s, 3H, OCH_3), 6.90-7.15 (m, 1H, H-6), 8.10-8.31 (m,

2H, H-5, H-3); IR ($CHCl_3$) 2220 (C≡C) cm^{-1}; mass spectrum m/z 219.09028 (calcd for $C_{12}H_{13}NO_3$, 219.08955).

2-Methoxydiphenylacetylene (16): yield 53%; bp 120-122°C (0.1 mm Hg) (lit. (151) bp 144-145°C (0.2 mm Hg)); ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, OCH_3), 6.41-8.02 (m, 9H, C_6H_4, C_6H_5); IR (neat) 2215 (C≡C) cm^{-1}; GC/MS, m/z (relative intensity) 208 (100, M^+), 131 (61).

Methyl 2-(1-pentynyl)benzoate (41): yield 54%; bp 180-182°C (16 mm Hg); ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H, J=6 Hz, CH_3), 1.61 (m, 2H, CH_2), 2.45 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 3.90 (s, 3H, OCH_3), 7.11-8.00 (m, 4H, C_6H_4); IR (neat) 2240 (C≡C), 1730 (C=O) cm^{-1}; mass spectrum m/z 202.09861 (calcd for $C_{13}H_{14}O_2$, 202.09938).

2-(1-Pentynyl)thioanisole (53): yield 70%; bp 177-180°C (16 mm Hg); ^1H NMR ($CDCl_3$) δ 1.05 (t, 3H, J=7 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.38 (s, 3H, SCH_3), 2.41 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 6.91-7.59 (m, 4H, C_6H_4); IR (neat) 2220 (C≡C) cm^{-1}; mass spectrum m/z 190.08173 (calcd for $C_{12}H_{14}S$, 190.08163).

N-Acetyl-2-(1-pentynyl)-aniline (60a): yield 37%; mp 63-65°C; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, J=6 Hz, CH_3), 1.63 (m, 2H, CH_2), 2.20 (s, 3H, $NCOCH_3$), 2.45 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 6.79-8.42 (m, 5H, C_6H_4, NH); IR (CCl_4) 3410 (NH), 2220 (C≡C), 1700 (C=O), cm^{-1}; mass spectrum m/z 201.11559 (calcd for $C_{13}H_{15}NO$, 201.11537).

N,N-Dimethyl-2-(1-pentynyl)aniline (60b): yield 46%; isolated by column chromatography using hexanes-ethyl acetate (20:1), R_f 0.28; ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H, J=6 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.45 (t, 2H, J=6 Hz, $C{\equiv}CCH_2$), 2.85 (s, 6H, $N(CH_3)_2$), 6.59-7.40 (m, 4H, C_6H_4); IR (neat)

2240 (C≡C) cm^{-1}; mass spectrum (M^+-H) m/z 186.12796 (calcd for $C_{13}H_{16}N$, 186.12827). The reaction also produced 1-methyl-2-propylindole (61): yield 30%; bp 170-174°C (17 mm Hg); ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, J=7 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.65 (t, 2H, J=7 Hz, $C=CCH_2$), 3.55 (s, 3H, NCH_3), 6.20 (s, 1H, H-3), 6.79-7.55 (m, 4H, C_6H_4); mass spectrum m/z 173.11997 (calcd for $C_{12}H_{15}N$, 173.12045).

2-(1-Pentynyl)nitrobenzene: yield 53%; ^1H NMR ($CDCl_3$) δ 1.01 (t, 3H, J=7 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.41 (t, 2H, J=7 Hz, $C≡CCH_2$), 7.08-8.06 (m, 4H, C_6H_4); IR (neat) 2230 (C C) cm^{-1}. This compound was reduced using the procedure of Schofield and Swain (152) for the reduction of 2-nitrodiphenylacetylene to provide 2-(1-pentynyl)aniline (60c): yield 38%; bp 170-173°C (17 mm Hg); ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, J=6 Hz, CH_3), 1.59 (m, 2H, CH_2), 2.40 (t, 2H, J=6 Hz, $C≡CCH_2$), 4.10 (br s, 2H, NH_2), 6.39-7.29 (m, 4H, C_6H_4); IR (neat) 3490 (NH), 3400 (NH), 2240 (C≡C) cm^{-1}; mass spectrum m/z 159.10443 (calcd for $C_{11}H_{13}N$, 159.10480).

N-Acetyl-N-methyl-2-(1-pentynyl)aniline (60d): yield 29%; isolated by column chromatography using hexanes-ethyl acetate (2:1) as the eluent (R_f 0.25); ^1H NMR ($CDCl_3$) δ 1.01 (t, 3H, J=7 Hz, CH_3), 1.60 (m, 2H, CH_2), 1.82 (s, 3H, $NCOCH_3$), 2.42 (t, 2H, J=7 Hz, $C≡CCH_2$), 3.23 (s, 3H, NCH_3), 6.92-7.62 (m, 4H, C_6H_4); IR (neat) 2220 (C≡C), 1655 (C=O) cm^{-1}; mass spectrum m/z 215.13056 (calcd for $C_{14}H_{17}NO$, 215.13102). This reaction also produced 1-acetyl-2-propylindole (63): yield 32%; mp 68-71°C; ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7 Hz, CH_3), 1.65 (m, 2H, CH_2), 2.73 (s, 3H, $NCOCH_3$), 2.97 (t, 2H, J=7 Hz, $C=CCH_2$), 6.40 (s, 1H, H-3), 6.90-7.90 (m, 4H, C_6H_4); IR (film) 1660 (C=O) cm^{-1}; mass spectrum m/z 201.11607 (calcd

for $C_{13}H_{15}NO$, 201.11537).

Methyl 2-(1-pentynyl)benzyl ether (67): yield 80%; isolated by column chromatography using hexanes-ethyl acetate (10:1) as the eluent (R_f 0.41); ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H, J=7 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.42 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 3.42 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2O), 6.91-7.52 (m, 4H, C_6H_4); IR (neat) 2240 ($C{\equiv}C$) cm^{-1}; mass spectrum m/z 188.12038 (calcd for $C_{13}H_{16}O$, 188.12012).

Methyl 4-methyl-2-(1-pentynyl)phenylacetate (68): yield 50%; isolated by column chromatography using hexanes-ethyl acetate (5:1) as the eluent (R_f 0.42); ^1H NMR ($CDCl_3$) δ 1.05 (t, 3H, J=7 Hz, CH_3), 1.62 (m, 2H, CH_2), 2.30 (s, 3H, $ArCH_3$), 2.41 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 3.70 (s, 3H, OCH_3), 3.78 (s, 2H, $ArCH_2$), 7.04-7.41 (m, 3H, C_6H_3); IR (neat) 2210 ($C{\equiv}C$), 1730 (C=O) cm^{-1}; mass spectrum m/z 230.13020 (calcd for $C_{15}H_{18}O_2$, 230.13068).

Methyl β-(4-methyl-2-(1-pentynyl))phenethyl ether (69): yield 63%; isolated by column chromatography using hexanes-ethyl acetate (10:1) as the eluent (R_f 0.37); ^1H NMR ($CDCl_3$) δ 1.03 (t, 3H, J=7 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.21 (s, 3H, $ArCH_3$), 2.36 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 2.91 (t, 2H, J=7 Hz, $ArCH_2$), 3.30 (s, 3H, OCH_3), 3.55 (t, 2H, J=7 Hz, CH_2O), 6.89-7.25 (m, 3H, C_6H_3); IR (neat) 2210 ($C{\equiv}C$) cm^{-1}; mass spectrum m/z 216.15131 (calcd for $C_{15}H_{20}O$, 216.15142).

1-(3-Cyclohexenyl)-2-(2-anisyl)acetylene (17). In a flame-dried 50 mL round-bottom flask with a septum inlet was placed 3.0 g (10.3 mmol) of 1-(2-anisyl)-2,2-dibromoethylene (prepared from 2-anisaldehyde using the procedure of Rameriz, Desai and McKelvie (153)) in 25 mL of dry

tetrahydrofuran. The solution was cooled to -78°C and 10.8 mL of 2.2 M n-butyllithium (23.76 mmol) was added dropwise. The resulting solution was stirred at -78°C for 1 h, then warmed to room temperature and stirred for 45 min. The reaction mixture was cooled back down to -78°C, and 2.45 g (15.2 mmol) of 3-bromocyclohexene and 1.0 g (5.25 mmol) of cuprous iodide were added. The solution was allowed to warm to room temperature and stirred overnight, followed by acidification with 10% hydrochloric acid. The reaction mixture was extracted with 2 x 30 mL of ether, and the ether extracts were washed with 3 x 30 mL of saturated ammonium chloride, dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography using hexanes-ethyl acetate (20:1) as the eluent to yield 1.10 g (5.19 mmol, 50%) of the desired acetylene (R_f 0.25): ^1H NMR ($CDCl_3$) δ 1.41-2.29 (m, 6H, C_3H_6), 3.31 (m, 1H, C≡CCH), 3.80 (s, 3H, OCH_3), 5.75 (s, 2H, CH=CH), 6.59-7.48 (m, 4H, C_6H_4); IR (neat) 2220 (C≡C) cm^{-1}; mass spectrum m/z 212.12036 (calcd for $C_{15}H_{16}O$, 212.12012).

2,2'-Dimethoxydiphenylacetylene (18). In a 100 mL round-bottom flask, 13.6 g (100 mmol) of 2-anisaldehyde and 1.38 g (21.2 mmol) of potassium cyanide were refluxed for 4 h in 25 mL of 50% ethanol. The reaction mixture was cooled to room temperature and placed in the freezer. The solid was filtered, washed with 50% ethanol, and recrystallized from ether to provide 5.74 g (21.1 mmol, 42%) of 2,2'-dimethoxybenzoin (23): mp 97-99°C (lit. (67) mp 101.5°C); ^1H NMR ($CDCl_3$) δ 3.70 (s, 6H, OCH_3), 4.45 (d, 1H, J=6 Hz, OH), 6.05 (d, 1H, J=6 Hz, -CHO-), 6.60-7.70 (m, 8H, C_6H_4). In a 100 mL round-bottom flask fitted with a reflux condenser, 5.50 g (20.22 mmol) of the benzoin

compound and 10.0 g (40.05 mmol) of copper (II) sulfate pentahydrate were refluxed in 12 mL of pyridine with 4 mL of water for approximately 2 h. After refluxing, the solution was allowed to cool and poured into 100 mL of water. The water was extracted with 3 x 75 mL of ether, and the ether extracts were washed with 1 x 25 mL of 10% hydrochloric acid and 2 x 25 mL of water, dried ($MgSO_4$) and concentrated. The solid residue was recrystallized from 80% ethanol to provide 3.48 g (12.89 mmol, 64%) of 2,2'-dimethoxybenzil (24): mp 128-129°C (lit. (68) mp 128-129°C); ^1H NMR ($CDCl_3$) δ 3.6 (s, 3H, OCH_3), 6.91-8.29 (m, 4H, C_6H_4). The benzil derivative was refluxed for 60 h with 2.04 g (34.6 mmol) of 85% hydrazine hydrate in 12 mL of n-propyl alcohol to provide 1.92 g (6.44 mmol, 50%) of 2,2'-dimethoxybenzil dihydrazone (25): mp 232-234°C (dec) (lit. (69) mp ~230°C (dec)); ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H, OCH_3), 5.25 (br s, 2H, NH_2), 6.80-7.51 (m, 4H, C_6H_4). The dihydrazone was refluxed with 3.43 g (15.84 mmol) of yellow mercuric oxide in 10 mL of xylenes for 2 h. The hot solution was filtered through Celite and the Celite was washed with 30 mL of hot benzene. The filtrate was dried ($MgSO_4$) and the solvent was removed by vacuum. The crude solid was chromatographed through 10 g of silica gel using hexanes-ethyl acetate (4:1) as the eluent to isolate the crude acetylene (R_f 0.31). The solid was recrystallized from 85% ethanol to yield 0.252 g (1.066 mmol, 17%) of 2,2'-dimethoxydiphenylacetylene (18): mp 124-126°C (lit. (69) mp 126°C); ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.79-7.70 (m, 4H, C_6H_4).

1-(2-Anisyl)-2-hexyn-1-one (42). In a flame-dried 100 mL round-bottom flask under a nitrogen atmosphere was added 2.07 g (30.4 mmol) of

1-pentyne in 45 mL of dry tetrahydrofuran. The solution was cooled to -78°C, and 12.5 mL of 2.42 M n-butyllithium (30.3 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 10 min and at room temperature for 30 min. After cooling to -78°C, a solution of 4.07 g (30.0 mmol) of 2-anisaldehyde in 15 mL of tetrahydrofuran was added dropwise. The reaction mixture was stirred at -78°C for 10 min and at room temperature for 1 h, acidified with 10% hydrochloric acid and extracted with 2 x 50 mL of ether. The organic layers were washed with 2 x 50 mL of saturated sodium bicarbonate and 2 x 50 mL of water, dried ($MgSO_4$) and concentrated to give 4.60 g (22.5 mmol, 75%) of the crude alcohol. The crude alcohol was treated with 6 mL of 4 M Jones reagent (24 mmol) in 30 mL of acetone at 0°C for 30 min. The reaction mixture was poured into 200 mL of water and extracted with 2 x 100 mL of ether. The ether extracts were washed with 2 x 50 mL of water, 2 x 50 mL of saturated sodium bicarbonate and 2 x 50 mL of brine, dried ($MgSO_4$) and concentrated. The crude concentrate was purified by column chromatography using hexanes-ethyl acetate (5:1) as the eluent to provide 4.25 g (21.04 mmol, 70% for two steps) of the desired acetylene 42 (R_f 0.30): ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, J=7 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.41 (t, 2H, J=7 Hz, $C{\equiv}CCH_2$), 3.90 (s, 3H, OCH_3), 6.87-8.18 (m, 4H, C_6H_4); IR (neat) 2210 (C≡C), 1640 (C=O) cm^{-1}; mass spectrum m/z 202.09888 (calcd for $C_{13}H_{14}O_2$, 202.09938).

1-(2-Anisyl)-3-phenyl-2-propyn-1-one (43). In a 25 mL round-bottom flask, 3.04 g (20.0 mmol) of 2-anisic acid and 3.60 g (30.3 mmol) of thionyl chloride were refluxed for 30 min. The excess thionyl chloride

was then removed under vacuum. In a 100 mL round-bottom flask under nitrogen was added 2.68 (20.0 mmol) of lithium iodide in 10 mL of dry ether to a suspension of 3.3 g (20.1 mmol) of cuprous phenylacetylide in 20 mL of dry ether. The acid chloride was added to this suspension via a double-ended needle, and the reaction mixture was stirred at room temperature for 1 h. To the mixture, 7 mL of hexamethylphosphoramide was added and stirring was continued for 20 h. The reaction mixture was treated with 10% hydrochloric acid, poured into 100 mL of water and extracted with 3 x 75 mL of ether. The ether extracts were washed with 2 x 50 mL of saturated ammonium chloride, 2 x 50 mL of saturated sodium bicarbonate, 1 x 50 mL of 5% sodium hydroxide and 2 x 50 mL of water, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography using hexanes-ethyl acetate (3:1) as the eluent provided 2.20 g (9.32 mmol, 47%), of the acetylene (R_f 0.30): ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.85-8.05 (m, 9H, C_6H_5); IR (neat) 2200 (C≡C), 1630 (C=O) cm^{-1}; mass spectrum m/z 236.08358 (calcd for $C_{16}H_{12}O_2$, 236.08373).

1-(2-Anisyl)-2-hexyne (66). To a -78°C solution of 1.70 g (25.0 mmol) of 1-pentyne in 50 mL of dry tetrahydrofuran was slowly added 11.85 mL of 2.11 M n-butyllithium (25.0 mmol). The mixture was stirred at -78°C for 10 min and at room temperature for 1 h. Then, the solution was cooled back to -78°C and 4.40 g (21.9 mmol) of 2-methoxybenzyl bromide was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 d at room temperature. Ether was added and the mixture was then washed with 3 x 50 mL of brine, dried ($MgSO_4$) and concentrated. The concentrate was distilled to provide 3.52 g (18.7

mmol, 85%) of the acetylene 66: bp 156-160°C (16 mm Hg); ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J=6 Hz, CH_3), 1.52 (m, 2H, CH_2), 2.2 (m, 2H, C≡CCH_2), 3.48 (br s, 2H, $ArCH_2$), 3.81 (s, 3H, OCH_3), 6.65-7.50 (m, 4H, C_6H_4); IR (neat) 2220 (C≡C) cm^{-1}; mass spectrum m/z 188.12030 (calcd for $C_{13}H_{16}O$, 188.12012).

The following compound was prepared in identical fashion, 1-(3-anisyl)-2-hexyne (77a): yield 38%; isolated by column chromatography using hexanes-ethyl acetate (10:1) as the eluent (R_f 0.46); ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J=7 Hz, CH_3), 1.55 (m, 2H, CH_2), 2.23 (m, 2H, C≡CCH_2), 3.54 (t, 2H, J=2 Hz, $ArCH_2$), 3.80 (s, 3H, OCH_3), 6.63-7.40 (m, 4H, C_6H_4); IR (neat) 2220 (C≡C) cm^{-1}.

2-Butynyl phenyl ether (74). In a flame-dried 100 mL round-bottom flask was placed 0.240 g (10.0 mmol) of sodium hydride (hexanes washed and vacuum dried) in 20 mL of dry tetrahydrofuran. To the suspension, 0.940 g (10.0 mmoles) of phenol was added under a nitrogen sweep, and the resulting mixture was stirred for 30 min. Then, 1.80 g (10 mmol) of 1-iodo-2-butyne was added dropwise, and the reaction mixture was stirred overnight at room temperature, acidified with 10% hydrochloric acid and extracted with 3 x 25 mL of ether. The ether extracts were washed with 40 mL of brine, 40 mL of 10% sodium hydroxide, 40 mL of saturated sodium bicarbonate, and 60 mL of brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography yielded 1.44 g (9.86 mmol, 100%) of the desired ether 74 (hexanes-ethyl acetate (15:1), R_f 0.36): ^{1}H NMR ($CDCl_3$) δ 1.82 (t, 3H, J=2 Hz, CH_3), 4.60 (q, 2H, J=2 Hz, CH_2), 6.75-7.47 (m, 5H, C_6H_5); IR (neat) 2210 (C≡C) cm^{-1}; mass spectrum

m/z 146.07332 (calcd for $C_{10}H_{10}O$, 146.07317).

1-(3-Anisyl)-3-heptyne (77b). The acetylene was prepared using the procedure of Suzuki and co-workers for the preparation of acetylenes from trialkylboranes (116). In a dry 100 mL round-bottom flask under nitrogen was placed 4 mL of 1 M borane-tetrahydrofuran (4 mmol) in 5 mL of dry tetrahydrofuran. The solution was cooled to 0°C and 1.60 g (11.94 mmol) of 3-methoxystyrene (154), prepared from 3-methoxybenzyltriphenylphosphonium bromide and aqueous formaldehyde (155), in 5 mL of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred at 0°C for 1 h and at room temperature for 1 h. Then, the solution was cooled back down to 0°C and 5 mmol of preformed 1-lithio-1-pentyne was added by a double-ended needle. The reaction mixture was warmed to room temperature and stirred for 2 h. Then, the solution was cooled to -78°C and 1.27 g (5.0 mmol) of iodine in 25 mL of dry tetrahydrofuran (or ether) was slowly added. The mixture was stirred at -78°C for 30 min and at room temperature for 1 h. The crude reaction mixture was washed with 2 x 20 mL of 3 N sodium hydroxide (containing 1-2 ml of saturated sodium thiosulfate) and the aqueous washes were combined and re-extracted with 25 mL of ether. The etheral layers were combined and treated with 12 mL of 3 N sodium hydroxide followed by 4 mL of 30% hydrogen peroxide. The resulting aqueous layer was saturated with potassium carbonate and removed. The organic phase was washed with 20 mL of saturated sodium bicarbonate and 30 mL of brine, dried ($MgSO_4$) and concentrated. The desired product was isolated by first distilling off the volatile components (1-iodo-1-pentyne) followed by column chromatography using

hexanes-ethyl acetate (15:1) as the eluent (R_f 0.40): yield 0.580 g (2.87 mmol, 72% based on BH_3); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=6 Hz, CH_3), 1.48 (m, 2H, CH_2), 2.00-2.46 (m, 4H, $CH_2C{\equiv}CCH_2$), 2.65 (t, 2H, J=7 Hz $ArCH_2$), 3.78 (s, 3H, OCH_3), 6.61-6.89 (m, 3H, H-2, H-4, H6), 7.12 (d, 1H, J=8 Hz, H-5); IR (neat) 2210 (C≡C) cm^{-1}; mass spectrum m/z 202.13551 (calcd for $C_{14}H_{18}O$, 202.13577).

