1983

# Synthesis of heterocycles via organopalladium intermediates

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SYNTHESIS OF HETEROCYCLES VIA ORGANOPALLADIUM INTERMEDIATES

*Iowa State University* PH.D. 1983

# Synthesis of heterocycles via organopalladium intermediates

by

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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

1983

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# I. GENERAL INTRODUCTION

In recent years, remarkable advances in organic syntheses via transition metal complexes have occurred. Among the transition metal complexes used for organic syntheses, those of palladium have had a unique position since 1960. For a long time, palladium had been used in organic synthesis only as a catalyst for hydrogenation. After the epoch-making introduction in 1960 of the Wacker process, by which acetaldehyde is produced from ethylene using palladium as a catalyst [1,2], palladium was recognized as a versatile reagent for organic syntheses. Since then, many synthetic reactions using palladium have been discovered.

The transmetallation of organotransition metal compounds with palladium (II) halides is an established method of forming organopalladium compounds. The insertion of carbon monoxide, olefins, acetylenes, or other unsaturated molecules into palladium-carbon or palladium-hydrogen bonds has established the importance of organopalladium chemistry in synthetic organic chemistry. Although this area of palladium chemistry is well known [3,4,5], current research interest is still high.

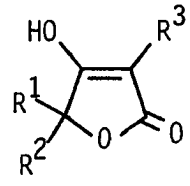
The aim of the work in this dissertation has been to study the synthesis of heterocycles via organopalladium intermediates. The following chapters of this dissertation will describe the syntheses of various heterocycles. First, furans have been prepared by mercuration and, subsequently, palladium-promoted carbonylation of 4-hydroxy-2-alkyn-1-ones. Second, a new approach to tetronic acid via mercuration-

acetoxylation of allenic acid and ester has been examined. Third, a new approach to the synthesis of tetracyclic sesquiterpenes via vinylation-carbonylation of 2,3-dimethylnorbornadiene-palladium dichloride was explored. Finally, lactones, lactams, and indoles have been prepared by palladium-assisted olefination of thallated _p_-tolylacetic acid, benzamide, _N_-methylbenzamide, and acetanilide.

# II. MERCURATION AND SUBSEQUENT CARBONYLATION OF 4-HYDROXY-2-ALKYN-1-ONES

## A. Introduction

Unsaturated five-membered ring lactones, butenolides, occur widely in nature [6], especially in cardenolides and tetronic acids (1) [7].



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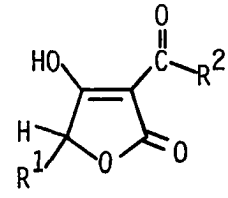
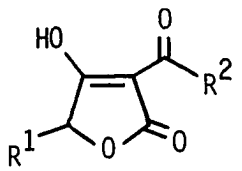
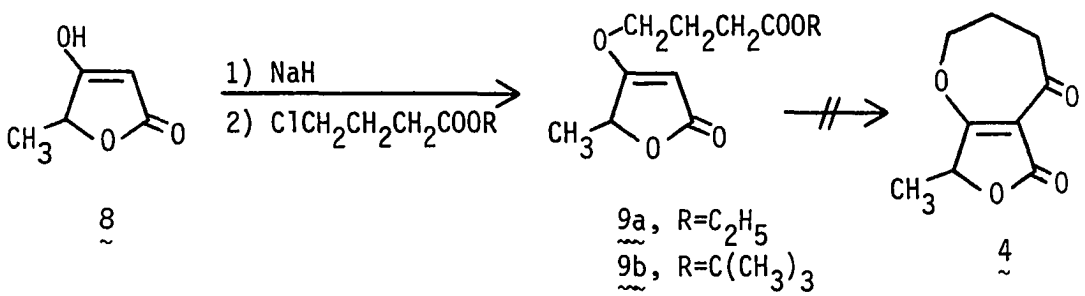


2

The chemistry of tetronic acids has been reviewed earlier by Haynes and Plimmer [7]. α-Acyltetronic acids (2), an important class of biologically active compounds [7-18], are also found as mold metabolites. Clutterback and his co-workers [9] have isolated a series of related α-acyltetronic acids: carolinic (3), carolic (4), carlic (5), and carlosic (6) acids. Birkinshaw and Raistrick [10] have also obtained terrestric acid (ethylcarolic acid) (7) from P. terrestre Jensen. Recently, the attempted synthesis of carolic acid (4, anhydrous form) from O-alkylated 5-methyltetronic acid (9) has been studied by Pollet and Gelin [19]. Unfortunately, closure of the seven-membered ring by various methods failed (eq. 1). This result suggests that the introduction of the α-acyl group at an earlier stage in the synthesis is necessary.



| | $R^1$ | $R^2$ |
|---|---|---|
| 3 | $CH_3$ | $CH_2CH_2COOH$ |
| 4, hydrated form | $CH_3$ | $CH_2CH_2CH_2OH$ |
| 5, hydrated form | $CH_2COOH$ | $CH_2CH_2CH_2OH$ |
| 6 | $CH_2COOH$ | $CH_2CH_2CH_3$ |
| 7, hydrated form | $CH_3$ | $CH_2CH_2CH(OH)CH_2CH_3$ |



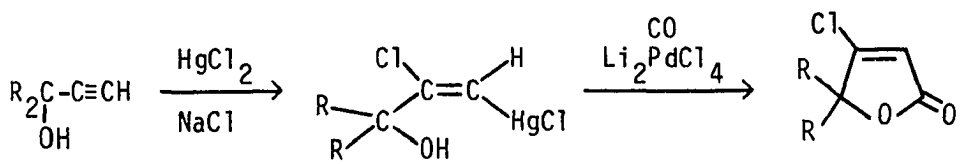

8

9a, R=$C_2H_5$
9b, R=$C(CH_3)_3$

4

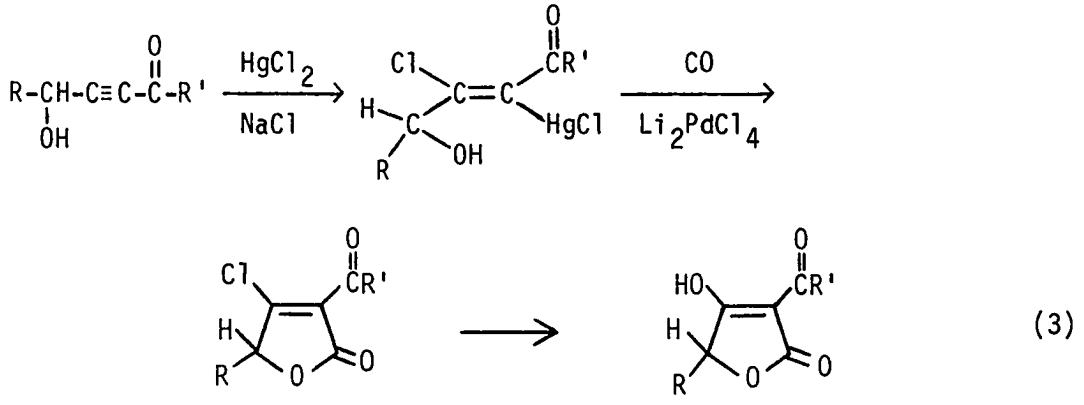
(1)

Recent work in our laboratory has provided a novel route to butenolides (eq. 2) [20, 21], which with suitable modifications appeared to hold

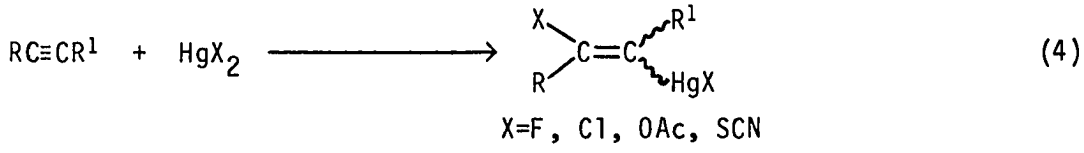



(2)

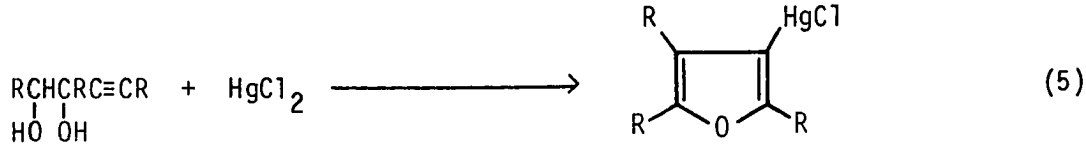
promise of providing a convenient new route to α-acyltetronic acids (eq. 3).



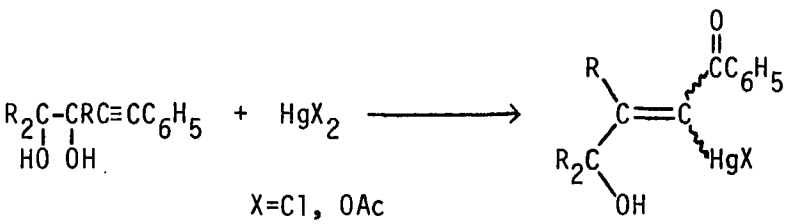
Mercury (II) salts are known to readily add to a variety of acetylenes to afford vinylmercurials (eq. 4). Thus, mercuric halides are



reported to add acetylene (anti) [22-27]; propyne (anti) [28]; cyclooctyne [29]; vinylacetylene (anti?) [28, 30-32]; alkynyl ethers [33-35]; propargylic alcohols (anti) [20, 21, 36] and halides (anti) [36, 37]; and α,β-unsaturated ketones [38], acids (anti) [39-41], and esters (anti?) [39, 42, 43] with the stereochemistry indicated. While the stereochemistry of addition has not always been determined, there appear to be no examples of mercuric halides adding to acetylenes in a syn fashion. Mercuric chloride also adds to certain acetylenic diols to afford furylmercurials (eq. 5) [44-50]. On the other hand, phenyl-

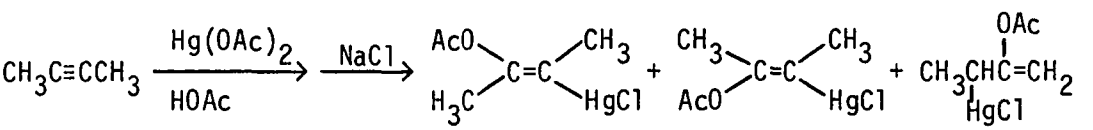


substituted acetylenic tertiary diols react with mercuric chloride and mercuric acetate to give vinylmercurials (eq. 6) [51-53]. The reaction



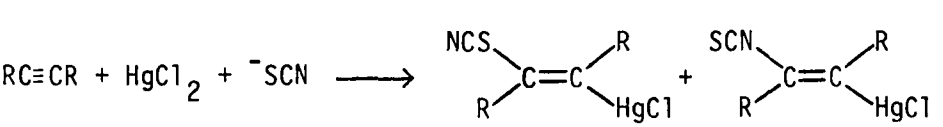
(6)

of acetylenes and mercuric acetate in acetic acid is reported to generate several different types of addition compounds. Terminal alkynes generally give dialkynylmercurials [54-56]. Simple internal aliphatic acetylenes appear to afford both regio- and stereochemical mixtures of vinylmercurials with anti adducts predominating [57-60], as illustrated by the reaction of 2-butyne (eq. 7) [61-63], while arylalkylacetylenes



(7)

yield regiochemical mixtures of exclusively anti adducts [55, 64, 65]. Diphenylacetylene affords both syn and anti addition compounds, but in this case the former predominates [61, 63, 64, 66]. Recently, mercuric chloride and thiocyanide anion have been reported to add to internal acetylenes to give both sulfur- and nitrogen-bonded anti addition products (eq. 8) [67].



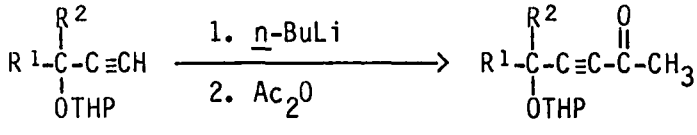
(8)

In attempting to extend our butenolides approach (eq. 2) to the synthesis of α-acyltetronic acids (eq. 3), we have examined the mercuration and subsequent carbonylation of 4-hydroxy-2-alkyn-1-ones. We wish to report here that the reaction of these acetylenes with mercuric chloride does not proceed as expected, but apparently affords the first example of the syn addition of mercuric chloride to an acetylene and provides a novel route to furylmercurials, which upon carbonylation afford furan-containing compounds.

## B. Results and Discussion

### 1. Preparation of 4-hydroxy-2-alkyn-1-ones

Several 4-hydroxy-2-alkyn-1-ones were prepared by the method of Duranti and Balsamini [68] with only slight modification. The commercially available acetylenic alcohols propargyl alcohol, 1-butyn-3-ol, and 3-methyl-1-butyn-3-ol were protected as the corresponding tetrahydropyranyl (THP) ethers, deprotonated by n-butyllithium, and then reacted with excess acetic anhydride at -78°C (eq. 9). The desired



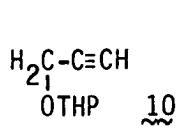
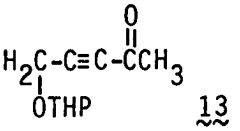
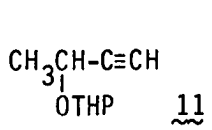
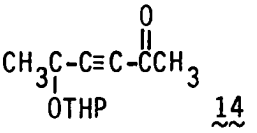
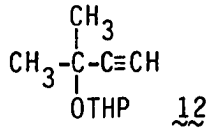
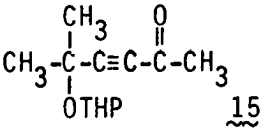

(9)

10, $R^1=R^2=H$ 13, $R^1=R^2=H$

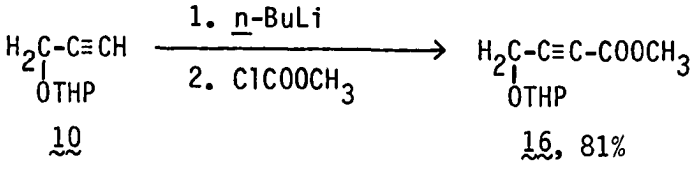
11, $R^1=H$, $R^2=CH_3$ 14, $R^1=H$, $R^2=CH_3$

12, $R^1=R^2=CH_3$ 15, $R^1=R^2=CH_3$

Table I. Preparation of 4-hydroxy-2-alkyn-1-ones

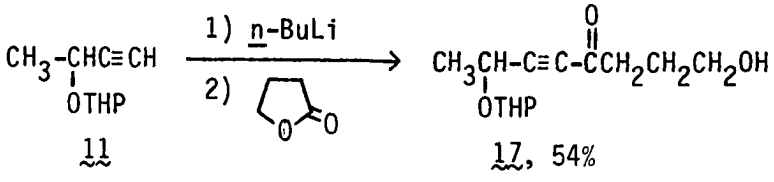
| Starting acetylene | Product | % Isolated yield | % Recovery of starting acetylene |
|---|---|---|---|
|  10 |  13 | 54 | 19 |
|  11 |  14 | 61 | 9 |
|  12 |  15 | 54 | 17 |

acetylenic ketones were obtained in modest yields, with 9~19% yields of recovered starting acetylenes (see Table I). We have also studied the reaction with acetyl chloride and found that the reaction with acetic anhydride gave cleaner results (two spots by thin layer chromatographic analysis). The reaction with acetyl chloride gave a mixture of four products which are both THP protected and deprotected starting acetylene and the desired products. The cleavage of the THP ether might be due to the small amount of hydrochloric acid generated during aqueous work-up. Since the corresponding 4-hydroxy-2-alkyn-1-ones are quite sensitive to light, heat and air, and can be stored for only short periods of time at -20°C in the dark [68], they are isolated and stored as their tetrahydropyranyl derivatives. The THP derivatives were deprotected only immediately prior to mercuration. Methyl 4-tetrahydropyranoxy-2-



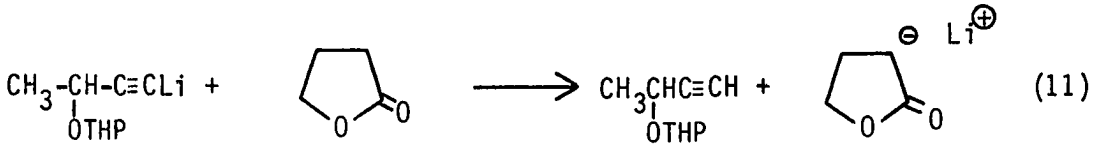

(9a)

butynoate (16) was prepared similarly (eq. 9a). 4-Oxo-7-tetrahydropyranyloxy-5-octyn-1-ol (17) has been synthesized by reaction of the appropriate lithium acetylide and γ-butyrolactone (eq. 10) [69, 70].



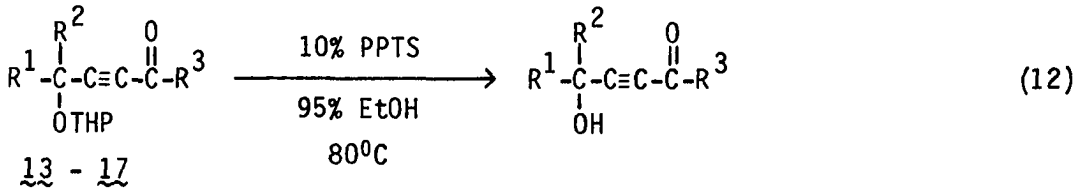

(10)

Here, 25% of the starting material was recovered from the reaction. The high percentage recovery of starting acetylene (11) suggested that an anion exchange reaction might have occurred to a certain extent (eq. 11).




(11)

The desired acetylenic alcohols can be obtained in almost quantitative yield by reacting the corresponding THP ethers with 10% pyridinium p-toluenesulfonate (PPTS) in 95% ethanol at 80°C (eq. 12) [71]. This reaction can be monitored by thin layer chromatography (TLC). After the reaction is complete, the reaction mixture was cooled to room temperature and solvent was removed under reduced pressure. The alcohols were isolated by passage through a short silica gel column to




13 - 17 (12)

18, $R^1=R^2=H$, $R^3=CH_3$
19, $R^1=H$, $R^2=R^3=CH_3$
20, $R^1=R^2=R^3=CH_3$
21, $R^1=R^2=H$, $R^3=OCH_3$
22, $R^1=H$, $R^2=CH_3$, $R^3=CH_2CH_2CH_2OH$

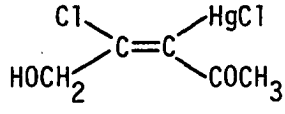
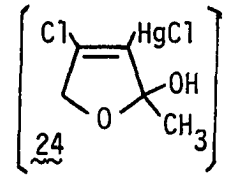
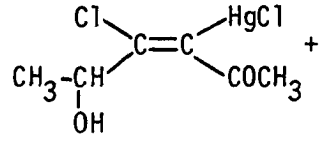
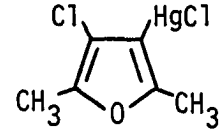
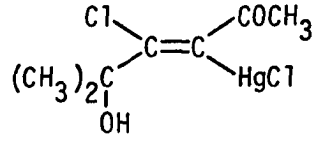
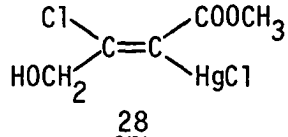
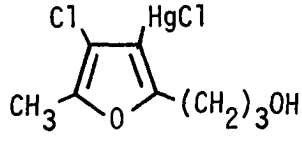
remove pyridinium p-toluenesulfonate (PPTS). Without further purification, the alcohols were used directly for the mercuration studies.

2. Mercuration of 4-hydroxy-2-alkyn-1-ones

The 4-hydroxy-2-alkyn-1-ones dissolved in a small amount of methanol were then treated in the dark at 0°C for 10-12 hours with an aqueous solution saturated with both mercuric chloride and sodium chloride. Simple filtration and a cold aqueous wash generally afforded high yields of a variety of interesting organomercurials, as summarized in Table II. The structures of the resulting products have been assigned on the basis of a variety of spectroscopic and analytical techniques as well as from the products resulting from their carbonylation (to be discussed later).

The initial product from the mercuration of 18 has been tentatively assigned structure 23. While we were unable to obtain a correct elemental analysis for this compound, $^1H$ NMR spectroscopy suggested that

Table II. Mercuration of 4-hydroxy-2-alkyn-1-ones

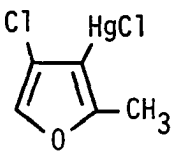
| 4-hydroxy-2-alkyn-1-one | Product(s) | % Yield[a] |
|---|---|---|
| 18 |  23 +  24 | 75 (30)[b] |
| 19 |  25 +  26 | 90 (63)[c] |
| 20 |  27 | 100 (72) |
| 21 |  28 | 100 (72) |
| 22 |  29 | 17 (13) |

[a]Isolated yield (recrystallized yield).

[b]After recrystallization, a small amount of 24 is formed.

[c]The recrystallized product is 26 only.

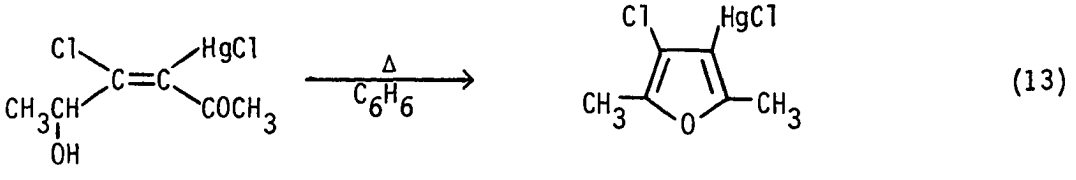
it is one pure compound and not a mixture of isomers. The infrared spectrum shows a strong carbonyl absorption. $^{13}C$ NMR analysis of this compound dissolved in acetone-$d_6$ overnight, however, showed peaks assignable to compound 24 and a furylmercurial 30. Subsequent $^{1}H$ NMR




30

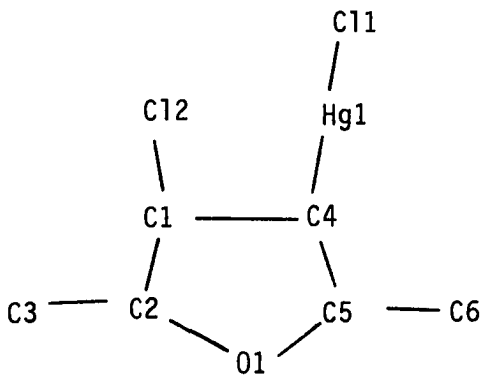
analysis of this same sample confirms this assignment. After recrystallization of the crude product 23, the $^{1}H$ NMR peak assigned to the methylene group in 23 changes from a clean doublet (coupled to the OH triplet) to an overlapping singlet and doublet, which suggests to us that compound 23 has partially isomerized to the corresponding hemiketal 24. The similar chemical shifts of these two peaks appear to rule out isomerization of an E isomer of 23 to the hemiketal 24, since one might expect significantly different chemical shifts for the methylene groups in two such different compounds. The furylmercurial 30 is not observed upon recrystallization. Unfortunately, neither 23 nor 24 can be isolated pure even after several recrystallizations. While the present evidence does not allow us to conclusively establish the stereochemistry of 23, the apparent formation of a cyclic hemiketal and furylmercurial and the furan-containing products obtained upon carbonylation (to be discussed later) are strongly suggestive of the Z isomer 23, which is shown.

The mercuration of 19 proceeds in high yield to give a mixture of an acyclic vinylmercurial (25) and a furylmercurial (26) in a ratio of 95:5 as judged by $^1$H NMR analysis. The ratio changes to 70:30 if the mercuration is run in 0.01 M HCl. Pure compound 25 can be obtained in low yield by very carefully recrystallizing the crude reaction mixture from benzene at low temperature and collecting only the first crystals formed. This compound gives a satisfactory elemental analysis and shows a strong carbonyl absorption in the infrared spectrum, thus tending to rule out a possible hemiketal structure. The Z stereochemistry shown is based on the formation of furyl-containing products upon carbonylation and the quantitative conversion of compound 25 to 26 upon refluxing in benzene (eq. 13). Pure 26 can also be obtained easily by twice




25 26 (13)

recrystallizing the crude mixture from benzene. The furan structure is supported by $^1$H NMR, elemental analysis, X-ray crystallography, and subsequent carbonylation results to be discussed later. The results of X-ray crystallographic analysis for compound 26 are shown in Figure 1 and selected bond angles and distances are listed in Table III. While it is conceivable that compound 25 has stereochemistry opposite to that shown, the addition of mercuric chloride to the carbon-carbon triple bond must then be readily reversible as it is difficult to see how the furan




Chemical formula: $C_6H_6HgCl_2O$

Crystal system: triclinic

Cell constants: a=7.582(2)Å b=13.912(3)Å c=4.181(1)Å

$\alpha$=93.91(3)° $\beta$=97.86(3)° $\gamma$=99.80(3)°

Z=2

P (2 $C_6H_6HgCl_2O$/cell) 2.75 g/cm$^3$

Fig. 1. Crystal data for compound 26

Table III. Selected bond angles and distances in compound 26

| | | | | | |
|---|---|---|---|---|---|
| | | angles,deg | | | |
| Cl(1)-Hg(1)-C(4) | 173.9(1) | | | Hg(1)-C(4)-C(1) | 122.4(1) |
| Hg(1)-C(4)-C(5) | 127.3(5) | | | Cl(2)-C(1)-C(4) | 126.1(3) |
| Cl(2)-C(1)-C(2) | 126.2(3) | | | C(1)-C(4)-C(5) | 109.5(4) |
| C(4)-C(1)-C(2) | 107.3(7) | | | C(1)-C(2)-O(1) | 108.0(2) |
| C(1)-C(2)-C(3) | 134.5(1) | | | C(3)-C(2)-O(1) | 117.4(1) |
| C(2)-O(1)-C(5) | 109.4(2) | | | O(1)-C(5)-C(6) | 113.3(4) |
| O(1)-C(5)-C(4) | 105.6(2) | | | C(4)-C(5)-C(6) | 141.1(2) |
| | | distances, Å | | | |
| Cl(1)-Hg(1) | 2.32(3) | Hg(1)-C(4) | 2.09(3) | Cl(2)-C(1) | 1.76(0) |
| C(1)-C(4) | 1.40(1) | C(1)-C(2) | 1.30(4) | C(2)-C(3) | 1.53(3) |
| C(2)-O(1) | 1.37(3) | O(1)-C(5) | 1.36(1) | C(5)-C(6) | 1.48(2) |
| C(5)-C(4) | 1.32(4) | | | | |

products can come from any compound other than the Z isomer shown. It therefore appears that mercuric chloride undergoes syn addition to both compounds 18 and 19, contrary to all previous reports of mercuric halide addition to acetylenes, including simple acetylenic alcohols [20,21,36] and ketones [38].

On the other hand, compound 20 appears to afford the more normal anti adduct, 27, upon mercuration. Only one pure compound is obtained, as judged by the $^{1}H$ and $^{13}C$ NMR spectra and elemental analysis. The presence of a strong carbonyl stretch in the infrared spectrum tends to rule out a hemiketal syn addition compound analogous to 24. Unfortunately, we have been unable to grow crystals of this compound suitable for X-ray crystallographic analysis. Carbonylation of 27 proceeds to give a mixture of products, most important of which is the expected butenolide. Mercuration, therefore, appears to either proceed

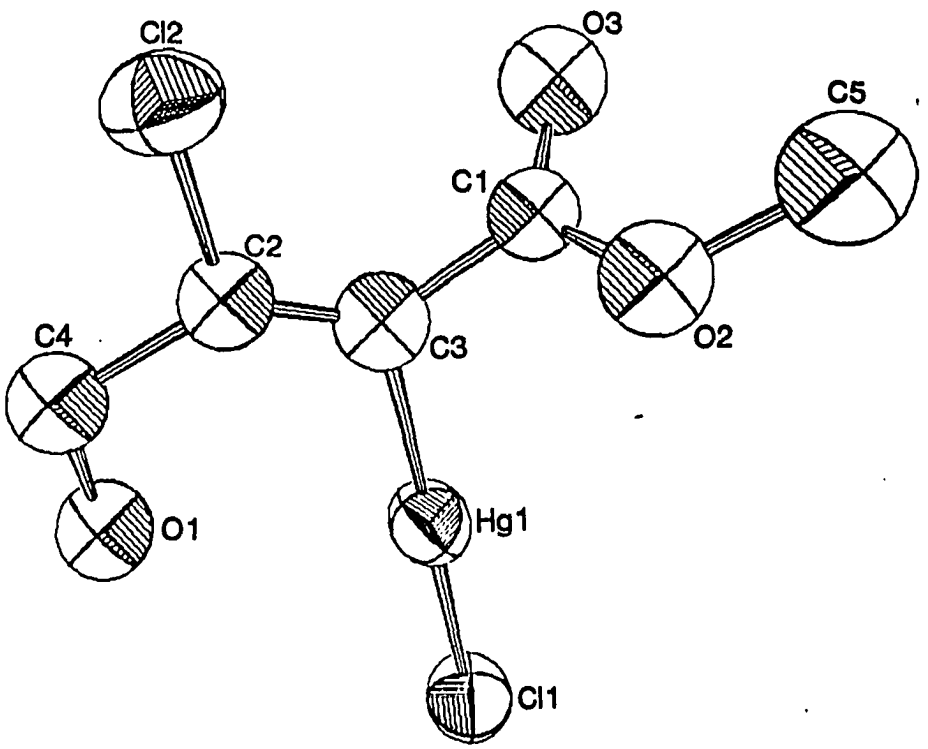
directly to the anti addition adduct 27 or forms the syn adduct, which isomerizes during carbonylation.