The acetylenes 77c and 80 were prepared in the same manner starting with 3-allylanisole (156) and styrene, respectively.

1-(3-Anisyl)-4-octyne (77c): yield 86% based on BH_3; isolated by column chromatography using hexanes-ethyl acetate (15:1), R_f 0.42; ^1H NMR ($CDCl_3$) δ 1.01 (t, 3H, J=7 Hz, CH_3), 1.15-1.90 (m, 4H, CH_2), 1.99-2.32 (m, 4H, $C{\equiv}CCH_2$), 2.68 (t, 2H, J=7 Hz, $ArCH_2$), 3.77 (s, 3H, OCH_3), 6.55-7.01 (m, 3H, H-2, H-4, H-6), 7.50 (d, 1H, J=8 Hz, H-5); IR (neat) 2215 (C≡C) cm^{-1}.

1-Phenyl-3-heptyne (80): yield 100% based on BH_3; isolated by column chromatography using hexanes-ethyl acetate (20:1), R_f 0.45; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=7 Hz, CH_3), 1.50 (m, 2H, CH_2), 1.97-2.44 (m, 4H, $C{\equiv}CCH_2$), 2.79 (t, 2H, J=6 Hz, $ArCH_2$), 7.26 (m, 5H, C_6H_5); IR (neat) 2200 (C≡C) cm^{-1}.

1-(2-Anisyl)-1-hexyn-3-one (99). To a -78°C solution of 3.0 g (10.27 mmol) of 1-(2-anisyl)-2,2-dibromoethylene in 25 mL of dry tetrahydrofuran was added 11.0 mL of 1.9 M n-butyllithium (20.9 mmol). The solution was stirred at -78°C for 30 min and at room temperature for 1 h. Then, the solution was cooled back down to -78°C and 0.80 g (13.77 mmol) of freshly distilled propionaldehyde was added. The reaction

mixture was allowed to slowly warm to room temperature and stirred overnight at room temperature, followed by acidification with 10% hydrochloric acid and extraction with 2 x 30 mL of ether. The ether extracts were washed with saturated ammonium chloride, dried ($MgSO_4$) and concentrated to provide crude 1-(2-anisyl)-3-hydroxy-1-hexyne in 64% yield: ^1H NMR ($CDCl_3$) δ 1.05 (t, 3H, J=7 Hz, CH_3), 1.80 (m, 2H, CH_2), 2.75 (br s, 1H, OH), 3.88 (s 3H, OCH_3), 4.56 (t, 1H, J=7 Hz, CHOH), 6.75-7.59 (m, 4H, C_6H_4). The alcohol was oxidized with Jones reagent in acetone to provide 0.936 g (4.98 mmol, 49% for the two steps) of the acetylenic ketone 99 after purification by column chromatography (hexanes-ethyl acetate (5:1), R_f 0.28); ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H, J=7 Hz, CH_3), 2.66 (q, 2H, J=7 Hz, CH_2), 3.88 (s, 3H, OCH_3), 6.75-7.89 (m, 4H, C_6H_4); IR (neat) 2200 (C≡C), 1670 (C=O) cm^{-1}; mass spectrum m/z 188.08364 (calcd for $C_{12}H_{12}O_2$, 188.08373).

1-(2-t-Butyldimethylsilyloxyphenyl)-1-propyne (100). This compound was prepared by alkylation of the corresponding gem-dibromoolefin with dimethyl sulfate using the procedure described above: yield 68%; isolated by column chromatography using hexanes + 2% ethyl acetate as the eluent (R_f 0.32); ^1H NMR ($CDCl_3$) δ 0.25 (s, 6H, $SiCH_3$), 1.02 (s, 9H, t-C_4H_9Si), 2.01 (s, 3H, CH_3), 6.59-7.45 (m, 4H, C_6H_4); IR (neat) 2240 (C≡C) cm^{-1}; mass spectrum m/z 246.14373 (calcd for $C_{15}H_{22}OSi$, 246.14400).

Preparation of organomercurials. Most of the acetylene mercuration reactions were performed under the same conditions. The following preparation of 3-chloromercuri-2-propylbenzofuran (2) is representative. To a suspension of 0.637 g (2.0 mmol) of mercuric

acetate in 6 mL of glacial acetic acid at room temperature was added 0.350 g (2.0 mmol) of 2-(1-pentynyl)anisole (1). The resulting solution was stirred at room temperature for 30 min, then poured into a saturated sodium chloride-ice mixture and allowed to warm to room temperature. The solid was collected by filtration, washed with hexanes and dissolved in hot chloroform. The chloroform solution was filtered through Celite, and the crude mercury compound was isolated by evaporation of the chloroform. The solid was recrystallized from 90% ethanol to yield 0.551 g (1.4 mmol, 70%) of 3-chloromercuri-2-propylbenzofuran (2): mp 119-120°C; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, J=7 Hz, CH_3), 1.73 (m, 2H, CH_2), 2.84 (t, 2H, J=7 Hz, $C=CCH_2$), 7.09-7.70 (m, 4H, C_6H_4), IR ($CHCl_3$), 3030 (C=CH), 1580 (C=C) cm^{-1}. Anal. Calcd for $C_{11}H_{11}ClHgO$: C, 33.43; H, 2.81; Hg, 50.75. Found: C, 33.47; H, 2.92; Hg, 50.93. The following mercurials were prepared in an identical fashion.

3-Chloromercuri-5-methoxy-2-propylbenzofuran (19): yield 60%; mp 147-148°C; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, J=7 Hz, CH_3), 1.73 (m, 2H, CH_2), 2.75 (t, 2H, J=7 Hz, $C=CCH_2$), 3.85 (s, 3H, OCH_3), 6.80-7.20 (m, 3H, C_6H_3); IR (nujol) 3010 (C=CH), 1600 (C=C) cm^{-1}. Anal. Calcd for $C_{12}H_{13}ClHgO_2$: C, 33.89; H, 3.08; Hg, 47.17. Found: C, 33.63; H, 3.04; Hg, 47.31.

3-Chloromercuri-5-nitro-2-propylbenzofuran (20): yield 45%; mp 116-118°C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J=7 Hz, CH_3), 1.72 (m, 2H, CH_2), 2.81 (t, 2H, J=7 Hz, $C=CH_2$), 7.40 (d, 1H, J=10 Hz, H-7), 8.11 (dd, 1H, J=10 Hz, J=3 Hz, H-6), 8.49 (d, 1H, J=3 Hz, H-4); IR (nujol) 3080 (C=CH), 1570 (C=C), 1510 (NO_2) cm^{-1}. Anal. Calcd for $C_{11}H_{10}ClHgNO_3$: C, 30.01;

H, 2.29; Hg, 45.56. Found: C, 30.22; H, 3.08; Hg, 45.32.

3-Chloromercuri-2-phenylbenzofuran (21): yield 59%; mp 205°C (dec); ^{1}H NMR ($CDCl_3$) δ 6.89-7.80 (m, Ar); IR (nujol) 3060 (C=CH), 3030 (C=CH), 1580 (C=C), cm^{-1}; Anal. Calcd for $C_{14}H_9ClHgO$: C, 39.17; H, 2.12; Hg, 46.73. Found: C, 39.26; H, 2.35; Hg, 46.94.

3-Chloromercuri-2-(3-cyclohexenyl)benzofuran (22): yield 30%; mp 123-125°C; ^{1}H NMR ($CDCl_3$) δ 1.40-2.32 (m, 6H, C_3H_6), 3.75 (m, 1H, C=CCH), 6.08 (m, 2H, HC=CH), 7.00-7.55 (m, 4H, C_6H_4); IR (nujol) 3060 (C=CH), 1600 (C=C), 1580 (C=C) cm^{-1}; Anal. Calcd for $C_{14}H_{13}ClHgO$: C, 38.81; H, 3.02; Hg, 46.29. Found: C, 38.53; H, 3.12; Hg, 46.37.

2-(2-Anisyl)-3-chloromercuribenzofuran (26): yield 58%; mp 205°C; ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H, OCH_3), 6.89-8.02 (m, 8H, C_6H_4); IR (nujol) 3010 (C=CH), 1600 (C=C), 1580 (C=C) cm^{-1}; Anal. Calcd for $C_{15}H_{11}ClHgO_2$: C, 39.21; H, 2.41; Hg, 43.69. Found: C, 39.39; H, 2.52; Hg, 43.84.

4-Chloromercuri-3-propylisocoumarin (44): yield 65%; mp 195-197°C; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, $\underline{J}$=7 Hz, CH_3), 1.69 (m, 2H, CH_2), 2.65 (t, 2H, $\underline{J}$=7 Hz, $C{=}CCH_2$), 7.10-8.19 (m, 4H, C_6H_4); IR (nujol) 3020 (C=CH), 1720 (C=O), 1610 (C=C) cm^{-1}; Anal. Calcd for $C_{12}H_{11}ClHgO_2$: C, 34.05; H, 2.62; Hg, 47.39. Found: C, 34.17; H, 2.75; Hg, 47.63.

3-Chloromercuri-2-propylchromone (45): yield 60%; mp 136-138°C; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, $\underline{J}$=7 Hz, CH_3), 1.89 (m, 2H, CH_2), 2.70 (t, 2H, $\underline{J}$=7 Hz, $C{=}CCH_2$), 7.02-8.21 (m, 4H, C_6H_4); IR (nujol) 3060 (C=CH), 1615 (C=O), 1600 (C=C), 1585 (C=C) cm^{-1}; Anal. Calcd for $C_{12}H_{11}ClHgO_2$: C, 34.05; H, 2.62; Hg, 47.39. Found: C, 33.84; H, 2.76; Hg, 47.16.

3-Chloromercuriflavone (46): yield 58%; mp 254-255°C; ^{1}H NMR

($CDCl_3$) δ 7.19-8.25 (m, 9H, Ar); IR (nujol) 3070 (C=CH), 1615 (C=O, C=C), 1555 (C=C) cm^{-1}; Anal. Calcd for $C_{15}H_9ClHgO_2$: C, 39.38; H, 1.98; Hg, 43.88. Found: C, 39.43; H, 2.10; Hg, 43.90.

3-Chloromercuri-2-propylbenzothiophene (54): yield 66%; mp 134-135°C; ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, J=6 Hz, CH_3), 1.69 (m, 2H, CH_2), 2.90 (t, 2H, J=7 Hz, $C=CCH_2$), 7.18-7.93 (m, 4H, C_6H_4); IR (nujol) 3015 (C=CH), 1600 (C=C) cm^{-1}; Anal. Calcd for $C_{11}H_{11}ClHgS$: C, 32.12; H, 2.70; Hg, 48.77. Found: C, 32.06; H, 2.75; Hg, 48.88.

The following mercurials were prepared in the same manner except that the reaction time was 20 h instead of 30 min.

Mercurial 70: yield 39%; mp 201-203°C; ^1H NMR ($CDCl_3$) δ 1.04 (t, 3H, J=7 Hz, CH_3), 1.65 (m, 2H, CH_2), 2.67 (t, 2H, J=7 Hz, $C=CCH_2$), 5.16 (s, 2H, CH_2O), 6.82-7.70 (m, 4H, C_6H_4); IR (nujol) 3060 (C=CH), 1600 (C=C), 1550, 1500 cm^{-1}; Anal. Calcd for $C_{12}H_{13}ClHgO$: C, 35.22; H, 3.20; Hg, 49.01. Found: C, 34.98; H, 3.02; Hg, 49.27.

Vinylmercurial 73: yield 44%; mp 104-105°C; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=6 Hz, CH_3), 1.52 (m, 2H, CH_2), 2.05 (s, 3H, $COCH_3$), 2.23 (s, 3H, $ArCH_3$), 2.27 (t, 2H, J=7 Hz, $C=CCH_2$), 2.86 (t, 2H, J=7 Hz, $ArCH_2$), 3.25 (s, 3H, OCH_3), 3.55 (t, 2H, J=7 Hz, CH_2O), 6.93-7.21 (m, 3H, C_6H_3); IR (nujol) 3020 (C=CH), 1740 (C=O), 1650 (C=C) cm^{-1}; Anal. Calcd for $C_{17}H_{23}ClHgO_3$: C, 39.93; H, 4.53; Hg, 39.22. Found: C, 40.01; H, 4.64; Hg, 39.46.

Vinylmercurial 101: yield 12%; mp 126-128°C; ^1H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7 Hz, CH_3), 2.19 (s, 3H, $COCH_3$), 2.76 (q, 2H, J=7 Hz, CH_2), 3.90 (s, 3H, OCH_3), 6.79-7.61 (m, 4H, C_6H_4); IR (film) 3060 (C=CH), 1740

(C=O), 1665 (C=O), 1600 (C=C) cm^{-1}. Anal. Calcd for $C_{14}H_{15}HgClO_4$: C, 34.79; H, 3.13; Hg, 41.50. Found: C, 34.28; H, 3.20; Hg, 41.12.

Vinylmercurials 102 and 103 (48 h reaction time): yield 66%; isolated by column chromatography using hexanes-ethyl acetate (5:1) as the eluent (both mercurials are thick oils). For 102: ^1H NMR ($CDCl_3$) δ 0.24 (s, 6H, $SiCH_3$), 1.03 (s, 9H, t-C_4H_9Si), 2.02 (s, 3H, $J_{^{199}Hg-CH_3}$=194 Hz, CH_3), 2.15 (s, 3H, $COCH_3$), 6.69-7.48 (m, 4H, C_6H_4); For 103: ^1H NMR ($CDCl_3$) δ 0.24 (s, 6H, $SiCH_3$), 1.03 (s, 9H, t-C_4H_9Si), 1.91 (s, 3H, $COCH_3$), 2.24 (s, 3H, CH_3), 6.69-7.48 (m, 4H, C_6H_4); IR (film) 3060, 2030 (C=CH), 1745 (C=O), 1600 (C=C) cm^{-1}; Anal. Calcd for $C_{17}H_{25}ClHgO_3Si$: C, 37.71; H, 4.65; Hg, 37.04. Found: C, 37.97; H, 4.74; Hg, 36.59.

3-Chloromercuri-4-methyl-2H-1-benzopyran (76). In a 25 mL round-bottom flask were placed 1.28 g (3.0 mmol) of mercuric trifluoroacetate and 0.360 g (9.0 mmol) of magnesium oxide in 6 mL of tetrahydrofuran. To the mixture was added 0.440 g (3.0 mmol) of 2-butynyl phenyl ether (74) in 3 mL of tetrahydrofuran. The reaction mixture was stirred at room temperature for 1 h, filtered through Celite, washed with 2 x 40 mL of brine, dried ($MgSO_4$) and concentrated. The concentrate was triturated with ether to give a yellowish solid which was recrystallized from dichloromethane-hexanes at -78°C to give 0.454 g (1.19 mmol, 40%) of mercurial 76: mp 220°C (dec); ^1H NMR (DMSO-d_6) δ 2.21 (br s, 3H, CH_3), 4.84 (br s, 2H, CH_2), 6.60-7.26 (m, 4H, C_6H_4); IR (nujol) 3070 (C=CH), 3040, 1600 (C=C) cm^{-1}; Anal. Calcd for $C_{10}H_9ClHgO$: C, 31.49; H, 2.36; Hg, 52.64. Found: C, 31.63; H, 2.50; Hg, 52.49.

3-Chloromercuri-7-methoxy-4-propyl-1,2-dihydronaphthalene (79). In

a 25 mL round-bottom flask were placed 0.430 g (1.0 mmol) of mercuric trifluoroacetate and 0.120 (3.0 mmol) of magnesium oxide in 2 mL of tetrahydrofuran. To this mixture, 0.20 g (1.0 mmol) of 1-(3-anisyl)-3-heptyne (77b) in 1 mL of tetrahydrofuran was added. The resulting mixture was stirred at room temperature for 10 h, filtered through Celite, washed with 2 x 40 mL of brine, dried ($MgSO_4$) and concentrated. The concentrate was purified by column chromatography using hexanes-ethyl acetate (10:1) as the eluent to provide 0.126 g (0.62 mmol, 62%) of the starting acetylene and 0.130 g (0.30 mmol, 30%) of mercurial 79 (R_f 0.20): mp 126-128°C; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=6 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.29-2.92 (m, 6H, CH_2), 3.80 (s, 3H, OCH_3), 6.61-6.82 (m, 2H, H-6, H-8), 7.15 (d, 1H, J=8 Hz, H-5); IR (nujol) 3030 (C=CH), 3000, 1605 (C=C), 1590 (C=C) cm^{-1}; Anal. Calcd for $C_{14}H_{17}ClHgO$: C, 38.45; H, 3.92; Hg, 45.87. Found: C, 38.36; H, 4.00; Hg, 45.74.

3-Chloromercuri-1-methyl-2-propylindole (64). This reaction was performed using the procedure of Yudin, Kost and Pavlyuchenko (157) for the mercuration of substituted indoles. In a 250 mL round-bottom flask were placed 1.18 g (4.35 mmol) of mercuric chloride and 2.36 g (17.35 mmol) of sodium acetate in 130 mL of methanol. Then, 0.750 g (4.34 mmol) of 1-methyl-2-propylindole in 20 mL of methanol was added, and the mixture was stirred for 5 h at room temperature. The solid was removed by filtration and the filtrate was poured into water, and the resulting precipitate was removed by filtration. The solids were combined, washed with water and ether and dried at 3 mm Hg for 1.5 h to yield 1.42 g (3.48 mmol, 80%) of the mercurated indole: mp 143-145°C; ^1H NMR ($CDCl_3$) δ 1.02

(t, 3H, J=7 Hz, CH_3), 1.61 (m, 2H, CH_2), 2.68 (t, 2H, J=7 Hz, $C=CCH_2$), 3.56 (s, 3H, NCH_3), 6.79-7.52 (m, 4H, C_6H_4); IR (nujol) 3040 (C=CH), 1600 (C=C) cm^{-1}; Anal. Calcd for $C_{12}H_{14}ClHgN$: C, 35.30; H, 3.46; Hg, 49.13. Found: C, 35.43; H, 3.53; Hg, 49.35.

Reactions of organomercurials: 2-Propylbenzofuran (83). This compound was prepared from mercurial 2 using the conditions of Brown and Hammar (117) for the reduction of organomercurials. In a 25 mL round-bottom flask was placed 0.199 g (0.50 mmol) of 2 in 4 mL of a 1:1 tetrahydrofuran-water mixture. To this solution, 2 mL of 3 M sodium hydroxide and 4 mL of 0.5 M sodium borohydride in 3 M sodium hydroxide were added, and the resulting mixture was stirred for 1 h. Sodium chloride was added to saturate the water layer, and the mixture was filtered through Celite, extracted with 2 x 25 mL of ether, dried ($MgSO_4$) and concentrated. Bulb to bulb distillation of the concentrate at 125-130°C (16 mm Hg) provided 72 mg (0.45 mmol, 90%) of 2-propylbenzofuran (lit. (158) bp 107-110°C (12.5 mm Hg)): ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, J=7 Hz, CH_3), 1.70 (m, 2H, CH_2), 2.81 (t, 2H, J=7 Hz, $C=CCH_2$), 6.28 (s, 1H, H-3), 7.01-7.60 (m, 4H, C_6H_4); IR (neat) 3010, 1600 (C=C), 1550 (C=C) cm^{-1}; mass spectrum m/z 160.08888 (calcd for $C_{11}H_{12}O$, 160.08882).

The following compounds were prepared in an identical manner in order to determine the structure of the cyclized compound. Only the pertinent spectral data will be listed here.

3-Propylisocoumarin: ^1H NMR ($CDCl_3$) δ 1.01 (t, 3H, J=7 Hz, CH_3), 1.69 (m, 2H, CH_2), 2.67 (t, 2H, J=7 Hz, $C=CCH_2$), 6.21 (s, 1H, H-4), 7.11-8.20 (m, 4H, C_6H_4); IR (neat) 1725 (C=O), 1655 (C=C), 1610 (C=C) cm^{-1};

GC/MS m/z (relative intensity) 188 (48, M^+), 159 (15), 131 (59), 118 (100), 89 (100).

4-Methyl-2H-1-benzopyran: ^1H NMR ($CDCl_3$) δ 2.35 (br s, 3H, CH_3), 4.63 (d, 2H, J=6 Hz, CH_2), 5.96 (t, 1H, J=6 Hz, H-3), 6.75-7.50 (m, 4H, C_6H_4) (decoupling: irradiation at δ 4.63 causes δ 5.96 to collapse to a br s; irradiation at δ 5.96 causes δ 4.63 to collapse to a br s, but 2.35 remains the same; irradiation at δ 2.35 causes both δ 4.63 and δ 5.96 to sharpen, but their respective multiplicity remains the same); IR (neat) 1600 (C=C) cm^{-1}; GC/MS m/z (relative intensity) 146 (70, M^+), 145 (77), 131 (100).

7-Methoxy-4-propyl-1,2-dihydronaphthalene (84): ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=6 Hz, CH_3), 1.62 (m, 2H, CH_2), 2.29-2.94 (m, 6H, CH_2), 3.79 (s, 3H, OCH_3), 5.67 (br s, 1H, H-3), 6.56-6.83 (m, 2H, H-6, H-8), 7.16 (d, 1H, J=8.5 Hz); IR (neat) 1605 (C=C) cm^{-1}; GC/MS m/z (relative intensity) 202 (50, M^+), 187 (5), 174 (54), 159 (100), 144 (31).

3-Iodo-2-propylbenzofuran (86). The iodination of 2 was performed using the procedure of Whitmore and Hanson (159) for the iodination of 2-chloromercuriphenol. In a 25 mL round-bottom flask was stirred 0.395 g (1.0 mmol) of 2 in 5 mL of chloroform. Then, 0.254 g (1.0 mmol) of iodine in 5 mL of chloroform was added and the resulting mixture was stirred for 3 h, filtered through Celite, washed with aqueous sodium iodide (5 g/40 mL of water) and dried (Na_2SO_4). Removal of the chloroform yielded a yellowish oil which was purified by column chromatography using hexanes as the eluent to furnish 0.215 g (0.75 mmol, 75%) of the iodo compound (R_f 0.45): ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H, J=7

Hz, CH_3), 1.80 (m, 2H, CH_2), 2.89 (t, 2H, J=7 Hz, $C=CCH_2$), 7.20-7.62 (m, 4H, C_6H_4); IR (neat) 3070 (C=CH), 1590 (C=C) cm^{-1}; mass spectrus m/z 285.98514 (calcd for $C_{11}H_{11}IO$, 285.98547).

The following iodo compound was prepared using an identical procedure, 3-iodo-2-propylchromone (87): yield 93%; isolated by column chromatography (hexanes-ethyl acetate (2:1), R_f 0.50); ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, J=7 Hz, CH_3), 1.89 (m, 2H, CH_2), 2.78 (t, 2H, J=7 Hz, $C=CCH_2$), 7.03-8.20 (m, 4H, C_6H_4); IR (neat) 1615 (C=O), 1600 (C=C) cm^{-1}; mass spectrum m/z 313.98051 (calcd for $C_{12}H_{11}IO_2$, 313.98038).

3-Acetyl-2-propylbenzofuran (88). The acylation of 2 was accomplished using the experimental procedure described by Larock and Bernhardt (119) for the acylation of alkenylmercurials. To a mixture of 0.135 g (1.0 mmol) of anhydrous aluminum trichloride and 0.080 g (1.0 mmol) of acetyl chloride in 10 mL of dry dichloromethane was added 0.395 g (1.0 mmol) of 2. The resulting mixture was stirred at room temperature for 15 min, poured into 30 mL of water and extracted with dichloromethane. The combined dichloromethane extracts were washed with 20 mL of 5% sodium bicarbonate, 20 mL of 3 M sodium thiosulfate and 30 mL of water. All the aqueous layers were combined and re-extracted with 2 x 30 mL of dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated. Bulb to bulb distillation produced 0.152 g (0.75 mmol, 75%) of the title compound: bp 123-127°C (0.05 mm Hg); ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, J=7 Hz, CH_3), 1.69 (m, 2H, CH_2), 2.61 (s, 3H, $COCH_3$), 3.08 (t, 2H, J=7 Hz, $C=CCH_2$), 7.08-8.03 (m, 4H, C_6H_4); IR (neat) 1675 (C=O), 1560 (C=C) cm^{-1}; mass spectrum m/z 202.09933 (calcd for

$C_{13}H_{14}O_2$, 202.09938). 2,4-DNP derivate: mp 165-167°C; mass spectrum m/z 382.12627 (calcd for $C_{19}H_{18}N_4O_5$, 382.12773).

Ester 89. This compound was prepared using the procedure of Heck (120). In a 25 mL round-bottom flask was stirred 0.395 g (1.0 mmol) of 2 and 0.354 g (4.1 mmol) of methyl acrylate in 7 mL of dry acetonitrile. After stirring for a short time, a solution of lithium tetrachloropalladite (1 mmol) in 7 mL of dry acetonitrile was added, and the reaction mixture was stirred at room temperature for 24 h. Then, ether and activated carbon were added, and the mixture was filtered through Celite. The filtrate was washed with 2 x 25 mL of saturated ammonium chloride, dried ($MgSO_4$) and concentrated. Bulb to bulb distillation at 200-205°C (0.025 mm Hg) provided 0.159 g (0.65 mmol, 65%) of the desired unsaturated ester 89: ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, J=7 Hz, CH_3), 1.79 (m, 2H, CH_2), 2.92 (t, 2H, J=7 Hz, $C=CCH_2$), 3.90 (s, 3H, OCH_3), 6.51 (d, 1H, J=17 Hz, C=CH), 7.09-7.62 (m, 4H, C_6H_4), 7.85 (d, 1H, J=17 Hz, HC=C); IR (neat) 1720 (C=O), 1635 (C=C), 1580 (C=C) cm^{-1}; mass spectrum m/z 244.10974 (calcd for $C_{15}H_{16}O_3$, 244.10995).

3-Carbomethoxy-2-propylbenzofuran (90). The preparation of this compound was accomplished using the procedure of Larock (121) for the carbonylation of organomercurials. In a 50 mL round-bottom flask were stirred 0.045 g (1.1 mmol) of anhydrous lithium chloride, 0.088 g (0.50 mmol) of palladium chloride and 0.040 g (1.0 mmol) of magnesium oxide in 6 mL of dry methyl alcohol. After stirring for a short time, the contents of the flask were cooled to -78°C. While the system was being flushed with carbon monoxide at -78°C, 0.198 g (0.50 mmol) of 2 was

added. A balloon filled with carbon monoxide was connected to the top of the flask, and the reaction mixture was allowed to slowly warm to room temperature and then stirred at room temperature overnight. Activated carbon was added and the reaction mixture was diluted with ether, filtered through Celite, washed with saturated ammonium chloride, dried ($MgSO_4$) and concentrated. The concentrate was purified by column chromatography using hexanes-ethyl acetate (10:1) as the eluent to provide 0.097 g (0.445 mmol, 89%) of 3-carbomethoxy-2-propylbenzofuran (90) (R_f 0.33): ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H, $\underline{J}$=7 Hz, CH_3), 1.71 (m, 2H, CH_2), 3.02 (t, 2H, $\underline{J}$=7 Hz, $C{=}CCH_2$), 3.89 (s, 3H, OCH_3), 7.02-7.91 (m, 4H, C_6H_4); IR (neat) 1715 (C=O), 1560 (C=C) cm^{-1}; mass spectrum m/z 218.09411 (calcd for $C_{13}H_{14}O_3$, 218.09430).

The following esters were prepared in an identical fashion.

2-(2-Anisyl)-3-carbomethoxybenzofuran: yield 100%; isolated by column chromatography using hexanes-ethyl acetate (4:1) as the eluent (R_f 0.30); ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H, OCH_3), 3.80 (s 3H, OCH_3), 6.91-7.75 (m, 7H, Ar), 7.95-8.20 (m, 1H, H-4); IR (neat) 1715 (C=O), 1600 (C=C) cm^{-1}; mass spectrum m/z 282.08838 (calcd for $C_{17}H_{14}O_4$, 282.08921).

Vinyl ester 104 (three-day reaction time): yield 70%; isolated by column chromatography using hexanes-ethyl acetate (5:1) as the eluent (R_f 0.40); ^1H NMR ($CDCl_3$) δ 0.18 (s, 6H, $SiCH_3$), 0.98 (s, 9H, $\underline{t}$-C_4H_9Si), 1.94 (s, 3H, CH_3), 2.14 (s, 3H, $COCH_3$), 3.49 (s, 3H, OCH_3), 6.67-7.30 (m, 4H, C_6H_4); IR (neat) 1745 (C=O), 1720 (C=O), 1600 (C=C) cm^{-1}; mass spectrum (M^+-$\underline{t}$-C_4H_9) m/z 307.10118 (calcd for $C_{15}H_{19}O_5Si$, 307.10018).

6H-Benzofuro(3,2-c)(1)-benzopyran-6-one(coumestan) (91). The

cyclization of 2-(2-anisyl)-3-carbomethoxybenzofuran was performed under the conditions of Ho and Olah (160) for the demethylation of esters and ethers. In a 25 mL round-bottom flask, 0.130 g (0.87 mmol) of phenyltrimethylsilane, 0.08 g (0.28 mmol) of the ester, and 0.216 g (0.85 mmol) of iodine were heated at 110°C for a period of 3 h. Then, the reaction mixture was quenched by the addition of water and extracted with 2 x 50 mL of ether. The ether extracts were washed with 2 x 20 mL of glacial acetic acid, 2 x 20 mL of saturated sodium bicarbonate and 1 x 50 mL of brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography using hexanes-ethyl acetate (4:1) as the eluent to give 0.059 g (0.25 mmol, 90%) of compound 91 (R_f 0.35): mp 179-181°C (lit. (161) mp 181-182°C); ^1H NMR ($CDCl_3$) δ 7.09-7.88 (m, 7H, Ar), 7.95-8.15 (m, 1H, H-7); IR (film) 1735 (C=O), 1625 (C=C), 1600 (C=C) cm^{-1}. ^1H NMR and IR spectral data are identical with that reported in the literature (161).

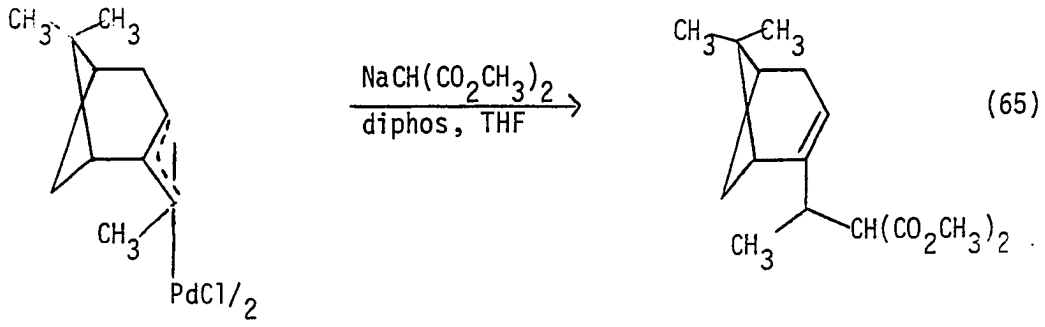
4-Acetoxy-3-methylcoumarin (105). In a 100 mL round-bottom flask was placed 0.325 g (0.89 mmol) of ester 104 in 6 mL of a mixture of 48% hydrofluoric acid:glacial acetic acid:tetrahydrofuran:water (1:3:1:1). The contents were heated at 55°C for 20 h, diluted with water and stirred with potassium carbonate for 1 h at room temperature. The reaction mixture was acidified with 10% hydrochloric acid, filtered through Celite, and the filtrate was extracted with 2 x 40 mL of ether. The ether extracts were washed with 20 mL of brine, 30 mL of dilute potassium hydroxide, 20 mL of saturated ammonium chloride and 40 mL of water, dried ($MgSO_4$) and concentrated. Isolation of the desired compound by column

chromatography (hexanes-ethyl acetate (2:1)) provided 0.138 g (0.633 mmol, 71%) of the coumarin 105: mp 149-151°C (lit. (162) mp 154°C); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3), 2.41 (s, 3H, $COCH_3$), 7.03-7.46 (m, 4H, C_6H_4); IR (nujol) 1750 (C=O), 1700 (C=O), 1640 (C=C), 1600 (C=C) cm^{-1}; mass spectrum m/z 218.05820 (Calcd for $C_{12}H_{10}O_4$, 218.05791). When the reaction was performed on a 7 mmol scale, compound 105 was isolated in 36% yield, and, upon acidification of the potassium hydroxide wash, the hydroxy compound 106 was also obtained in a 28% yield: mp 226-227°C (lit. (163) mp 226°C). The hydroxy compound can be acylated to provide 105.

PREPARATION OF HETEROCYCLES BY INTRAMOLECULAR NUCLEOPHILIC ATTACK ON A π-ALLYLPALLADIUM COMPOUND

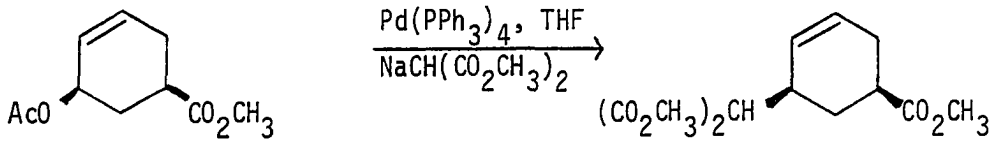
Introduction

There have been many examples of nucleophilic attack on π-allylpalladium complexes reported in the literature. The majority of these reactions involve the use of carbon nucleophiles to form new carbon-carbon bonds. Trost (164) and Tsuji (165) have found that various π-allylpalladium complexes can be alkylated with stabilized carbanions when the reaction is performed in the presence of strongly coordinating ligands such as phosphines (eq. 65).



(65)

Through the use of allylic acetates as the starting material, Trost (164) has developed an efficient catalytic system for the alkylation. The nucleophile attacks the π-allyl ligand on the face opposite the palladium. Since π-allylpalladium formation also proceeds with inversion, the product that results has a net retention of stereochemistry (eq. 66). By using an intramolecular reaction of this type, a novel method for the preparation of large ring lactones has been developed (166) (eq. 67).



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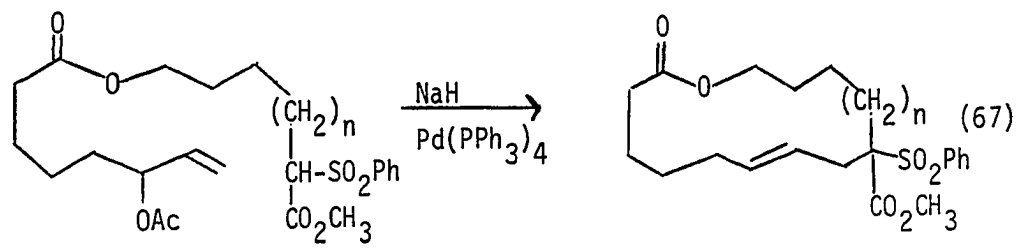
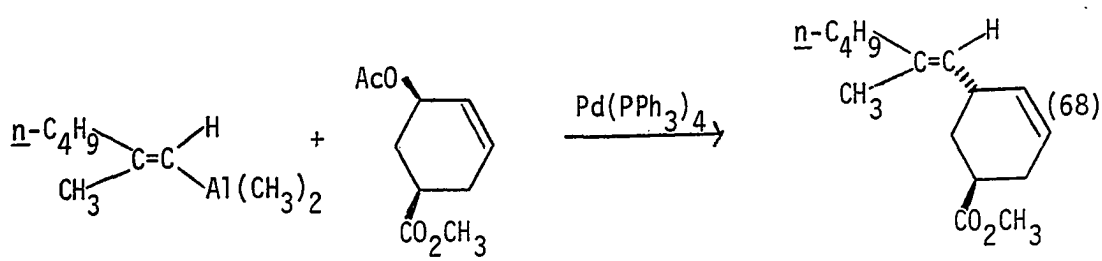


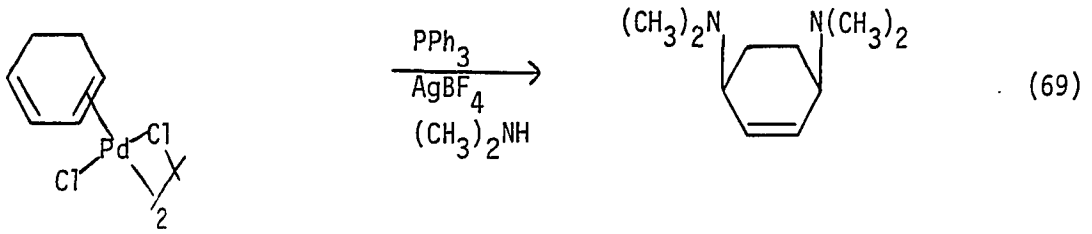
(67)

Alkenylzirconium complexes (167) and alkenylaluminum compounds (168) have also been used to alkylate the π-allyl ligand. These reactions proceed by initial attack of the alkenylmetal compound at palladium followed by reductive elimination to give a net inversion of stereochemistry (eq. 68).



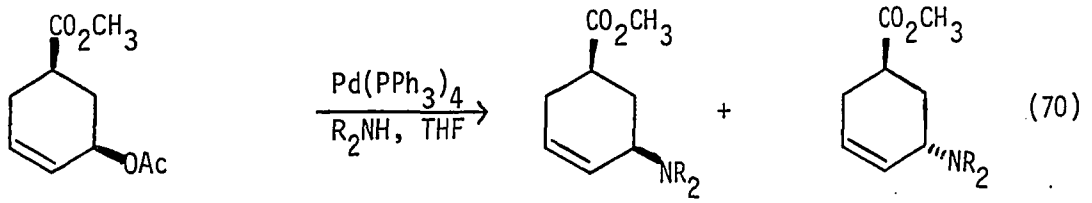
(68)

Amine nucleophiles have also been shown to react with π-allylpalladium complexes. Akermark and coworkers (169) have developed a procedure for the cis-1,4-diamination of cyclohexadiene (eq. 69). The



(69)

fact that the cis compound is the only product observed suggests that the amine is attacking the π-allyl ligand on the face opposite the palladium. However, Trost and Keinan (170, 171) have observed a cis-trans mixture in the amination of allylic acetate 108. They state that there is a competition between external amine attack (cis product) or prior coordination to palladium followed by reductive elimination (trans product) (eq. 70) (172).