The mercuration of compound 21 affords a high yield of a vinylmercurial, 28, whose stereochemistry we have established by X-ray crystallographic analysis. The crystal structure of compound 28 is shown in Figure 2, and selected bond angles and distances are listed in Table IV. Elemental analysis and $^{1}H$ and $^{13}C$ NMR spectra also indicate that only one isomer is formed. Upon attempted carbonylation of 28, 50-60% of the starting mercurial is recovered and no other products are observed.

Table IV. Selected bond angles and distances in compound 28

| | angles, deg | | |
|---|---|---|---|
| Cl(1)-Hg(1)-C(3) | 176.7(8) | C(1)-O(2)-C(5) | 119.8(24) |
| O(2)-C(1)-O(3) | 123.1(25) | O(2)-C(1)-C(3) | 114.2(23) |
| O(3)-C(1)-C(3) | 122.7(24) | Cl(2)-C(2)-C(3) | 119.4(22) |
| Cl(2)-C(2)-C(4) | 107.8(17) | Hg(1)-C(3)-C(1) | 113.7(18) |
| Hg(1)-C(3)-C(2) | 118.8(21) | C(1)-C(3)-C(2) | 127.6(26) |
| O(1)-C(4)-C(2) | 109.6(21) | | |
| | distances, Å | | |
| Hg(1)-C(3) | 2.13(3) | Hg(1)-Cl(1) | 2.33(1) |
| Cl(2)-C(2) | 1.76(3) | O(1)-C(4) | 1.46(3) |
| O(2)-C(1) | 1.30(3) | O(2)-C(5) | 1.49(4) |
| O(3)-C(1) | 1.24(3) | C(1)-C(3) | 1.46(4) |
| C(2)-C(3) | 1.27(4) | C(2)-C(4) | 1.55(4) |

Finally, the mercuration of 22, a possible precursor for the synthesis of carolic acid [9], has been examined. The only product to precipitate from solution is the furylmercurial 29 isolated in 17% unoptimized yield. The structure of 29 has been confirmed by elemental

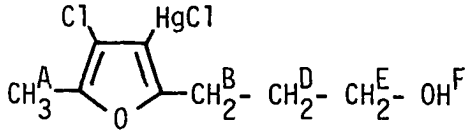



Chemical Formula: $C_5H_6Cl_2HgO_3$
Crystal System: Monoclinic
Space Group: $P2_1/n$
Cell Constants: a = 4.342(1) b = 7.876(1) c = 25.656(5) A
β = 91.81(4)°
R-factor: 7.4%
Least-Squares Refinement: Hg, Cl - anisotropic
All other atoms - isotropic
No hydrogens included
Number of pieces of data used - 1176
4 molecules/cell

Figure 2. Crystal structure of compound 28

analysis as well as infrared and high-resolution $^1$H NMR spectroscopy. The high-resolution $^1$H NMR (300 MHz) spectral data for compound 29 are listed in Table V. This product (29) apparently arises from mercuric chloride syn addition to the carbon-carbon triple bond followed by cyclic hemiketal formation and dehydration.

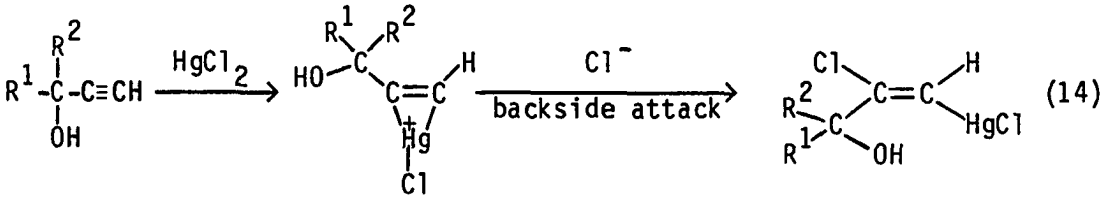
Table V. High-resolution $^1$H NMR spectrum data of 29




| | Chemical shifts of hydrogens, δ | | | | |
|---|---|---|---|---|---|
| | A | B | D | E | F |
| | 2.24(s) | 2.73 (t) J=6.81 Hz | 1.80-1.88(m) J=6.81 Hz J=5.85 Hz | 3.69(dt) J=5.85 Hz J=4.89 Hz | 1.57 (t) J=4.89 Hz |
| irradiated at δ 3.69 | 2.24(s) | 2.73(t) J=6.81 Hz | 1.84(t) J=6.81 Hz | --- | 1.61(s) |
| irradiated at δ 1.57 | 2.24(s) | 2.73(t) J=6.81 Hz | 1.80-1.88(m) J=6.81 Hz J=5.85 Hz | 3.69(t) J=5.85 Hz | --- |

3. Mechanism of mercuration

The chloromercuration of simple propargylic alcohols gives trans-β-chloromercuri anti adducts exclusively (eq. 2) [20,21,36]. The mechanism of their formation is expected to be very similar to oxymercuration of an alkene (eq. 14). The stereochemistry of the mercuric chloride addition

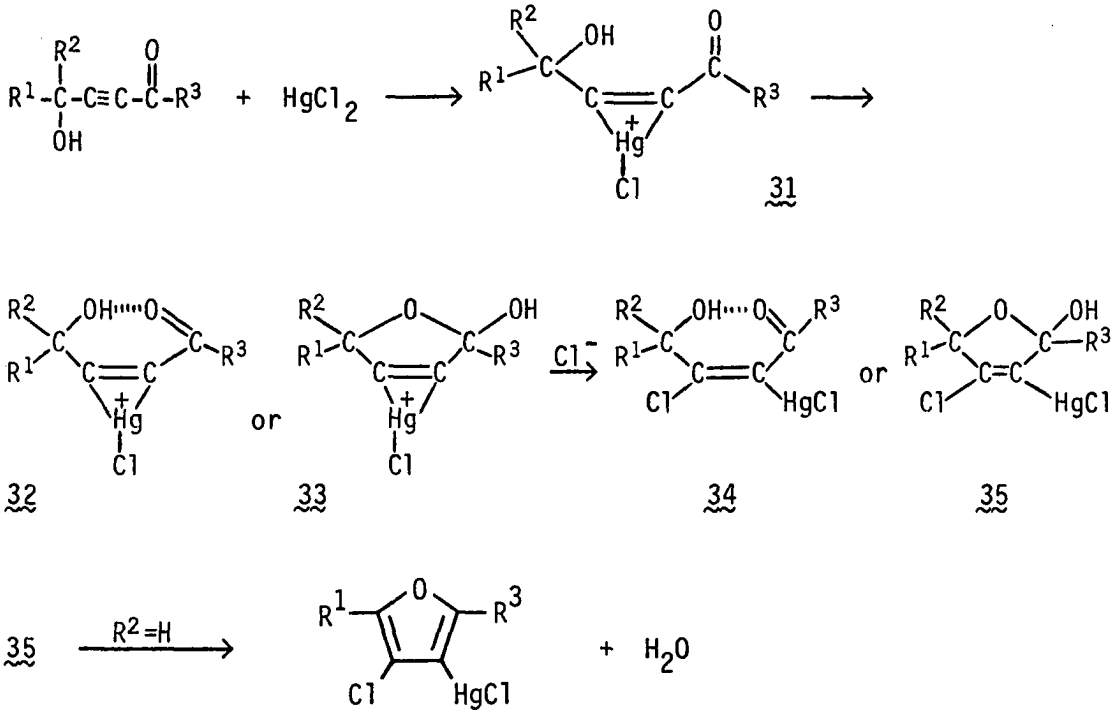



(14)

to 1-phenyl-1-butyn-3-one has not been established [38]. Obviously, the presence of the carbonyl group in 4-hydroxy-2-alkyn-1-ones plays an important role in effecting syn addition. While the present evidence does not allow one to make any definitive statements on the mechanism of these mercuration reactions, it is, we believe, worthwhile speculating on why the mercuration of 4-hydroxy-2-alkyn-1-ones apparently proceeds in a syn manner at least with primary and secondary alcohols, but affords anti addition compounds with simple propargylic alcohols and compounds 21 and 22.

We assume that the mercuration of acetylenes parallels that of simple alkenes and that an initial π-complex or mercurinium ion-like structure is initally produced (Scheme I). With 4-hydroxy-2-alkyn-1-ones, such an intermediate, 31, might be additionally stabilized by the presence of an intramolecular hydrogen bond between the alcohol and carbonyl group (32) or by intramolecular hemiketal formation (33). Such cyclic structures would prevent backside attack of chloride anion on the carbon β to the carbonyl and allow only formation of the syn addition compounds by frontside attack on the mercury-stabilized cation, resulting in products such as 34 and 35 for which we have presented evidence in this chapter. Furan formation is easily envisioned from such products by dehydration of the hemiketal 35. Neither simple acetylenic alcohols nor

Scheme I. Possible mechanism for the mercuration of 18, 19, and 22.



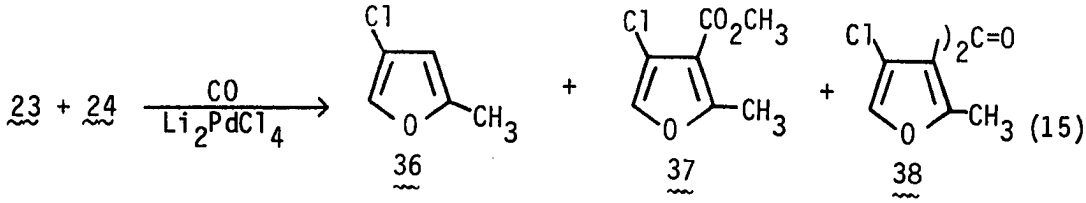
ketones are capable of forming such hydrogen-bonded or cyclic structures. To examine the effect of hydrogen bonding we have examined the mercuration of the tetrahydropyranyl ethers 15 and 14 and the acetate corresponding to 14. Unfortunately, 15 gave only a very small amount of white solid initially and then decomposed, and 14 gave only 26 in 28% yield after considerable reaction time. Presumably, 14 is first hydrolyzing to the corresponding alcohol 19, which only then undergoes mercuration. The acetate corresponding to 14 gave no reaction with aqueous mercuric chloride. We are, therefore, unable to assess the role of hydrogen bonding in these reactions. We have also examined the reaction of mercuric chloride and 3-hexyn-2-one and found no addition product at

all. So we can conclude that the free OH group is necessary for mercuration. The mechanism as shown nicely explains the majority of our results. It does not, however, provide an answer as to why the tertiary alcohol 20 or ester 21 apparently afford anti addition products. One can only surmise that cyclic structures such as 32 and 33 might be less favorable with the more highly crowded tertiary alcohol of 20 or the ester carbonyl of 21 and do not form to any significant extent, therefore, allowing chloride anion to attack the mercury cation from the backside.

4. Carbonylation

Much of the information used to help establish the structure of the various organomercurials prepared in the previous section has been obtained by studying the palladium-promoted carbonylation of these compounds. This approach has previously proven valuable for the synthesis of β-chloro-$\Delta^{\alpha,\beta}$-butenolides from the anti adducts obtained from mercuric chloride addition to simple propargylic alcohols (eq. 2) [20, 21]. It was, in fact, with the expectation that we would obtain butenolides that the present carbonylation studies were initiated. This work has resulted instead in a novel new route to furan-containing carbonyl compounds, as well as providing the first evidence for the syn addition of mercuric chloride to acetylenes.

Since neither vinylmercurial 23 nor 24 can be isolated in pure form, a mixture of these two compounds of unknown ratio has been carbonylated using 1 equiv. of $Li_2PdCl_4$, 1 atmosphere of carbon monoxide, and either methanol or diethyl ether as the solvent (eq. 15). Only furan-containing




compounds 36, 37 and 38 have been observed, and the first two compounds have been identified by gas chromatography/mass spectral analysis only (Table VI). In ether, compound 36 is the major product, but it proved

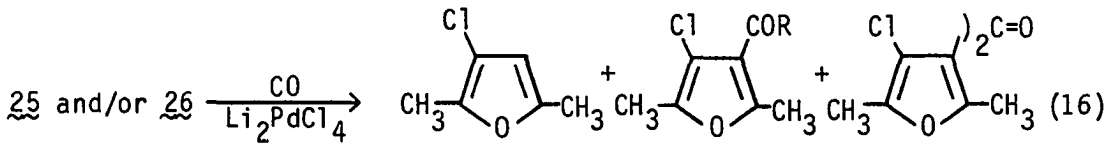
Table VI. Carbonylation of 23 + 24

| Solvent | Base added | Products (Ratio[a]) | % Isolated yield |
|---|---|---|---|
| $Et_2O$ | --- | 36 : 38 (3 : 1) | 30 (38) |
| MeOH | --- | 36 : 37 : 38 (130 : 25 : 1) | |
| MeOH | 2 $Et_3N$ | decomposed | |

[a]The ratio indicates the relative peak areas as determined from GLC analysis.

too volatile to easily isolate. Compound 38 is also formed in 30% isolated yield in this reaction. In methanol, all three compounds, 36, 37, and 38, are formed in the approximate ratio 130:25:1, respectively, based on relative peak areas in the gas chromatograph.

Pure vinylmercurial 25, a 95:5 mixture of 25 and 26, and pure 26 have also been carbonylated (eq. 16). Furan-containing products analogous to those obtained upon carbonylation of 23 and 24 have been obtained. The results are summarized in Table VII. Compounds 39, 41, and 42 have been characterized by gas chromatography/mass spectrometry




(16)

39 40, R=OCH 43
41, R=$OC_2H_5$
42, R=Cl

Table VII. Carbonylation of organomercurials 25 and/or 26

| Organo-mercurial(s) | Solvent | Base added | Products (Ratio[a]) | % Yield[b] |
|---|---|---|---|---|
| 25 | MeOH | --- | 39:40:43 (4.6:2.2:1) | 11 (40) |
| | | | | 4 (43) |
| | | MgO | 40 | 12 |
| | $Et_2O$ | --- | 39:41:43 (12.4:1:3.7) | |
| | | $2Et_3N$ | 39:41:43 (1:3.6:28) | |
| | $CH_3CN$ | --- | 39:43 (1:1.7) | |
| | | $2Et_3N$ | 43 | (8) |
| 25 + 26[c] | MeOH | --- | 39:40:43 (7:1:1.2) | |
| | | $2Et_3N$ | 40 | (9) |
| | | MgO | 40 | (10) |
| | $CH_3CN$ | MgO | 39:42:43 (1.2:1:3.6) | (10)(43) |
| | | $4Et_3N$ | 43 | (3) |
| 26 | MeOH | $2Et_3N$ | 40 | (97) |
| | $CH_3CN$ | $2Et_3N$ | 43 | (93) |

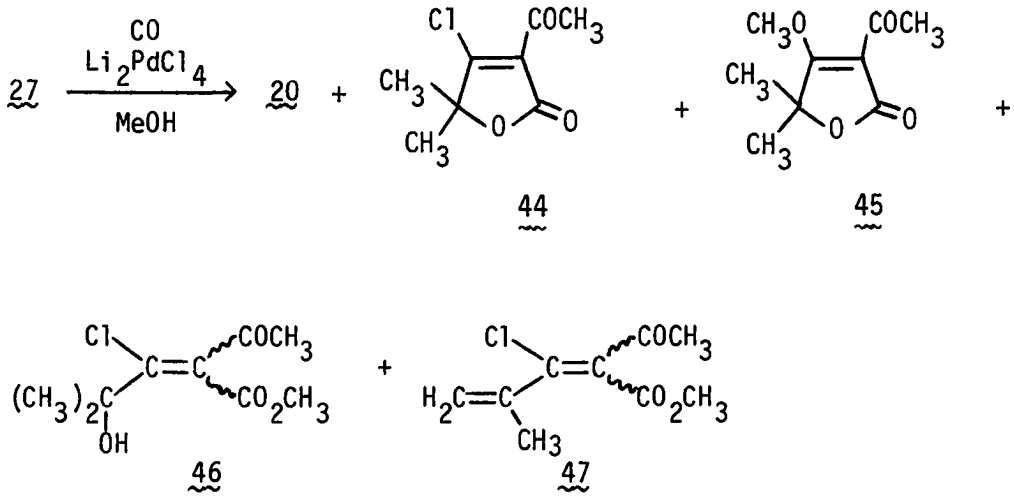
[a]The ratio indicates the relative peak areas as determined from GLC analysis.

[b]Isolated yield (yield determined by GLC analysis).

[c]Ratio of 25 to 26 is approximately 95:5.

only. Unfortunately, only low yields of products could be isolated from 25 or 25 + 26. While the addition of a base greatly reduces the amount of 39 in these reactions, the isolated yields of 40 or 43 are not significantly improved. In diethyl ether, ethyl esters are actually observed, indicating that the ether is being cleaved in some fashion. Starting with pure 26, one can obtain near quantitative yields of the methyl ester 40 in methanol or the corresponding ketone 43 in acetonitrile.

The carbonylation of 27 leads to a variety of products (eq. 17).



(17)

The results are summarized in Table VIII. Compound 20 has been characterized by comparison of its gas chromatographic retention time and mass spectrum with that of authentic 20. Compounds 44 and 45 have been isolated and fully characterized, while evidence for 46 and 47 rests solely on gas chromatography/mass spectral data. In the absence of a base, 20, 44, 45, and 46 are formed in the ratio 16:3:1:2 (relative peak

Table VIII. Carbonylation of 27

| Solvent | Base added | Products (Ratio[a]) | % Yield[b] |
|---|---|---|---|
| MeOH | MgO | 44 | 12 |
| | | 45 | 4 |
| MeOH | --- | 20:44:45:46 (16.3:3:1:2) | |
| MeOH | $Et_3N$ | 20:44:46 (10.2:1.2:1) | |
| $CH_3CN$ | 2 $Et_3N$ | decomposed | |

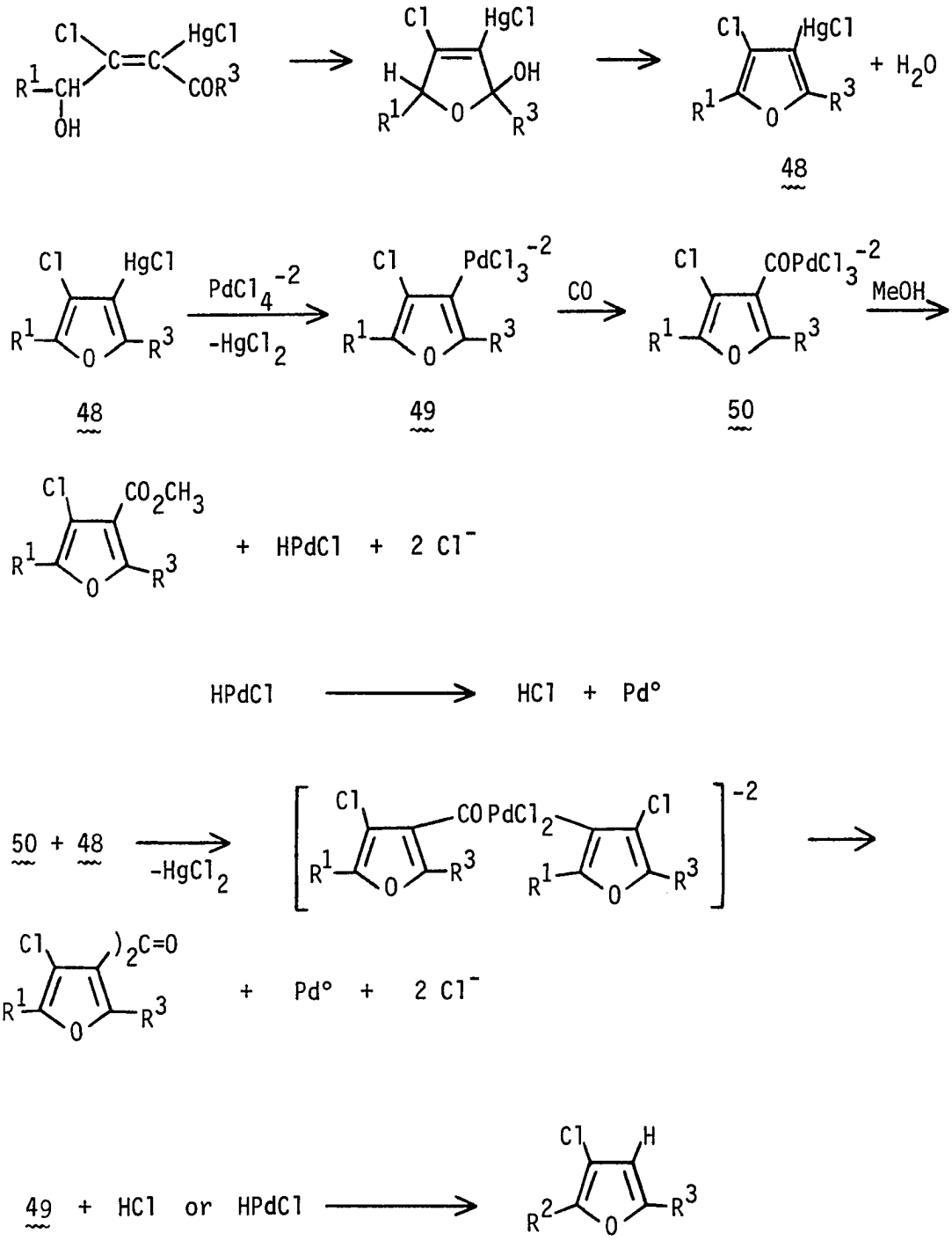
[a]The ratio indicates the relative peak areas as determined from GLC analysis.

[b]Isolated yield.

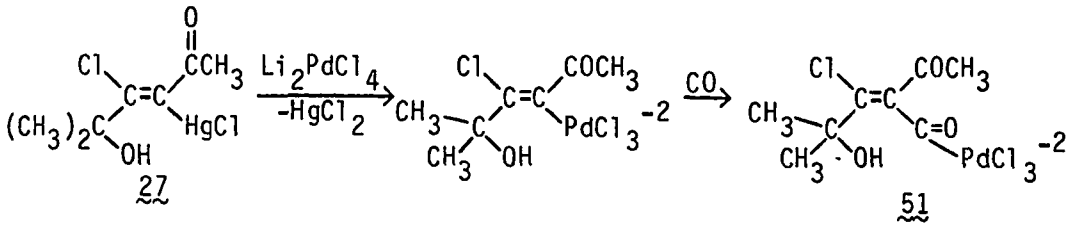
areas obtained by GLC analysis). With 1 equiv. of MgO added, all five compounds are observed by GLC analysis in the following relative amounts 46 > 20 > 44 > 47 > 45. However, only compounds 44 (12%) and 45 (4%) could be isolated and identified. With 1 equiv. of triethylamine added, compounds 20, 44, and 46 were observed in the ratio 10:1:1 (GLC peak areas). Compound 27 is the only organomercurial to afford both starting acetylene and butenolide products upon carbonylation. This suggests that 27 probably has stereochemistry opposite to that of 23 or 25.

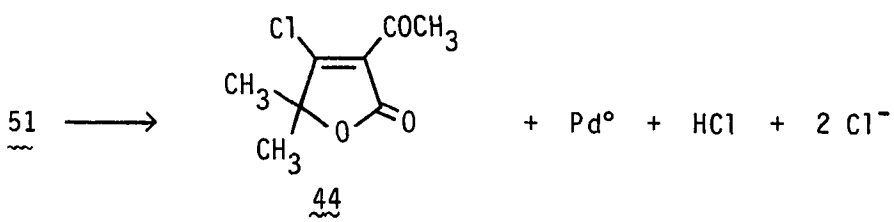
The carbonylation of compound 28 has been studied under a variety of reaction conditions. No carbonylation products were observed and 50-60% of the starting vinylmercurial could be recovered.

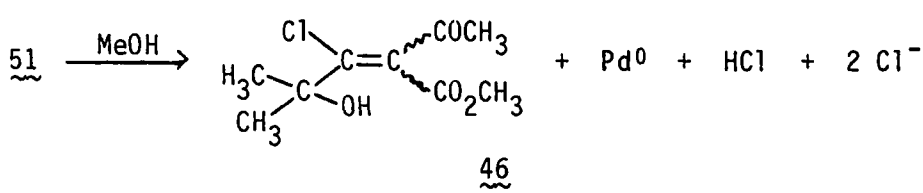
Scheme II. Mechanism for carbonylation of 23 and 25



Scheme III. Mechanism for the formation of compounds 44 and 46







The carbonylation of furylmercurial 29 has not been studied. We assumed that furan-containing products analogous to those obtained upon carbonylation of pure 26 could be obtained.

The furan-containing carbonyl products are most likely formed by cyclic dehydration of the vinylmercurials to furylmercurials followed by carbonylation according to Scheme II. Compounds 44 and 46 presumably arise as shown in Scheme III.

## C. Conclusion

The addition of mercuric chloride to acetylenes has been reported to give vinylmercuric chlorides where the chlorine and mercury groups are anti to each other. We have examined the mercuration of 4-hydroxy-2-alkyn-1-ones and observed that, at least with primary and secondary alcohols, mercuric chloride appears to add syn to the carbon-carbon triple bond. These vinylmercurials undergo facile cyclic dehydration to furylmercuric chlorides in the presence of dilute HCl or upon simple recrystallization. This provides a unique approach to 3-substituted furans since the mercury moiety can be readily converted into a variety of other substituents. For instance, carbonylation affords either the corresponding methyl ester or symmetrical ketone in near quantitative yields. With a tertiary alcohol, it appears that mercuric chloride adds anti to the acetylene. Carbonylation affords the corresponding butenolide plus other products. The exact reason for the difference in products remains obscure.

## D. Experimental Section

### 1. Equipment

The infrared spectra were recorded on a Beckman IR-4250 infrared spectrophotometer and the $^{1}H$ NMR spectra on a Varian Associates A-60 NMR or a Hitachi Perkin-Elmer R-20 B NMR spectrometer. High-resolution $^{1}H$ NMR spectra were recorded on a Bruker WM-300 NMR spectrometer. Carbon-13 NMR spectra were recorded on a JEOL FX-90Q $^{13}C/^{1}H$ Fourier Transform 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 Merk 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). Diffraction data for X-ray crystallographic analysis were collected at ambient temperature on an AL (Ames Laboratory) automatic diffractometer. Elemental analyses were performed by Galbraith Laboratories.

## 2. Reagents

All chemicals were used directly as obtained unless otherwise indicated. Propargyl alcohol was purchased from Aldrich and 3-hydroxy-1-butyne and 3-hydroxy-3-methyl-1-butyne from Farchan. Acetic anhydride, mercuric chloride, and sodium chloride were used directly as obtained from Fisher. Dihydropyran (Eastman Kodak) and γ-butyrolactone (Aldrich) were distilled before using. Methanol was distilled from magnesium methoxide; acetonitrile was distilled from phosphorus pentoxide; diethyl ether and tetrahydrofuran were distilled from calcium hydride; and triethylamine was 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.

3. Preparation of tetrahydropyranyl ethers of propargylic alcohols

All preparations were carried out under conditions identical with those described by Parham and Anderson [72]. The preparation of 3-(tetrahydropyranyloxy)-1-propyne (10) is representative. To a mixture of 3-hydroxy-1-propyne (1.12 mol) and dihydropyran (1.12 mol) was added a few drops of concentrated hydrochloric acid, and the mixture was allowed to stand for 3 h with occasional shaking. Ether was then added and the solution was shaken vigorously with 10% aqueous sodium hydroxide to ensure removal of all traces of acid. The ethereal extract was dried ($Na_2SO_4$), concentrated, and distilled, giving 148.6 g (91%) of the tetrahydropyranyl ether 10 : bp 40-43°C (1 mmHg); $^1$H NMR ($CCl_4$) δ 1.3-2.0 (br m, 6 H, $CH_2$), 2.35 (t, 1 H, J = 2.5 Hz, C≡CH), 3.2-4.0 (m, 2 H, -$CH_2$O-), 4.15 (d, 2 H, J = 2.5 Hz, $CH_2$C≡C), 4.76 (br s, 1 H, -OCHO-); IR (neat) 3300 (C≡C-H), 2120 (C≡C), 1120 (C-O) $cm^{-1}$.

The following two tetrahydropyranyl ethers were prepared in identical fashion. 3-(Tetrahydropyranyloxy)-1-butyne (11) : yield 85%; bp 28-30°C (0.2 mmHg); $^1$H NMR ($CCl_4$) δ 1.42 (d, 3 H, J = 6.8 Hz, $CH_3$), 1.61 (m, 6 H, $CH_2$), 2.27 (d, 1 H, J = 2.3 Hz, C≡CH), 3.20-3.97 (m, 2 H, -$CH_2$O-), 4.42 (qd, 1 H, J = 6.8 Hz, J = 2.3 Hz, -OCH-), 4.64-4.96 (br m, 1 H, OCHO); IR (neat) 3284 (C≡CH), 2098 (C≡C) $cm^{-1}$. 3-Methyl-3-(tetrahydropyranyloxy)-1-butyne (12) : yield 89%; bp 45-48°C (1.5 mmHg); $^1$H NMR ($CCl_4$) δ 1.20-2.0 (br m, 6 H, $CH_2$), 1.44 (s, 3 H, $CH_3$), 1.49 (s, 3

H, $CH_3$), 2.37 (s, 1 H, C≡CH), 3.15-4.10 (m, 2 H, $-CH_2O-$), 4.94-5.17 (br m, 1H, -OCHO-); IR (neat) 3300 (C≡CH), 2104 (C≡C) $cm^{-1}$.