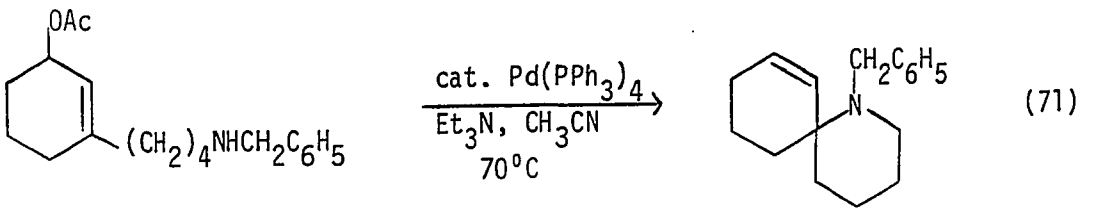


108

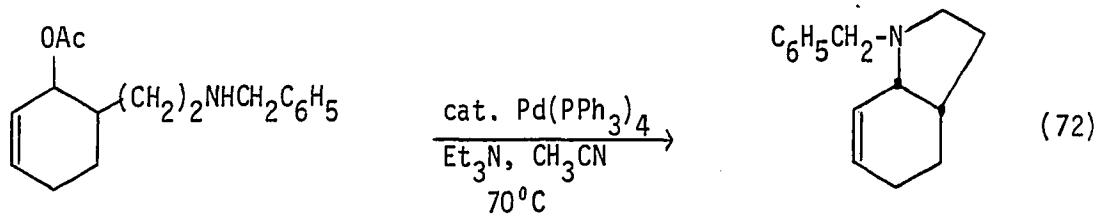
65 : 35

(70)

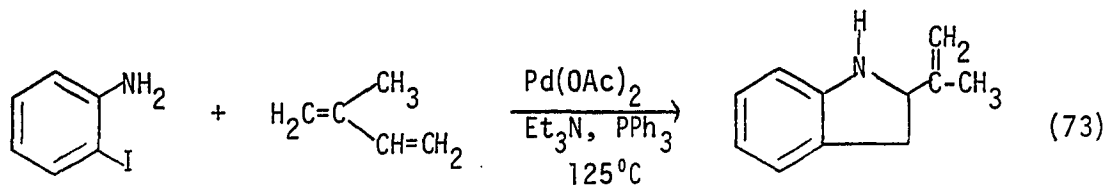
Several groups (173-175) have used an intramolecular amine attack to prepare several interesting nitrogen heterocycles (eqs. 71-73).



(71)

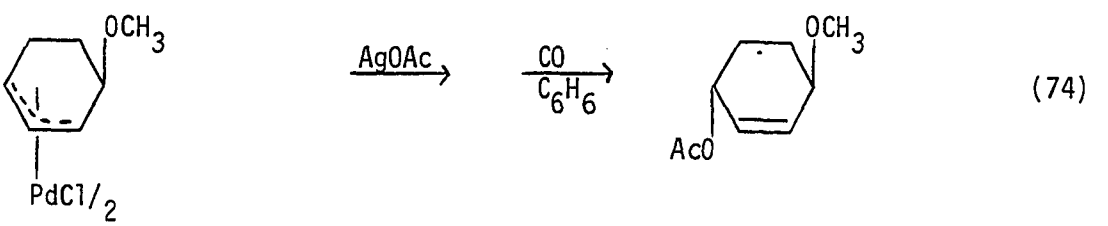


(72)

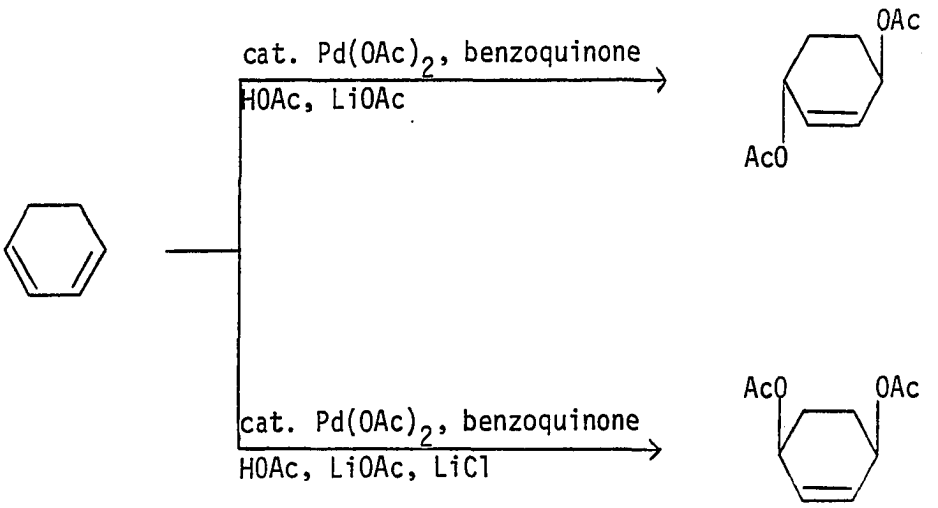


(73)

Less work has been done with respect to acetate or alkoxide attack on the π-allyl ligand. Bäckvall and coworkers (176, 177) have shown that the reaction of an acetate with a π-allylpalladium complex can proceed by either external attack or by prior coordination to palladium depending on the reaction conditions employed (eqs. 74, 75).

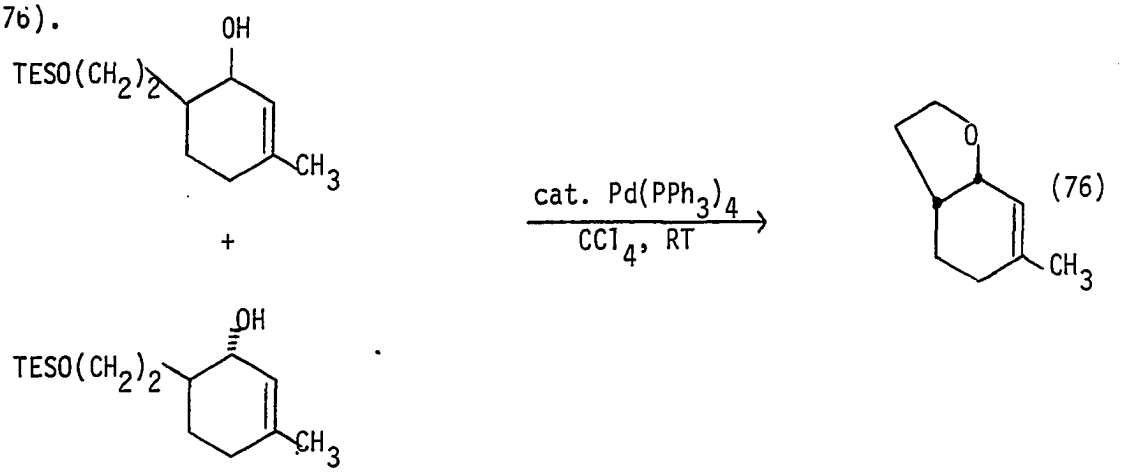


(74)



(75)

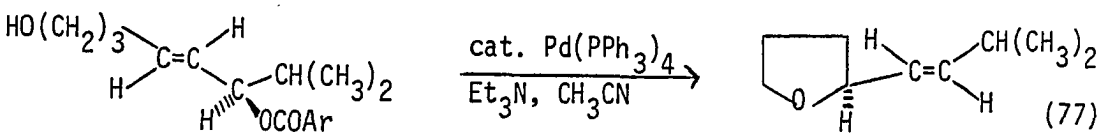
Alkoxides have been of only limited utility as nucleophiles in π-allylpalladium chemistry. The first example of an alkoxide nucleophile was that of Takahashi et al. (178) who used the sodium salts of methanol, benzyl alcohol and phenol in a transetherification reaction. Recently, Stanton and coworkers have developed a method for the preparation of oxygen heterocycles based on an intramolecular alkoxide attack (179) (eq. 76).



(76)

TES= $(C_2H_5)_3Si$

The authors state that alkoxides may exhibit a relatively small energy difference between backside attack on the π-allyl ligand and attack at the metal center followed by reductive elimination. Stork and Poirier (180) have also used an intramolecular alkoxide attack in their method for the preparation of 2-substituted tetrahydrofurans of known absolute stereochemistry (eq. 77).

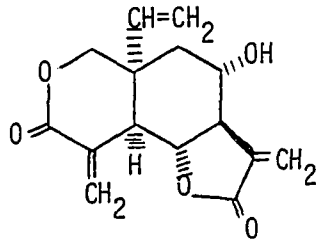


(77)

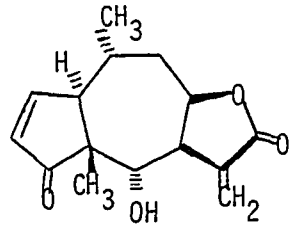
In all the cyclizations described in this introduction, one must first synthesize the desired allylic substrate, sometimes via a multi-step sequence, before cyclization can be effected. The work described in this chapter involves a novel synthesis of heterocyclic ring systems in which formation of the desired π-allylic substrate and subsequent cyclization occur in the same flask.

Results and Discussion

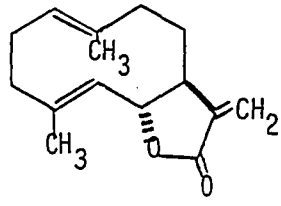
α-Methylene-γ-butyrolactone and α-methylene-δ-valerolactone units are found in various cytotoxic sesquiterpenes. Generally, these moieties are either cis- or trans-fused to 6-, 7-, or 10-membered rings. A few of the more important examples of these compounds are vernolepin (109) (181), helenalin (110) (182), and costunolide (111) (183). As a consequence of the wide range of biological activity, particularly the cytotoxic and antitumor activity (184), fungitoxicity (185), and plant growth



109



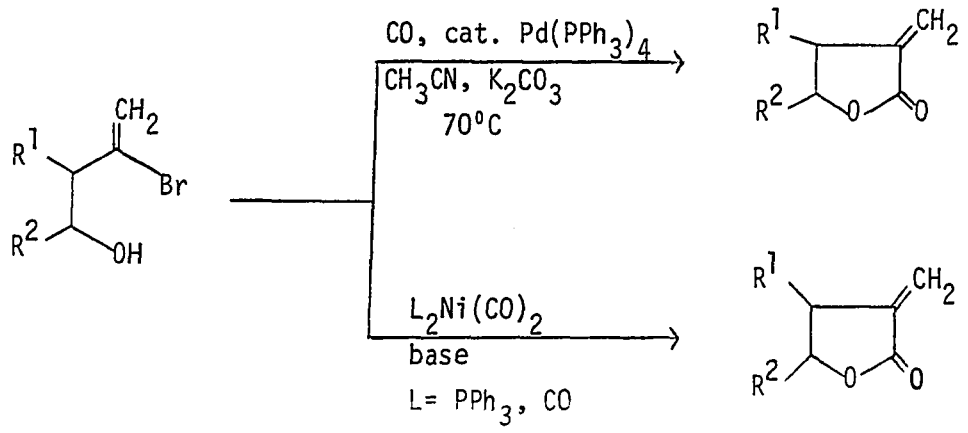
110



111

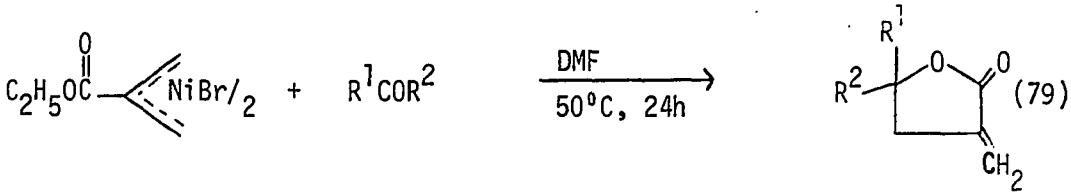
inhibition (186) possessed by α-methylene-γ-butyrolactones, this class of compounds has been the object of considerable synthetic activity (187).

There have been several transition metal assisted syntheses of α-methylene-γ-lactones developed recently. Semmelhack and Brickner (188) and Matsuda (189) have both found that alcoholic vinyl bromides can be carbonylated to the corresponding unsaturated lactone by the use of an excess of a nickel complex. Martin and Stille (190) have also observed that tetrakis(triphenylphosphine)palladium(0) will catalyze this transformation (eq. 78).



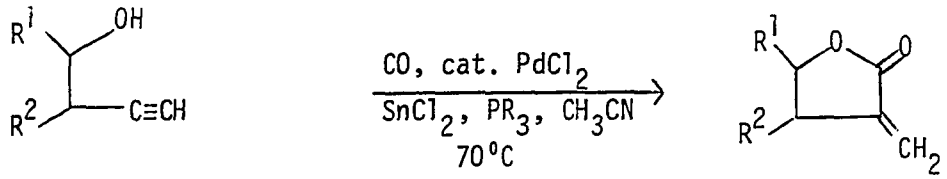
(78)

Hegedus et al. (191) have developed a synthesis of α-methylene-γ-butyrolactones by the use of a π-allylnickel complex (eq. 79).



(79)

One of the more useful transition metal catalyzed syntheses of lactones involves the palladium catalyzed cyclocarbonylation of acetylenic alcohols (192). This method has been used to prepare several α-methylene-γ-butyrolactones (eq. 80).



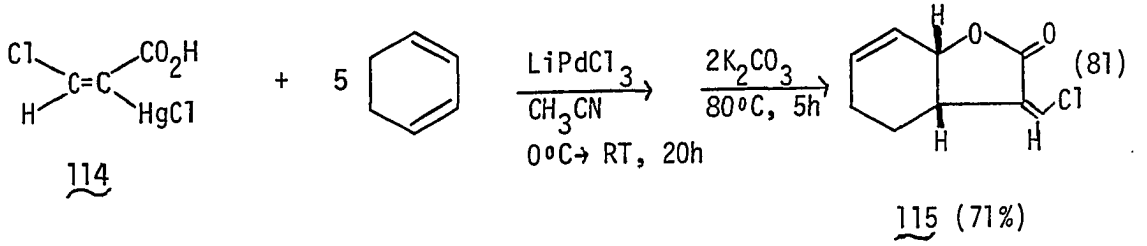
(80)

Since it is known that organomercurials will react with 1,3-dienes

in the presence of a palladium salt to produce π-allylpalladium complexes (193), and that carboxylates can attack π-allylpalladium complexes; it was believed that the reaction of a 1,3-diene with an organomercurial containing the carboxylate function might be used to prepare lactones.

The first organomercurial examined was chloromercuriacetic acid (112). This compound was easily prepared by the reaction of 1,1-difluoroethylene with mercuric acetate in water (194). The reaction of 112 with 1,3-cyclohexadiene in the presence of lithium tetrachloropalladate in tetrahydrofuran followed by treatment of the reaction mixture with potassium carbonate failed to produce any of the desired lactone. The compound that was produced appeared to be the acid 113 by both infrared and gas chromatographic-mass spectral analysis. Several other conditions were examined to see if 112 could be transformed into the desired lactone, but all proved unsuccessful (Scheme VIII).

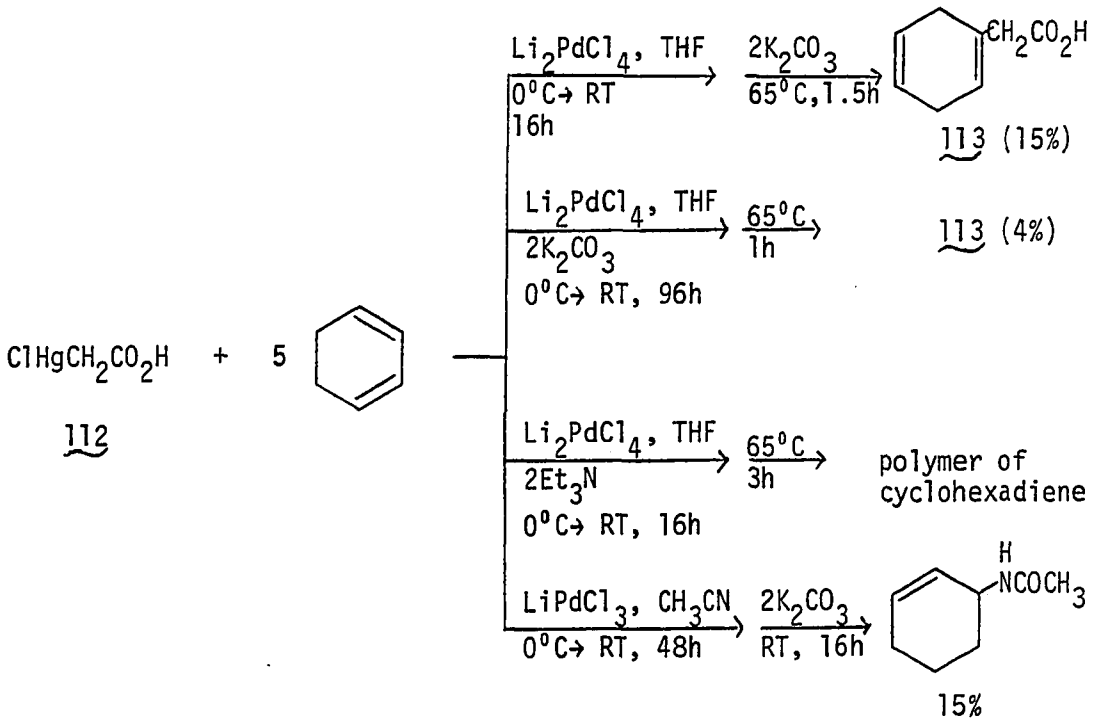
The vinylmercurial 114 was prepared in quantitative yield by the reaction of propiolic acid with mercuric chloride (22). The reaction of this compound with 1,3-cyclohexadiene (5 equivalents) in the presence of lithium trichloropalladate(II), followed by treatment of the reaction mixture with two equivalents of potassium carbonate did produce the desired lactone 115 in a 71% yield (eq. 81). Other variations in the reaction conditions, such as using two equivalents of 1,3-cyclohexadiene

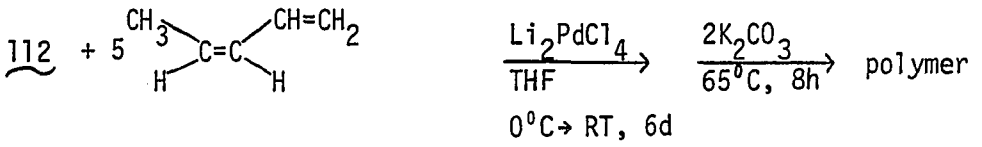


114

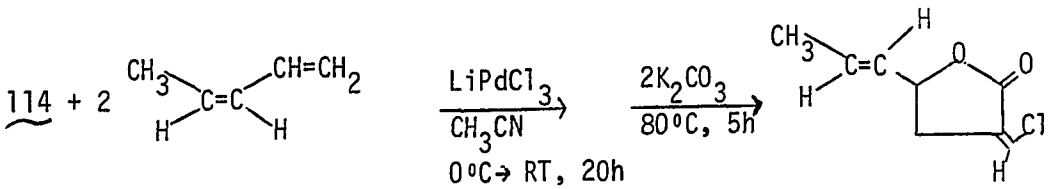
115 (71%)

Scheme VIII

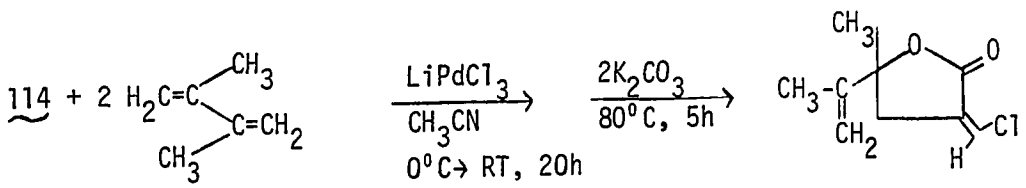

ClHgCH2CO2H
112
+ 5
Li2PdCl4, THF
0°C→ RT
16h
2K2CO3
65°C, 1.5h
CH2CO2H
113 (15%)
Li2PdCl4, THF
2K2CO3
0°C→ RT, 96h
65°C
1h
113 (4%)
Li2PdCl4, THF
2Et3N
0°C→ RT, 16h
65°C
3h
polymer of cyclohexadiene
LiPdCl3, CH3CN
0°C→ RT, 48h
2K2CO3
RT, 16h
H
NCOCH3
15%


112
+ 5
CH3
C=C
CH=CH2
H
H
Li2PdCl4
THF
0°C→ RT, 6d
2K2CO3
65°C, 8h
polymer

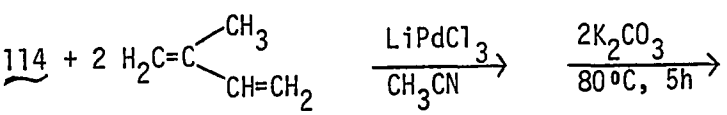
or using triethylamine as the base, did produce 115 but in lower yields (22% and 46%, respectively). Since the reaction with 1,3-cyclohexadiene worked well, several other dienes were examined to see if the corresponding lactones could be produced (eqs. 82-86). In the case of acyclic dienes, it was found that two equivalents of diene were sufficient to obtain good yields.