4. Preparation of 4-(tetrahydropyranyloxy)-2-alkyn-1-ones 13 - 17

All preparations were carried out according to the method of Duranti and Balsamini with only slight modifications [68]. The following preparation of 1-(tetrahydropyranyloxy)-4-oxo-2-pentyne (13) is representative of the general procedure used for the synthesis of compounds 13 - 15. To a -78°C solution of 56.0 g (0.4 mol) of 10 in 400 ml of tetrahydrofuran (THF) was slowly added 160 ml of 2.5 M n-butyllithium (0.4 mol). The mixture was stirred at -78°C for 1 h and at -20°C for 20 min. Then the solution was cooled back to -78°C and transferred via a double-ended needle into a solution of acetic anhydride (0.48 mol) in 300 ml of THF also kept at -78°C. The reaction mixture was allowed to slowly warm up to room temperature over a period of 3 h and stirred overnight at room temperature. Ether (500 ml) was added and the mixture was then washed with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted 3 times with ether. The organic extracts were combined, dried ($MgSO_4$), concentrated, and distilled, giving 10.6 g (19%) of starting material (10) and 39.3 g (54%) of compound 13: bp 89-92°C (0.3 mmHg) (lit. [68] bp 93°C (1 mmHg)); $^1H$ NMR ($CCl_4$) δ 1.10-1.90 (m, 6 H, $CH_2$), 2.27 (s, 3 H, $COCH_3$), 3.4-4.0 (m, 2 H, $-OCH_2-$), 4.32 (s, 2 H, $-OCH_2C\equiv C$), 4.72 (br s, 1 H, -OCHO-); IR (neat) 2200 (C≡C), 1683 (C=O) $cm^{-1}$.

Compounds 14 and 15 were prepared in identical fashion. Compound 14: yield 61% (9% recovery of starting material 11); bp 77-78°C (0.16 mmHg); $^1$H NMR ($CDCl_3$) δ 1.40-2.00 (br m, 6 H, $CH_2$), 1.5 (d, 3 H, J = 6.9 Hz, $CH_3$), 2.34 (s, 3 H, $COCH_3$), 3.35-4.15 (m, 2 H, $-OCH_2-$), 4.71 (q, 1 H, J = 6.9 Hz, CHOTHP), 4.88 (br s, 1 H, -OCHO-); IR (neat) 2220 (C≡C), 1686 (C=O) $cm^{-1}$. Mass spectrum ($M^+$-H), m/z calcd for $C_{11}H_{15}O_3$ 195.10212, obsd 195.10302. Compound 15: yield 54% (17% recovery of starting material 12); bp 69-71°C (0.25 mmHg); $^1$H NMR ($CCl_4$) δ 1.20-2.00 (m, 6 H, $CH_2$), 1.47 (s, 3 H, $CH_3$), 1.52 (s, 3 H, $CH_3$), 2.26 (s, 3 H, $COCH_3$), 3.18-4.10 (m, 2 H, $-OCH_2-$), 4.25-5.14 (br m, 1 H, -OCHO-); IR (neat) 2204 (C≡C), 1680 (C=O) $cm^{-1}$. Mass spectrum ($M^+-CH_3$), m/z calcd for $C_{11}H_{15}O_3$ 195.10212, obsd 195.10283.

Compound 16 was prepared as follows. To a solution of 14.0 g (0.1 mol) of 10 in 400 ml of THF was added 0.1 mole of n-butyllithium (hexane solution) at -78°C. The mixture was allowed to slowly warm up to -20°C and then cooled back down to -78°C. The above solution was transferred via a double-ended needle into a solution of 18.9 g (0.2 mol) of methyl chloroformate in 300 ml of THF at -78°C. The reaction mixture was stirred at -78°C for 10 min and at 0°C for 100 min. Ether (500 ml) was added and the reaction mixture was washed with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer extracted three times with ether. The organic extracts were combined, concentrated, and distilled, giving 16.0 g (81%) of the ester 16: bp 100-101°C (0.30 mmHg); $^1$H NMR ($CCl_4$) δ 1.3-2.07 (br m, 6 H, $CH_2$), 3.24-4.20 (m, 2 H, $-OCH_2-$), 3.77 (s, 3 H, $OCH_3$), 4.34 (s, 2 H, $CH_2C{=}C$), 4.76 (br s,

1 H, -OCHO-); IR ($CCl_4$) 2240 (C≡C), 1726 (C=O) $cm^{-1}$. Mass spectrum ($M^+$-H), m/z calcd for $C_{10}H_{13}O_4$ 197.08138, obsd 197.08100.

Compound 17 was prepared as follows. To a solution of 3.08 g (20 mmol) of 11 in 70 ml of THF was added 9 ml of n-butyllithium (2.27 M solution in hexane) (20.4 mmol) at -78°C. The mixture was allowed to slowly warm up to -20°C and then cooled back down to -78°C. The above solution was added slowly to a solution of 2.07 g (24 mmol) of γ-butyrolactone in 80 ml of THF at -78°C. The reaction mixture was stirred at -78°C for 2 h, 0°C for 1 h and room temperature for 30 min. Ether (200 ml) was added and the reaction mixture was washed with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with ether three times. The organic extracts were combined and concentrated, and the residue was flash chromatographed (silica gel column, eluting solvent 1:1 EtOAc:hexanes) to afford 2.60 g (54%) of compound 17: $^1H$ NMR ($CDCl_3$) δ 1.33-2.20 (m, 8 H, $CH_2$), 1.53 (d, 3 H, J = 7 Hz, $CH_3$), 2.46 (br s, 1 H, OH), 2.72 (t, 2 H, J = 7.2 Hz, $CH_2C$=O), 3.34-4.14 (m, 2 H, -$OCH_2$-), 3.66 (t, 2 H, J = 6.5 Hz, $CH_2OH$), 4.70 (q, 1 H, J = 7 Hz, CH), 4.90 (br s, 1 H, -OCHO-); IR (neat) 3100-3650 (OH), 2224 (C≡C), 1665 (C=O) $cm^{-1}$. Mass spectrum ($M^+$-$H_2O$), m/z calcd for $C_{12}H_{18}O_3$ 222.12559, obsd 222.12603.

5. Preparation and mercuration of compound 18 - 22

The following preparation of compound 25 is representative. To a solution of 1.96 g (10 mmol) of 14 in 50 ml of 95% EtOH was added 0.252 g (1 mmol) of pyridinium p-toluenesulfonate (PPTS). The mixture was

stirred at 80°C (bath temperature) for 5 h. Analysis by TLC at this stage showed no starting THP ether. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was passed through a short column of silica gel (10-15 g, 1:1 EtOAc/hexanes as eluant) to remove PPTS. Without further purification compound 19 was dissolved in 2 ml of MeOH and then added to 50 ml of a saturated aqueous solution of mercuric chloride and sodium chloride at room temperature. The reaction mixture was stored in the refrigerator for 10-12 h. The white solid that precipitated from solution was collected by vacuum filtration and washed with a small amount of cold water. The white solid was dried under vacuum for 24 h to afford 3.45 g (90%) of compound 25 containing a small amount of compound 26. Fractional recrystallization of the crude product from benzene and collection of the first crop of crystals afforded pure compound 25: recrystallized yield 27%; mp 119-120.5°C; $^1$H NMR (acetone-$d_6$) δ 1.50 (d, 3 H, J = 6.7 Hz, $CH_3$), 2.38 (s, 3 H, $COCH_3$), 4.68 (dq, 1 H, J = 6.7 Hz, J = 3.2 Hz, CH), 6.07 (br d, 1 H, J = 3.2 Hz, OH); IR ($HCCl_3$) 3590 (free OH), 3100-3520 (OH), 1674 (C=O), 1606 (C=C) $cm^{-1}$. Anal. Calcd for $C_6H_8Cl_2HgO_2$: C, 18.79; H, 2.10; Hg, 52.29; Cl, 18.48. Found: C, 18.75; H, 2.12; Hg, 52.28; Cl, 18.50. The mother liquor was concentrated and recrystallized from benzene again to afford compound 26: yield 40%; mp 185-185.5°C; $^1$H NMR (acetone-$d_6$) δ 2.22 (s, 3 H, $CH_3$), 2.36 (s, 3 H, $CH_3$); IR (kBr) 1590, 1560, and 1520 (furan) $cm^{-1}$. Anal. Calcd for $C_6H_6HgCl_2O$: C, 19.71; H, 1.65; Hg, 54.86; Cl, 19.39. Found: C, 19.90; H, 1.61; Hg, 54.64; Cl, 19.53.

The following mercurials were prepared by the procedure described above and characterized. Compound 23 contains a small amount of compound 24: yield 75% (recrystallized yield 30%); mp 154-155°C; $^1$H NMR (acetone-$d_6$) δ 2.43 (s, 3 H, $CH_3$), 4.52 (d, 2 H, J = 5.5 Hz, $CH_2$), 6.20 (t, 1 H, J = 5.5 Hz, OH); IR (KBr) 3200-3600 (OH), 1659 (C=O), 1633 (C=C) $cm^{-1}$. Compound 27: yield 100% (recrystallized yield 72%); mp 139-140°C (decomp); $^1$H NMR (acetone-$d_6$) δ 1.56 (s, 6 H, $CH_3$), 2.32 (s, 3 H, $COCH_3$), 5.80 (s, 1 H, OH); IR (kBr) 3200-3600 (OH), 1670 (C=O), 1610 (C=C) $cm^{-1}$. $^{13}$C NMR (acetone-$d_6$) δ 28.37 (2 $CH_3$), 29.47 ($\underline{C}H_3CO$), 73.76 (COH), 144.71 and 148.02 (C=C), 203.5 (C=O). Anal. Calcd for $C_7H_{10}HgCl_2O_2$: C, 21.14; H, 2.53; Hg, 50.44; Cl, 17.83. Found: C, 21.48; H, 2.61; Hg, 49.97; Cl, 17.55. Compound 28: yield 100% (recrystallized yield 72%); mp 155.5-156°C; $^1$H NMR (acetone-$d_6$) δ 3.71 (s, 3 H, $OCH_3$), 4.39 (s, 2 H, $CH_2$), 6.00 (br S, 1 H, OH); IR ($HCCl_3$) 3200-3600 (OH), 1722 (C=O), 1610 (C=C) $cm^{-1}$. $^{13}$C NMR (acetone-$d_6$) δ 52.2 ($OCH_3$), 64.4 ($CH_2O$), 137.5 and 144.6 (C=C), 169.0 (C=O). Anal. Calcd for $C_5H_6HgCl_2O_3$: C, 15.57; H, 1.57; Hg, 52.02; Cl, 18.39. Found: C, 15.65; H, 1.60; Hg, 51.71; Cl, 18.05. Compound 29: yield 17% (recrystallized yield 13%); mp 130.5-131°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.57 (t, 1 H, J = 4.9 Hz, OH), 1.80-1.88 (tt, 2 H, J = 6.8 Hz, J = 5.85 Hz, $CH_2$), 2.24 (s, 3 H, $CH_3$), 2.73 (t, 2 H, J = 6.8 Hz, $CH_2$), 3.69 (dt, 2 H, J = 5.85 Hz, J = 4.89 Hz, $CH_2O$); IR (KBr) 3050-3600 (OH), 1597, 1560, and 1513 (furan) $cm^{-1}$. Anal. Calcd for $C_8H_{10}Cl_2HgO_2$: C, 23.46; H, 2.46; Hg, 48.96; Cl, 17.31. Found: C, 23.62; H, 2.50; Hg, 48.83; Cl, 17.14.

6. Carbonylation

All carbonylation reactions were carried out according to the following representative procedure. Two millimoles of anhydrous lithium chloride (0.085 g), 1 mmol of palladium chloride (0.1774 g), 1 mmol of magnesium oxide (or 2 mmol of triethylamine, if base was used), and 10 ml of dry solvent were placed in a round bottom flask with a septum inlet. While the system was being flushed with carbon monoxide at -78°C, 1 mmol of the appropriate organomercurial was added. A balloon filled with CO was connected to the top of the flask, and the reaction mixture was allowed to slowly warm up to room temperature and then stirred at room temperature for 24-48 h. One milliliter of saturated ammonium chloride solution, 30 ml of ether, and a small amount of activated carbon were added, and stirring was continued for an additional 30 min. The reaction mixture was filtered through Celite and washed with saturated ammonium chloride. The organic layer was dried ($Na_2SO_4$), concentrated, and the reaction products were isolated by either liquid column chromatography or flash chromatography.

Carbonylation of compound 23 in diethyl ether (no base added) gave compounds 36 and 38 in a 3:1 ratio. Compound 36: GC/MS, m/z (relative intensity, assignment) 118 (31.90, $M^+ + 2$), 116 (100, $M^+$), 87 (38.81, $M^+$-HCO), 81 (12.57, $M^+$-Cl), 53 (91.22, $M^+$-CO-Cl). Compound 38: yield 30%; mp 54-56°C; $^1H$ NMR ($CDCl_3$) $\delta$ 2.48 (s, 6 H, $CH_3$), 7.48 (s, 2 H, CH); IR ($HCCl_3$) 3180 (C=CH), 1650 (C=O), 1590 and 1540 (furan) $cm^{-1}$; mass spectrum, m/z calcd for $C_{11}H_8Cl_2O_3$ 257.98505, obsd 257.98450. Anal. Calcd for $C_{11}H_8Cl_2O_3$: C, 50.99; H, 3.11. Found: C, 50.59; H, 3.44. The

analogous reaction in methanol (no base added) gave products 36, 37, and 38 in the ratio 130:1:25. Compound 37: GC/MS, m/z (relative intensity, assignment) 176 (13.24, $M^+ + 2$), 174 (41.85, $M^+$), 159 (16.72, $M^+-CH_3$), 143 (100, $M^+-OCH_3$), 114 (14.82, $M^+-HCO_2CH_3$), 51 (70.88, $M^+-115$). The analogous reaction in methanol with 2 equiv. of triethylamine added gave no products at all.

Carbonylation of compound 25 in methanol (no base added) gave products 39, 40, and 43 in the ratio 4.6:2.2:1. Compound 39: GC/MS, m/z (relative intensity, assignment) 132 (30.88, $M^+$+2), 131 (32.87, $M^+$+1). 130 (100, $M^+$), 129 (85.97, $M^+$-1), 115 (28.79, $M^+-CH_3$), 95 (24.81, $M^+$-Cl), 87 (33.82, $M^+-CH_3-CO$). Compound 40: yield 11%; $^1$H NMR ($CDCl_3$) δ 2.25 (s, 3 H, $CH_3$), 2.52 (s, 3 H, $CH_3$), 3.86 (s, 3 H, $OCH_3$); IR ($HCCl_3$) 1719 (C=O), 1625 and 1572 (furan) $cm^{-1}$; mass spectrum, m/z calcd for $C_8H_9ClO_3$ 188.02402, obsd 188.02476. Compound 43: yield 4%; mp 109-110°C; $^1$H NMR ($CDCl_3$) δ 2.28 (s, 3 H, $CH_3$), 2.40 (s, 3 H, $CH_3$); IR ($HCCl_3$), 1640 (C=O), 1570 (furan) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{12}Cl_2O_3$ 286.01635, obsd 286.01623. The analogous reaction in methanol (1 equiv. of MgO added) gave compound 40 (12%) as the only product. Carbonylation in diethyl ether (no base added) gave compounds 39, 41, and 43 in the ratio of 12.4:1:3.7. Compound 41: GC/MS, m/z (relative intensity, assignment) 204 (14.61, $M^+$+2), 202 (46.85, $M^+$), 173 (100, $M^+-C_2H_5$), 157 (72.58, $M^+-OC_2H_5$), 128 (24.59, $M^+-HCO_2C_2H_5$). The same reaction in diethyl ether with 2 equiv. of triethylamine added gave 39, 41, and 43 in the ratio 1:3.6:28. Reaction in acetonitrile (no base added) gave two products

39 and 43, in the ratio 1:1.7. Carbonylation in acetonitrile (2 equiv. of triethylamine added) afford only one product, 43, in 8% GLC yield.

Carbonylation of 26 in methanol (2 equiv. of triethylamine added) gave only one product, 40, in 97% yield. Reaction in acetonitrile (2 equiv. of triethylamine added) yielded compound 43 in 93% yield.

Carbonylation of a mixture containing compounds 25 and 26 in methanol (no base added) afforded three products, 39, 40, and 43, in the ratio 7:1:1.2. The same reaction with 2 equiv. of triethylamine added afforded only one product, 40, in a 9% yield. One equivalent of MgO yielded 10% of compound 40 as the only product. Carbonylation in acetonitrile (1 equiv. of MgO added) gave three products, 39, 42, and 43, in the ratio 1.2:1:3.6. Compound 43 was obtained in 10% GLC yield. Compound 42: GC/MS (relative intensity, assignment) 194 (6.07, $M^+$+2), 192 (10.34, $M^+$), 159 (31.79, $M^+$+2-Cl), 157 (100, $M^+$-Cl), 129 (3.42, $M^+$-COCl). Reaction in acetonitrile (4 equiv. of triethylamine added) gave compound 43 as the only product in 3% GLC yield. The results of the carbonylation of 25 and/or 26 are summarized in Table VII.

Carbonylation of compound 27 in methanol (1 equiv. of MgO added) gave products 20 and 44 - 47. Compound 20: GC/MS, m/z (relative intensity, assignment) 126 (100, $M^+$), 111 (3.05, $M^+$-$CH_3$), 68 (88.86, $M^+$-$C_3H_6O$). Compound 44: yield 12%; $^1H$ NMR ($CCl_4$) $\delta$ 1.57 (s, 6 H, $CH_3$), 2.47 (s, 3 H, $COCH_3$); IR ($CCl_4$) 1777 (lactone), 1703 (ketone), 1607 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_7H_9ClO_3$ 188.02403, obsd 188. 02437. Compound 45: yield 4%; $^1H$ NMR ($CCl_4$) $\delta$ 1.45 (s, 6 H, $CH_3$), 2.47 (s, 3 H, $COCH_3$), 4.12 (s, 3 H, $OCH_3$); IR ($CCl_4$) 1760 (lactone), 1684 (ketone),

1604 (C=C) $cm^{-1}$; GC/MS, m/z (relative intensity, assignment) 184 (100, $M^+$), 169 (82.19, $M^+-CH_3$), 141 (24.06, $M^+-CH_3CO$). Compound 46: GC/MS, m/z (relative intensity, assigment) 222 (1.01, $M^+$+2), 220 (3.30, $M^+$), 219 (35.93, $M^+$-1), 203 (100, $M^+$-OH), 187 (8.66, $M^+-H_2O-CH_3$), 171 (7.38, $M^+-H_2O-OCH_3$), 143 (4.48, $M^+-H_2O-CO_2CH_3$). Compound 47: GC/MS, m/z (relative intensity, assigment) 204 (31.51, $M^+$+2), 202 (100, $M^+$), 187 (66.13, $M^+-CH_3$), 170 (52.16, $M^+$-MeOH), 167 (18.32, $M^+$-Cl), 143 (40.28, $M^+-CO_2CH_3$). Carbonylation in methanol (no base added) gave products 20, 44, 45, and 46 in the ratio 16.3:3:1:2, while addition of 1 equiv. of triethylamine gave 20, 44, and 46 in the ratio 10.2:1.2:1. Reaction in acetonitrile (2 equiv. of triethylamine added) gave no organic product at all.

# III. MERCURATION AND SUBSEQUENT ACETOXYLATION OR CARBONYLATION OF ALLENIC ACIDS OR ESTERS

## A. Introduction

Since the mercuration-carbonylation of 4-hydroxy-2-alkyn-1-ones led only to furan derivatives (for primary and secondary alcohols), we sought other methods for construction of the tetronic acid skeleton. The cyclization of unsaturated carboxylic acids appeared to offer a promising new route to tetronic acids and many other unsaturated lactones. Our approach involved the mercuration of allenic acids and esters. Allenic acids or esters are readily available from propargylic halides (eq. 18)

$$\underset{\text{Cl}}{\text{R-CHC}\equiv\text{CH}} \xrightarrow[\text{or } Ni(CO)_4]{Mg/CO_2} \text{RCH=C=CHCOOH} \qquad (18)$$

[73-75], propargylic alcohols (eq. 19) [75], β-ketoesters (eq. 20) [76],

$$Me_2C(OH)C\equiv CH \xrightarrow[BuOH]{HCl,\ Ni(CO)_4} Me_2C=C=CHCOOBu \qquad (19)$$

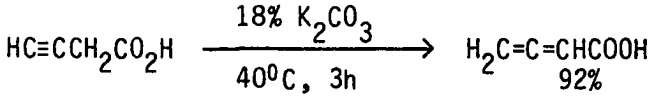
$$RCH_2\overset{O}{\overset{\|}{C}}CHCOOR \xrightarrow[Tl(NO_3)_3]{N_2H_4} RCH=C=\overset{R}{\overset{|}{C}}-COOR \qquad (20)$$

ketenes (eq. 21) [77], acid chlorides (eq. 22) [78-80], and acetylenic

$$R^1R^2C=C=PPh_3 + R^3R^4C=O \longrightarrow R^1R^2C=C=CR^3R^4 + Ph_3P=O \qquad (21)$$

acids (eq. 23) [81].

(22)



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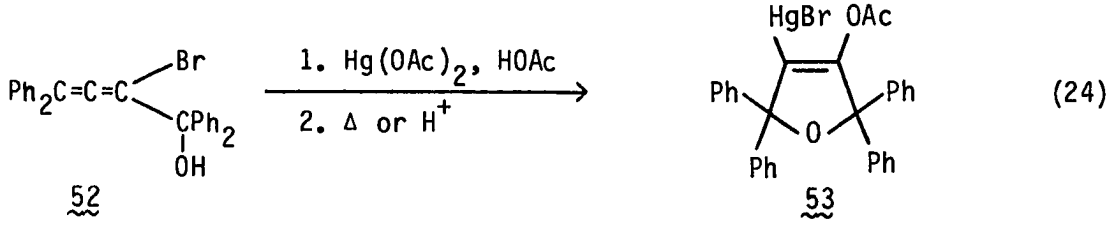
The mercuration of allenic alcohols was first reported by Toda and Akagi (eqs. 24 and 25) [82]. The mercuration of allenic alcohols with



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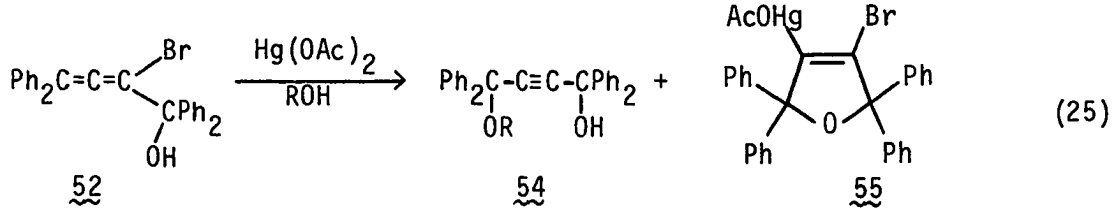
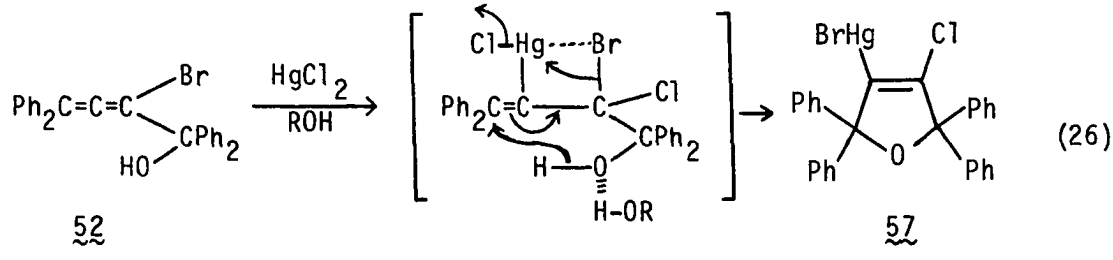


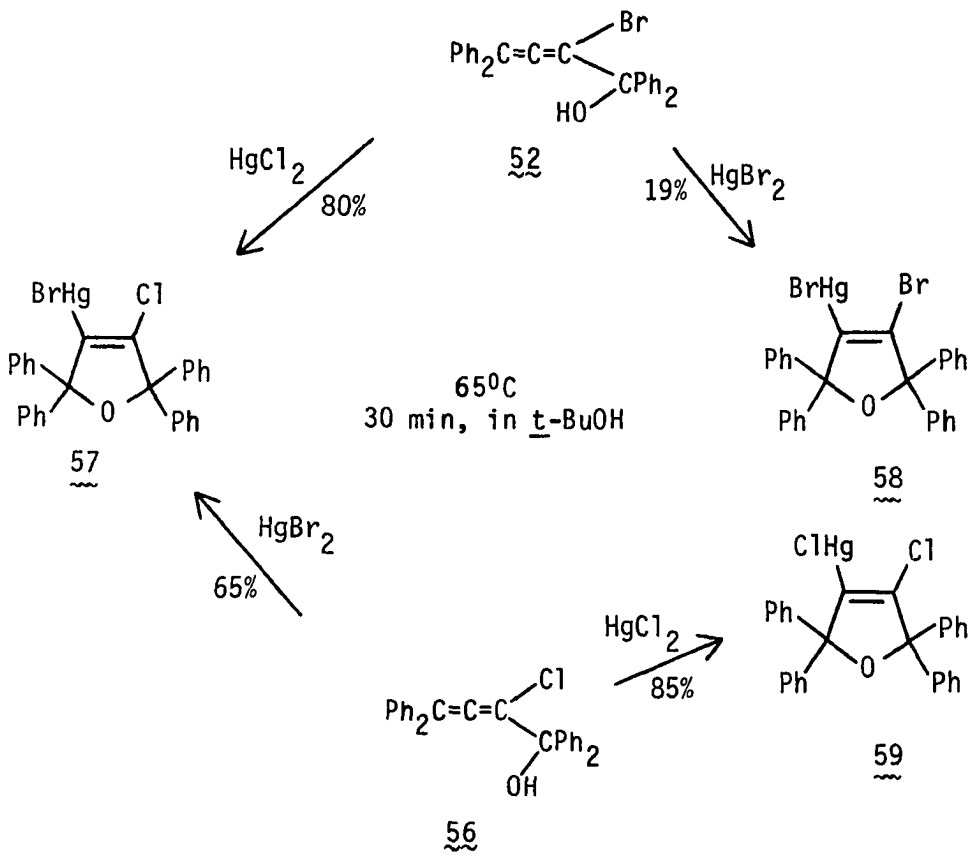
(25)

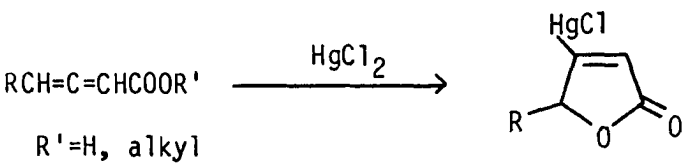
mercuric chloride has also been reported (Scheme IV) [83]. The mechanism for the conversion of compound 52 to 57 is shown in equation 26. In analogy to the mercuration of allenic alcohols, mercuration of allenic acids or esters should afford cyclized β-chloromercuributenolides (eq.



(26)

Scheme IV. Mercuration of 52 and 56

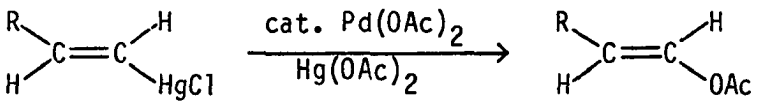



(27)

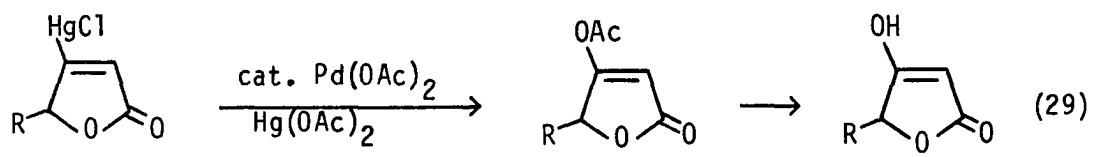
27). To complete the synthesis of tetronic acids, one needs a method for substitution of the chloromercuri moiety by an oxygen group. Larock and

co-workers have developed a convenient catalytic method to effect this transformation (eq. 28) [84]. When carried out on β-chloromercuri-



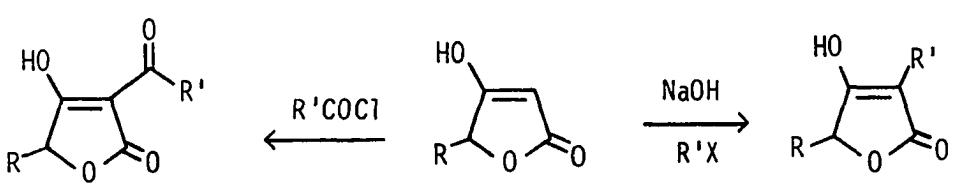

(28)

butenolides, this procedure should afford β-acetoxy derivatives readily hydrolyzed to tetronic acids (eq. 29). Since tetronic acids can




(29)

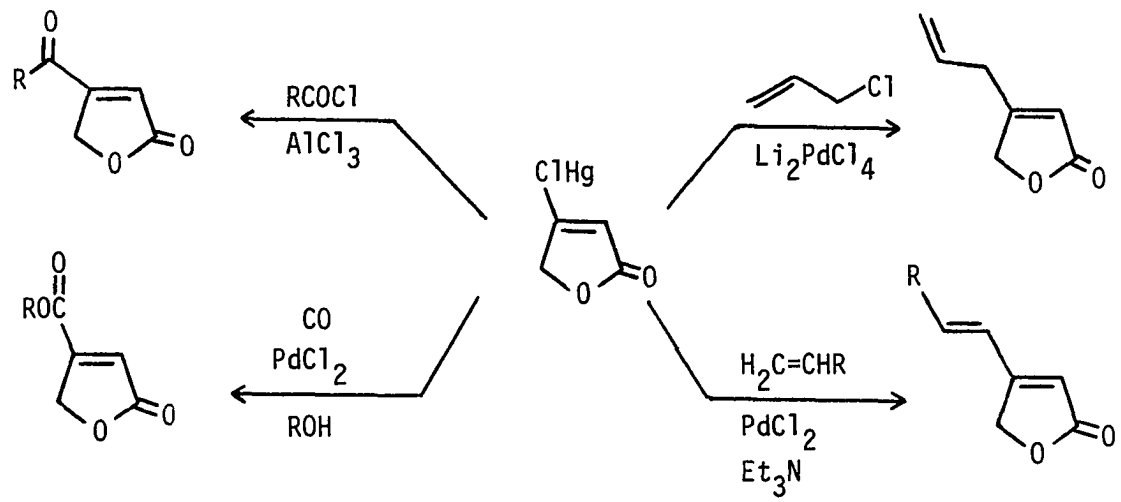
themselves be acylated [85-88] or alkylated [89] in the α-position (eq. 30), this approach affords a highly versatile route to tetronic acids.