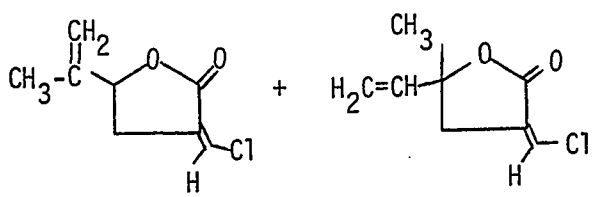
(82)

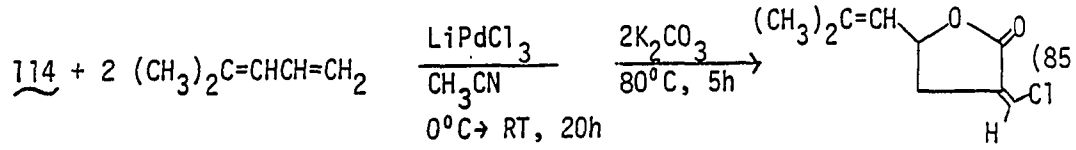


(83)

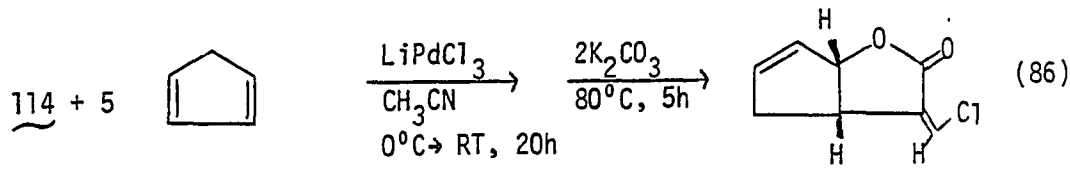


(84)



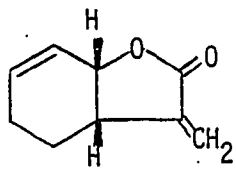


120 (67%)

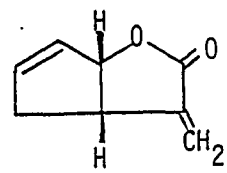


121 (59%)

The cis-ring fusion in compounds 115 and 121 was determined by comparison of the spectral data of these two lactones with the spectral data reported for lactones 122 and 123 (195). The cis stereochemistry



122

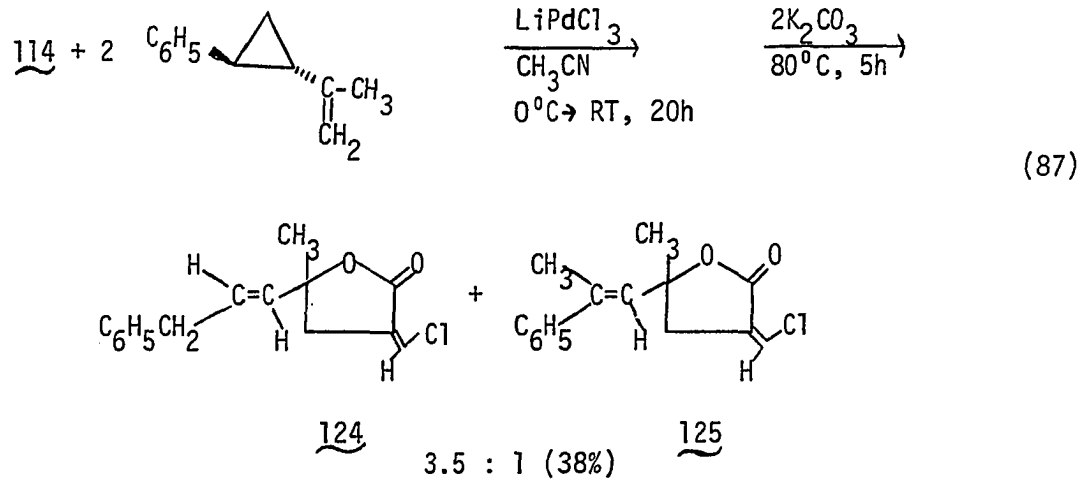


123

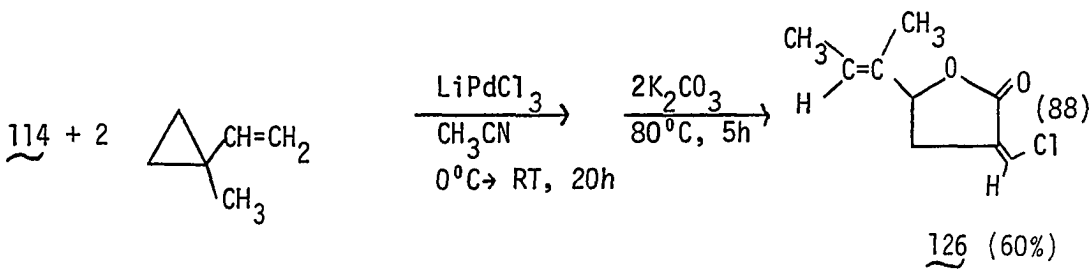
observed in compounds 115 and 121 is presumably arising from carboxylate attack on palladium followed by reductive elimination.

Since it has been observed in our group (196) that organomercurials will react with vinylcyclopropanes in the presence of a palladium(II) salt to produce π-allylpalladium complexes, the possibility of using

vinylcyclopropanes instead of dienes in this lactone synthesis was examined (eqs. 87, 88).

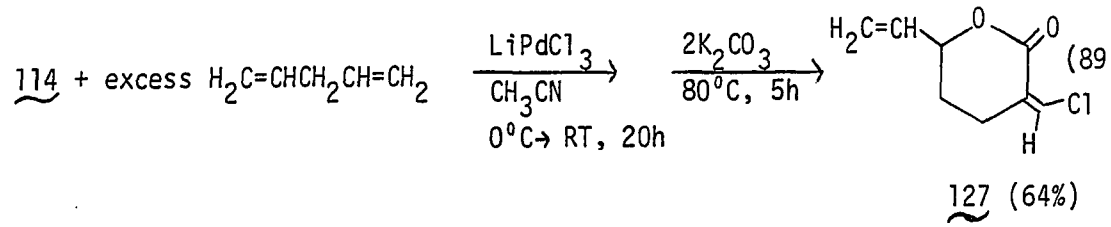


(87)



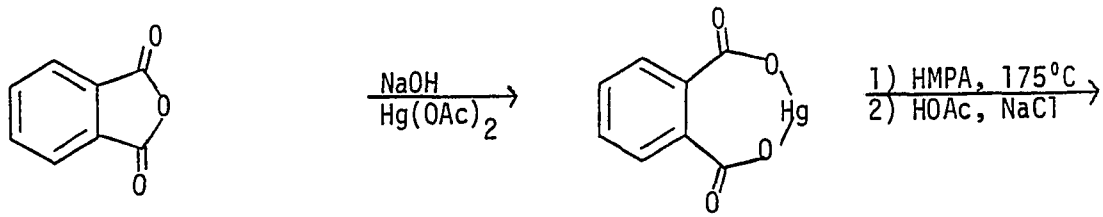
(88)

Larock and Takagi (197) have shown that π-allylpalladium compounds can be prepared by the reaction of lithium tetrachloropalladate(II), organomercurials and non-conjugated dienes such as 1,4-pentadiene or 1,5-hexadiene. The use of a non-conjugated diene in the lactone preparation would enable one to make larger ring lactones. The reaction of mercurial 114 with 1,4-pentadiene under the usual conditions did produce the desired α-methylene-δ-valerolactone 127 in a yield of 64% (eq. 89). The extension of this reaction to 1,5-hexadiene proved unsuccessful.



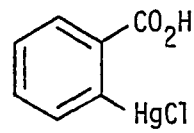
127 (64%)

The next mercurial examined was 2-chloromercuribenzoic acid (129) in order to determine if one could prepare dihydroisocoumarins by this methodology. The mercurated acid was prepared in low yield from phthalic anhydride (eq. 90) (198). The reaction of mercurial 129 with cis-1,3-



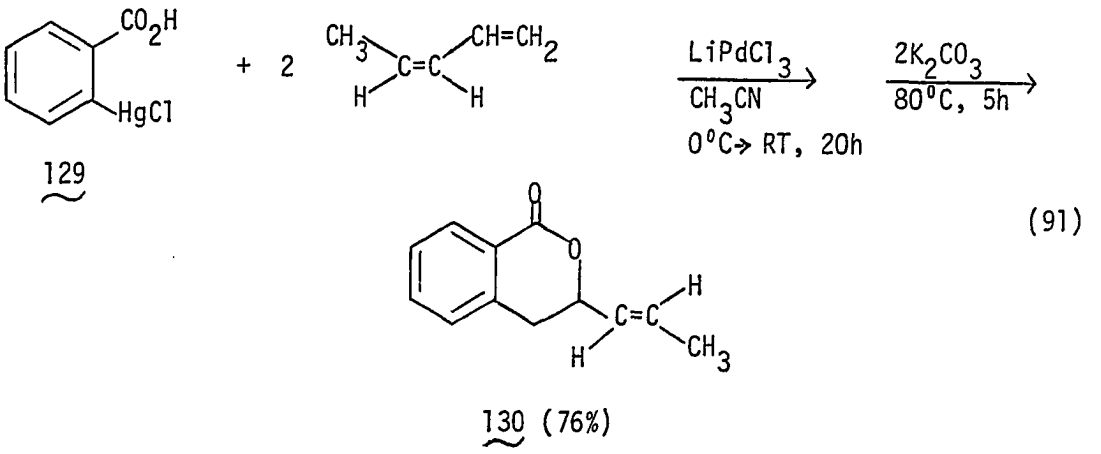
128 (80%)

(90)



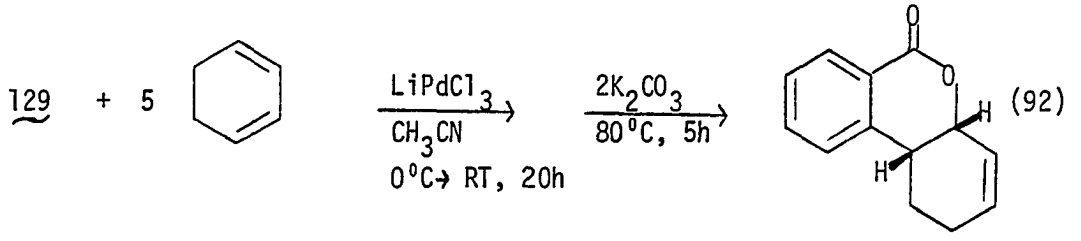
129 (14%)

pentadiene and 1,3-cyclohexadiene using the same conditions that were employed for 114 produced the dihydroisocoumarin derivatives 130 and 131 respectively (eqs. 91, 92).



129 (91)

130 (76%)

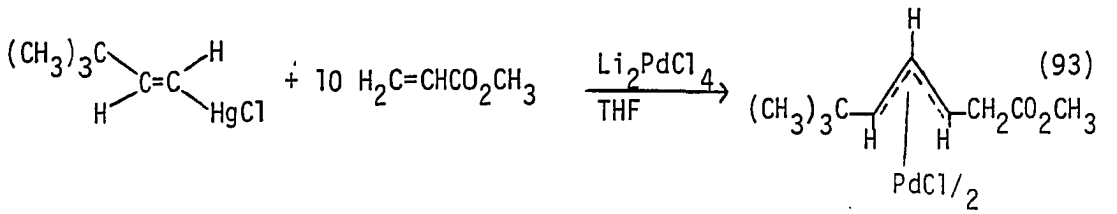


(92)

131 (33%)

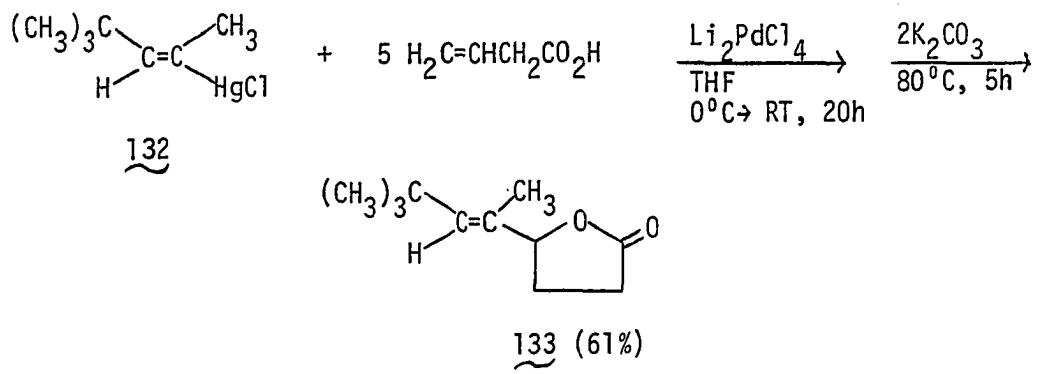
The cis-ring fusion in compound 131 was previously established by hydrogenation (196). The cis stereochemistry could again arise from initial attack of the carboxylate on the metal followed by reductive elimination.

Larock and Mitchell (199) have shown that the reaction of a vinylmercurial with olefins in the presence of a palladium(II) salt produces π-allylpalladium compounds (eq. 93). It was believed that if the olefin contained a carboxylate function, then, this method of π-allylpalladium synthesis could also be used as a method for the synthesis of lactones.



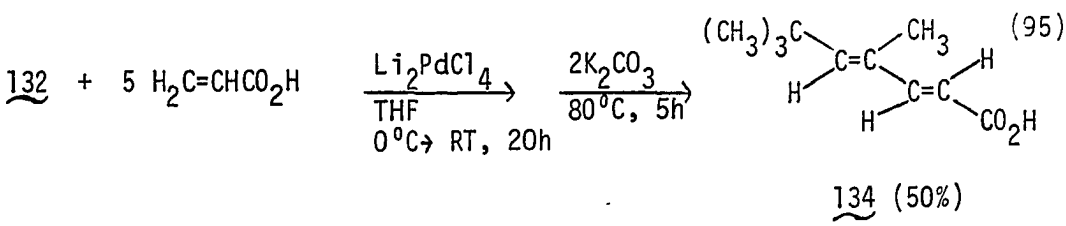
(93)

The first vinylmercurial that was examined was E-2-chloromercuri-4,4-dimethyl-2-pentene (132). The reaction of 132 with 3-butenoic acid (5 equivalents) in the presence of lithium tetrachloropalladate(II) followed by treatment with two equivalents of potassium carbonate led to the formation of the desired γ-butyrolactone 133 in a yield of 61% (eq.



(94)

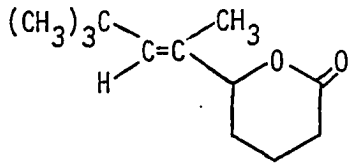
The mercury compound 132 was reacted with other olefinic acids to determine if this method was applicable to both larger and smaller ring lactones. The reaction with acrylic acid produced only the diene acid 134 in ~50% yield (eq. 95). When performed in tetrahydrofuran, the



(95)

reaction of 132 with 4-pentenoic acid produced no desired product, but, if the reaction was carried out using acetonitrile as the solvent, then the expected δ-valerolactone 135 could be isolated in 76% yield (eq. 96).

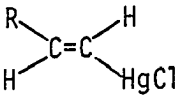
$$\underset{\sim}{132} + 5\ H_2C{=}CH(CH_2)_2CO_2H \xrightarrow[CH_3CN]{LiPdCl_3} \xrightarrow[0^\circ C \rightarrow RT,\ 20h]{} \xrightarrow[80^\circ C,\ 5h]{2K_2CO_3} \underset{\sim}{135}\ (76\%) \qquad (96)$$



Trying to extend this reaction to larger ring lactones by the use of 6-heptenoic acid or 10-undecenoic acid proved unsuccessful and led only to recovery of the starting acid.

In an effort to determine if this lactone synthesis was general for other vinylmercurials, trans-1-pentenylmercuric chloride (136) and trans-1-decenylmercuric chloride (137) were examined. Both of these mercurials did produce the corresponding γ-butyrolactone when reacted with 3-butenoic acid in acetonitrile (eq. 97).

Since the yields of both 138 and 139 were low and dimerization of the organomercurial was observed, other conditions using organomercurial 137 were examined (Scheme IX). Before the addition of the organomercurial, the reaction mixture was cooled to -20°C instead of 0°C; but, this produced little change in the isolated yield of 139. It was felt that removal of the lithium chloride from the reaction might decrease the amount of dimer formed; therefore, the reaction was

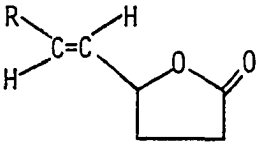


+ 5 $H_2C{=}CHCH_2CO_2H$ $\xrightarrow[CH_3CN]{LiPdCl_3}$ $\xrightarrow[80^\circ C,\ 5h]{2K_2CO_3}$

$0^\circ C \rightarrow$ RT, 20h

136: R=n-C_3H_7

137: R=n-C_8H_{17}



(97)

138: R=n-C_3H_7 (31%)

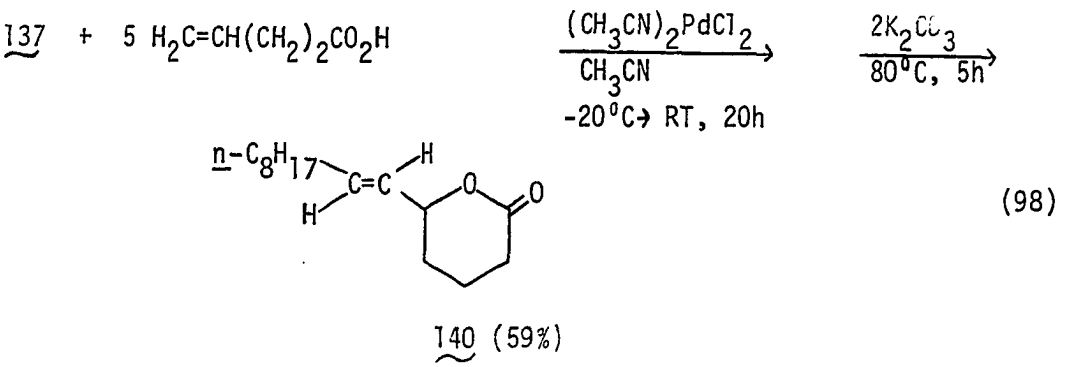
139: R=n-C_8H_{17} (40%)

Scheme IX

137 + 5 $H_2C{=}CHCH_2CO_2H$

$\xrightarrow[CH_3CN]{LiPdCl_3}$ $-20^\circ C \rightarrow$ RT, 20h	$\xrightarrow[80^\circ C,\ 5h]{2K_2CO_3}$	139 (35%)
$\xrightarrow[CH_3CN]{(CH_3CN)_2PdCl_2}$ $-20^\circ C \rightarrow$ RT, 20h	$\xrightarrow[80^\circ C,\ 5h]{2K_2CO_3}$	139 (63%)
$\xrightarrow[CH_3CN]{PdCl_2}$ $-20^\circ C \rightarrow$ RT, 20h	$\xrightarrow[80^\circ C,\ 5h]{2K_2CO_3}$	139 (54%)
$\xrightarrow[CH_2Cl_2]{PdCl_2}$ $-20^\circ C \rightarrow$ RT, 20h	$\xrightarrow[80^\circ C,\ 5h]{2K_2CO_3}$	139 (19%)

performed using bis(acetonitrile)dichloropalladium(II) in acetonitrile, palladium chloride in acetonitrile and palladium chloride in methylene chloride. The best conditions for the reaction involved the use of bis (acetonitrile)dichloropalladium(II) in acetonitrile and starting the reaction at -20°C. Using the best conditions, the reaction of 137 with acrylic acid, 4-pentenoic acid, 6-heptenoic acid and 10-undecenoic acid was examined. Again, the only other acid that produced the desired product was 4-pentenoic acid (eq. 98). Recently, it has been found that

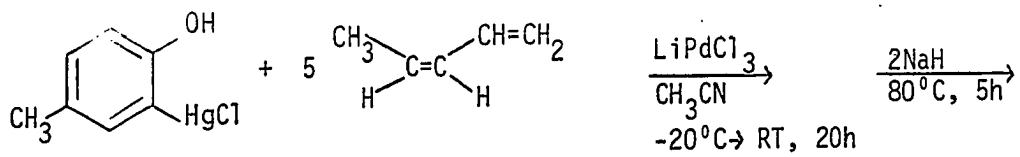


(98)

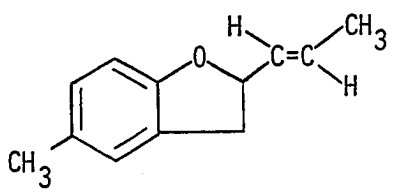
the reaction of mercurial 132 with 3-butenoic acid and 4-pentenoic acid using bis(acetonitrile)dichloropalladium(II) produced the lactones 133 and 135 in 83% and 70% yield, respectively (200).