(30)

Furthermore, with numerous new synthetic transformations of vinylmercurials now available [90], the butenolide mercurials should prove to be valuable intermediates in a number of new butenolide syntheses (Scheme V). To prepare β-chloromercuributenolides, we have examined the mercuration of 2,3-butadienoic acid (60) and methyl 2,3-butadienoate (61) and the results will be reported later.

Scheme V. Reactions of β-chloromercuributenolide




B. Results and Discussion

1. Preparation of allenic acid and esters

Our model system 2,3-butadienoic acid (60), was prepared by the method of Eglinton and co-workers (eq. 31) [81]. The commercially

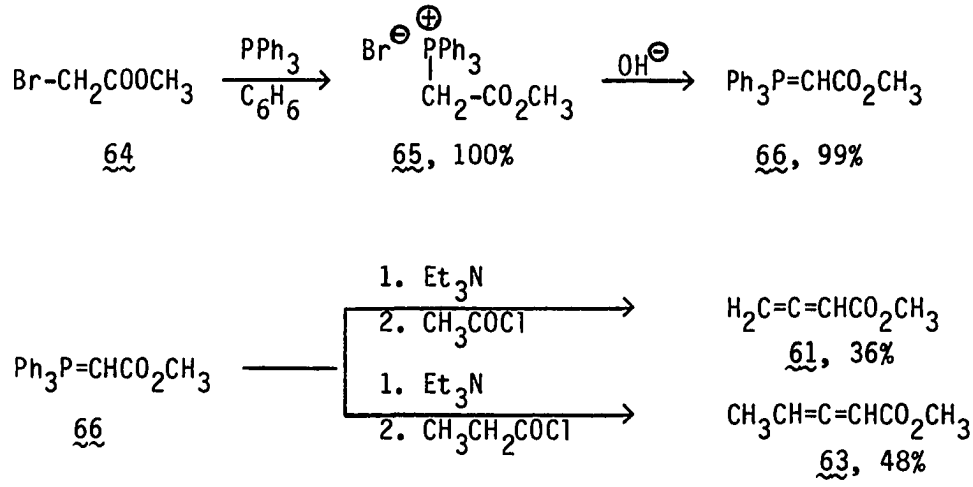
$$HC{\equiv}CCH_2CH_2OH \xrightarrow[\text{acetone}]{CrO_3/H_2SO_4} HC{\equiv}CCH_2CO_2H \xrightarrow[40^{\circ}C,\ 3\ h]{18\%\ K_2CO_3} H_2C{=}C{=}CHCO_2H \qquad (31)$$

62, 42% 60, 93%

available 3-butyn-1-ol was oxidized with Jones' reagent to yield the corresponding acetylenic acid, 62, in 42% yield. Acid 62 was then isomerized with 18% aqueous potassium carbonate to afford compound 60 in 93% yield.

Methyl 2,3-butadienoate (61) and methyl 2,3-pentadienoate (63) were prepared by the method of Lang and Hansen [80]. The preparations are

Scheme VI. Preparations of esters 63 and 64




shown in Scheme VI. Methyl bromoacetate was allowed to react with triphenylphosphine in benzene to afford the phosphonium salt 65 in quantitative yield. Compound 65 was then converted to ylid 66 with sodium hydroxide. Ylid 66 was treated with acetyl and propionyl chlorides in the presence of triethylamine to yield esters 61 and 63.

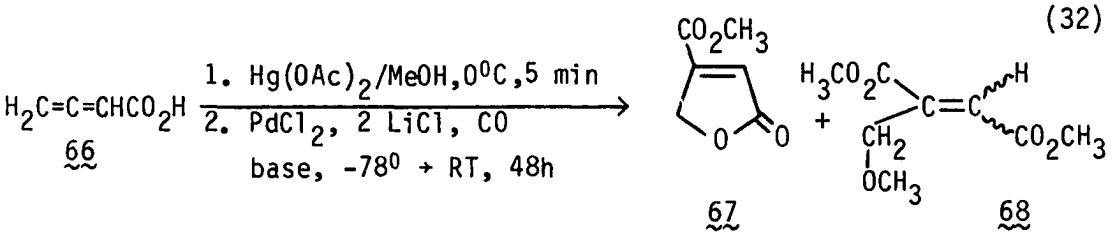
2. Mercuration of 2,3-butadienoic acid (60)

The mercuration of compound 60 with mercuric chloride in various solvents (100% EtOH, 95% EtOH, and MeOH) has been examined. None of these reactions gave mercurated product. Only starting acid 60 and mercuric chloride could be isolated from the reaction mixture. We then changed to mercuric acetate as the mercurating agent. The reaction of acid 60 and mercuric acetate in methanol at room temperature gave a yellow solid. This yellow solid is not soluble in most organic solvents

and shows no proton absorption by $^1H$ NMR analysis in DMSO-$d_6$. This compound was not further characterized. When the reaction was run at 0°C, same yellow solid again formed after the reaction mixture was treated with aqueous sodium chloride. Since mercuric acetate is not very soluble in methanol, we added a suspension of mercuric acetate in methanol to a methanol solution of compound 60. The solution turned clear immediately after the above two solutions were mixed together. This phenomenon suggests that mercuration has occurred and that the mercuration product decomposed upon attempted isolation. This assumption has been proven by examining the mercuration-carbonylation reaction of compound 60 (to be discussed later). Mercuration of compound 60 has also been conducted in tert-amyl alcohol and tetrahydrofuran and yellow solids were obtained in both cases.

3. Mercuration and subsequent carbonylation of compound 60

Although the mercuration product from compound 60 cannot be isolated, it has been characterized by its carbonylation product(s) (eq. 32).




(32)

The results are summarized in Table IX. The reaction gave both intra- and intermolecular mercuration products, 67 and 68. Although the overall yields are low, this study does prove that compound 60 can be

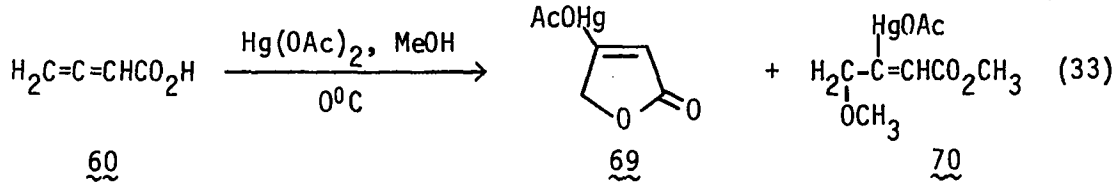
Table IX. Mercuration-carbonylation of compound 60

| Base added | % yield[a] | |
|---|---|---|
| | 67 | 68[b] |
| --- | 26 | 2 |
| MgO | 19 (14% isolated) | 1.6 |
| 2 MgO | 0 | 0 |

[a]GLC yield using n-$C_{14}H_{30}$ as the internal standard.

[b]GLC yields for compound 68 are based on the assumption that it has the same GLC response factor as compound 67.

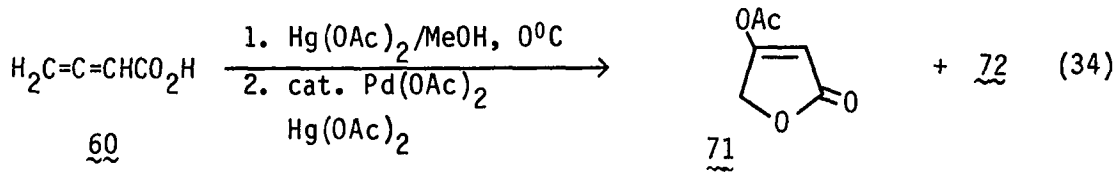
mercurated with mercuric acetate. The intermediate mercurial which led to compound 67 should have the structure 69 (eq. 33). Apparently,



$$H_2C{=}C{=}CHCO_2H \xrightarrow[0^0C]{Hg(OAc)_2,\ MeOH} \underset{69}{\text{AcOHg-cyclic}} + \underset{70}{H_2C(HgOAc)(OCH_3)-C{=}CHCO_2CH_3} \quad (33)$$

60

neither compound 69 nor 70 is stable. Neither compound can be isolated or converted to the corresponding chloromercury compound. To overcome this difficulty, we have examined the possibility of generating intermediate 69 *in situ* and subsequently converted it to 4-acetoxy-2(5H)-furanone (71) according to the method of Larock (eq. 34) [84]. By



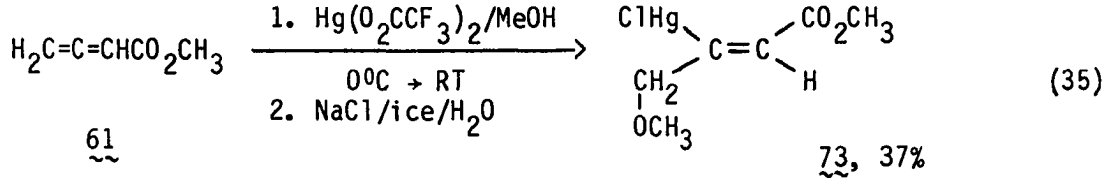
$$H_2C{=}C{=}CHCO_2H \xrightarrow[2.\ cat.\ Pd(OAc)_2,\ Hg(OAc)_2]{1.\ Hg(OAc)_2/MeOH,\ 0^0C} \underset{71}{\text{OAc-cyclic}} + 72 \quad (34)$$

60

comparing the proton NMR spectrum of the crude reaction mixture with that of an authentic sample, we concluded that compound 71 has formed. GC/mass spectral analysis of the reaction mixture shows two major products, 71 and 72, in the ratio 1:5.6. The total yield for 71 and 72 is ca. 17%. We were unable to identify compound 72 (molecular weight 122). Neither compound 71 nor 72 could be easily isolated and characterized. Thus we turned our attention to the corresponding allenic esters.

## 4. Mercuration of methyl 2,3-butadienoate (61)

The reaction of compound 61 and mercuric acetate gave no recognizable product. However, mercuration of compound 61 with mercuric trifluoroacetate in methanol gives a stable mercurial, 73, (eq. 35). The



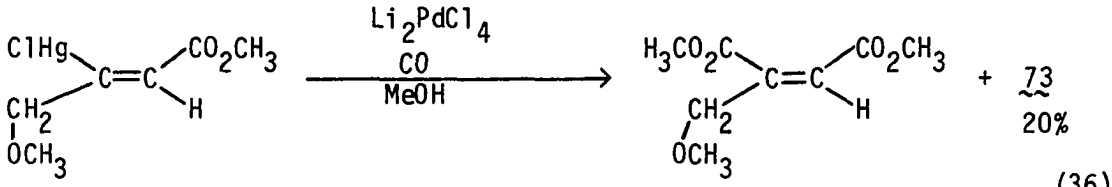

61 73, 37% (35)

stereochemistry of compound 73 has been assigned as shown based on the structure of its carbonylation product (to be discussed later). $^1H$ NMR spectrum of compound 73 shows that the mercury-proton spin-spin coupling constant, $J_{^{199}Hg-H}$, between Hg and olefinic proton is 490 Hz. The typical coupling constant for an E isomer (i.e., Hg and olefinic H are cis to each other) is 300 Hz and that for a Z isomer (i.e., Hg and olefinic H are trans to each other) is 600 Hz. So the stereochemistry of

compound 73 cannot be assigned by comparing its mercury-proton spin-spin coupling constant with the typical values.

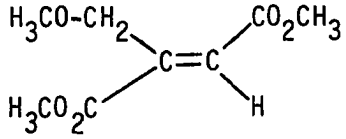
5. Carbonylation of compound 73

In order to determine its stereochemistry, compound 73 was carbonylated (eq. 36) and the structure of reaction product (74) was then




73 → 74, 68% (36)

determined by comparing its $^1$H NMR spectrum with that of a known compound. Here, we assume that palladium-promoted carbonylation proceeds stereospecifically to afford the product with retention of configuration. Although compound 74 has not been reported in the literature, its E isomer (75) has been reported [91]. The $^1$H NMR




75

spectral data of E-dimethyl α-(methoxymethyl)fumarate (75) and compound 74 are listed in Table X. The chemical shifts for the olefinic protons in both compounds 74 and 75 are very close to the calculated values. The calculated chemical shift for the olefinic proton in compound 74 is δ

Table X. $^1H$ NMR spectral data of compounds 74 and 75

| Compound | Boiling point (air-bath temp.) | $^1H$ NMR ($CDCl_3$), δ values |
|---|---|---|
| 74 | 80-86°C (0.25 mmHg) | 3.40 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.18 (d, 2 H, J = 1.7 Hz), 6.16 (t, 1 H, J = 1.7 Hz) |
| 75 | 55°C (0.25 mmHg) | 3.33 (s, 3 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 4.55 (d, 2 H, J = 0.8 Hz), 6.81 (t, 1 H, J = 0.8 Hz) |

6.27 and that in compound 75 is δ 6.91 [92]. So we are sure that the diester 74 obtained from mercurial 73 has the Z configuration. This also explains why we could not obtain the expected butenolide derivative.

## C. Conclusion

Mercuric acetate adds to 2,3-butadienoic acid to give mercurial 69 which can then be carbonylated to afford the corresponding ester 67 (eq. 33). Unfortunately, the intermediate mercurial, 69, could not be isolated. Palladium-assisted acetoxylation of mercurial 69 (generated *in situ*) affords only a very low yield of β-acetoxytetronic acid. This approach to tetronic acids does not at present appear to be synthetically useful.

The reaction of methyl 2,3-butadienoate and mercuric trifluoroacetate in methanol gave a stable mercurial 73. Mercurial 73 has been shown to be the Z isomer based on its carbonylation product.

This result eliminates the possibility of synthesizing tetronic acids from allenic esters.

## D. Experimental Section

### 1. Equipment

The infrared spectra were recorded on a Beckman IR-4250 infrared spectrophotometer and the $^{1}H$ NMR spectra on a Varian Associates A-60 NMR spectrometer. Carbon-13 NMR spectra were recorded on a JEOL FX-90Q $^{13}C/^{1}H$ Fourier Transform NMR spectrometer. The GC/mass spectra were recorded on a Finnegan 4023 GC/MS data system. Silica gel (230-400 mesh) for column chromatography was purchased from MCB Manufacturing Chemists, Inc. Elemental analyses were performed by Galbraith Laboratories.

### 2. Reagents

All chemicals were used directly as obtained unless otherwise indicated. Triphenylphosphine and 3-butyn-1-ol were purchased from Aldrich. Reagent grade acetone, potassium carbonate, and mercuric acetate were used directly as obtained from Fisher. Chromium trioxide and mercuric chloride were purchased from Mallinckrodt and carbon monoxide from Matheson Gas Products. Mercuric trifluoroacetate was prepared by a literature procedure [93]. Methanol was distilled from magnesium methoxide; dichloromethane was distilled from phosphorus pentoxide; and triethylamine was distilled from barium oxide before using. Palladium chloride and palladium acetate were generously supplied by Johnson Matthey, Inc., and Engelhard Industries.

3. Preparation of 3-butynoic acid (62)

Preparation of compound 62 was carried out according to the method of Heilbron and co-workers [94] with only slight modification. To a 0°C solution of 38.0 g (0.54 mol) of 3-butyn-1-ol in 350 ml of acetone was added 350 ml of chromic acid solution (prepared by diluting a mixture of 100 g of chromium trioxide and 160 g of conc. $H_2SO_4$ to 500 ml with water) during 10 min, the temperature being kept at about 20°C. After stirring for another 45 min., 100 ml of water was added to the above reaction mixture. The solution was saturated with sodium chloride and the two layers were separated. The aqueous layer was continuously extracted with ether for 19 h. The organic layer and ethereal extract were combined, dried ($Na_2SO_4$), and concentrated, giving a dark green solid. The dark green solid was then continuously extracted with hexanes. The hexanes extract was concentrated to afford 19.2 g (42%) of compound 62. The crude product was recrystallized from hexanes to afford 12.46 g (27.3% recrystallized yield) of pure compound 62: mp 83-84.5°C (lit. [94] mp 83-83.5°C); $^1H$ NMR ($CDCl_3$) $\delta$ 2.24 (t, 1 H, J = 3 Hz, C≡CH), 3.39 (d, 2 H, J = 3Hz, $CH_2$), 11.43 (s, 1 H, OH); IR (Nujol) 3330 (C≡C-H), 2500-3300 (OH), 2125 (C≡C), 1716 (C=O) $cm^{-1}$.

4. Preparation of 2,3-butadienoic acid (60)

The preparation was carried out under conditions identical with those described by Jones and co-workers [75]. To 200 ml of 18% $K_2CO_3$ was added 5.0 g (59.5 mmol) of compound 62. The solution was stirred at 40°C for 3 h. After acidifying with 6N HCl, the reaction product was extrac-

ted with ether. The ethereal extract was dried ($Na_2SO_4$), and concentrated, giving 4.66 g (93.1%) of compound 60. The crude product, 60, was recrystallized from hexanes to afford 3.76 g (75.2%) of pure compound 60: mp 63-64°C (lit. [75] mp 65-66°C); $^1H$ NMR ($CDCl_3$) δ 5.28 (d, 1 H, J = 7.3 Hz, =C$\underline{H}_2$), 5.30 (d, 1 H, J = 5.3 Hz, =C$\underline{H}_2$), 5.68 (dd, 1 H, J = 7.3 Hz, J = 5.3 Hz, =CHCOO), 11.63 (s, 1 H, OH); IR (Nujol) 2500-3300 (OH), 1970 (C=C=C), 1695 (C=O) $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) δ 79.53 ($H_2C$=), 87.60 (=CH), 171.94 (C=O), 216.88 (=C=) (lit. [95] δ 80.0, 88.1, 172.3, 217.7).

5. Preparation of allenic esters 61 and 63

Both preparations were carried out under conditions identical with those described by Lang and Hansen [80]. The preparation of methyl 2,3-butadienoate (61) is representative. To a solution of 13.38 g (40 mmol) or carbomethoxymethylenetriphenylphosphorane (66) [80] in 160 ml of $CH_2Cl_2$ was added a solution of 4.05 g (40 mmol) of triethylamine in 40 ml of $CH_2Cl_2$ at room temperature. Then, a solution of 3.14 g (40 mmol) of acetyl chloride in 40 ml of $CH_2Cl_2$ was added slowly. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure ($\leq$ 20°C/12-14 mmHg) and the residue was extracted with pentane. The pentane extract was concentrated ($\leq$ 20°C/14 mmHg), and distilled, giving 1.40 g of compound 61: yield 36%; bp 90-91°C (23 mmHg) (air bath temperature) (lit. [80] bp 40°C (14 mmHg)); $^1H$ NMR ($CDCl_3$) δ 3.87 (s, 3 H, $CH_3$), 5.32 (d, 1 H, J = 7.3 Hz, =C$\underline{H}_2$), 5.34 (d, 1 H, J = 6 Hz, =C$\underline{H}_2$), 5.77 (dd, 1 H, J = 7.3 Hz, J = 6 Hz, =CHCO); IR (neat) 1970 (C=C=C), 1718 (C=O) $cm^{-1}$.

Compound 63 was prepared in identical fashion. Methyl 2,3-pentadienoate (63): yield 48%; bp 110°C (22 mmHg) (air bath temperature) (lit. [80] bp 60°C (14 mmHg)); $^1$H NMR ($CDCl_3$) δ 1.80 (dd, 3 H, J = 5Hz, J = 4.2 Hz, $CH_3$), 3.77 (s, 3 H, $OCH_3$), 5.46-5.84 (m, 2 H, =CH); IR (neat) 1967 (C=C=C), 1720 (C=O) $cm^{-1}$.

6. Mercuration and subsequent carbonylation of 60

To a 0°C suspension of 1.5934 g (5 mmol) of mercuric acetate in 25 ml of MeOH was added 0.42 g (5 mmol) of compound 60. The mixture was stirred at 0°C for 30 min. The above reaction mixture was then added to a -78°C suspension of 0.887 g (5 mmol) of palladium chloride, 0.4245 g (10 mmol) of lithium chloride and 0.2016 g (5 mmol) of magnesium oxide in 30 ml of methanol. While the system was being flushed with carbon monoxide at -78°C, a balloon filled with CO was connected to the top of the flask, and the reaction mixture was allowed to slowly warm up to room temperature and then stirred at room temperature for 20 hr. Fifty milliliters of ether and a small amount of activated carbon was added and stirring was continued for an additional 30 min. The reaction mixture was filtered through Celite. The filtrate was concentrated and extracted with ether. The ethereal extract was washed with saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$) and concentrated. The reaction product was isolated by flash chromatography to afford 0.1 g of compound 67: yield 14.1%; mp 83.5-85°C (lit. [96] mp 83°C); $^1$H NMR ($CDCl_3$) δ 4.03 (s, 3 H, $OCH_3$), 5.14 (d, 2 H, J = 2 Hz, $CH_2$), 6.88 (t, 1 H, J = 2 Hz, =CH); IR ($HCCl_3$) 3020 (C=C-H), 1788 and

1752 (lactone), 1737 (ester), 1635 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_6H_6O_4$ 142.02661, obsd 142.02684. GLC analysis of the reaction mixture shows two products: compound 67 (GLC yield, 19%) and compound 68 (GLC yield, 1.6%). For compound 68: GC/MS, m/z (relative intensity, assignment) 188 (5.88, $M^+$), 157 (43.41, $M^+$-$OCH_3$), 156 (35.33, $M^+$-H-$OCH_3$), 129 (11.15, $M^+$-$CO_2CH_3$), 128 (83.85, $M^+$-H-$CO_2CH_3$), 125 (76.92, $M^+$-$CH_3OH$-$OCH_3$), 59 (100, $^+\cdot CO_2CH_3$). The same reaction with no base added gave the same two products 67 (26% GLC yield) and 68 (2% GLC yield).

7. Preparation of 4-acetoxy-2(5H)-furanone (71)

To a 0°C solution of 0.6374 g (2 mmol) of mercuric acetate in 100 ml of THF was added 0.168 g (2 mmol) of 2,3-butadienoic acid (60). The mixture was stirred at 0°C for 20 min and then 0.0449 g (0.2 mmol) of palladium acetate was added to the above solution. The reaction mixture was stirred at 0°C for 3h and at 25°C for 28 h. Another 0.6374 g (2 mmol) of mercuric acetate was added and the mixture was stirred at room temperature for another 24 h. One milliliter of saturated ammonium chloride solution, 20 ml of ether and a small amount of activated carbon were added and stirring was continued for an additional 30 min. The reaction mixture was filtered through Celite. The filtrate was concentrated and extracted with ether. The ethereal extract was washed with saturated ammonium chloride solution. The organic layer was separated, dried ($Na_2SO_4$), and concentrated, giving 47.8 mg of crude products containing 71 and 72. Compound 71: GC/MS, m/z (relative intensity, assignment) 142 (2.37, $M^+$), 100 (8.23, $M^+$-$CH_2$=C=O), 99 (1.04,

$M^+$-$CH_3CO$), 83 (0.54, $M^+$-$CH_3CO_2$), 69 (100, $O{=}C{=}CH{-}C{\equiv}O^{\bullet+}$). Compound 72: GC/MS, m/z (relative intensity, assignment) 122 (51.44, $M^+$), 93 (100, $M^+$-29), 64 (97.62, $M^+$-58). The authentic sample of compound 71 has been prepared by the method of Lehmann and Wamhoff [97]. For pure compound 71: $^1H$ NMR ($CDCl_3$) δ 2.38 (s, 3 H, $CH_3$), 4.98 (d, 2 H, J = 2 Hz, $CH_2$), 6.07 (t, 1 H, J = 2 Hz, CH); IR ($HCCl_3$) 1788 (lactone), 1748 (ester) $cm^{-1}$; mass spectrum, m/z calcd for $C_6H_6O_4$ 142.02661, obsd 142.02682.

## 8. Mercuration of methyl 2,3-butadienoate (61)

To a 0°C solution of 7.835 g (18.37 mmol) of mercuric trifluoroacetate in 100 ml of methanol was added 1.8 g (18.37 mmol) of compound 61. The mixture was stirred under $N_2$ at 0°C for 1 h and then at 25°C for 1.5 h. An ice-cold saturated aqueous sodium chloride solution (10 ml) was added to the above reaction mixture. The white solid formed from the reaction mixture was collected by vacuum filtration and washed with cold water to afford 2.4501 g (36.5%) of compound 73: mp 119.5-120°C; $^1H$ NMR ($CDCl_3$) δ 3.42 (s, 3 H, $OCH_3$), 3.84 (s, 3 H, $CO_2CH_3$), 4.27 (d, 2 H, J = 2 Hz, $J_{^{199}Hg-CH_2}$ = 126.6 Hz, $CH_2$), 6.68 (t, 1 H, J = 2 Hz, $J_{^{199}Hg-CH}$ = 490.2 Hz, CH); IR (KBr) 3004 (C=C-H), 1690 (C=O), 1617 (C=C) $cm^{-1}$. Anal. Calcd for $C_6H_9HgClO_3$: C, 19.73; H, 2.48; Hg, 54.93; Cl, 9.71. Found: C, 19.88; H, 2.52; Hg, 55.28; Cl, 9.62.

## 9. Carbonylation of mercurial 73

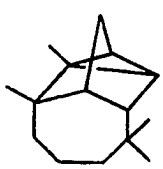
Five millimole of anhydrous lithium chloride (0.2125 g), 2.5 mmol of palladium chloride (0.4435 g), 5 mmol of magnesium oxide (0.2016 g) and

25 ml of dry methanol were placed in a round bottom flask with a septum inlet. While the system was being flushed with carbon monoxide at -78°C, 2.5 mmol of mercurial 73 (0.9128 g) was added. A balloon filled with CO was connected to the top of the flask and the reaction mixture was allowed to slowly warm up to room temperature and then stirred at room temperature for 18 h. One milliliter of saturated ammonium chloride solution and a small amount of activated carbon was added and stirring was continued for an additional 30 min. The reaction mixture was filtered through Celite. The filtrate was concentrated and the residue was extracted with ether. The ethereal extract was washed with saturated ammonium chloride. The organic layer was separated, dried ($MgSO_4$), and concentrated, giving a mixture containing a white solid and a colorless liquid. Hexanes were added to the above product mixture. The white solid was collected by filtration to afford 0.182 g (20%) of starting mercurial 73. The filtrate was concentrated and distilled to give 0.32 g of compound 74: yield 68%; bp 80-86°C (0.25 mmHg) (air bath temperature); $^1H$ NMR ($CDCl_3$) $\delta$ 3.40 (s, 3 H, $OCH_3$), 3.76 (s, 3 H, $CO_2CH_3$), 3.83 (s, 3 H, $CO_2CH_3$), 4.18 (d, 2 H, J = 1.7 Hz, $CH_2$), 6.16 (t, 1 H, J = 1.7 Hz, CH); IR (neat) 1730 (C=O), 1610 (C=C) $cm^{-1}$. GC/MS, m/z (relative intensity, assignment) 188 (0.02, $M^+$), 157 (33.56, $M^+$-$OCH_3$), 156 (93.15, $M^+$-$HOCH_3$), 129 (63.75, $M^+$-$COOCH_3$), 113 (37.60, $M^+$-$HCO_2CH_3$-$CH_3$), 101 (88.44, $M^+$-87), 98 (37.99, $M^+$-$CO_2CH_3$-$OCH_3$), 75 (100, $M^+$-113).

# IV. ATTEMPTED SYNTHESIS OF TETRACYCLIC SESQUITERPENES

## A. Introduction

In 1963, Nayak and Dev reported the structure of the first identified tetracyclic sesquiterpene, longicyclene (76) [98,99]. More recently other tetracyclic sesquiterpenes have been both characterized [100] and synthesized. The tetracyclic sesquiterpenes comprise a select class of natural products of which cyclosativene (77) [101-103], cyclocopacamphene (78) [104], longicyclene (76), (epi)cyclocopacamphenol (79) [104], and (epi)cyclocopacamphenic acid (80) [104] bear close structural resemblance [105-106]. The complex molecular architecture of



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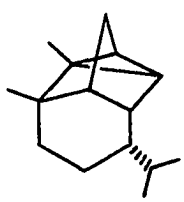

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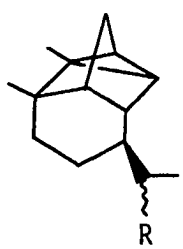
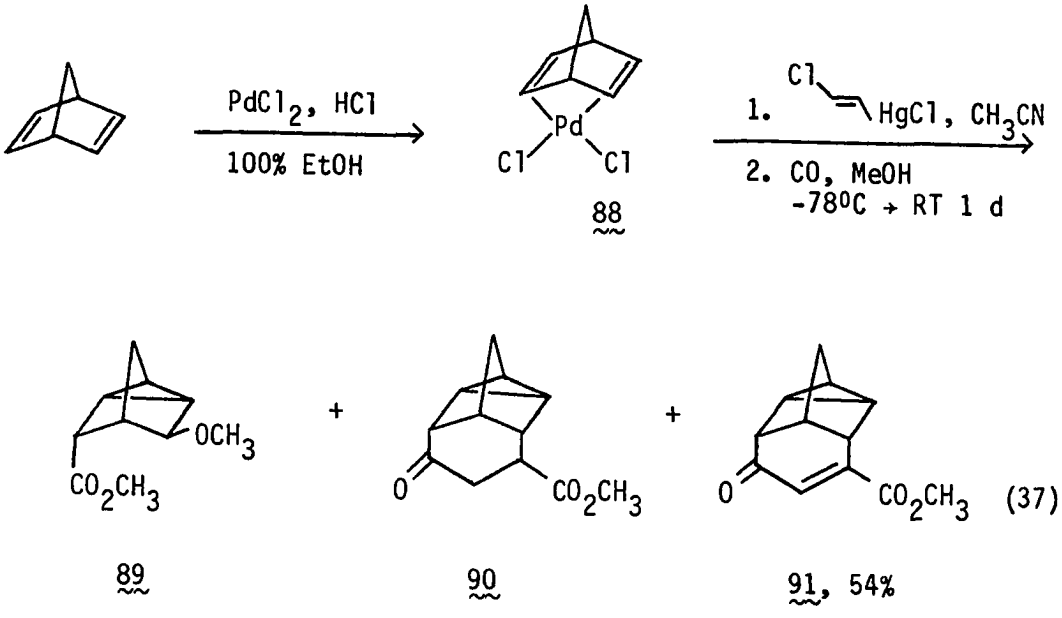


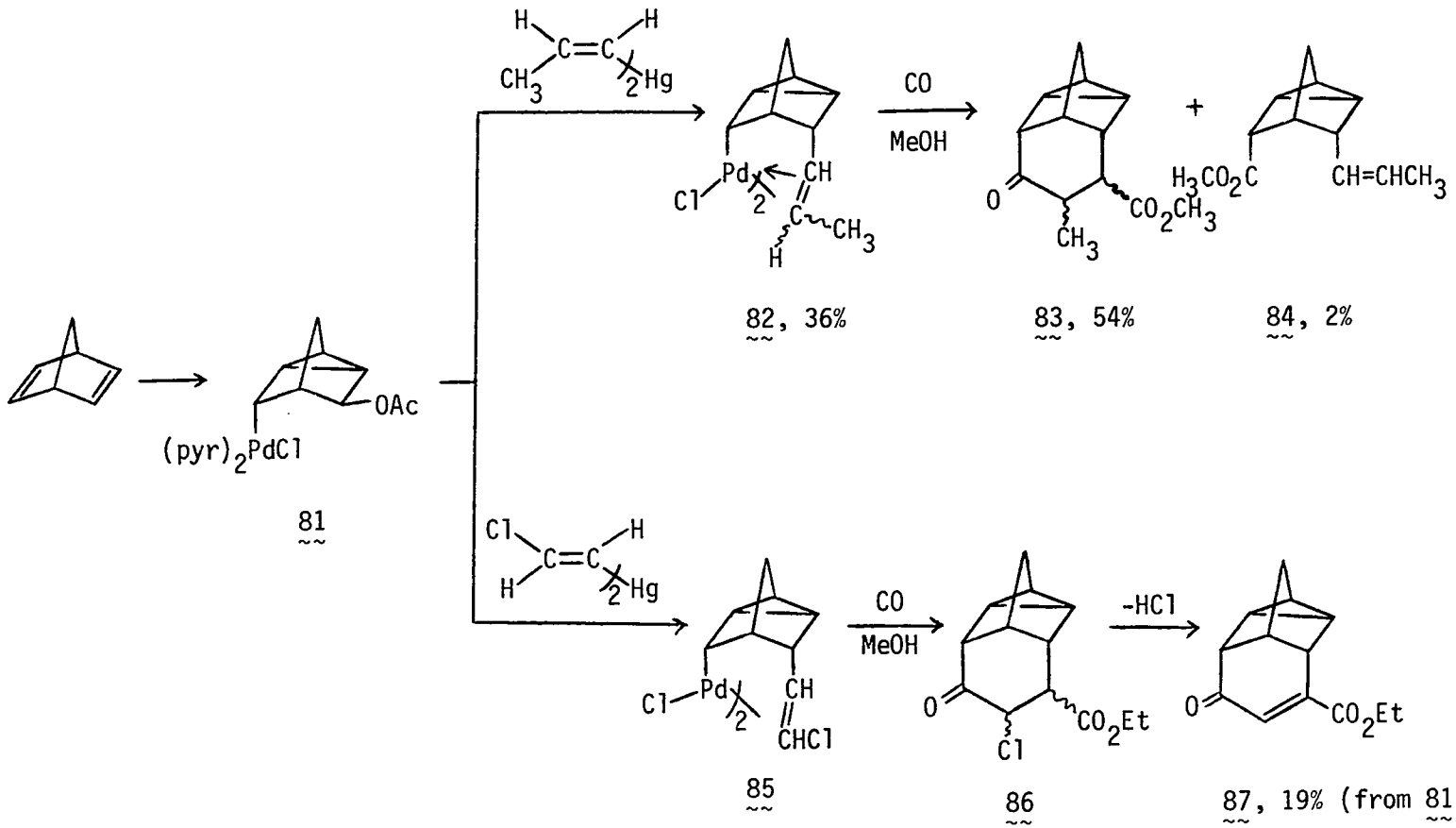

78, R=$CH_3$
79, R=$CH_2OH$
80, R=$CO_2H$

these tetracyclic sesquiterpenes has challenged synthetic organic chemists. While syntheses of the simple hydrocarbons have been reported [103], they tend to be rather lengthy. The alcohols and acids have not yet been synthesized.

Recent work in our laboratory and others [107] has provided a new route to the tetracyclic carbon skeleton, which with suitable modifications appeared to hold promise of providing a convenient new route to these sesquiterpenes (76 to 80). Vedejs and Weeks [107] have observed that vinylpalladation and subsequent carbonylation of norbornadiene affords the desired tetracyclic system (Scheme VII). We have examined the same reaction and found that the methyl ester analogue to compound 87 can be obtained from norbornadiene palladium dichloride, 88, in higher yield (eq. 37). It was our wish to extend this approach to

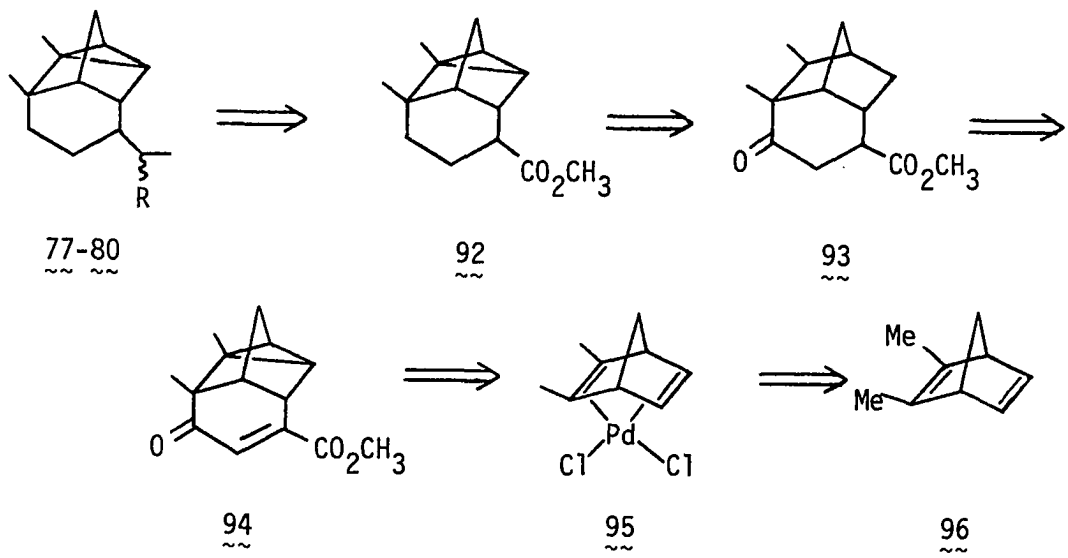


Scheme VII. Vinylpalladation-carbonylation of norbornadiene



the synthesis of tetracyclic sesquiterpenes. The retro-synthetic analysis of compounds 77 to 80 is shown in Scheme VIII. The intermediate

Scheme VIII. Retro-synthetic analysis of compounds 77 to 80




77-80 92 93

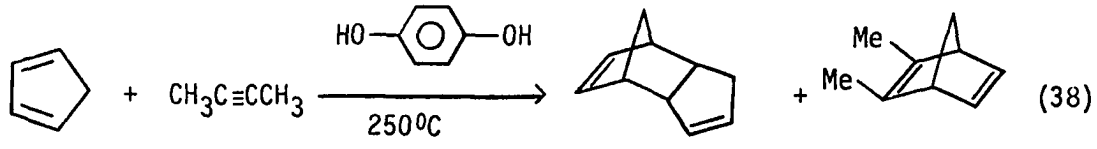
94 95 96

92 should be easily carried on to any of the six membered ring tetracyclic sesquiterpenes using standard synthetic organic techniques. By controlling the stereochemistry of the ester group by epimerization, we hoped to be able to prepare either cyclosativene or cyclocopacamphene and its derivatives. The key intermediate, keto ester 93, should also prove valuable for the synthesis of longicyclene by ring expansion. If successful this basic approach to the tetracyclic sesquiterpenes would greatly simplify present syntheses of all of these compounds and provide the first syntheses of cyclocopacamphenol, epicyclocopacamphenol, cyclocopacamphenic acid, and epicyclocopacamphenic acid.

## B. Results and Discussion

### 1. Preparation of 2,3-dimethylbicyclo[2.2.1]hepta-2,5-diene (96) and its reaction with $PdCl_2$

A direct Diels-Alder approach to the synthesis of compound 96 has been reported by two research groups [108,109]. However, this reaction gave a very low yield of compound 96 which can only be purified by preparative gas chromatography. When we repeated the reported procedures, only trace amounts of the desired compound 96 could be detected by GC/mass spectral analysis (eq. 38). We were unable to

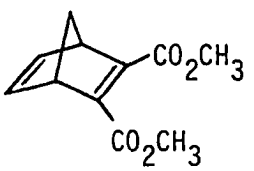



(38)

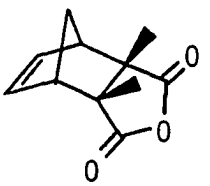
97 : 96

94 : 6

isolate compound 96 from the reaction mixture. Since the direct Diels-Alder approach gave only an abysmal yield of compound 96, it became necessary to develop other less direct routes to compound 96. We have examined four possible precursors to 96. These precursors are 2,3-dicarbomethoxybicyclo[2.2.1]hepta-2,5-diene (98), 2-exo, 3-exo-dimethylbicyclo[2.2.1]hepta-5-en-2-endo, 3-endo-dicarboxylic anhydride (99), 2-methyl-3-formylbicyclo[2.2.1]hepta-2,5-diene (100), and 2-methyl-3-carbomethoxybicyclo[2.2.1]hepta-2,5-diene (101).



98



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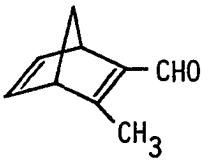

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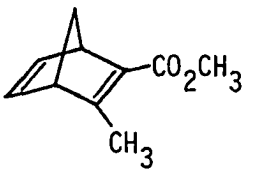
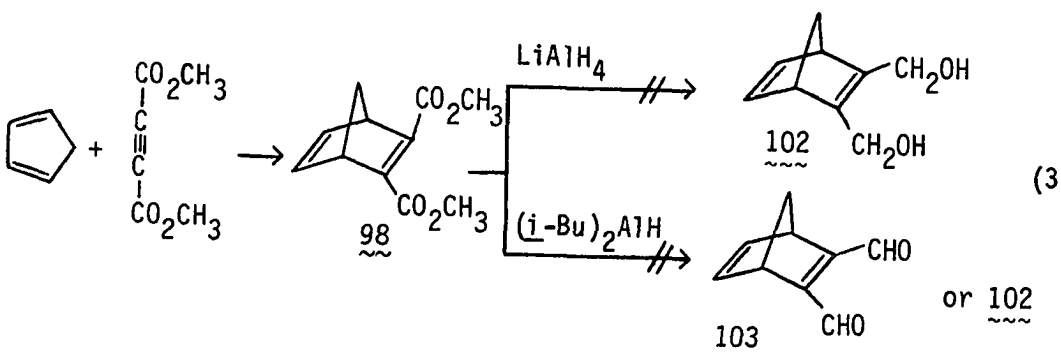


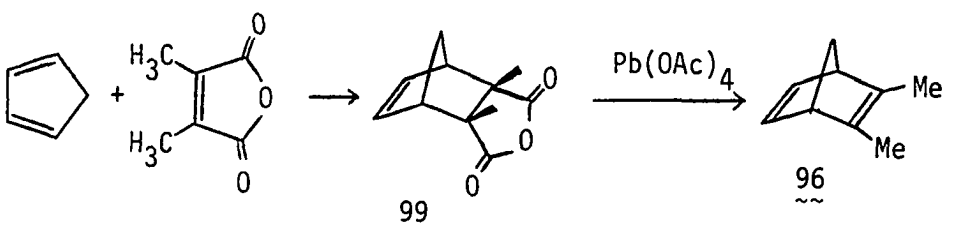
101

Reduction of compound 98 to the corresponding diol or dialdehyde has been examined by Larock and Takagi (eq. 39) [110]. Unfortunately, none of the expected product was detected in the reaction mixture.



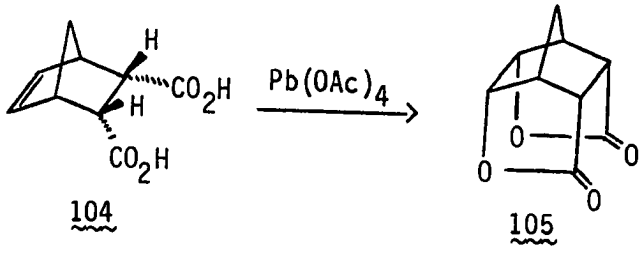
(39)

A combination of a Diels-Alder reaction using maleic anhydride followed by bisdecarboxylation with lead tetraacetate represents a convenient synthesis of a wide variety of bicyclic alkenes [111]. Our approach to the synthesis of compound 96 from 99 is shown in Equation 40.



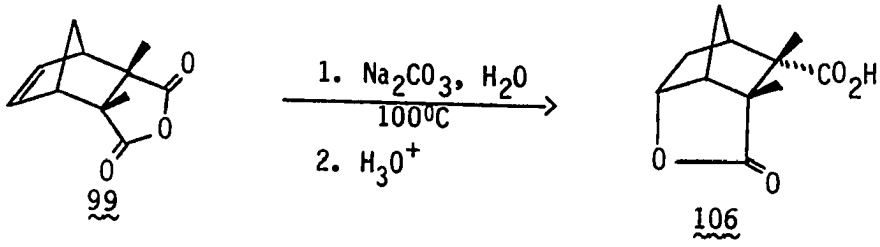
(40)

Compound 99 has been prepared from cyclopentadiene and 2,3-dimethylmaleic anhydride [112] in 81% recrystallized yield (based on reacted 2,3-dimethylmaleic anhydride). Bisdecarboxylation of compound 99 or the corresponding diacid with lead tetraacetate appeared promising as a route to 96. However, many competing side reactions have been observed when a double bond is in close proximity to the carboxyl groups [111-113]. For example, the only product isolated from the reaction of the bicyclic acid, 104, and lead tetraacetate is a dilactone (105) (eq. 41). Actually, Corey and Gross have utilized the same reaction (eq. 41) to synthesize bislactones from unsaturated diacids and lead tetraacetate [114].



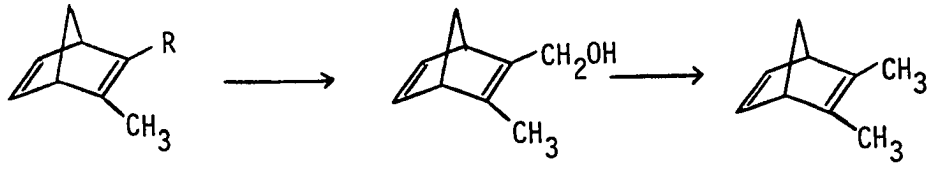

104 105 (41)

We decided to examine bisdecarboxylation of both compounds 99 and the corresponding diacid. Unfortunately, the reaction of compound 99 and lead tetraacetate gave no product and the starting material 99 could be recovered quantitatively. Hydrolysis of compound 99 in boiling water gave starting material only. Hydrolysis of compound 99 with sodium carbonate gave tricyclic lactone 106 instead of the expected diacid (eq. 42). We, therefore, turned our attention to other approaches.




99 106 (42)

An α,β-unsaturated aldehyde or ester of structure 107 seemed attractive as a precursor to 96 for two good reasons: (i) its relative ease of synthesis and (ii) the abundance of methods available for the reduction of 107 to alcohol 108 and eventually to 96. We first examined the synthesis of 107a. The Diels-Alder reaction of cyclopentadiene and

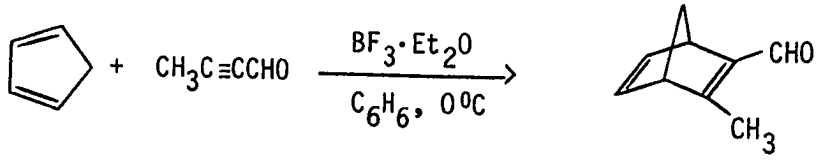



(43)

107 a R=CHO
b R=$CO_2CH_3$

108 96

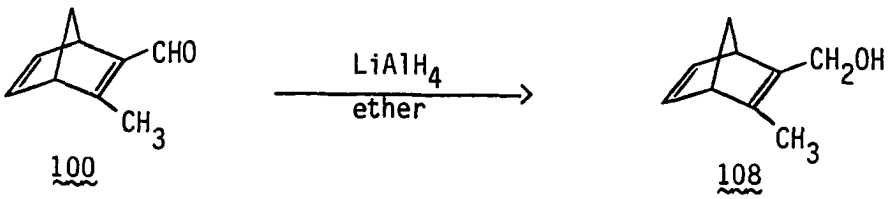
2-butynal gave an unstable product 100 as the only product (analyzed by GLC) (eq. 44). The reduction of compound 100 with lithium aluminum




(44)

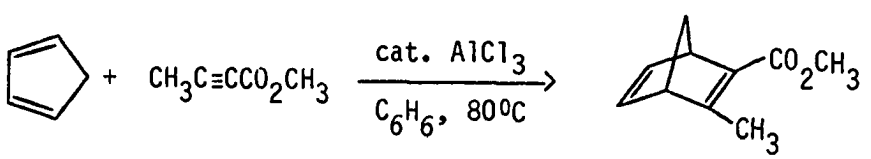
100 (31% isolated)

hydride ($LiAlH_4$) in diethyl ether gave the corresponding alcohol 108 in 25% isolated yield (eq. 45). Reductions of compound 100 with $LiAlH_4$ in




100 108 (45)

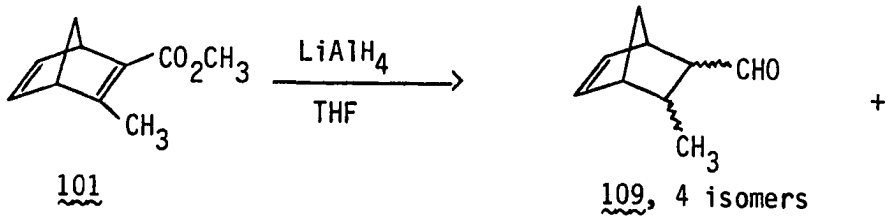
THF or with diisobutyl aluminum hydride in THF gave comparable yields. Since both steps, the Diels-Alder reaction and reduction, proceeded in low yields and the same reaction sequence when carried out on α,β-unsaturated ester (101) gave a higher yield (to be discussed later), we switched our attention to compound 101. We have been able to synthesize compound 101 in 67% yield from cyclopentadiene and methyl-2-butynoate in the presence of catalytic amounts of aluminum chloride (eq. 46). We have



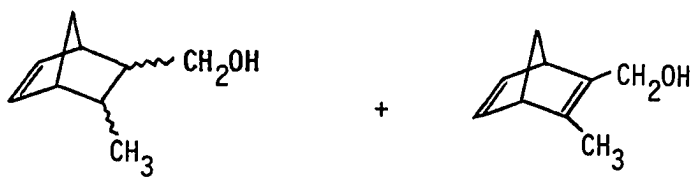

(46)

101, 67%

also found that boron trifluoride etherate has no effect on this reaction. The reduction of compound 101 with lithium aluminum hydride in THF gave products 109 (41%), 110, and 108 (yield of 110 + 108: 16%; ratio of 110:108 is 5.7:1) (eq. 47). Product 109 contains all four possible isomers and product 110 contains three isomers (identified by GC/mass spectral analysis). Changing the solvent from THF to diethyl ether gave



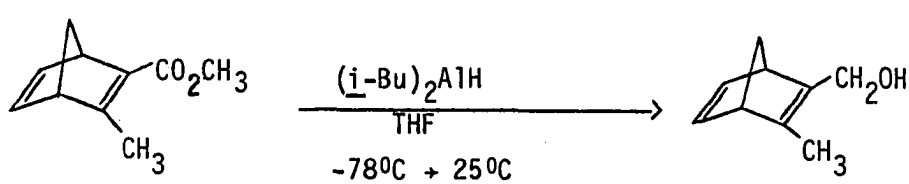

101 109, 4 isomers




(47)

110, 3 isomers 108

only a very small amount of product 109 and the major product was unreacted starting material 101. Aluminum hydride (prepared from $LiAlH_4$ and $AlCl_3$) also did not reduce ester 101 at all after 1 h at 25°C. However, reduction of compound 101 with diisobutylaluminum hydride gave the desired alcohol as the only product in 96% isolated yield (eq. 48).

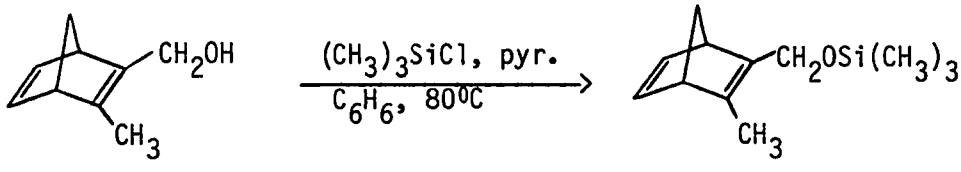



(48)

101 108

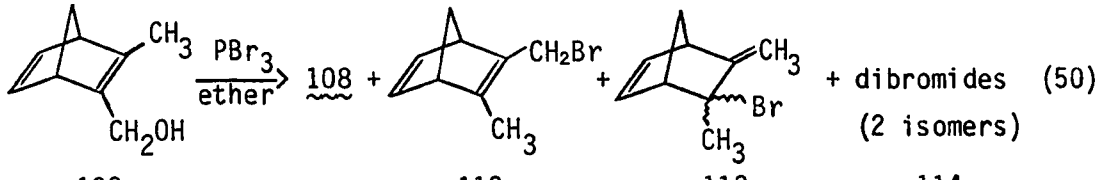
The deoxygenation of alcohol 108 was not as easy as anticipated. The replacement of the allylic hydroxyl group by hydrogen using hydride displacement is complicated by difficulties in the conversion of the hydroxyl function into a suitable leaving group. The most commonly used

derivatives, the p-toluenesulfonate, methanesulfonate, iodide, bromide, and chloride have all been examined. Tosylation and mesylation [115] of alcohol 108 under various conditions gave only unidentified product. For the hydride displacement reaction, an iodide is more reactive than the corresponding bromide or chloride. We therefore examined the iodination of compound 108 first. Iodination of alcohol 108 by the method of Olah ($Me_3SiCl/NaI/CH_3CN$) [116] gave unidentifed product. Iodination of the trimethylsilyl ether of alcohol 108 has also been examined. Compound 108 has been converted to the trimethylsilyl ether (111) in 67% yield (eq. 49). Unfortunately, both Morita's method ($NaI/Me_3SiCl/CH_3CN$) [117]



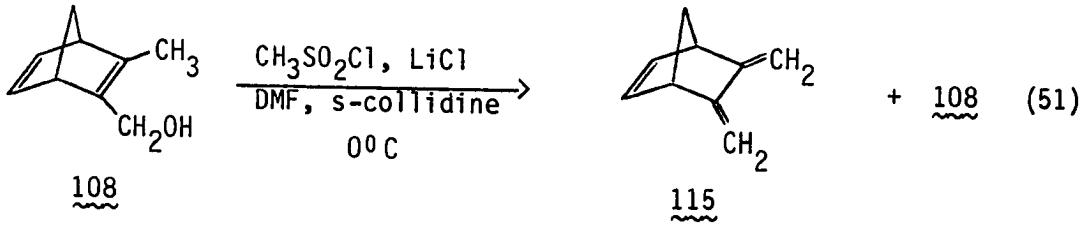

108 111 (49)

and Jung's method ($Me_3SiI/HCCl_3$) [118] failed to convert compound 111 to the corresponding iodide. The bromination of compound 108 with phosphorus tribromide gave two monobromides and two dibromides (eq. 50) [119]. The relative GLC peak areas for 108:112:113:114 is 1:1.6:4.1:1.8.



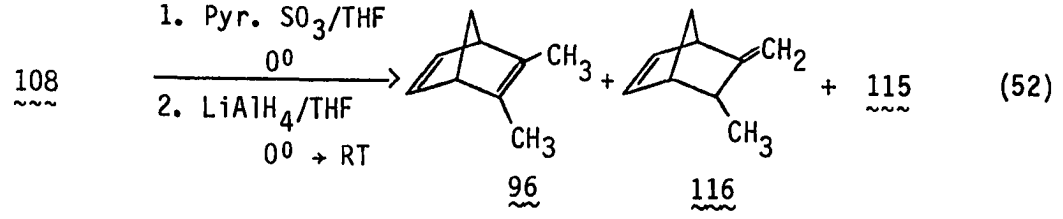

108 112 113 114 (50)

Bromination of 108 with phosphorus tribromide in the presence of a catalytic amount of pyridine [120] gave the same products in the ratio 1:1.2:9.1:1.9. The proton NMR spectrum of the reaction mixture showed that the major product was the rearranged monobromide (113). Bromination of alcohol 108 with carbon tetrabromide-triphenylphosphine ($CBr_4/PPh_3$) under various conditions [121] also gave compound 113 as the major product. In 1971, Collington and Meyers reported a mild procedure to convert allylic alcohols to the corresponding chlorides without allylic rearrangement [122]. We applied the same reaction conditions to alcohol 108 and found that the major product is triene 115 (eq. 51). The proton NMR spectrum of the reaction mixture showed that it contained only compound 115 [123,124], small amounts of compound 108 and several unidentified products.




108 115

Finally, we found that the method for deoxygenation of allylic alcohols reported by Corey and Achiwa [125] works well for our system (eq. 52). Although Corey claimed that neither cis-trans isomerization nor allylic transposition was observed to a significant extent, we found that allylic transposition and 1,4-elimination products were formed in

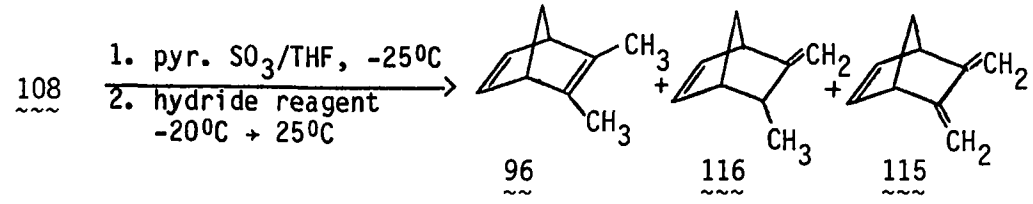



(52)

addition to the desired product. The ratio of 96:116:115 as judged by their GLC relative peak areas is 4.9:1:9.7. The ratio changed to 3.5:1:1.5 when the reaction temperature was kept at -25°C. The effect of various hydride reagents has been examined and the results are summarized in Table XI. The best reaction conditions involved a clear solution of lithium aluminum hydride in tetrahydrofuran [126] at -20°- -25°C. The isolation and purification of compound 96 from the reaction mixture was very difficult.