Since alkoxides and amines are also known to attack π-allylpalladium compounds, one should be able to prepare other heterocyclic ring systems by the reaction of a suitably functionalized organomercurial with a diene. The preparation of dihydrobenzofuran derivatives was examined using 2-chloromercuri-4-methylphenol (141). The reaction of 141 and cis-1,3-pentadiene using the conditions developed for organomercurials for 114 and 129 resulted in a low mass recovery and 3 spots by TLC

analysis. It was found that the cyclization to the dihydrobenzofuran could be accomplished, however, if five equivalents of cis-1,3-pentadiene were used, the initial temperature of addition was -20°C, and sodium hydride was used at the base (eq. 99). Other dienes such as 1,3-



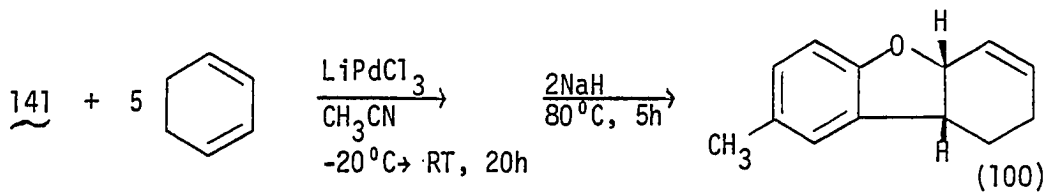
141 (99)



142 (88%)

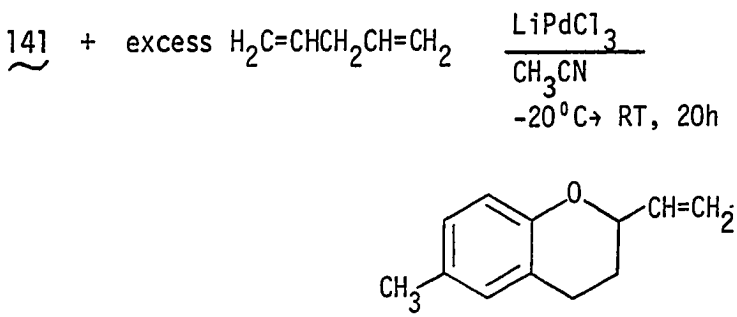
cyclohexadiene, 1,4-pentadiene, and isoprene work equally well with this substrate to furnish compounds 143, 144, 145, and 146 respectively (eqs. 100-102).

There have been a couple of other interesting palladium approaches to dihydrobenzofurans. Horino and Inoue (201) have also made use of 2-chloromercuriphenol to prepare dihydrobenzofuran derivatives. Their approach involves the addition of an intermediate phenolic palladium compound across the carbon-carbon double bond of 2H-1-benzopyran (eq. 103). Hosokawa et al. (202, 203) have made use of the palladium catalyzed cyclization of 2-allylphenols to prepare dihydrobenzofurans (eq. 104).



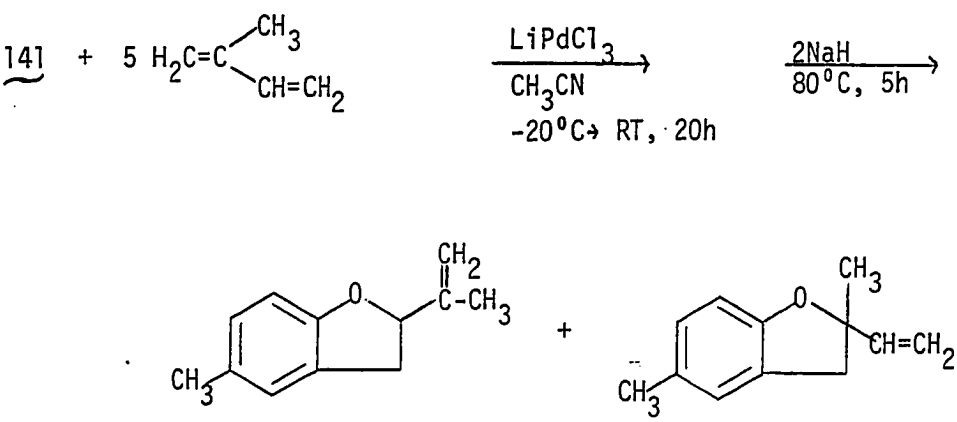
(100)

143 (86%)



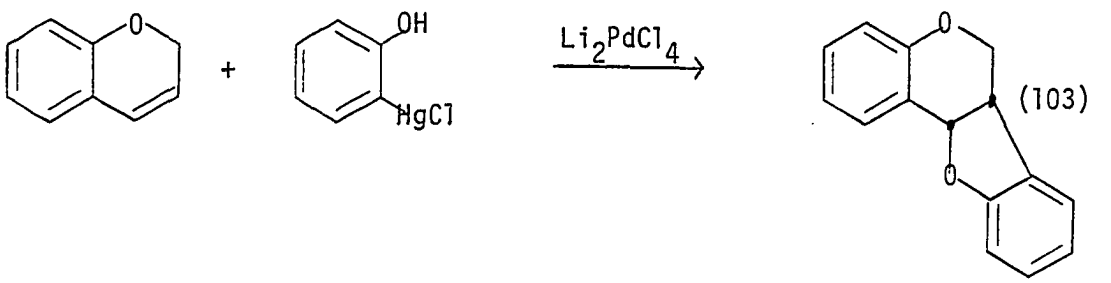
(101)

144 (62%)

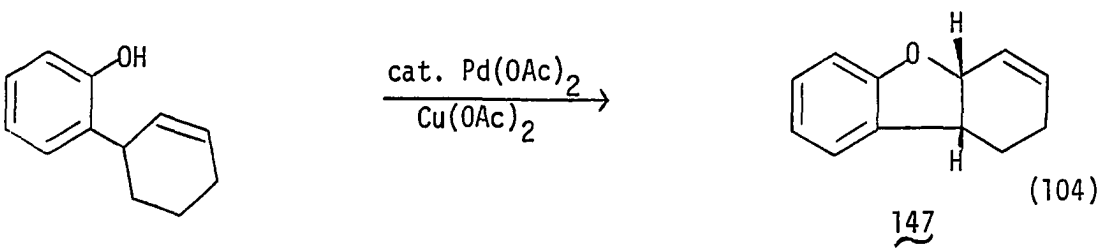


(102)

145 4:1 (83%) 146



(103)

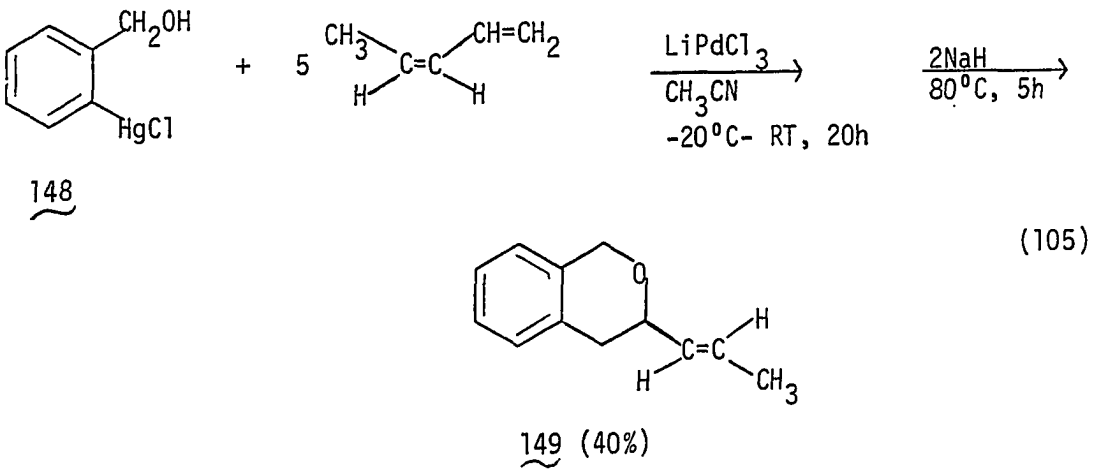


(104)

147

The stereochemistry of the ring junction in compound 143 was determined by comparison of its spectral data with that reported by Hosokawa for compound 147. The cis stereochemistry observed in 143 could again arise from the attack of the alkoxide on palladium followed by reductive elimination, although other alternate pathways are possible.

Several mercurated alcohols were examined to determine if other oxygen heterocycles could be prepared by this method. The mercurated benzyl alcohol 148 was synthesized by refluxing benzyl alcohol with mercuric acetate in water for six hours (204). The reaction of 2-chloromercuribenzyl alcohol (148) with cis-1,3-pentadiene in the presence of lithium trichloropalladate(II) produced the dihydroisocoumarin derivative 149 in a 40% yield (eq. 105).

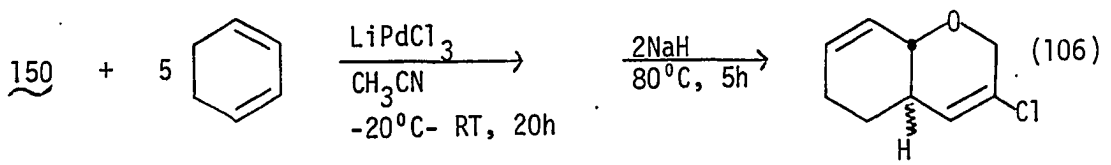


148

149 (40%)

(105)

The allylic alcohol 150 was prepared by the reaction of propargyl alcohol with mercuric chloride (16). The reaction of this alcohol with lithium trichloropalladate(II) and cis-1,3-pentadiene (Table III) or 1,3-cyclohexadiene (eq. 106) produced the cyclized compounds in very poor yield.

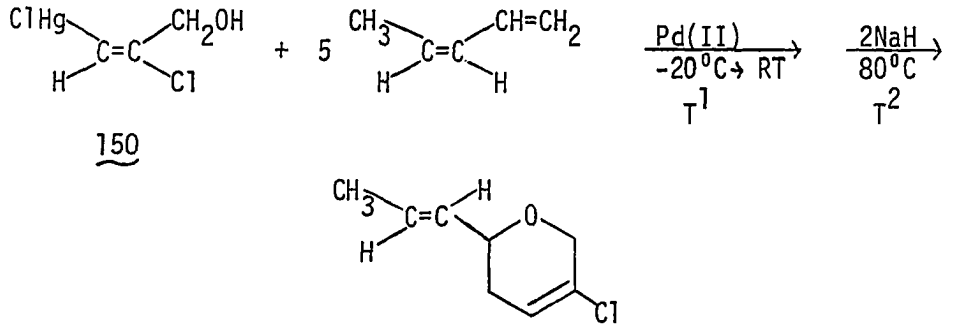


152 (24%)

(106)

One reason for the low yield of cyclized product might possibly be some form of hydride elimination from the allylic alcohol to form an aldehyde. Therefore, allylic alcohol 153 was examined. When reacted with cis-1,3-pentadiene, this mercurial produced the desired compound 154 in good yield under a variety of conditions (Scheme X). The reaction of organomercurial 153 with 1,3-cyclohexadiene was successful only if the

Table III. Reaction Conditions for the Reaction of Alcohol 150 and cis-1,3-Pentadiene



150

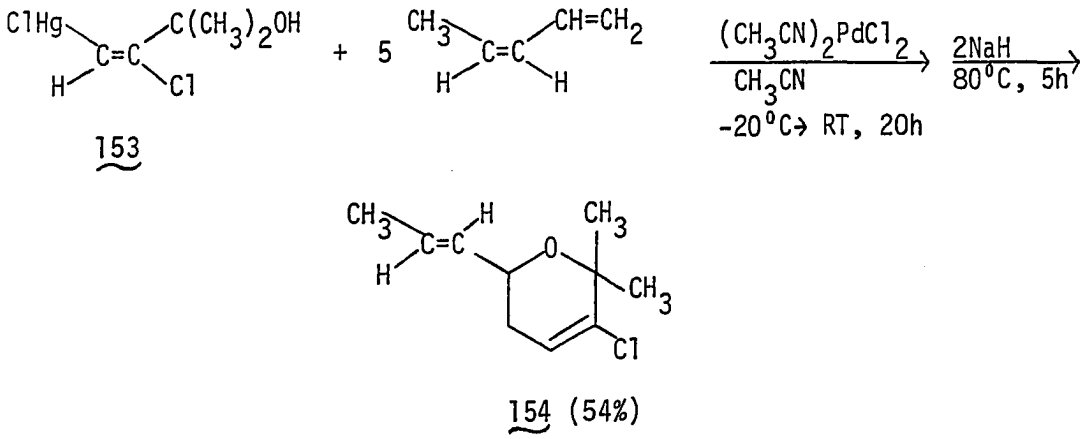
151

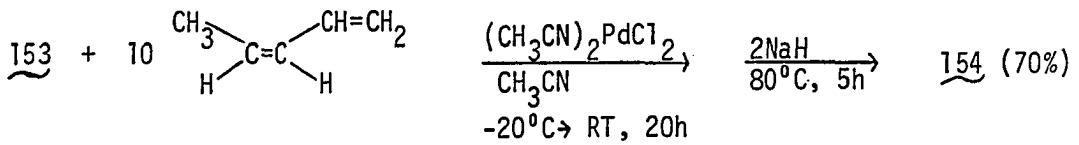
Pd(II) salt	solvent	T^1 (h)	T^2 (h)	Yield of 151 (%)
$LiPdCl_3$	CH_3CN	20	5	10
$(CH_3CN)_2PdCl_2$				13
			24	10
Li_2PdCl_4	THF		5	<5
$Pd(OAc)_2$	CH_3CN	48		10
$(CH_3CN)_2PdCl_2 + 2PPh_3$		20		<5

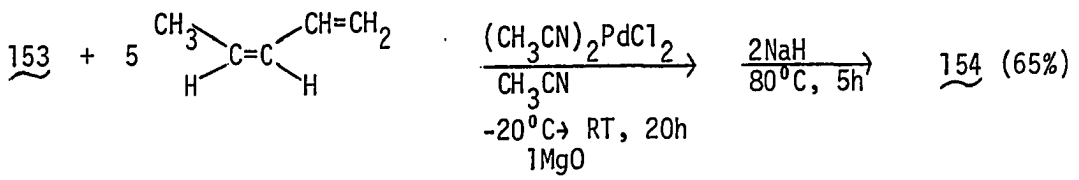
reaction was performed in the presence of one equivalent of magnesium oxide. This condition produced the cyclized compound 155 in a yield of 51% (eq. 107). Without magnesium oxide, the yield was <30%.

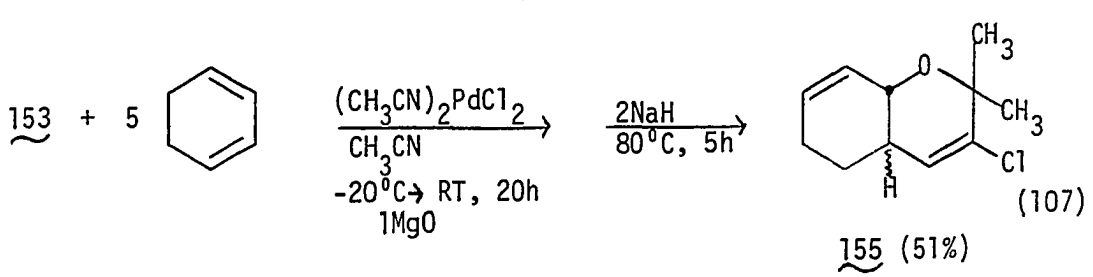
In an attempt to extend this cyclization to nitrogen heterocycles, the reactions of 2-acetoxymercuri-4-methylaniline were studied. The

Scheme X


ClHg
C(CH3)2OH
C=C
H
Cl
153
+ 5
CH3
CH=CH2
(CH3CN)2PdCl2
CH3CN
-20°C→ RT, 20h
2NaH
80°C, 5h
CH3
H
O
Cl
154 (54%)


153 + 10
CH3
CH=CH2
C=C
H
(CH3CN)2PdCl2
CH3CN
-20°C→ RT, 20h
2NaH
80°C, 5h
154 (70%)

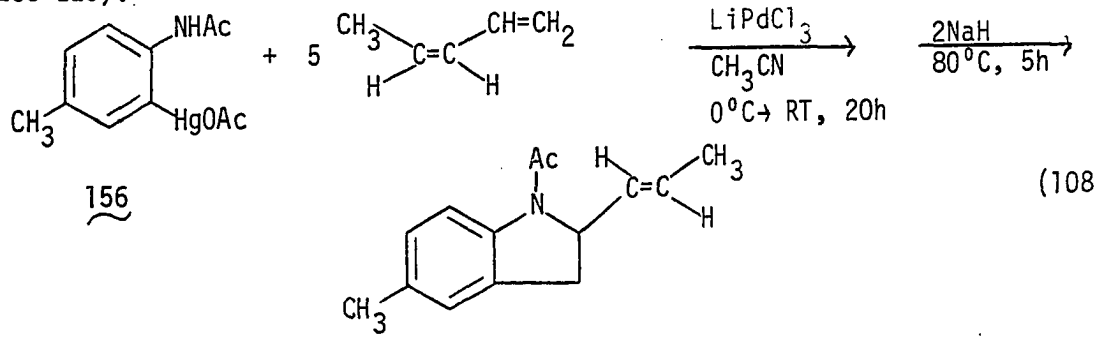

153 + 5
CH3
CH=CH2
C=C
H
(CH3CN)2PdCl2
CH3CN
-20°C→ RT, 20h
1MgO
2NaH
80°C, 5h
154 (65%)


153 + 5
(CH3CN)2PdCl2
CH3CN
-20°C→ RT, 20h
1MgO
2NaH
80°C, 5h
CH3
O
CH3
Cl
H
(107)
155 (51%)

reaction of this mercurial with cis-1,3-pentadiene under various conditions produced three different cyclization products in a combined yield of ~25%. Because of this low yield, no further work was attempted using the mercurated aniline.