After searching the literature, we found no indication that compounds similar to 115 or 116 would form a solid complex with $PdCl_2$. So compound 96 should be separable as the $PdCl_2$ complex. Thus, compound 108 was allowed to react with the sulfur trioxide pyridine complex (2 equiv.) in THF at -25°C for 7 h and then the mixture was reduced with a crystal-clear solution of $LiAlH_4$ (5 equiv.) in THF for 16 h at -25°C to afford a mixture of 96, 115, and 116. As expected, only one product (95) was isolated as a yellow solid from the reaction of $PdCl_2$ and the mixture of 96, 115, and 116 (eq. 53) [127]. Complex 95 precipitated from the reaction mixture as a pure compound. It has been characterized by both

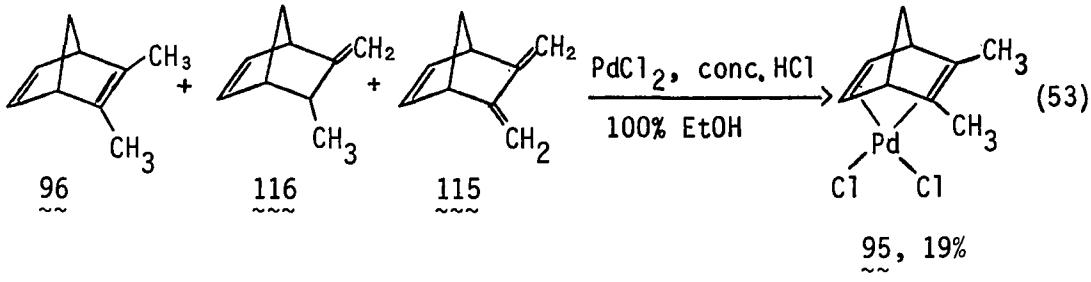
Table XI. Deoxygenation of alcohol 108




96 116 115

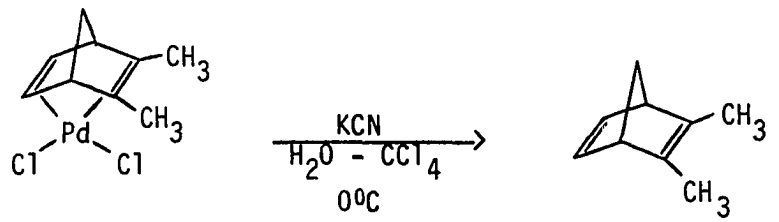
| Hydride Reagent | Ratio of 96:116:115[a] |
|---|---|
| $LiAlH_4$ | 3.5:1:1.5 |
| | 2.5:1.2:1 |
| $(i\text{-Bu})_2AlH$ | 1.6:1:3 |
| clear THF solution of $LiAlH_4$ | 4.4:1:1.3 |
| $NaAlH_2(OCH_2CH_2OCH_3)$ (Vitride) | only compound 115 can be detected by GLC analysis |
| $LiHBEt_3$ | 5.4:1:3.4 |

[a]Relative GLC peak areas




96 116 115 95, 19% (53)

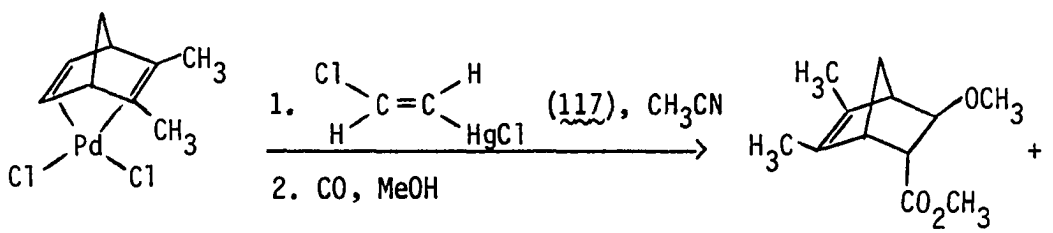
chemical (eq. 54) [128] and physical methods (elemental analysis, see Experimental Section). After treating the complex with potassium cyanide, only compound 96 was observed by capillary gas chromatography analysis.



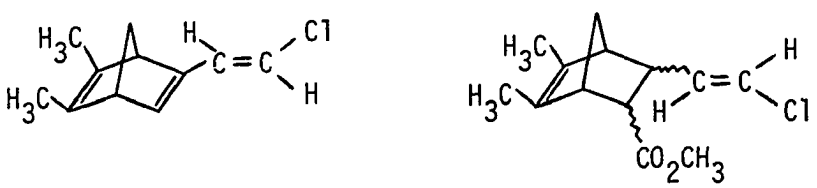

95 96 (54)

2. Vinylation and subsequent carbonylation of compound 95

The reaction of compound 95 with trans-2-chlorovinylmercuric chloride (117) and subsequently with CO/MeOH gave compound 118 as the major product, together with two vinylated products 119 and 120 (eq. 55). The results are summarized in Table XII. These results suggest



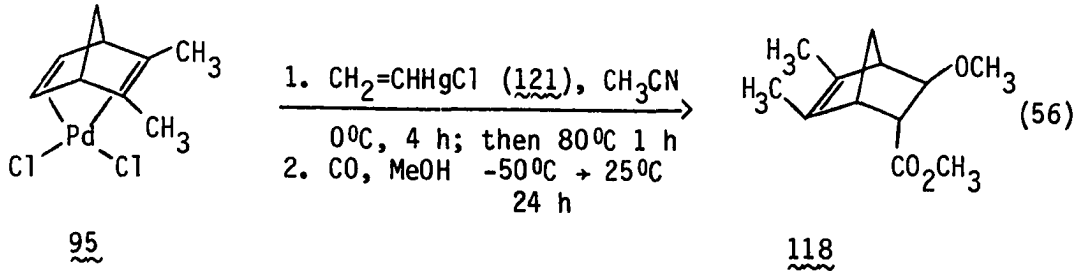

95 118, major product




119 120 (55)

that mercurial 117 is not reactive enough toward compound 95. Heating does not help the vinylation step (see entry 2, Table XII). The results

also suggest that a more reactive vinylating agent should be employed. The reaction of compound 95 with vinylmercuric chloride (121) and subsequently with carbon monoxide in methanol also gave compound 118 as the only product (eq. 56). No vinylated product could be detected in the




95 118

Table XII. Vinylation and subsequent carbonylation[a] of compound 95

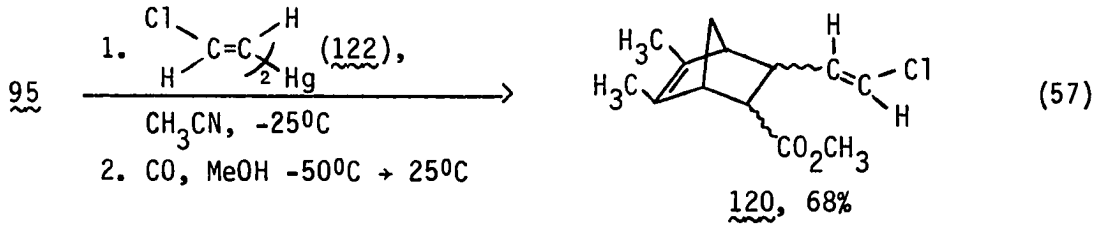
| Entry | Reaction conditions for the vinylation step | Ratio of product(s)[b] |
|---|---|---|
| 1 | 0°C, 4h; 25°C, 24 h | 118[c]:119:120=10.6:1:5 |
| 2 | 0°C, 30 min; 25°C, 5h; 80°C, 1 h | 118 only |
| 3 | 0°C, 1.5 h | 118:119:120=8:3.6:1 |
| 4 | -25°C, 3.5 h | 118 only |
| 5 | -25°C, 5 h | 118 only |
| 6 | -50°C, 2 h | 118 only |
| 7 | 0°C, 1.5 h | 118:120=1.7:1 |

[a]Carbonylation was effected at -50°C → 25°C for 1 day.

[b]Relative peak area ratio by GLC analysis.

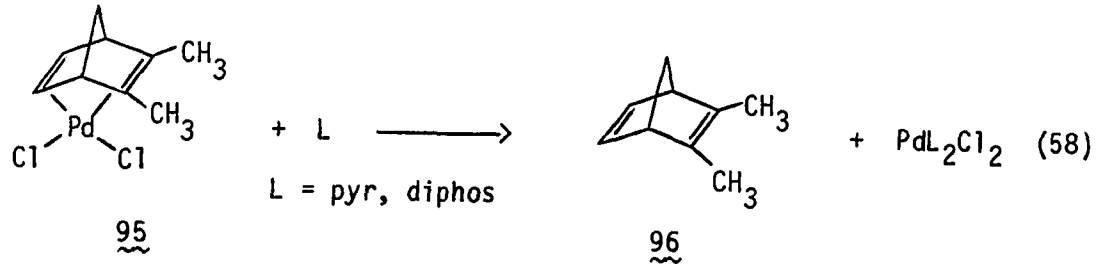
[c]Compound 118 could be isolated in 13% yield.

reaction mixture by GLC analysis. The reaction of compound 95 with the more reactive mercurial di(trans-2-chlorovinyl)mercury (122) and subsequently with CO in MeOH gave compound 120 as the only product (2 isomers in a ratio of 10:1) (eq. 57.). Neither tetracyclic nor tricyclic products could be detected by GC/mass spectral analysis. Subsequent work indicated that the solvent used for the vinylation step has no effect on

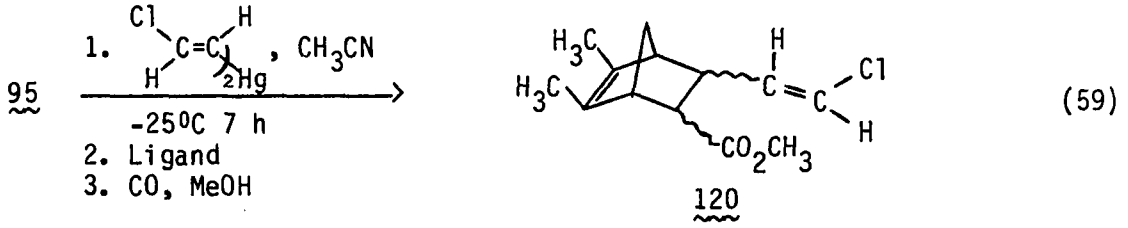



(57)

the structure of the product. Running the reaction in acetonitrile (68% isolated yield), THF (75%) or $CH_2Cl_2$ (no yield determined) still gave only compound 120. The effect of added ligand has also been examined. When pyridine or 1,2-bis(diphenylphosphino)ethane (diphos) and compound 95 were stirred together for 30 min and then vinylation (with mercurial 122) and subsequent carbonylation were carried out, no organic product could be detected from the reaction mixture. This might be due to the destruction of compound 95 to form a palladium(II) salt and compound 96 (eq. 58). When compound 95, mercurial 122, and ligand (CO and/or 2 equiv. pyridine) were mixed together at the beginning of the reaction, still only compound 120 could be detected. We also examined the effect of adding the ligand after the vinylation step is complete (eq. 59) and found that only compound 120 was formed when pyridine (8




95 96



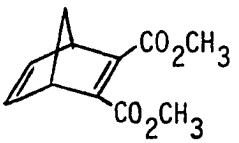

120

equiv.) was used and no organic product could be detected when diphos (2 equiv.) was used. We conclude that the tetrasubstituted double bond of compound 95 fails to participate in the cyclization and one obtains only bicyclic products.

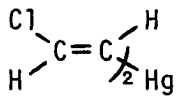
3. Attempted vinylpalladation and subsequent carbonylation of compounds 98 and 101

Since vinylation and subsequent carbonylation of the palladium chloride complex of 2,3-dimethylbicyclo[2.2.1]hepta-2,5-diene gave only bicyclic products, we wanted to examine the possibility of preparing $PdCl_2$ complexes of compounds 98 and 101 for possible applications in the synthesis of tetracyclic sesquiterpenes. When treated with $PdCl_2$ in the presence of conc. HCl, neither compound 98 nor 101 gave a solid product. So our next approach was to examine the possibility of generating the $PdCl_2$ complexes *in situ* ($Li_2PdCl_4$/THF) and follow that by

vinylation-carbonylation. Both compounds 98 and 101 gave the same products as determined by gas chromatography and mass spectral analysis (eqs. 60 and 61). Unfortunately, none of the desired product could be detected by GC/mass spectral analysis. These results suggest that no

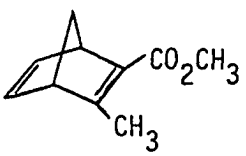


98

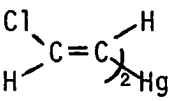
1. $Li_2PdCl_4$, THF
2. 
3. CO, MeOH

$\rightarrow C_4H_4Cl_2 + C_5H_2Cl_2O + C_6Cl_2O_2$ (60)

| 123 | | 124 | | 125 |
|---|---|---|---|---|
| 83.7 | : | 11.6 | : | 4.7 |

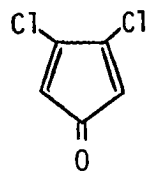


101

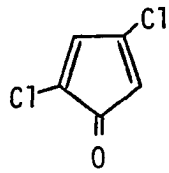
1. $Li_2PdCl_4$, THF
2. 
3. CO, MeOH

| 123 | + | 124 | + | 125 | (61) |
|---|---|---|---|---|---|
| 78 | : | 17 | : | 5 | |

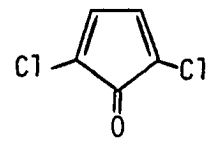
$PdCl_2$ complex has been formed in either case. These two reactions were analyzed by GC/mass spectroscopy and the ratios are relative GLC peak areas. Compound 123 is actually two isomers, presumably 1,3- and 1,4-dichloro-1,3-butadiene or *cis* and *trans* isomers of one of these compounds. The most reasonable structure for product 124 would appear to be 126 and its formation can be explained as shown in Scheme IX. At this stage, we cannot rule out the other two possible structures 127 and 128. One possible structure for compound 125 is 131.



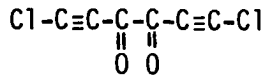
126



127

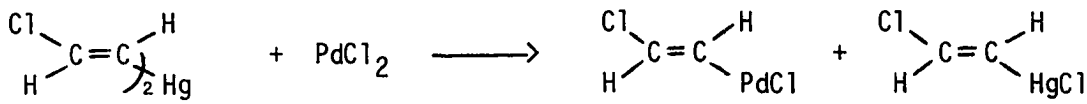


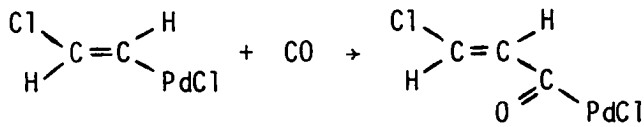
128



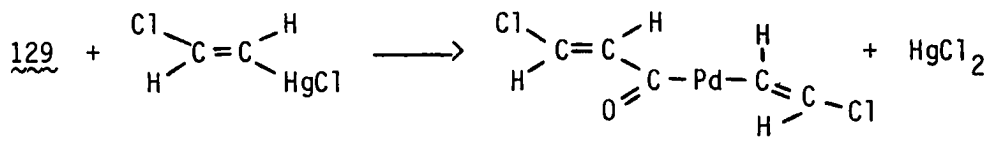
131

Scheme IX. Formation of compound 126

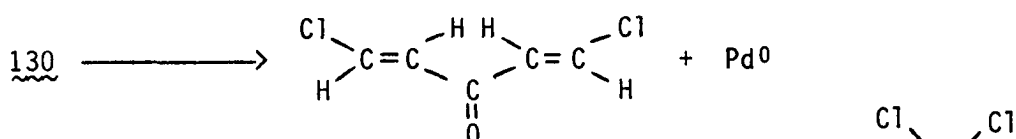


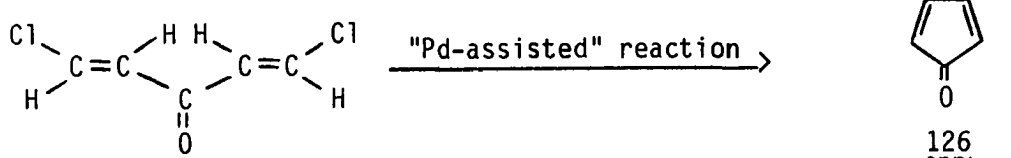


129



130

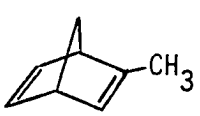




126

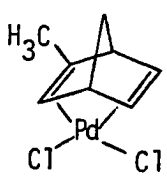
4. Preparation of 2-methylbicyclo[2.2.1]hepta-2,5-diene (132) and its reaction with $PdCl_2$

Since the 2,3-dimethylnorbornadiene-palladium dichloride complex led only to bicyclic products, we examined the possibility of first constructing the tetracyclic carbon skeleton from 2-methylbicyclo[2.2.1]-hepta-2,5-diene-palladium dichloride (133) and introducing the second methyl group later on. From a mechanistic view, vinylpalladation should introduce the vinyl moiety at the least hindered site and subsequent carbonylation should give tetracyclic product 134 (eq. 62). Hopefully, compound 134 could be methylated alpha to the ketone, and the resulting

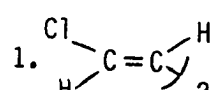


132

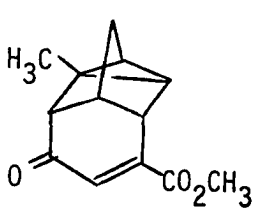
$PdCl_2$, conc. HCl, 100% EtOH



133

1.  Hg, $CH_3CN$

2. CO, MeOH

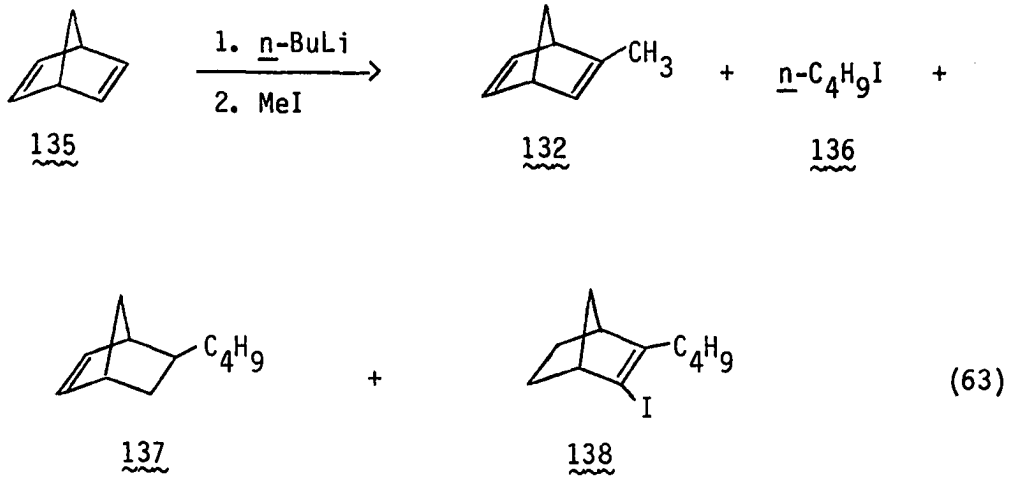


134

(62)

product should be easily carried on to the tetracylic sesquiterpenes using standard synthetic organic techniques.

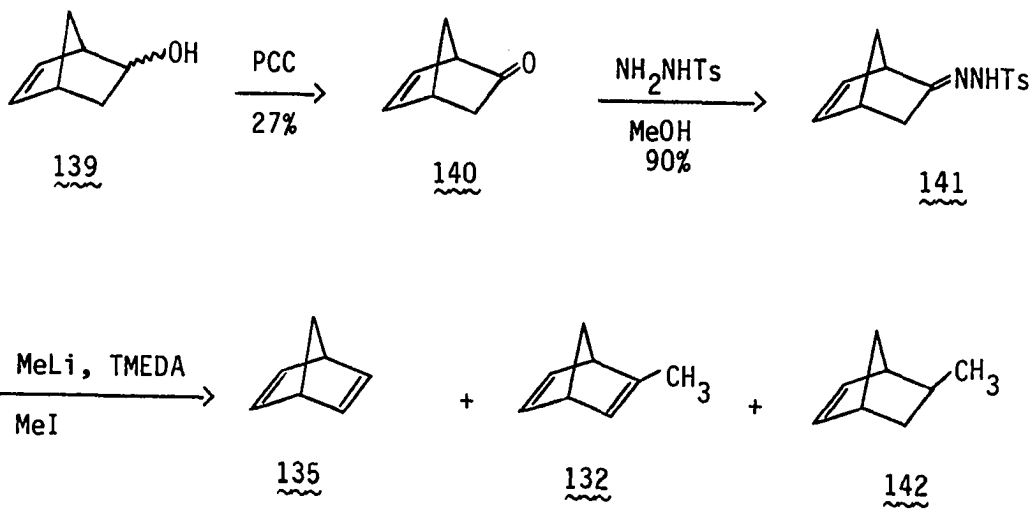
A direct route to the synthesis of 2-methylbicyclo[2.2.1]hepta-2,5-diene (132) [129] gave only trace amounts of compound 132 together with large amounts of 136, 137, and 138 (contains 3 isomers) (eq. 63). The



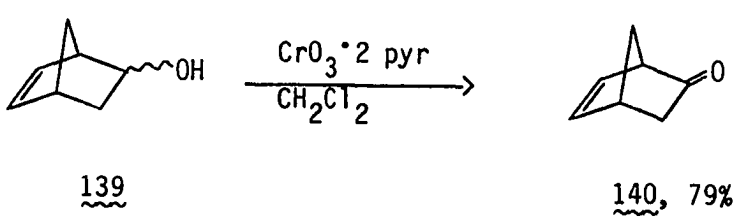

135 132 136 137 138 (63)

relative GLC peak areas of 132:136:137:138 were 1:24.4:1.3:9.4. Changing the base from n-butyllithium to t-butyllithium gave no better yield of compound 132. A literature procedure for the synthesis of compound 132 has been published recently [130]. An identical reaction sequence has been examined (Scheme X). This reaction sequence suffers two difficulties. First, the oxidation of compound 139 to 140 with pyridinium chlorochromate (PCC) proceeds in very low yield (27%; lit. [130] yield 24%). Second, the Shapiro reaction (141 → 132) always gives norbornadiene (135) as a by-product even when all reagents and solvents

Scheme X. Preparation of compound 132




were purified. Since the separation of compound 132 from compounds 135 and 142 is difficult and both compounds 132 and 135 can react with $PdCl_2$ to form solid complexes, this approach was not very promising. Although we were able to improve the yield for the oxidation step (eq. 64)

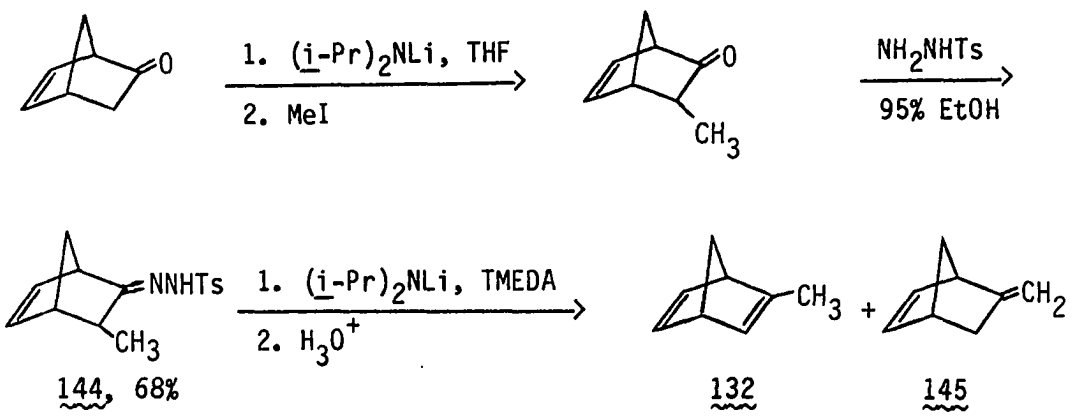



(64)

[131,132], we were still unable to eliminate the formation of compound 135 from the reaction (since compound 142 will not form a solid complex with $PdCl_2$, we were not worried about it at the moment). Although the addition of benzene as co-solvent for the Shapiro reaction reduces the

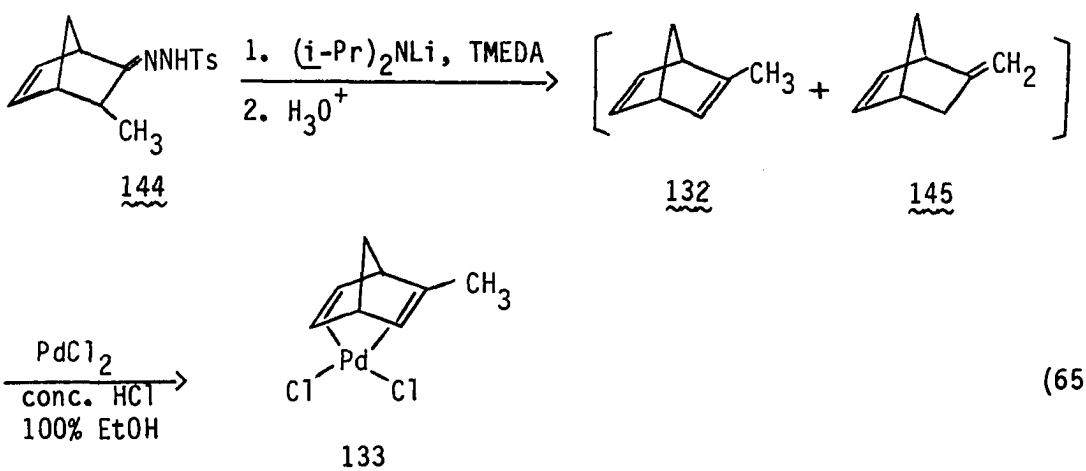
amount of compound 135 relative to 132 from 1:25 to 1:50, we were unable to completely eliminate the formation of compound 135. We have, therefore, adopted a new route [133] to compound 132 (Scheme XI). This new route

Scheme XI. A new route to compound 132




144, 68% 132 145

gave two products 132 and 145 in a ratio 6.8:1 (relative GLC peak areas). Without further separation, the mixture of 132 and 145 was treated with $PdCl_2$ to afford a solid complex 133 in 31% yield from compound 144 (eq. 65). The yellow solid which precipitated from the

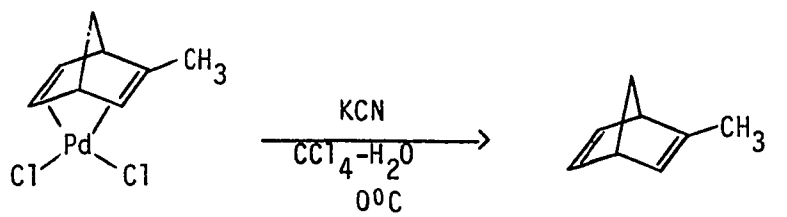



144 132 145

133

(65)

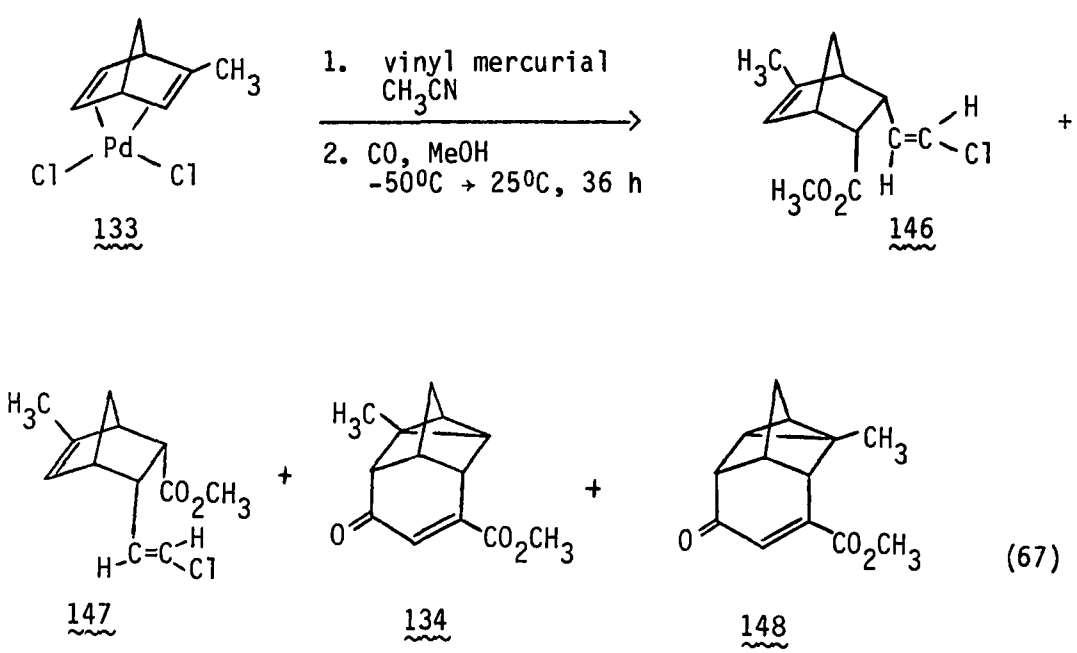
reaction mixture was pure compound 132 as shown by elemental analysis (see Experimental Section) and its conversion to compound 132 (eq. 66) [128].




133 132 (66)

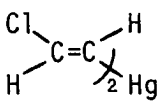
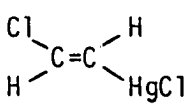
5. Vinylation and subsequent carbonylation of compound 133

The vinylation and subsequent carbonylation of compound 133 gave four major products (eq. 67). The results are summarized in Table XIII.




147 134 148 (67)

Table XIII. Vinylation and subsequent carbonylation of 133

| Vinylating agent and reaction condition | Ratio[a] of 146:147:134:148 | % yield[b] 146 | 147 | 134 | 148 |
|---|---|---|---|---|---|
|  (122) | 1.28:1:2.62:148 | | | | |
| 0°C, 7 h | | | | | |
| 122 | 3.7:1:11.2:7.3 | 3.4 | 0.9 | 10 | 6.9 |
| 25°C, 7 h | | | | | |
| 122 | 1:28:4.8:2.9 | 1.7 | 4.7 | 8.3 | 5.0 |
| -40°C → -50°C, 9 h | | | | | |
|  (117) | 3.6:1:4.2:3.0 | | | | |
| 0°C, 7 h | | | | | |
| 117 | 2.3:1.2:4.0:1 | 4.5 | 2.2 | 8.2 | 3.1 |
| 25°C, 24 h | | | | | |
| 117 | 1:2.1:4.6:1.3 | 1.6 | 3.3 | 7.6 | 2.1 |
| 25°. 48 h | | | | | |
| $H_2C$=CHHgCl (121) | ---[c] | | | | |
| 25°C, 24 h | | | | | |

[a]GLC relative peak areas.

[b]GLC yields with n-$C_{13}H_{28}$ as the internal standard and assuming that the response factors are equal to one for all products.

[c]No peak can be detected by GLC analysis.

The isolation of these 4 products has been attempted using trans-2-chlorovinylmercuric chloride (117) as the vinylating agent. We found that the combined yields for compounds (146 + 147) and (134 + 148) varied depending on the reaction condition used in the vinylation step. The results are summarized in Table XIV. Compounds 146 and 147 have the same

Table XIV. Vinylation-carbonylation of compound 133

| Reaction conditions for the vinylation step | Isolated Yield (%) 146 + 147 | 134 + 148 |
|---|---|---|
| 25°C, 36 h | 19 | 26 |
| 25°C, 24 h | 21 | 21 |
| 0°C, 48 h | 25 | 16 |

Rf value (TLC analysis) and they can be separated by GLC only. GC/MS analysis of the mixture shows two peaks with the same molecular ion at m/z 226 and both have the base peak at m/z 80 ($C_5H_5CH_3^{+\cdot}$). The stereochemistry of 146 and 147 is tentatively assigned as endo, endo for both the ester and vinyl substituents. Compounds 134 and 148 cannot be separated by liquid column chromatography. GC/MS analysis of the mixture shows two peaks, both peaks have the molecular ion at m/z 218. The proton NMR spectrum of the mixture shows two singlets corresponding to the olefinic protons. The relative peak intensities for these two singlets varied from reaction to reaction. The above results strongly suggested that there must be two isomers in the mixture. By comparing

the proton NMR spectrum of the mixture of 134 and 148 to that of compound 91, we tentatively assigned the structures of the two isomers as shown.

6. Methylation of the mixture of 134 and 148

The observation of a mixture of tetracyclic products was discouraging. Nevertheless, several methylation reactions have been examined. However, none of them gave the desired product 94. When deprotonated with lithium diisopropylamide (LDA) and then quenched with methyl iodide, the mixture of compounds 134 and 148 gave unidentified products (eq. 68). When the base was changed from lithium

$$\underset{\text{134}}{\text{}} + \underset{\text{148}}{\text{}} \xrightarrow[\text{2. 3~5 equiv. } CH_3I \\ -78^0 \rightarrow 25^0C,\ 18\ h]{\text{1. base/THF}} \underset{\text{134}}{\text{}} + \underset{\text{148}}{\text{}} + \underset{\text{149}}{\text{}} + \underset{\text{150}}{\text{}} \qquad (68)$$

diisopropylamide to lithium 2,2,6,6-tetramethylpiperidide (LiTMP), the reaction gave no organic product at all (analyzed by GLC). The results of methylation are summarized in Table XV. The reaction products were analyzed by GC/mass spectrometry. Product 149 contains two isomers; both have a molecular ion of m/z=246. Product 150 contains three isomers, all of which have a molecular ion of m/z=260. The fragmentation patterns at m/z $\leq$ 186 ($M^+$-$CH_3OH$ of 134 or 148) for all isomers of 149 and 150 are very similar to the starting material (see Experimental Section). From this result, we concluded that there was no methylation reaction occurring on the tetracyclic ring. The possible structures for the two

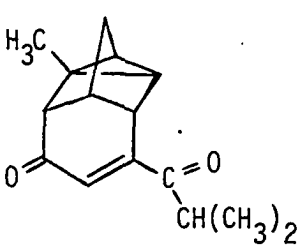
Table XV. Methylation of compounds 134 + 148

| Reagent and reaction conditions for the deprotonation step | Products and ratio[a] |
|---|---|
| 1.1 equiv LDA; -78°C, 1 h | 134 + 148 |
| 1.2 equiv LDA; -78°C, 1 h and then 25°C, 10 min | (134 + 148):149:150 =5:1:20 |
| 2.2 equiv LDA; -78°C, 30 min and then 25°C, 1.5 h | (134 + 148):149:150=10.3:1:9.8 |
| 1.2 equiv LiTMP; -78°C, 1 h and then 25°C, 10 min | no organic product[b] |

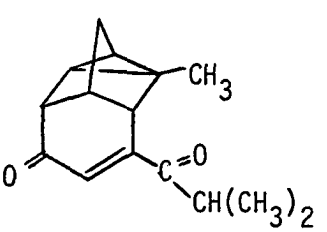
[a]Ratios are the relative GLC peak areas.

[b]No organic product can be detected by GLC analysis.

isomers of 149 are 149a and 149b. A mixture of three isomers (150a, 150b, and 150c) of product 150 has been isolated and its proton NMR spectrum shows that neither a methoxy nor an isopropyl group is present. We are unable to assign structure to these compounds at this time.




149a




149b

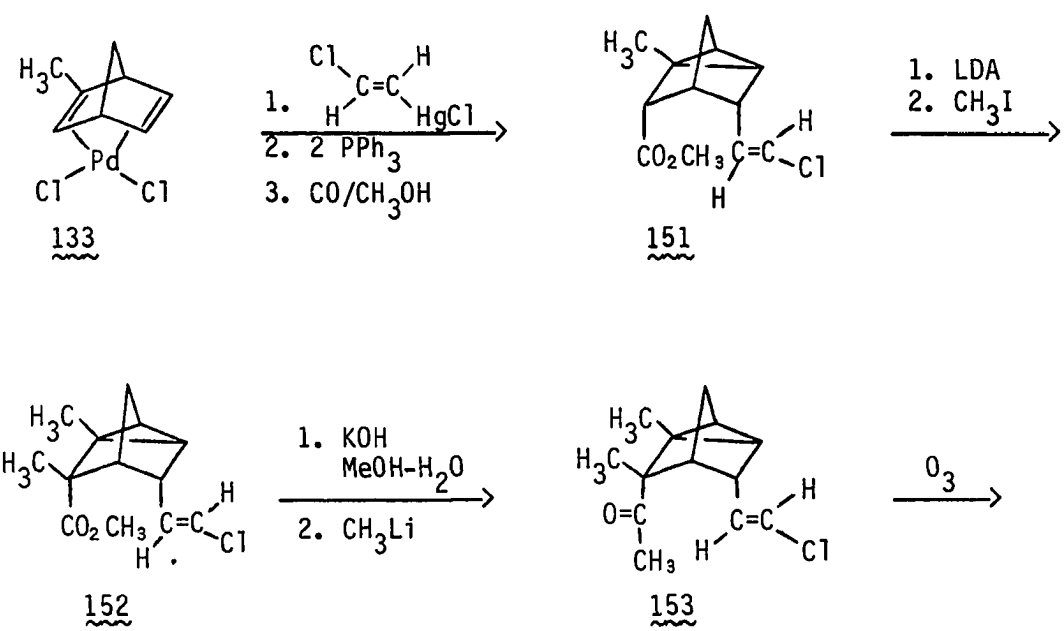
Another possible route to introduce the methyl group is to generate the enol silyl ether first. Unfortunately, only the starting keto ester could be isolated from the silylation reaction (eq. 69).

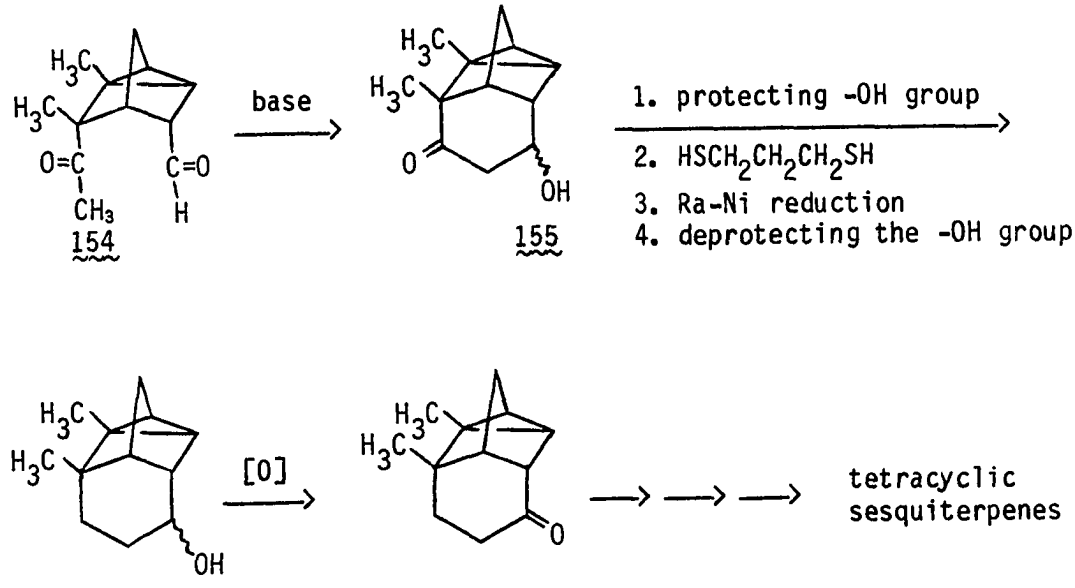
$$\underset{\sim}{134} + \underset{\sim}{148} \xrightarrow[\text{2. 1.2 equiv. } Me_3SiI \\ -20^0C,\ 20\ min;\ 25^0C,\ 20\ h]{\text{1. 1.2 equiv. } (Me_3Si)_2NH/CH_2Cl_2,\ -20^0C} \underset{\sim}{134} + \underset{\sim}{148} \qquad (69)$$

## 7. Two possible approaches to tetracyclic sesquiterpenes

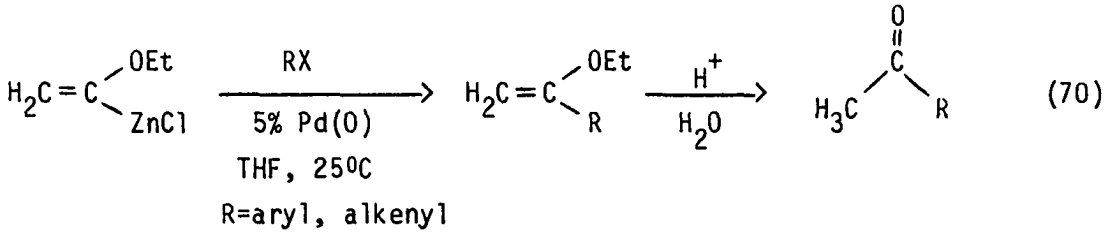
There are two more new approaches which might lead to the synthesis of tetracyclic sesquiterpenes. The first approach is shown in Scheme XII.

Scheme XII. First new approach to tetracyclic sesquiterpenes



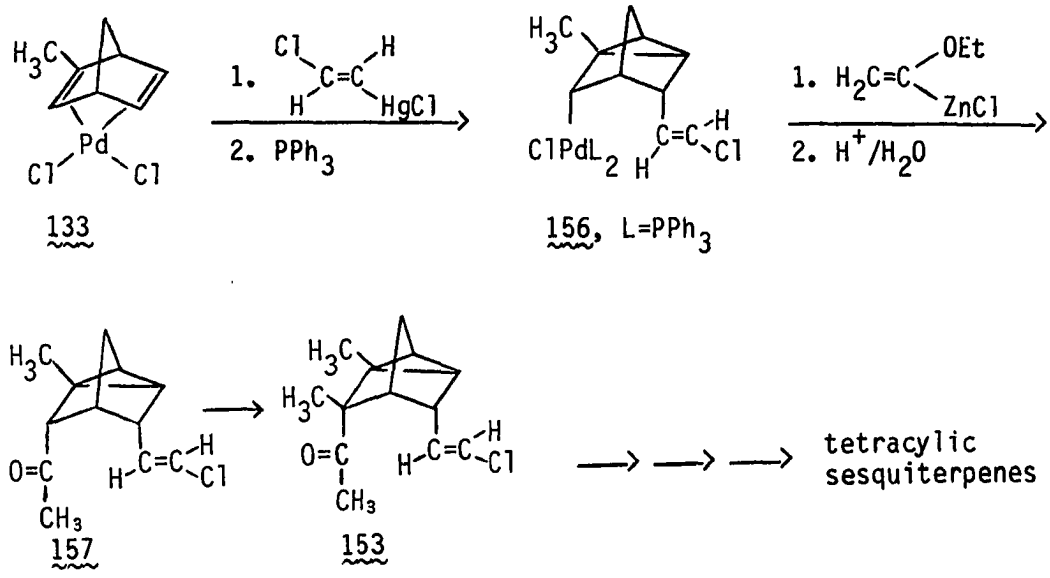



The second approach is to utilize one of the reactions reported by Hegedus. Russell and Hegedus have reported that zinc salts of enol ether anions can be coupled to aryl and alkenyl halides by use of a palladium catalyst (eq. 70) [134]. Our second possible approach is shown in Scheme XIII. The generation of the more thermodynamically stable enolate and subsequent stereospecific methylation of compound 157 should not give




(70)

Scheme XIII. Second new approach to tetracyclic sesquiterpenes




problems. After compound 153 is prepared, it should be easily carried on to the tetracyclic sesquiterpenes as shown in Scheme XII.

Although these two new approaches might lead to the synthesis of tetracylic sesquiterpenes, they tend to be rather lengthy. Also for the preparation of either compound 151 or 157, the regioisomer may be formed. Since these approaches are not as attractive or efficient as our original proposal (Scheme VIII), we have decided not to examine them at this stage.

## C. Conclusion

After much effort and time being spent on the synthesis of 2,3-dimethylbicyclo[2.2.1]hepta-2,5-diene (96) and its $PdCl_2$ complex 95, we were frustrated to learn that the tetrasubstituted double bond of compound 95 fails to participated in the cyclization. As an alternative

route, vinylation and subsequent carbonylation of the 2-methylbicyclo[2.2.1]hepta-2,5-diene palladium dichloride complex (133) does give the desired tetracyclic product in very low yield. Unfortunately, methylation of this tetracylic product failed to give the expected product. Although two new possible approaches have been proposed, they are rather lengthy and have not been examined.

## D. Experimental Section

### 1. Equipment

Proton NMR spectra were recorded on a Varian EM-360 spectrometer. Infrared spectra were recorded on either a Beckman IR-4250 or a Beckman Acculab 2 infrared spectrometer. Mass spectra were obtained on an AEI MS-902 high resolution mass spectrometer, while GC/mass spectra were recorded on a Finnegan 4023 GC/MS data system. A Varian 3700 gas chromatograph equipped with a Varian CDS-111 chromatography data system was used for gas chromatography analyses. The elemental analyses were performed by Galbraith Laboratories.

### 2. Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. THF and diethyl ether were distilled from calcium hydride. Acetonitrile and dichloromethane were distilled from phosphorus pentaoxide before using. Pyridine and triethylamine were distilled from barium oxide. Methyllithium and n-butyllithium were purchased from Alfa. Methyllithium was titrated by the method of Watson and Eastham

[135], while n-butyllithium was titrated with 2,5-dimethoxybenzyl alcohol [136]. 5-norbornen-2-one and sulfur trioxide-pyridine were purchased from Aldrich. Norbornadiene-palladium dichloride (88) was prepared using a literature procedure [127]. Vinylmercuric chloride was obtained from ICN Pharmaceuticals, Inc. trans-2-Chlorovinylmercuric chloride (117) [137,138] and di(trans-2-chlorovinyl)mercury (122) [139,140] were prepared using literature procedures. Carbon monoxide was purchased from Matheson Gas Products. Palladium chloride was generously supplied by Johnson Matthey, Inc. and Engelhard Industries.

3. Vinylation and subsequent carbonylation of compound 88

To a 0°C solution of 0.2694 g (1 mmol) of norbornadiene-palladium dichloride in 15 ml of dry acetonitrile was added 0.2975 g (1 mmol) of trans-2-chlorovinylmercuric chloride. The reaction mixture was stirred at 0°C under $N_2$ for 1 h. There was no color change at this stage. The mixture was then slowly warmed up to room temperature and stirred at that temperature for 1 day. Some gray precipitate formed and the solution turned greenish-yellow. While the system was being flushed with carbon monoxide at -78°C, a balloon filled with carbon monoxide was connected to the top of the flask. The reaction mixture was allowed to slowly warm up to room temperature and stirring was continued for another 24 h. Three milliliters of saturated ammonium chloride solution and a small amount of activated carbon was added and stirring was continued for an additional 30 min. The reaction mixture was filtered through Celite. The filtrate was concentrated and the residue was extracted with ether. The ethereal

extract was washed with saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$), and concentrated to afford products 89, 90, and 91 in the ratio 1:6.2:19.5 (relative GLC peak areas). For compound 89: GC/MS, m/z (relative intensity, assignment) 182 (11.50, $M^+$), 167 (52.14, $M^+-CH_3$), 151 (2.41, $M^+-OCH_3$), 123 (100, $M^+-CO_2CH_3$). For compound 90: GC/MS, m/z (relative intensity, assignment) 208 (0.17, $M^+$), 193 (0.76, $M^+-CH_3$), 177 (5.04, $M^+-OCH_3$), 149 (0.98, $M^+-CO_2CH_3$), 75 (100, $M^+-133$). For compound 91: yield 54%; $^1H$ NMR ($CDCl_3$) $\delta$ 0.66-1.90 (m, 5 H, cyclopropane CH and bridgehead $CH_2$), 2.08 (br s, 1 H, bridge CH), 2.47 (t, J = 2 Hz, 1 H, CHC=O), 3.63 (br s, 1 H, CHC=C), 3.78 (s, 3 H, $OCH_3$), 6.33 (s, 1 H, C=CH); IR ($HCCl_3$) 3007 (C=CH), 1733 (C=O, ester), 1711 (C=O, ketone), 1665 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{12}H_{12}O_3$ 204.07865, obsd 204.07792.

4. Preparation of compound 96 and its reaction with $PdCl_2$

a. Diels-Alder reaction of cyclopentadiene and 2-butyne The direct Diels-Alder reaction of cyclopentadiene and 2-butyne was carried out under conditions identical to those described by Baldwin and co-workers [108]. Fifty grams (0.926 mol) of 2-butyne, 16.5 g (0.25 mol) of freshly distilled cyclopentadiene, and 1 g (0.009 mol) of hydroquinone were put in a stainless steel autoclave. The autoclave was heated to 250°C and maintained at this temperature for 30 min. The reaction container was cooled and reaction products were distilled under vacuum (until no volatile material was left). This gave 45.2 g of 2-butyne (90.4% recovery) and a mixture of dicyclopentadiene (97) and 2,3-

dimethylbicyclo[2.2.1]hepta-2,5-diene (96) in a ratio of 16.3:1 (relative GLC peak areas). For compound 97: GC/MS, m/z (relative intensity, assignment) 132 (16.82, $M^+$), 66 (100, $C_5H_6^{+\cdot}$). For compound 96: GC/MS, m/z (relative intensity, assignment) 120 (85.09, $M^+$), 105 (100, $M^+-CH_3$), 94 (11.70, $M^+-C_2H_2$), 79 (17.23, $M^+-C_2H_2CH_3$), 66 (63.48, $C_5H_6^{+\cdot}$).

b. Preparation of compound 99 Compound 99 was prepared under conditions identical to those reported in the literature [141]. To a solution of 10.089 g (0.08 mol) of 2,3-dimethylmaleic anhydride in 100 ml of benzene was added 10.56 g (0.16 mol) of freshly distilled cyclopentadiene. The mixture was heated to reflux and kept refluxing for 24 h. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure to afford a mixture of a white solid and an oil (dimer, trimer, or polymer of cyclopentadiene). The white solid was collected by filtration and washed with cyclohexane. The filtrate was washed three times with dilute KOH and the aqueous layer was separated and washed with ether. The aqueous layer was separated and acidified with dilute HCl at 0°C and then extracted with ether. The ethereal extract was dried ($Na_2SO_4$) and concentrated to afford additional white solid. The white solids (a mixture of 2,3-dimethylmaleic anhydride and compound 99) were combined and distilled to afford 7.8 g (77% of recovery) of 2,3-dimethylmaleic anhydride and 3.12 g of residue (crude product of 99). The residue was recrystallized from cyclohexane to yield 2.81 g of compound 99: recrystallized yield 18.3% (81% based on reacted 2,3-dimethylmaleic anhydride); mp 153-154°C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.44 (s, 6

H, $CH_3$), 1.79 (br m, 2 H, $CH_2$), 2.96 (m, 2 H, CH), 6.28 (dd, J = 2 Hz, J = 1.7 Hz, 2 H, HC=CH); IR ($HCCl_3$) 3020 (C=C-H), 1830 and 1766 (anhydride) $cm^{-1}$.

c. Hydrolysis of compound 99 To a solution of 1.92 g (10 mmol) of compound 99 in 60 ml of water was added 1.06 g (10 mmol) of sodium carbonate. The mixture was heated to reflux and kept refluxing for 18 h. After having cooled to room temperature, the reaction mixture was acidified with 6 N HCl. The acidic solution was cooled to 0°C and a white solid precipitated. The white solid was collected by filtration and washed with cold water to give 0.19 g (10% recovery) of compound 99. The filtrate was extracted three times with a 1:1 mixture of chloroform and methylene chloride. The extract was combined, dried ($Na_2SO_4$), and concentrated to afford 1.679 g of compound 106: yield 80%; mp 312-314°C (sealed tube); $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$) $\delta$ 1.19 (s, 3 H, $CH_3$), 1.37 (s, 3 H, $CH_3$), 1.43-2.17 (m, 4 H, $CH_2$), 2.17-2.52 (br m, 1 H, CH), 2.59-2.97 (br m, 1 H, CH), 4.66 (t, J = 6 Hz, 1 H, CH-O-), 11.0 (br s, 1 H, OH); IR (KBr) 2500-3350 (OH), 1767 ($\delta$-lactone), 1703 (C=O of acid) $cm^{-1}$; mass spectrum for $M^+-H_2O$, m/z calcd for $C_{11}H_{12}O_3$ 192.07864, obsd 192.07929.

d. Preparation of compound 100 To a 0°C solution of 3.96 g (60 mmol) of freshly distilled cyclopentadiene and 0.68 g (10 mmol) of 2-butynal (prepared from pyridinium chlorochromate oxidation of 2-butyn-1-ol) in 70 ml of benzene was added 1.5 mmol of $BF_3 \cdot Et_2O$. After being stirred at 0°C for 2 h, the reaction mixture was poured into 20 ml of

saturated sodium bicarbonate solution. The mixture was extracted with ether (3 x 100 ml). The ethereal extracts were combined, dried ($Na_2SO_4$), and concentrated to give 0.94 g of crude product 100 (70%). The crude product was purified by flash chromatography to afford 0.48 g of pure compound 100: yield 31%; $^1H$ NMR ($CDCl_3$) $\delta$ 2.0 (m, 2 H, $CH_2$), 2.27 (s, 3 H, $CH_3$), 3.47 (br m, 1 H, CH), 3.99 (br s, 1 H, CH), 6.55-6.99 (m, 2 H, HC=CH), 9.79 (s, 1 H, CHO); IR (neat) 3059 (C=C-H), 1692 (C=O), 1640 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_9H_{10}O$ 134.07317, obsd 134.07349.

e. Reduction of compound 100 with $LiAlH_4$ A solution of 0.0379 g (1.0 mmol) of $LiAlH_4$ in 5 ml of diethyl ether was heated to reflux and kept refluxing for 5 min and then the solution was cooled to 0°C. One millimole (0.134 g) of compound 100 was added to the above solution. The reaction mixture was stirred at 0°C for 4 h. To the reaction mixture was added in the following order 0.1 ml of $H_2O$, 0.1 ml of 15% NaOH, and 0.3 ml of $H_2O$. A dry granular precipitate appeared and the mixture was filtered. The filtrate was washed with a saturated solution of NaCl. The organic layer was dried ($Na_2SO_4$) and concentrated to yield 80.7 mg of crude product. The product was purified by flash chromatography to afford 34.2 mg of pure alcohol 108: yield 25%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.49 (br s, 1 H, OH), 1.77 (s, 3 H, $CH_3$), 1.91 (br s, 2 H, $CH_2$), 3.30 (br m, 1 H, CH), 3.58 (br m, 1 H, CH), 4.23 (s, 2 H, $CH_2$-O-), 6.88 (m, 2 H, HC=CH); IR (neat) 3100-3700 (OH), 3060 (C=C-H), 1656 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_9H_{12}O$ 136.08882, obsd 136.08847.

f. Preparation of compound 101 To a solution of 3.92 g (40 mmol) of methyl 2-butynoate and 15.84 g (240 mmol) of freshly distilled cyclopentadiene in 400 ml of benzene was added 1.068 g (8 mmol) of $AlCl_3$. The reaction mixture was heated under reflux for 1 day. The mixture was then cooled to room temperature. Ether (200 ml) was added to the reaction mixture first, followed by 100 ml of dilute HCl. The organic layer was separated and washed with water. The layers were separated and the organic layer was dried ($Na_2SO_4$) and concentrated. The reaction product was isolated by flash chromatography to afford 4.4 g of compound 101: yield 67%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.83-2.18 (m, 2 H, $CH_2$), 2.23 (s, 3 H, $CH_3$), 3.29-3.50 (br m, 1 H, CH), 3.74 (s, 3 H, $OCH_3$), 3.82-4.03 (br m, 1 H, CH), 6.64-7.05 (m, 2 H, HC=CH); IR (neat) 3060 (C=C-H), 1700 (C=O), 1624 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{10}H_{12}O_2$ 164.08373, obsd 164.08320.

g. Reduction of compound 101 with $LiAlH_4$ A solution of 0.1706 g (4.5 mmol) $LiAlH_4$ in 20 ml of THF was heated under reflux for 5 min and then cooled to 25°C. To the above solution was added 0.492 g (3 mmol) of compound 101 and the reaction mixture was stirred at 25°C for 4 h under $N_2$. To destroy the excess amount of $LiAlH_4$, 0.2 ml of $H_2O$ was added to the reaction mixture first followed by 0.2 ml of 15% NaOH and finally 0.6 ml of $H_2O$. A dry granular precipitate appeared and the mixture was filtered through Celite. The filtrate was concentrated and then extracted with ether. The ethereal extract was washed with a saturated NaCl solution. The organic layer was separated, dried ($Na_2SO_4$) and

concentrated. At this stage, TLC analysis of the crude mixture showed two spots with $R_f$ = 0.50 and 0.13 (ethyl acetate:hexanes = 1:4). These two components were separated by flash chromatography to afford 0.1673 g (55.8%) of compound 109 and 0.066 g of compounds 110 and 108 (16% total yield). For compound 109: GC/MS analysis showed that it contained four isomers with molecular ions at m/z 136 and all of them had very similar fragmentation patterns. GC/MS, m/z (assignment) 136 ($M^+$), 121 ($M^+$-$CH_3$), 107 ($M^+$-CHO), 66 ($C_5H_6^{+\cdot}$); $^1$H NMR ($CDCl_3$) $\delta$ 0.90 (d, J = 7 Hz, 3 H, $CH_3$), 1.03-1.94 (m, 3 H, CHMe and $CH_2$), 2.08-2.70 (m, 1 H, CHC=O), 2.64-2.92 (m, 1 H, CH), 2.90-3.20 (br m, 1 H, CH), 5.90-6.45 (m, 2 H, HC=CH), 9.34 (d, J = 3.8 Hz) and 9.76 (d, J = 2.6 Hz) (1 H, CHO); IR (neat) 3080 (C=C-H), 1725 (C=O) $cm^{-1}$. For compound 110: GC/MS analysis showed that it contained three isomers all of which had a molecular ion at m/z 138 and the same fragmentation pattern. GC/MS, m/z (assignment) 138 ($M^+$), 121 ($M^+$-OH), 120 ($M^+$-$H_2O$), 66 ($C_5H_6^{+\cdot}$); IR (neat) 3100-3600 (OH), 3062 (C=C-H) $cm^{-1}$.

h. Reduction of compound 101 with (i-Bu)$_2$AlH To a -78°C solution of 3.28 g (20 mmol) of compound 101 in 150 ml of THF was added 53.2 ml of a 1.24 M (66 mmol) heptane solution of (i-Bu)$_2$AlH. The reaction mixture was stirred at -78°C for 5 h and allowed to slowly warm up to room temperature. Then 100 ml of methanol was added to destroy any excess (i-Bu)$_2$AlH. After 100 ml of $H_2O$ was added, the reaction mixture was filtered through Celite. The filtrate was concentrated and extracted with ether (3 x 100 ml). The ethereal extracts were combined and washed

with saturated sodium chloride solution. The organic layer was separated, dried ($MgSO_4$), and concentrated. The product was isolated by flash chromatography to give 2.61 g (96%) of compound 108.

i. Silylation of compound 108 To a solution of 0.6516 g (6 mmol) of trimethylchlorosilane in 40 ml of benzene was slowly added a solution of 0.68 g (5 mmol) of compound 108 in 0.97 ml (12 mmol) of pyridine. The mixture was heated under reflux for 2 h and then cooled to room temperature. The mixture was filtered through Celite and the Celite pad was washed with ether (10 ml). The filtrate and ether washing were combined and distilled to afford 0.7 g of compound 111: yield 67%; bp 100-110 °C/15-20 mmHg; $^1H$ NMR ($CDCl_3$) δ (relative to $-OSiMe_3$) 0 (s, 9 H, $SiCH_3$), 1.63 (s, 3 H, $CH_3$), 1.65-2.0 (m, 2 H, $CH_2$), 3.0-3.20 (br m, 1 H, CH), 3.2-3.48 (br m, 1 H, CH), 3.90 (d, J = 12 Hz, 1 H, diastereotopic proton of $CH_2O$-), 4.18 (d, J = 12 Hz, 1 H, diastereotopic proton of $CH_2O$-), 6.40-6.70 (m, 2 H, HC=CH); IR (neat) 3070 (C=C-H), 1665 (C=C) $cm^{-1}$.

j. Reaction of compound 108 and $PBr_3$ To a solution of 0.408 g (3 mmol) of compound 108 in 15 ml of diethyl ether was added 0.298 g (1.1 mmol) of $PBr_3$ in the dark. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 2 h. The mixture was cooled to room temperature and poured into an ice-water mixture. The mixture was extracted 3 times with diethyl ether. The ethereal extracts were combined and washed with saturated $NaHCO_3$ solution and then with water. The organic layer was dried ($MgSO_4$) and concentrated to afford compounds 108, 112, 113, and 114 (contains 2 isomers 114a and 114b) in the ratio

1:1.6:4.1:1.8. For compound 112: GC/MS, m/z (relative intensity, assignment) 200 (1.21, $M^+$+2), 198 (1.25, $M^+$), 119 (89.74, $M^+$-Br), 105 (16.62, $M^+$-$CH_2Br$), 91 (100, $C_7H_7^{+\cdot}$). For compound 113: GC/MS, m/z (relative intensity, assignment) 200 (3.01, $M^+$+2), 198 (3.25, $M^+$), 185 (0.73, $M^+$+2 - $CH_3$), 183 (0.75, $M^+$-$CH_3$), 119 (100, $M^+$-Br), 91 (47.87, $C_7H_7^{+\cdot}$), 66 (46.62, $C_5H_6^{+\cdot}$). For compound 114a: GC/MS, m/z (relative intensity, assignment) 282 (0.03, $M^+$+4), 280 (0.08, $M^+$+2), 278 (0.04, $M^+$), 201 (40.23, $M^+$+2-Br), 199 (43.93, $M^+$-Br), 120 (45.61, $M^+$-2 Br), 119 (100, $M^+$-HBr-Br). For compound 114b: GC/MS, m/z (relative intensity, assignment) 282 (0.07, $M^+$+4). 280 (0.15, $M^+$+2), 278 (0.08, $M^+$), 201 (1.95, $M^+$+2-Br), 199 (2.07, $M^+$-Br), 120 (3.36, $M^+$-2Br), 119 (15.67, $M^+$-HBr-Br), 66(100, $C_5H_6^{+\cdot}$).

k. Chlorination of compound 108 The chlorination of compound 108 was carried out under conditions identical to those described by Collington and Meyers [122]. A stirred mixture of 0.136 g (1 mmol) of compound 108 and 0.1331 g (1.1 mmol) of s-collidine under nitrogen was treated with 0.0425 g (1 mmol) of lithium chloride dissolved in a minimum amount of dry dimethylformamide. On cooling to 0°C, a suspension formed which was treated dropwise with 0.1260 g (1.1 mmol) of methanesulfonyl chloride. Stirring was continued at 0°C for 2 h, then the pale yellow reaction mixture was poured into an ice-water mixture. The aqueous layer was extracted with cold ether-pentane (1:1) and the combined extracts were washed successively with saturated copper nitrate solution. This was continued until no further intensification of the blue copper

solution occurred, indicating complete removal of s-collidine. The organic layer was dried ($Na_2SO_4$) and analyzed by GC/MS. The reaction gave a mixture of compounds 115, 108, and a small amount of unidentified products in a ratio of 2.5:1:1.7 (GLC relative peak areas). For compound 115: GC/MS, m/z (relative intensity, assignment) 118 (81.00, $M^+$), 117 (100, $M^+$-1), 103 (10.53, $M^+$-$CH_3$), 91 (16.32, $C_7H_7^{+\cdot}$), 66 (59.50, $C_5H_6^{+\cdot}$).