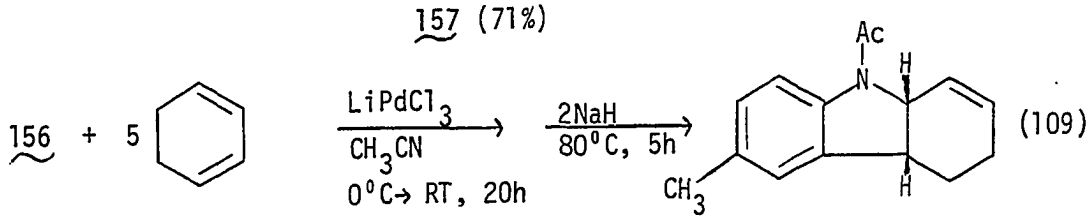
Horino and Inoue (205) have found that acetanilide can be ortho palladated with palladium acetate to produce a stable arylpalladium compound. This compound can then be reacted with olefins to produce the coupling product. With this in mind, the reaction of dienes and a 2-mercurated acetanilide was examined.

The mercurated acetanilide 156 was easily prepared by the reaction of 2-acetoxymercuri-4-methylaniline with acetic anhydride (206). The reaction of compound 156 with various dienes using the same conditions that were used for compound 141, except that the initial temperature was 0°C, provided the desired nitrogen heterocycles 157. 158, and 159 (eqs. 108-110).



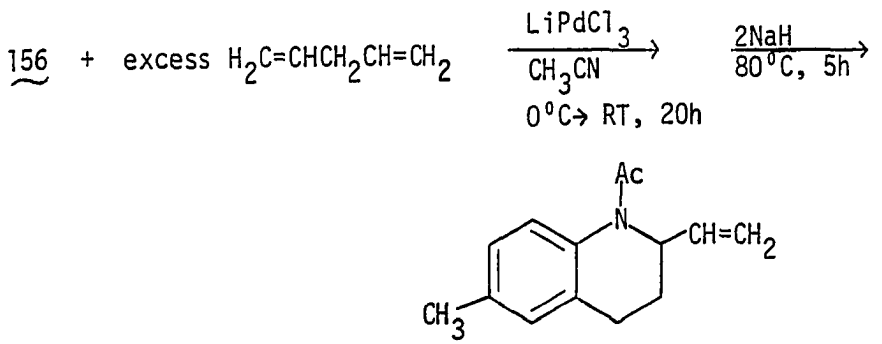
156 (108)

157 (71%)



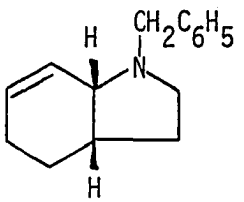
(109)

158 (74%)



(110)

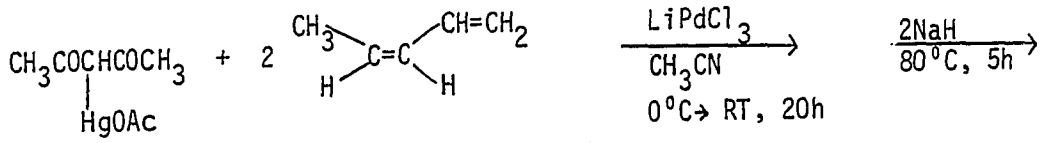
The cis ring fusion in 158 was established by comparison of the NMR coupling constant of the ring junction hydrogens with that reported by Trost and Genet (174) for compound 160. The cis-fusion could again be a



160

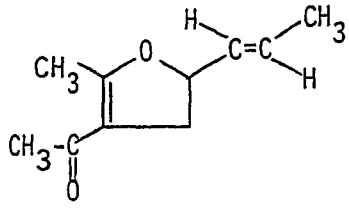
result of initial attack of the amide anion on the metal center followed by reductive elimination.

By selecting the appropriate organomercurial, it was believed that this methodology might be applicable to the preparation of carbocyclic ring systems. The mercurial that was used for this study was 3-acetoxymercuri-2,4-pentanedione (161). The reaction of this mercurial with cis-1,3-pentadiene did produce the cyclized compound, but the product was one resulting from O-alkylation rather than C-alkylation (eq. 111). The best procedure for this reaction involved filtering the



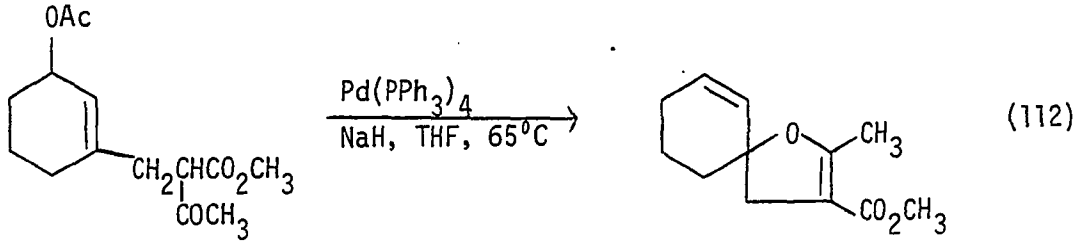
161

(111)

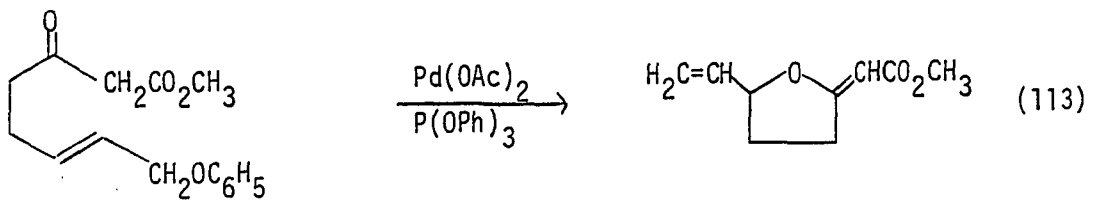


162 (28%)

reaction mixture through Celite and washing with saturated ammonium chloride before the addition of sodium hydride. This produced the cyclic ether 162 in a yield of 33%. Attempted isomerization of the O-alkylated product to the C-alkylated compound by using the conditions of either Trost and coworkers (207) or Tsuji and coworkers (208) was unsuccessful. The isolation of the O-alkylated product in systems such as this has also been observed (208, 209) (eqs. 112, 113).



(112)



(113)

Conclusion

The results presented in this chapter provide a novel one-pot route to several heterocyclic ring systems. The methodology is based upon the ability of π-allylpalladium compounds to undergo intramolecular nucleophilic attack by heteroatoms. In the reaction, one forms both a new carbon-carbon bond and a new carbon-heteroatom bond. By simply changing the organomercurial, one can prepare lactones, other oxygen-containing heterocycles, and nitrogen-containing heterocycles in good yields.

Experimental Section

Equipment The infrared spectra were recorded on a Beckman IR-4250 spectrophotometer or a Beckman Acculab 2 spectrophotometer, and the ^1H NMR spectra on a Varian Associates EM-360 NMR spectrometer or a Nicolet NT-300 NMR spectrometer. The mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer, while the GC/mass spectra were recorded on a Finnegan 4023 GC/MS data system. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected.

Reagents All chemicals were used directly as obtained commercially unless otherwise indicated. Propargyl alcohol, 2-methyl-3-butyn-2-ol, propiolic acid, 3-butenoic acid, 1,3-cyclohexadiene (96%), isoprene (99%), 2,3-dimethyl-1,3-butadiene (98%), and 1,5-hexadiene (98%) were all purchased from Aldrich Chemical. cis-1,3-Pentadiene (99%), 1,4-pentadiene (99%), and 4-methyl-1,3-pentadiene (99%) were purchased from Wiley Organics and 4-pentenoic acid from Alfa Products. The vinyl cyclopropanes and 2-acetoxymercuri-4-methylaniline were generously supplied by Dr. Sudarsanan Varaprath, and 2-chloromercuri-4-methylphenol was supplied by Mr. David Leuck. trans-1-Pentenylmercuric chloride, trans-1-decenylmercuric chloride and E-2-chloromercuri-4,4-dimethyl-2-pentene were previously prepared according to the procedure of Larock and Brown (210) and were recrystallized from 95% ethanol before use. Acetonitrile was distilled from phosphorus pentoxide before use. Palladium chloride was generously supplied by Johnson Matthey, Inc., and Engelhard Industries.

Chloromercuriacetic acid (112). The acid was prepared using a variation of the procedure developed by Knunyants, Perova, and Tyuleneva (194). In a 100 mL round-bottom flask was placed 4.78 g (15 mmol) of mercuric acetate in 20 mL of water. Then, 1,1-difluoroethylene was slowly bubbled into the solution and addition was continued until the reaction mixture showed a negative test for mercuric ion. Ice and saturated sodium chloride were added to the reaction mixture followed by 15 mL of ether; and, the mixture was stirred at $0^{o}C$ for 30 min. The solid was removed by filtration, washed with ether and air-dried to yield

3.80 g (12.9 mmol, 86%) of the acid: mp 195-196°C (lit. (211) mp 194-195°C); ^{1}H NMR (DMSO-d_6) δ 2.38 (CH_2); IR (nujol) 3300-2500 (OH), 1685 (C=O) cm^{-1}.

E-β-Chloro-α-chloromercuriacrylic acid (114). This compound was prepared using the method of Nesmeyanov et al. (22). In a 50 mL Erlenmeyer flask, 1.0 g (14.3 mmol) of propiolic acid was mixed with 10 mL of a solution saturated with both mercuric chloride and sodium chloride. The precipitate began to form after 5 min. of scratching the side of the flask with a glass rod. The reaction mixture was let stand for 2 h, filtered, washed with a little water and dried to provide 4.80 g (14 mmol, 100%) of the title compound: mp 177-180°C (lit. (22) mp 178-179°C); ^{1}H NMR (DMSO-d_6) δ 6.50 (s, $J_{^{199}Hg-H}$ = 180 Hz, HC=C); IR (nujol) 3400-2800 (OH), 1660 (C=O) cm^{-1}.

2-Chloromercuribenzoic acid (129). In a 250 mL round-bottom flask, 2.96 g (20 mmol) of phthalic anhydride was dissolved in 100 mL of 0.4 N sodium hydroxide. To this solution, a solution of 6.37 g (20 mmol) of mercuric acetate in 100 mL of water containing 1 mL of acetic acid was added; and, the resulting mixture was stirred for 10 min. The solid was filtered, washed with absolute ethanol and dried to yield 5.85 g (16 mmol, 80%) of salt 128. The crude salt was decarboxylated using the procedure of Newman and Vander Zwan (198). In a 250 mL round-bottom flask with a reflux condenser, 128 and 4 g of powdered soft glass were suspended in 35 mL of hexamethylphosphoramide. This suspension was placed in a 175°C oil bath and heated until the evolution of carbon dioxide ceased (~ 1 h). The mixture was diluted with 200 mL of water and

solid was dissolved in acetic acid and saturated sodium chloride was added. The mixture was extracted with hot chloroform, dried ($MgSO_4$) and concentrated to yield 0.80 g (2.24 mmol, 14%) of the desired mercurial 129: mp 250-252°C (with dec.); ^1H NMR (DMSO-d_6) δ 7.24-7.85 (m, 3H, H-3, H-4, H-5), 8.19 (d, 1H, J=7.5 Hz, H-6); IR (nujol) 3400-2500 (OH), 1665 (C=O) cm^{-1}.

2-Chloromercuribenzyl alcohol (148). This compound was prepared by the mercuration of benzyl alcohol using the procedure of Ukai, Yamamoto and Yotsuzuka (204). In a 100 mL round-bottom flask, 9.7 g (30.4 mmol) of mercuric acetate and 3.24 g (30 mmol) of benzyl alcohol were refluxed in 60 mL of water for 6 h. The hot reaction mixture was filtered and poured into saturated sodium chloride. The resulting solid was filtered and treated with hot water to separate the 2-mercurated isomer (soluble) from the 4-mercurated isomer (insoluble) to provide 0.390 g (1.14 mmol, 3.8%) of the desired isomer: mp 119-121°C (lit. (204) mp 120-120.5°C).

E-2-Chloro-3-chloromercuri-2-propen-1-ol (150). This compound was prepared from propargyl alcohol using the procedure of Nesmeyanov and Kochetkov (16). In a 50 mL Erlenmeyer flask, 0.96 g (17.1 mmol) of propargyl alcohol was mixed with 10 mL of a solution saturated with both mercuric chloride and sodium chloride. The reaction mixture was stirred for 1 h, and the resulting solid was filtered, washed with a little cold water and allowed to air dry. Recrystallization of the crude solid from benzene provided 3.35 g (10.2 mmol, 60%) of the desired mercurial: mp 105-107°C (lit. (16) mp 105°C); ^1H NMR (acetone-d_6) δ 3.21 (br s, 1H, OH), 4.30 (d, 2H, J=1.8 Hz, CH_2), 6.27 (t, 1H, J=1.8 Hz, HC=C).

E-3-Chloro-4-chloromercuri-2-methyl-3-buten-2-ol (153) was prepared in identical fashion: yield 34%; mp 69-70°C (lit. (16) mp 70°C); ^{1}H NMR (acetone-d_6) δ 1.51 (s, 6H, CH_3), 5.05 (s, 1H, OH), 6.01 (s, 1H, HC=C).

2-Acetoxymercuri-4-methylacetanilide (156). The title compound was prepared according to the procedure of Bell (206). In a 50 mL round-bottom flask, 3.66 g (10 mmol) of 2-acetoxymercuri-4-methylaniline was stirred overnight with 20 mL of acetic anhydride. The solid was filtered, washed with 10 mL of water and 15 mL of cold ether and dried to give 2.67 g (6.55 mmol, 66%) of compound 156: mp 175-178°C (lit. (206) 178°C); ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 2.31 (s, 3H, $ArCH_3$), 6.85-7.78 (m, 3H, C_6H_3), 9.36 (br s, 1H, NH).

3-Acetoxymercuri-2,4-pentanedione (161). This mercurial was prepared from 2,4-pentanedione using the procedure of Allmann and coworkers (212). To a solution of 2.50 g (25.0 mmol) of 2,4-pentanedione in 50 mL of ethanol was added a solution of 8.0 g (25.1 mmol) of mercuric acetate in 100 mL of water. The reaction mixture was stirred for 1 h and the resulting precipitate was filtered, washed with cold water and cold ether, and allowed to air dry for 5 h: yield 69%; mp 251°C (dec.); IR (nujol) 1690 (C=O), 1660 (C=O), 1635 (C=O) cm^{-1}.

Lactones 115-127 were all prepared in a similar manner. In the case of acyclic dienes and vinylcyclopranes only two equivalents of diene were used. The preparation of lactone 115 is representative.

Lactone 115. To a solution of 0.178 g (1.0 mmol) of palladium chloride and 0.043 g (1.0 mmol) of lithium chloride in 20 mL of dry acetonitrile at 0°C under nitrogen were added 0.40 g (5 mmol) of 1,3-

cyclohexadiene and 0.340 g (1.0 mmol) of mercurial 114. The solution was allowed to warm to room temperature and stirred overnight. Potassium carbonate (2 mmol) was then added and the reaction mixture was refluxed for 5 h, diluted with 5 mL of ether and a small amount of activated carbon was added. The mixture was filtered through Celite, washed with saturated ammonium chloride, dried ($MgSO_4$) and concentrated. The concentrate was purified by column chromatography using hexanes-ethyl acetate (2:1) as the eluent to provide 0.130 g (0.71 mmol, 71%) of lactone 115 (R_f 0.33): mp 70-71°C; ^1H NMR ($CDCl_3$) δ 1.34-2.33 (m, 4H, CH_2), 2.94-3.46 (m, 1H, CH), 4.82 (dd, 1H, J=7 Hz, J=2.6 Hz, -CHO-), 5.62-6.33 (m, 2H, HC=CH), 6.64 (d, 1H, J=2 Hz, C=CHCl); IR (neat) 3060 (C=CH), 3030 (C=CH), 1760 (C=O), 1635 (C=C) cm^{-1}; mass spectrum m/z 186.02537 (calcd for $C_9H_9\,^{37}ClO_2$, 186.02616).

Lactone 116: yield 74%; ^1H NMR ($CDCl_3$) δ 1.75 (d, 3H, J=5.8 Hz, CH_3), 2.51-3.49 (m, 2H, CH_2), 4.91 (q, 1H, J=6.8 Hz, -CHO-), 5.38-6.01 (m, 2H, CH=CH), 6.67 (dd overlapping, 1H, J=2.4 Hz, J=2.0 Hz, C=CHCl) (the 300 MHz spectrum in the region 5.37-6.14 indicated compound 116 to be the trans isomer J=15.37 Hz); IR (neat) 3045 (C=CH), 1760 (C=O), 1665 (C=C), 1620 (C=C) cm^{-1}; mass spectrum m/z 172.02892 (calcd for $C_8H_9ClO_2$, 172.02911).

Lactone 117: yield 32%; ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H, CH_3), 1.69 (d, 3H, J=1.2 Hz, $C=CCH_3$), 2.79-3.10 (m, 2H, CH_2), 4.89 (br s, 1H, C=CH), 5.05 (br s, 1H, C=CH), 6.64 (dd overlapping, 1H, J=2.3 Hz, J=2.0 Hz, C=CHCl); IR (neat) 3060 (C=CH), 1765 (C=O), 1640 (C=C), 1630 (C=C) cm^{-1}; mass spectrum m/z 186.04481 (calcd for $C_9H_{11}ClO_2$, 186.04476).

Lactones 118 and 119: yield 61%; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 3H, CH_3 of 119), 1.74 (s, 3H, CH_3 of 118), 2.86-3.25 (m, 2H, CH_2), 4.84-5.28 (m, olefin of 118 and 119, -CHO- of 118), 6.62 (dd overlapping, 1H, J=1.92 Hz, J=2.40 Hz, C=CHCl); IR (neat) 3050 (C=CH), 1760 (C=O), 1635 (C=C), 1620 (C=C) cm^{-1}; mass spectrum m/z 172.02884 (calcd for $C_8H_9ClO_2$, 172.02911).

Lactone 120: yield 67%; ^{1}H NMR ($CDCl_3$) δ 1.77 (br s, 6H, CH_3), 2.42-3.41 (m, 2H, CH_2), 5.03-5.36 (m, 2H, C=CH and -CHO-), 6.68 (dd overlapping, 1H, J=2.5 Hz, J=2.0 Hz, C=CHCl); IR (neat) 3080 (C=CH), 1770 (C=O), 1645 (C=C) cm^{-1}; mass spectrum m/z 186.04525 (calcd for $C_9H_{11}ClO_2$, 186.04476).

Lactone 121: yield 59%; mp 93-95°C; ^{1}H NMR ($CDCl_3$) δ 2.13-3.28 (m, 2H, CH_2), 3.42-3.84 (m, 1H, CH), 5.43 (dd, 1H, J=7.0 Hz, J=2.0 Hz -CHO-), 5.64-6.12 (m, 2H, HC=CH), 6.63 (d, 1H, J=2.1 Hz, C=CHCl); IR (film) 3060 (C=CH), 1755 (C=O), 1660 (C=C), 1615 (C=C) cm^{-1}; mass spectrum m/z 170.01386 (calcd for $C_8H_7ClO_2$, 170.01346).

Lactones 124 and 125: yield 38%; ^{1}H NMR ($CDCl_3$) for 124: δ 1.50 (s, 3H, CH_3), 2.78-3.01 (m, 2H, CH_2), 3.37 (d, 2H, J=4.7 Hz, $ArCH_2$), 5.59-5.93 (m, 2H, HC=CH), 6.58 (dd overlapping, 1H, J=2.6 Hz, J=2.1 Hz, C=CHCl), 7.07-7.54 (m, 5H, C_6H_5); for 125: δ 1.42 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.76-3.00 (m, 2H, CH_2), 4.72 (br s, 1H, C=CH), 6.32 (dd overlapping, 1H, J=2.3 Hz, J=2.1 Hz, C=CHCl), 7.05-7.54 (m, 5H, C_6H_5); IR (neat) 3060 (C=CH), 3020 (C=CH), 1760 (C=O), 1635 (C=C) cm^{-1}; mass spectrum m/z 262.07640 (calcd for $C_{15}H_{15}ClO_2$, 262.07606). Capillary gas chromatographic analysis indicated that compound 125 was only one isomer.

Lactone 126: yield 60%; ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 3H, CH_3), 1.65 (d, 3H, J=6.8 Hz, CH_3), 2.76-3.13 (m, 2H, CH_2), 4.86 (t, 1H, J=7.1 Hz, -CHO-), 5.62 (q, 1H, J=6.4 Hz, C=CH), 6.65 (t, 1H, J=2.3 Hz, C=CHCl); IR (neat) 3080 (C=CH), 1760 (C=O), 1635 (C=C) cm^{-1}; mass spectrum m/z 186.04451 (calcd for $C_9H_{11}ClO_2$, 186.04476).

Lactone 127: yield 64%; ^{1}H NMR ($CDCl_3$) δ 1.64-2.97 (m, 4H, CH_2), 4.56-4.98 (m, 1H, -CHO-), 5.02-6.21 (m, 3H, $HC=CH_2$), 6.59 (t, 1H, J=2.1 Hz, C=CHCl); IR (neat) 3070 (C=CH), 1725 (C=O), 1640 (C=C), 1600 (C=C) cm^{-1}; mass spectrum m/z 172.02858 (calcd for $C_8H_9ClO_2$, 172.02911).

The following dihydroisocoumarin derivatives were prepared in the same manner starting from 2-chloromercuribenzoic acid (129).

Compound 130: yield 76%; isolated by column chromatography (hexanes-ethyl acetate (4:1) R_f 0.30); ^{1}H NMR ($CDCl_3$) δ 1.73 (d, 3H, J=4.5 Hz, CH_3), 2.99 (d, 2H, J=7.0 Hz, CH_2), 4.92 (q, 1H, J=6.8 Hz, -CHO-), 5.37-6.14 (m, 2H, CH=CH), 7.06-8.10 (m, 4H, C_6H_4) (the 300 MHz spectrum of the olefin region indicated compound 130 to be the trans isomer, J=15.3 Hz); IR (neat) 3020 (C=CH), 1720 (C=O) cm^{-1}; mass spectrum m/z 188.08439 (calcd for $C_{12}H_{12}O_2$, 188.08373).

Compound 131: yield 33%; ^{1}H NMR ($CDCl_3$) δ 1.56-2.52 (m, 4H, CH_2), 2.70-3.21 (m, 1H, CH), 4.98 (t, 1H, J=5 Hz, -CHO-), 5.81-6.32 (m, 2H, HC=CH), 7.13-8.28 (m, 4H, C_6H_4); IR (neat) 3030 (C=CH), 1725 (C=O), 1600 (C=C) cm^{-1}; mass spectrum m/z 200.08368 (calcd for $C_{13}H_{12}O_2$, 200.08373).

γ-Butyrolactone 133. To a 0°C mixture of 0.085 g (2.0 mmol) of anhydrous lithium chloride, 0.178 g (1.0 mmol) of palladium chloride and 0.430 g (5.0 mmol) of 3-butenoic acid in 20 mL of dry tetrahydrofuran was

added 0.333 g (1.0 mmol) of E-2-chloromercuri-4,4-dimethyl-2-pentene (132). The resulting mixture was allowed to warm to room temperature and stirred overnight. Then, 0.280 g (2.0 mmol) of potassium carbonate was added and the mixture was refluxed for 5 h, diluted with 5 mL of ether and a small amount of activated carbon was added. The resulting mixture was filtered through Celite, washed with ammonium chloride and saturated sodium bicarbonate, dried ($MgSO_4$) and concentrated. Column chromatography of the residue using hexanes-ethyl acetate (2:1) as the eluent provided 0.111 g (0.61 mmol, 61%) of the desired lactone (R_f 0.42). ^1H NMR ($CDCl_3$) δ 1.12 (s, 9H, t-C_4H_9), 1.72 (d, 3H, J=1 Hz, CH_3), 2.14-2.73 (m, 4H, CH_2), 4.75 (t, J=7.5 Hz, -CHO-), 5.52 (br s, 1H, C=CH); IR (neat) 1770 (C=O), 1650 (C=C) cm^{-1}; mass spectrum m/z 172.13034 (calcd for $C_{11}H_{18}O_2$, 182.13068).

δ-Valerolactone 135 was prepared in identical fashion using acetonitrile as the solvent: yield 76%; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H, t-C_4H_9), 1.81 (d, 3H, J=1 Hz, CH_3), 1.89-2.79 (m, 6H, CH_2), 4.80 (t, 1H, J=7.2 Hz, -CHO-), 5.79 (br s, 1H, C=CH); IR (neat) 1725 (C=O), 1640 (C=C) cm^{-1}; mass spectrum m/z 196.14671 (calcd for $C_{12}H_{20}O_2$, 196.14633).

γ-Butyrolactone 138 was prepared in the same manner using trans-1-pentenylmercuric chloride 136: yield 31%; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=6 Hz, CH_3), 1.07-2.79 (m, 8H, CH_2), 4.82 (q, 1H, J=7 Hz, -CHO-), 5.43-5.94 (m, 2H, HC=CH, from 300 M Hz J=15.3 Hz); IR (neat) 1770 (C=O), 1650 (C=C) cm^{-1}; mass spectrum m/z 154.09979 (calcd for $C_9H_{14}O_2$ 154.09938).

γ-Butyrolactone 139. In a 25 mL round-bottom flask, 0.130 g (0.5 mmol) of bis(acetonitrile)dichloropalladium(II) was dissolved in 15 mL of

dry acetonitrile. The solution was cooled to -20°C and 0.215 g (2.5 mmol) of 3-butenoic acid and 0.187 g (0.5 mmol) of trans-1-decenylmercuric chloride were added. The reaction was stirred at -20°C for ~2 hr, then, allowed to warm to room temperature and stirred overnight. To the solution, 0.140 g (1.0 mmol) of potassium carbonate was added and the mixture was refluxed for 5 h. Work-up as described for 133 provided 0.070 g (0.313 mmol, 63%) of the desired lactone: ^{1}H NMR ($CDCl_3$) δ 0.68-1.62 (m, 17H, C_8H_{17}), 1.76-2.73 (m, 4H, CH_2), 4.85 (q, 1H, J=6.3 Hz, -CHO-), 5.23-6.01 (m, 2H, HC=CH, from 300 M Hz J=15.4 Hz); IR (neat) 1765 (C=O), 1660 (C=C) cm^{-1}; mass spectrum m/z 224.17709 (calcd for $C_{14}H_{24}O_2$, 224.17764).

δ-Valerolactone 140 was prepared in the same manner: yield 59%; ^{1}H NMR ($CDCl_3$) δ 0.68-1.59 (m, 17H, C_8H_{17}), 1.63-2.71 (m, 6H, CH_2), 4.52-4.91 (m, 1H, -CHO-), 5.25-5.98 (m, 2H, HC=CH, 300 M Hz J=15.7 Hz); IR (neat) 1725 (C=O) cm^{-1}; mass spectrum m/z 238.19321 (calcd for $C_{15}H_{26}O_2$, 238.19329).

Dihydrobenzofuran 142. To a -20°C solution of 0.088 g (0.5 mmol) of palladium chloride and 0.022 g (0.5 mmol) of lithium chloride in 10 mL of dry acetonitrile under nitrogen were added 0.170 g (2.5 mmol) of cis-1,3-pentadiene and 0.164 g (0.5 mmol) of 2-chloromercuri-4-methylphenol. After stirring at -20°C for 1.5 h, the reaction mixture was slowly warmed to room temperature and stirred overnight. Sodium hydride (1.0 mmol) was then added and the reaction mixture was refluxed for 5 h, diluted with 5 mL of ether and a small amount of activated carbon was added. The mixture was filtered through Celite, washed with saturated ammonium

chloride, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography using hexanes-ethyl acetate (15:1) as the eluent to yield 0.077 g (0.44 mmol, 88%) of the desired heterocycle (R_f 0.47): ^1H NMR ($CDCl_3$) δ 1.69 (d, 3H, J=4.5 Hz, CH_3), 2.27 (s, 3H, $ArCH_3$), 2.81-3.32 (m, 2H, CH_2), 4.82-5.30 (m, 1H, -CHO-), 5.57-5.98 (m, 2H, HC=CH), 6.55-7.02 (m, 3H, C_6H_3); IR (neat) 3015 (C=CH), 1675 (C=C), 1615 (C=C) cm^{-1}; mass spectrum m/z 174.10384 (calcd for $C_{12}H_{14}O$, 174.10447).

The following compounds were prepared in identical fashion.

Compound 143: yield 86%; ^1H NMR ($CDCl_3$) δ 1.43-2.17 (m, 4H, CH_2), 2.25 (s, 3H, $ArCH_3$), 3.02-3.49 (m, 1H, CH), 4.87 (dd, 1H, J=8 Hz, J=2.0 Hz, -CHO-), 5.90-6.17 (m, 2H, HC=CH), 6.57-7.00 (m, 4H, C_6H_4); IR (neat) 3045 (C=CH), 1660 (C=C), 1625 (C=C) cm^{-1}; mass spectrum m/z 186.10455 (calcd for $C_{13}H_{14}O$, 186.10447).

Compound 144: yield 62%; ^1H NMR ($CDCl_3$) δ 1.73-2.08 (m, 2H, CH_2), 2.24 (s, 3H, $ArCH_3$), 2.55-2.93 (m, 2H, CH_2), 4.23-4.61 (m, 1H, -CHO-), 5.00-6.26 (m, 3H, $HC=CH_2$), 6.69-7.00 (m, 3H, C_6H_3); IR (neat) 3015 (C=CH), 1600 (C=C) cm^{-1}; mass spectrum m/z 174.10399 (calcd for $C_{12}H_{14}O$ 174.10447).

Compounds 145 and 146: yield 83%; ^1H NMR ($CDCl_3$) δ 1.50 (s, 3H, CH_3 of 146), 1.72 (d, 3H, J=1 Hz, CH_3 of 145), 2.27 (s, 3H, $ArCH_3$), 2.73-3.36 (m, 2H, CH_2), 4.68-5.41 (m, olefin of 145 and 146, -CHO- of 145), 6.52-7.13 (m, 3H, C_6H_3); IR (neat) 3020 (C=CH), 1635 (C=C), 1600 (C=C) cm^{-1}; mass spectrum m/z 174.10399 (calcd for $C_{12}H_{14}O$, 174.10447).

Compound 149. This compound was prepared similarly using 2-chloromercuribenzyl alcohol (148): yield 40%; ^1H NMR ($CDCl_3$) δ 1.73 (d,

3H, J=4.5 Hz, CH_3), 2.77 (d, 2H, J=6 Hz, CH_2), 4.13 (q, 1H, J=6 Hz, -CHO-), 4.82 (br s, 2H, CH_2O), 5.56-5.89 (m, 2H, HC=CH), 6.75-7.33 (m, 4H, C_6H_4); IR (neat) 3010 (C=CH), 1620 (C=C), 1600 (C=C) cm^{-1}; mass spectrum m/z 174.10431 (calcd for $C_{12}H_{14}O$, 174.10447).

Compound 152. To a -20°C solution of 0.088 g (0.5 mmol) of palladium chloride and 0.022 g (0.5 mmol) of lithium chloride in 10 mL of dry acetonitrile were added 0.20 g (2.5 mmol) of 1,3-cyclohexadiene and 0.164 g (0.5 mmol) of mercurial 150. The reaction mixture was stirred at -20°C for 2 h, then warmed to room temperature and stirred overnight. Sodium hydride (1.0 mmol) was then added and the reaction mixture was refluxed for 5 h, diluted with 5 mL of ether and a small amount of activated carbon was added. The mixture was filtered through Celite, washed with saturated ammonium chloride, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography using hexanes-ethyl acetate (15:1) to yield 0.020 g (0.12 mmol, 24%) of the cyclized compound (R_f 0.50): ^1H NMR ($CDCl_3$) δ 1.61-2.58 (m, 5H, CH_2 and CH), 3.83-4.02 (m, 1H, -CHO-), 4.13 (t, 2H, J=1.8 Hz, CH_2O), 5.70-6.18 (m, 3H, HC=CH and HC=C); IR (neat) 3030 (C=CH), 1630 (C=C) cm^{-1}; GC/MS, m/z (relative intensity) 172 (15.5, M + 2), 170 (51, M^+), 135 (94).

The following compounds were prepared in a similar manner using bis(acetonitrile)dichloropalladium(II) and the experimental changes indicated.

Compound 151: yield 13%; ^1H NMR ($CDCl_3$) δ 1.61 (d, 3H, J=5 Hz, CH_3), 2.1-2.5 (m, 2H, CH_2), 3.80-4.03 (m, 1H, -CHO-), 4.17 (t, 2H, J=2 Hz, CH_2O), 5.58-6.02 (m, 3H, HC=CH and HC=C); IR (neat) 3025 (C=CH), 1620

(C=C) cm^{-1}; GC/MS, m/z (relative intensity) 160 (1.15, M + 2), 158 (3.76, M^+).

Compound 154: 10 equivalents of diene; yield 70%; ^1H NMR ($CDCl_3$) δ 1.49 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.73 (d, 3H, J=5.2 Hz, CH_3), 2.28-2.75 (m, 2H, CH_2), 4.09-4.56 (m, 1H, -CHO-), 5.32-5.79 (m, 2H, HC=CH), 5.94 (t, 1H, J=2 Hz, HC=C); IR (neat) 3030 (C=CH), 1615 (C=C) cm^{-1}; mass spectrum m/z 186.08089 (calcd for $C_{10}H_{15}ClO$, 186.08115).

Compound 155: 1 equivalent of magnesium oxide; yield 51%; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.58-2.21 (m, 4H, CH_2), 2.50-2.88 (m, 1H, CH), 4.21-4.46 (m, 1H, -CHO-), 5.89-6.15 (m, 3H, HC=CH and HC=C); IR (neat) 3050 (C=CH), 3020 (C=CH), 1635 (C=C) cm^{-1}; mass spectrum m/z 198.08150 (calcd for $C_{11}H_{15}ClO$, 198.08115).

Dihydroindole 157. A solution of 0.178 g (1.0 mmol) of palladium chloride and 0.043 g (1.0 mmol) of lithium chloride in 20 mL of dry acetonitrile under nitrogen was cooled to 0°C and 0.340 g (5.0 mmol) of cis-1,3-pentadiene was added followed by 0.408 g (1.0 mmol) of mercurial 156. The solution was allowed to warm to room temperature and stirred overnight. Sodium hydride (2 mmol) was then added and the reaction mixture was refluxed for 5 h, diluted with 10 mL of ether and a small amount of activated carbon was added. The mixture was filtered through Celite, washed with saturated ammonium chloride, dried ($MgSO_4$) and concentrated. The concentrate was purified by column chromatography using hexanes-ethyl acetate (2:1) as the eluent to provide 0.152 g (0.71 mmol, 71%) of the pure dihydroindole (R_f 0.32); ^1H NMR ($CDCl_3$) δ 1.63 (d, 3H, J=5.0 Hz, CH_3), 2.18 (s, 3H, $COCH_3$), 2.26 (s, 3H, $ArCH_3$), 2.51-

3.48 (m, 2H, CH_2), 4.51-4.89 (m, 1H, CHN), 5.35-5.77 (m, 2H, HC=CH), 6.80-7.13 (m, 2H, H-4, H-6), 8.02 (br s, 1H, H-7); IR (neat) 3010 (C=CH), 1650 (C=O), 1605 (C=C) cm^{-1}; mass spectrum m/z 215.13047 (calcd for $C_{14}H_{17}NO$, 215.13102).

The following compounds were prepared in a similar manner.

Compound 158: yield 74%; mp 123-125°C; ^1H NMR ($CDCl_3$) δ 1.78-2.15 (m, 4H, CH_2), 2.30 (br s, 6H, $COCH_3$, $ArCH_3$), 3.42-3.84 (m, 1H, CH), 4.79 (d, 2H, J=7.5 Hz, CHN), 5.49-6.00 (m, 2H, HC=CH), 6.80-7.29 (m, 2H, H-4, H-6), 7.98 (d, 1H, J=8 Hz, H-7); IR (film) 3015 (C=CH), 1655 (C=O), 1600 (C=C) cm^{-1}; mass spectrum m/z 227.13027 (calcd for $C_{15}H_{17}NO$ 227.13102).

Compound 159: yield 20%; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H, $COCH_3$), 2.30 (s, 3H, $ArCH_3$), 2.41-2.73 (4H, m, CH_2), 4.79-4.98 (m, 1H, CHN), 5.01-5.81 (m, 3H, $HC=CH_2$), 6.84-7.30 (m, 3H, C_6H_3); IR (film) 3040 (C=CH), 1665 (C=O), 1600 (C=C) cm^{-1}; mass spectrum m/z 215.13068 (calcd for $C_{14}H_{17}NO$, 215.13102).

Compound 162. To a 0°C solution of 0.088 g (0.5 mmol) of palladium chloride and 0.022 g (0.5 mmol) of lithium chloride in 10 mL of acetonitrile were added 0.068 g (1.0 mmol) of cis-1,3-pentadiene and 0.180 g (0.5 mmol) of 3-acetoxymercuri-2,4-pentanedione. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was filtered through Celite, washed with 20 mL of saturated ammonium chloride and dried ($MgSO_4$). The solution was placed in a 50 mL round-bottom flask and sodium hydride (0.5 mmol) was added. The reaction mixture was refluxed for 5 h, diluted with ether and a small amount of activated carbon was added. The mixture was filtered through Celite,

washed with saturated ammonium chloride, dried ($MgSO_4$) and concentrated. The concentrate was purified by column chromatography using hexanes-ethyl acetate (3:1) as the eluent to provide 0.027 g (0.163 mmol, 33%) of compound 162: ^1H NMR ($CDCl_3$) δ 1.69 (d, 3H, J=5.0 Hz, CH_3), 2.18 (m, 6H, $COCH_3$ and CH_3), 2.50-3.17 (m, 2H, CH_2), 4.68-5.07 (m, 1H, -CHO-), 5.43-5.82 (m, 2H, HC=CH); IR (neat) 3010 (C=CH), 1650-1580 (C=C and C=O) cm^{-1}; GC/MS, m/z (relative intensity) 166 (63, M^+), 151 (5), 123 (100).

CONCLUSION

In this work, two new organometallic approaches to heterocyclic ring systems were developed. First, the mercuration of aryl acetylenes provides a broad range of naturally occurring, physiologically active heterocyclic ring systems, including benzofurans, benzothiophenes, isocoumarins, chromones, benzopyrans, coumarins, and coumestan. The mercury moiety in many of these compounds can be substituted by various methods to provide more highly functionalized heterocycles. The reaction of an organomercurial with a diene or an olefin in the presence of a palladium(II) salt provides another method for the preparation of heterocycles. The approach involves the intramolecular attack of an oxygen or a nitrogen mucleophile on a π-allylpalladium intermediate. In the reaction, both a new carbon-carbon bond and a new carbon-heteroatom bond are formed. Using this method, lactones, dihydrobenzofurans, dihydroindoles, and pyrans can be prepared in good yields.

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ACKNOWLEDGEMENTS

I wish to thank my major professor, Richard Larock, for his guidance and support during the course of this work. I would also like to thank my family for their encouragement. I wish to acknowledge the members of the Larock group and many others in the department for providing both valuable discussions and comic relief. I wish to express my gratitude to Deb Austin for her help in the preparation of the structures and to Deb Arneson for typing this manuscript.