1. Deoxygenation of alcohol 108 with $SO_3$·pyr/$LiAlH_4$ This reaction was carried out according to the method of Corey and Achiwa [125] with only slight modifications. To a -25°C solution of 1.496 g (11 mmol) of compound 108 in 100 ml of THF was added 3.498 g (22 mmol) of the sulfur trioxide-pyridine complex. The mixture was stirred at -25°C for 6.5 h and then a clear solution of 55 mmol of $LiAlH_4$ in THF (1.45 M solution) [126] was added to the above solution at -25°C. The reaction mixture was allowed to slowly warm up to room temperature and kept at room temperature overnight. To the reaction mixture was added in the following order 5.5 ml of $H_2O$, 5.5 ml of 15% NaOH, and 16.5 ml of $H_2O$. The mixture was filtered through Celite and the Celite pad was washed with 100 ml of diethyl ether. The filtrate and ether washing were combined and washed with dilute HCl (1.5 N) several times and then washed with water several times. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was distilled at 50°-60°C/50-60 mmHg to afford 1.265 g of a mixture of 96, 116, and 115 in the ratio 3.5:1:1.5. For compound 116: GC/MS, m/z (relative intensity, assignment)

120 (14.01, $M^+$), 105 (36.49, $M^+-CH_3$), 91 (47.58, $C_7H_7^{+\cdot}$), 78 (29.15, $C_6H_6^{+\cdot}$), 66 (100, $C_5H_6^{+\cdot}$).

m. Reaction of palladium chloride and a mixture of 96, 116, and 115

This reaction was carried out under conditions identical to those described by Drew and Doyle [127]. Palladium chloride (0.887 g, 5 mmol) was dissolved in 3 ml of conc. HCl by warming. The cold (25°C) solution was diluted with 67 ml of absolute ethanol, filtered, and the residue and filter paper washed with 12 ml of absolute ethanol. To the combined filtrate and washing was added the mixture of 96, 116, and 115 (obtained from the above step). The mixture was stirred under $N_2$ at room temperature. A yellow solid precipitated after 2-3 min of stirring. The stirring was continued for a total of 2.5 h. The yellow solid was collected by filtration and washed with three 10 ml portions of ether. The yellow solid was dried under vacuum to afford 0.6077 g of compound 95: yield 19% (overall yield from alcohol 108); FT $^1H$ NMR ($CDCl_3$) $\delta$ 1.55 (s, 6 H, $CH_3$), 1.85 (br s, 2 H, $CH_2$), 3.70 (br s, 2 H, CH), 6.30 (br s, 2 H, HC=CH). Anal. Calcd for $C_9H_{12}PdCl_2$: C, 36.34; H, 4.07. Found: C, 36.61; H, 4.36.

n. Reaction of compound 95 and KCN The characterization of compound 95 has been carried out under conditions identical to those described by Trebellas and co-workers [128]. To a solution of 0.0595 g (0.2 mmol) of compound 95 in 2 ml of $CCl_4$ was added 0.1302 g (2.0 mmol) of KCN in 4 ml of $H_2O$. The mixture was stirred at 0°C for 3.5 h. The organic layer was separated and analyzed by gas chromatography. Only one

peak corresponding to 2,3-dimethylbicyclo[2.2.1]hepta-2,5-diene (96) could be detected by GLC analysis. This result suggests that compound 95 is a pure compound from the reaction of compound 96 and palladium chloride.

5. Reaction of compound 95 with mercurial 117, 121, and 122 and subsequently with CO/MeOH

a. Reaction of compound 95 with mercurial 117 and subsequently with CO/MeOH To a suspension of 0.2379 g (0.8 mmol) of compound 95 in 10 ml of dry acetonitrile was added 0.2381 g (0.8 mmol) of mercurial 117 at 0°C. The reaction mixture was stirred at 0°C for 4 h and then slowly warmed up to room temperature and kept at that temperature for 15 h. The mixture was cooled to -50°C and a balloon containing carbon monoxide was connected to the top inlet of the reaction flask. Fifteen milliliters of dry methanol was added to the above solution at -50°C. The reaction mixture was allowed to slowly warm up to room temperature and kept at that temperature for 1 day. The mixture was filtered through Celite and the filtrate solvent was removed under reduced pressure. The residue was extracted several times with ether and the ethereal extracts were combined and washed with saturated ammonium chloride solution. The organic layer was separated and dried to afford four products, 118, 119a, 119b, and 120 in the ratio 10:1:2:5. For compound 118: isolated yield 13%; $^1$H NMR ($CDCl_3$) $\delta$ 1.54 (s, 2 H, $CH_2$), 1.67 (s, 6 H, $CH_3$), 2.54-2.78 (m, 2 H, bridgehead CH), 2.78-2.98 (m, 1 H, CHC=O), 3.38 (s, 3 H,

$OCH_3$), 3.6-3.84 (m, 1 H, CH-O-), 3.68 (s, 3 H, $OCH_3$); IR ($HCCl_3$) 1720 (C=O) $cm^{-1}$; GC/MS, m/z (relative intensity, assignment) 210 (2.06, $M^+$), 195 (0.01, $M^+-CH_3$), 179 (0.58, $M^+-OCH_3$), 151 (0.19, $M^+-CO_2CH_3$), 94 (100, dimethylcyclopentadiene). For compound 119a: GC/MS, m/z (relative intensity, assignment) 182 (30.61, $M^+$+2), 180 (100, $M^+$), 165 (2.04, $M^+-CH_3$), 145 (98, $M^+$-Cl), 94 (52.6, dimethylcyclopentadiene). For compound 119b: GC/MS, m/z (relative intensity, assignment) 182 (20.7, $M^+$+2), 180 (73.6, $M^+$), 165 (4.1, $M^+-CH_3$), 145 (100, $M^+$-Cl), 119 (15.7, $M^+$-CHCHCl), 94 (29.8, dimethylcyclopentadiene). For compound 120: GC/MS, m/z (relative intensity, assignment) 242 (0.09, $M^+$+2), 240 (0.41, $M^+$), 204 (0.46, $M^+$-HCl), 181 (0.07, $M^+-CO_2CH_3$), 94 (100, dimethylcyclopentadiene).

b. Reaction of compound 95 and mercurial 121 and subsequently with CO/MeOH To a suspension of 0.0297 g (0.1 mmol) of compound 95 in 3 ml of dry acetonitrile was added 0.0263 g (0.1 mmol) of vinylmercuric chloride (121) at 0°C. The reaction mixture was stirred at 0°C for 4 h and at 80°C for 1 h. The mixture was cooled to -50°C and a balloon containing carbon monoxide was connected to the top inlet of the reaction flask. Four milliliters of methanol was added to the above solution at -50°C and the reaction mixture was allowed to slowly warm up to room temperature and kept at that temperature for 1 day. The reaction mixture was filtered through Celite and the filtrate solvent was removed under reduced pressure. The residue was extracted several times with ether and the ethereal extracts were combined and washed with saturated ammonium

chloride solution. The organic layer was separated, dried ($MgSO_4$), and analyzed by GLC which showed that only one product 118 was formed.

c. Reaction of compound 95 with mercurial 122 and subsequently with CO/MeOH To a suspension of 0.0892 g (0.3 mmol) of compound 95 in 5 ml of dry acetonitrile was added 0.0971 g (0.3 mmol) of mercurial 122 at -25°C. The reaction mixture turned black within 1 min. The mixture was stirred at -25°C for 7 h and then cooled to -50°C. A balloon containing carbon monoxide was connected to the top inlet of the reaction flask and 10 ml of dry methanol was added to the reaction mixture at -50°C. The reaction mixture was allowed to slowly warm up to room temperature and kept at that temperature for 1 day. The mixture was filtered through Celite and the filtrate solvent was removed under reduced pressure. The residue was extracted with ether and washed with a saturated solution of ammonium chloride. The organic layer was separated, dried ($MgSO_4$), and concentrated. The reaction product was isolated by flash chromatography to give 49.1 mg of compound 120: yield 68%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.05-1.65 (m, 2 H, $CH_2$), 1.70 (s, 3 H, $CH_3$), 1.72 (s, 3 H, $CH_3$), 2.53 (br s, 1 H, CHC=O), 2.78 (br s, 1 H, CHC=C), 2.99-3.35 (m, 2 H, bridgehead CH), 3.61 (s, 3 H, $OCH_3$), 5.52 (dd, J = 13.2 Hz, J = 2 Hz, 1 H, HC=C-Cl), 6.00 (d, J = 13.2 Hz, 1 H, C=CHCl); IR ($HCCl_3$) 3010 (C=C-H), 1730 (C=O), 1613 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{17}O_2Cl$ 240.09171, obsd 240.09136.

6. Vinylpalladation and subsequent carbonylation of compounds 98 and 101

To a solution of 0.0887 g (0.5 mmol) of palladium chloride and 0.0425 g (1.0 mmol) of lithium chloride in 10 ml of dry THF was added 0.104 g (0.5 mmol) of compound 98 at room temperature. The mixture was stirred at room temperature overnight and then cooled to -25°C. Mercurial 122 (0.1618 g, 0.5 mmol) was added to the above solution at -25°C. The reaction mixture was allowed to slowly warm up to room temperature and kept at that temperature for 10 h. The mixture was then cooled to -50°C and a balloon containing carbon monoxide was connected to the top inlet of the reaction flask. Fifteen milliliters of dry methanol was added at -50°C. The mixture was allowed to slowly warm up to room temperature and ketp at that temperature for 1 day. The reaction mixture was filtered through Celite and the filtrate solvent was removed under reduced pressure. The residue was extracted with ether and washed with saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$) and analyzed by GC/MS. GC/MS analysis of the reaction products shows 4 products, 123 (contains 2 isomers 123a and 123b), 124, and 125 in the ratio 17.8:2.5:1. For compound 123a: GC/MS, m/z (relative intensity, assignment) 126 (11.42, $M^+$+4), 124 (70.67, $M^+$+2), 122 (100, $M^+$), 89 (26.70, $M^+$+2-Cl), 87 (83.35, $M^+$-Cl), 51 (7.02, $M^+$-HCl-Cl). For compound 123b: GC/MS, m/z (relative intensity, assignment) 126 (12.02, $M^+$+4), 124 (76.18, $M^+$+2), 122 (100, $M^+$), 89 (27.26, $M^+$+2-Cl), 87 (83.51, $M^+$-Cl), 51 (6.15, $M^+$-HCl-Cl). For compound 124: GC/MS, m/z (relative intensity, assignment) 152 (8.96, $M^+$+4), 150 (58.03, $M^+$+2), 148

(91.91, $M^+$), 115 (29.18, $M^+$+2-Cl), 113 (93.47, $M^+$-Cl), 77 (100, $M^+$-HCl-Cl). For compound 125: GC/MS, m/z (relative intensity, assignment) 178 (9.80, $M^+$+4), 176 (61.41, $M^+$+2), 174 (100, $M^+$), 141 (31.19, $M^+$+2-Cl), 139 (98.54, $M^+$-Cl), 103 (94.05, $M^+$-HCl-Cl).

Vinylpalladation and subsequent carbonylation of compound 101 under identical conditions gave products 123 (contains 2 isomers 123a and 123b), 124, and 125 in the ratio 16.8:4:1.

## 7. Preparation of compound 132 and its reaction with $PdCl_2$

a. Direct methylation of norbornadiene This reaction was carried out exactly as described by Jefford and Rimbault [129]. A solution of 18.4 g (0.2 mol) of freshly distilled norbornadiene in 120 ml of ether was added to 128 ml of 2.2 M n-butyllithium (0.4 mol) in hexane at 0°C. The mixture was allowed to slowly warm up to room temperature and kept at that temperature overnight. The above solution was slowly added to a solution of 60 g (0.42 mol) of methyl iodide in 50 ml of ether at -78°C. The reaction mixture was allowed to slowly warm up to room temperature over 2 h. The mixture was then poured into a mixture of ice and water. The organic layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and distilled to afford compounds 132, 136, 137, and 138 (contains 3 isomers, 138a, 138b, and 138c) in the ratio 1:24.4:1.3:9.4. For compound 132: GC/MS, m/z (relative intensity, assignment) 106 (100, $M^+$), 91 (68.34, $M^+$-$CH_3$), 80 (8.33, $M^+$-$C_2H_2$), 66 (32.66, $C_5H_6^{+\cdot}$). For compound 136: GC/MS, m/z (relative intensity, assignment) 184 (47.37, $M^+$), 155 (4.28, $M^+$-$C_2H_5$), 127 (2.29, $M^+$-$C_4H_9$) 57

(100, $M^+$-I). For compound 137: GC/MS, m/z (relative intensity, assignment) 150 (74.49, $M_+$); 135 (6.53, $M^+$-$CH_3$). 121 (16.18, $M^+$-$C_2H_5$), 107 (19.27, $M^+$-$C_3H_7$), 93 (92.09, $M^+$-$C_4H_9$), 80 (100, $M^+$-$C_3H_7$-$C_2H_4$ + 1), 66 (78.31, $C_5H_6^{+\cdot}$). For compound 138a: GC/MS, m/z (relative intensity, assignment) 276 (0.01, $M^+$), 149 (100, $M^+$-I), 121 (8.92, $M^+$-I-$C_2H_4$), 93 (17.14, $M^+$-I-$C_4H_9$ + 1), 79 (53.59, $C_6H_7^{+\cdot}$). For compound 138b: GC/MS, m/z (relative intensity, assignment) 276 (0.01, $M^+$), 149 (100, $M^+$-I), 121 (9.65, $M^+$-I-$C_2H_4$), 93 (20.24, $M^+$-I-$C_4H_9$ + 1), 79 (62.18, $C_6H_7^{+\cdot}$).

b. Oxidation of compound 139 with PCC This reaction was carried out under conditions identical to those described by Lightner and co-workers [130]. To a solution of 11.02 g (0.1 mol) of 5-norbornen-2-ol (139, a mixture of endo and exo isomers) in 300 ml of dichloromethane was added 32.44 g (0.1505 mol) of pyridinium chlorochromate (PCC) in one portion. The mixture was stirred at room temperature for 1 h and an additional 8.0 g (0.037 mol) of PCC was added. The reaction mixture was stirred for another 6 h and then filtered through a Florisil column. The filtrate was concentrated by distillation. The residue was distilled to afford 2.8 g of compound 140: yield 26% (lit. [130] 24%); bp 45°C (5 mm Hg); $^1$H NMR ($CDCl_3$) δ 1.91 (br s, 2 H, $CH_2$), 1.95-2.40 (m, 2 H, $CH_2C{=}O$), 2.97 (br m, 1 H, CH), 3.18 (br m, 1 H, CHC=O), 6.05 (br t, 1 H, C=CH), 6.51 (dd, J = 6 Hz, J = 3 Hz, 1 H, C=CH); IR (neat) 3060 (C=C-H), 1738 (C=O), 1634 (C=C) $cm^{-1}$.

c. Oxidation of compound 139 with dipyridine chromium (VI) oxide This reaction was carried out under conditions identical to those

described by Lambert and Mark [131]. A solution of 9.9144 g (0.09 mole) of 5-norbornen-2-ol in 100 ml of dry dichloromethane was added in one portion to a 3-necked flask fitted with a mechanical stirrer containing a solution of 140 g (0.542 mol) of dipyridine chromium(VI) oxide complex ($CrO_3 \cdot 2pyr$) in 1 l of anhydrous dichloromethane. A dark brown, viscous sludge precipitated on the sides and bottom of the flask. After stirring for 2 h at room temperature, the liquid was filtered through Celite and then washed with 500 ml of 5% NaOH, 3 times with 250 ml of 5% HCl, twice with 400 ml of saturated $NaHCO_3$ solution, and once with saturated NaCl solution. After drying ($MgSO_4$), the solvent was removed by distillation. The residue was distilled to afford 7.6 g of compound 140: yield 78%; bp 84-86°C (60 mmHg) (lit. [131] bp 86-88°C/60 mmHg).

d. Preparation of compound 141 The preparation of compound 141 was carried out under identical conditions to those described by Lightner and co-workers [130]. To a solution of 2.7864 g (25.8 mmol) of compound 140 in 25 ml of dry methanol was added 4.8528 g (26.1 mmol) of p-toluenesulfonylhydrazine ($TsNHNH_2$) and the mixture was gently warmed to dissolve $TsNHNH_2$. The clear solution was stirred at room temperature for 8 h and then cooled to 0°C. The white solid formed in the reaction was collected by filtration and washed with an ether-pentane mixture to yield 6.35 g of compound 141: yield 90%; mp 185-186°C (decomp.); $^1H$ NMR ($CDCl_3$) 1.34-2.10 (m, 4 H, $CH_2$), 2.39 (s, 3 H, $ArCH_3$), 3.06 (br s, 1 H, CH), 3.25 (br s, 1 H, CH), 6.05 (m, 1 H, C=CH), 6.20 (m, 1 H, C=CH), 7.25 and 7.80 (2 x d, J = 8 Hz, 2 x 2 H, ArH).

e. Preparation of compound 132 from compound 141 To a solution of 5.52 g (20 mmol) of compound 141 in a mixture of 25 ml of freshly distilled N, N, N', N'-tetramethylethylenediamine (TMEDA) and 25 ml of benzene was added 55 ml of 1.6 M methyllithium (88 mmol) at -78°C. The deep red colored solution was allowed to slowly warm up to room temperature and kept at that temperature for 1 day. The reaction mixture was cooled to -30°C and 14.2 g (100 mmol) of freshly distilled methyl iodide was added to the above solution. The mixture was allowed to slowly warm up to room temperature. The mixture was then extracted with a pentane-water mixture. The organic layer was washed with 2N HCl, then with 3 N NaOH. The organic layer was dried ($MgSO_4$), concentrated, and distilled to yield a mixture of compounds 135, 132 and 142 in the ratio of 1:50:5.5. For compound 142: GC/MS, m/z (relative intensity, assignment) 108 (12.83, $M^+$), 93 (2.72, $M^+-CH_3$), 66 (100, $C_5H_6^{+\cdot}$).

f. Preparation of compound 143 To a solution of 17 ml of 1.86 M n-butyllithium (31.5 mmol) in 300 ml of THF was slowly added 2.426 g (31.5 mmol) of diisopropylamine at -78°C and the mixture was stirred at -78°C for 40 min. A solution of 3.24 g (30 mmol) of compound 140 in 20 ml of THF was added slowly into the above lithium diisopropylamide (LDA) solution at -78°C. The mixture was stirred at -78°C for 50 min and 17.04 g (120 mmol) of freshly distilled methyl iodide was added at -78°C. The reaction mixture was allowed to warm up to room temperature and kept at that temperature for 1 day. At this stage, GLC analysis of the reaction mixture showed there is no starting material left. A small amount of

water was added to the above mixture and the THF was evaporated. The residue was extracted three times with ether. The ethereal extracts were combined, washed with 0.5 N HCl, and dried ($MgSO_4$). The solvent was removed by distillation and the residue was distilled to afford 2.572 g of compound 143: yield 70%; bp 54-57°C (12 mmHg); $^1H$ NMR ($CDCl_3$) δ 1.13 (d, J = 8 Hz, 3 H, $CH_3$), 1.67-2.30 (m, 3 H, $CH_2$ + CHMe), 2.71-3.09 (m, 2 H, CH), 6.0-6.29 (m, 1 H, C=CH), 6.50-6.77 (m, 1 H, CH=C); IR (neat) 3055 (C=C-H), 1740 (C=O), 1637 (C=C) $cm^{-1}$.

g. Preparation of compound 144 p-Toluenesulfonylhydrazine (5.22 g, 28 mmol) was dissolved in hot 95% EtOH. Ketone 143 (3.109 g, 25.5 mmol) and 2 drops of conc. HCl were then added to the above solution. The mixture was heated to reflux and kept refluxing for 15 min. The mixture was then cooled to room temperature and the tosylhydrazone precipitated was collected by filtration. The solid was washed with ether and dried under vacuum to afford 5.003 g of compound 144: yield 68%; mp 147-148°C; $^1H$ NMR ($CDCl_3$) δ 1.07 (d, J = 7.5 Hz) and 1.18 (d, J = 6.4 Hz) (3 H, $CH_3$, mixture of *endo* and *exo* methyl group), 1.5-1.9 (m, 2 H, $CH_2$), 1.9-2.38 (m, 1 H, CHMe), 2.43 (s, 3 H, $ArCH_3$), 2.67 (br s, 1 H, CH), 3.20 and 3.60 (br s, 1 H, CH), 5.85-6.12 (m, 1 H, C=CH), 6.13-6.46 (m, 1 H, C=CH), 7.1-7.9 (m, 5 H, 4 ArH + NH); IR ($HCCl_3$) 3209 (NH) 3005 (C=CH), 1660 (C=C), 1598 (C=N) $cm^{-1}$.

h. Preparation of compound 133 To a solution of 10.86 g (107.5 mmol) of diisopropylamine and 6.2292 g (53.7 mmol) of *N*, *N*, *N'*, *N'*-tetramethylethylenediamine (TMEDA) in 105 ml of dry ether was added 44.8 ml of

1.5 M methyllithium (67.18 mmol) at 0°C. After stirring at 0°C for 30 min, 7.79 g (26.87 mmol) of compound 144 was added. The cold bath was removed and the reaction mixture was stirred at room temperature for 24 h under a $N_2$ atmosphere. Enough water was carefully added to dissolve the lithium salts. The solution was poured into a separatory funnel, the layers were separated, and the aqueous phase was extracted three times with 30 ml of diethyl ether. The organic extracts were combined and washed eight times with 30 ml of water. The organic layer was then washed with 60 ml aliquots of 5% $CuSO_4$ solution until all of the diisopropylamine had been removed. The $CuSO_4$ extracts were suction filtered to remove a pasty emulsion, and the resulting filtrate was extracted twice with 30 ml of ether. The organic phases were combined, dried ($MgSO_4$), and the diethyl ether was removed by fractional distillation. The residue was distilled (bp 109-112°C) to afford 1.6 g of a mixture of 132 and 145 in a ratio of 6.8:1 (relative GLC peak areas). Without further separation, the mixture was added to a solution containing 3.335 g (18.8 mmol) of palladium chloride, 8.5 ml of conc. HCl in 240 ml of absolute ethanol. A yellow solid precipitated after several minutes of stirring. After stirring for 1 h, the yellow solid was collected by filtration and washed with ether to afford 2.36 g of compound 133: yield 31% (overall yield from compound 144). Anal. Calcd for $C_8H_{10}PdCl_2$: C, 33.90; H, 3.56. Found: C, 33.95; H, 3.69.

i. Reaction of compound 133 and KCN The characterization of compound 133 has been carried out under conditions identical to those described by Trebellas and co-workers [128]. To a solution of 0.0283 g (0.1 mmol) of compound 133 in 1 ml of $CCl_4$ was added 0.0651 g (1 mmol) of KCN in 1.5 ml of $H_2O$. The mixture was stirred at 0°C for 3 h. The organic layer was separated and analyzed by gas chromatography using a capillary column. Only one peak corresponding to 2-methylbicyclo[2.2.1]-hepta-2,5-diene (132) could be detected from the reaction.

8. Vinylation and subsequent carbonylation of compound 133

To a suspension of 2.1255 g (7.5 mmol) of compound 133 in 75 ml of dry acetonitrile was added 2.3436 g (7.875 mmol) of trans-2-chlorovinylmercuric chloride (117). The mixture was stirred at room temperature for 36 h under a $N_2$ atmosphere. The mixture was cooled to -50°C and a balloon containing carbon monoxide was connected to the top inlet of the reaction flask. After stirring for 30 min at -50°C, 75 ml of dry methanol was added. The reaction mixture was allowed to slowly warm up to room temperature and kept at that temperature for 36 h. A small amount of active carbon was added to the above reaction mixture. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was extracted three times with ether and the ethereal extracts were combined and washed with saturated ammonium chloride solution. The organic layer was dried ($MgSO_4$) and concentrated. The reaction products were isolated by flash chromatography to afford 0.3252 g of compounds 146 + 147 (19.2%) and

0.4247 g of compounds 134 + 148 (26%). For compound 146 (or 147): GC/MS, m/z (relative intensity, assignment) 228 (0.03, $M^+$+2), 226 (0.10, $M^+$), 195 (0.43, $M^+$-$OCH_3$), 191 (0.29, $M^+$-Cl), 167 (0.20, $M^+$-$CO_2CH_3$), 80 (100, $CH_3C_5H_5^{+\cdot}$). For compound 147 (or 146): GC/MS, m/z (relative intensity, assignment) 228 (0.13, $M^+$+2), 226 (0.50, $M^+$), 191 (20.36, $M^+$-Cl), 80 (100, $CH_3C_5H_5^{+\cdot}$). For compound 134: GC/MS, m/z (relative intensity, assignment) 218 (51.62, $M^+$), 203 (2.57, $M^+$-$CH_3$), 186 (39.59, $M^+$-$CH_3OH$), 159 (32.84, $M^+$-$CO_2CH_3$), 158 (100, $M^+$-$CO_2CH_3$-H). For compound 148: GC/MS, m/z (relative intensity, assignment) 218 (10.96, $M^+$), 186 (100, $M^+$-$CH_3OH$), 159 (30.82, $M^+$-$CO_2CH_3$), 158 (84.25, $M^+$-$CO_2CH_3$-H).

9. Attempted methylation of compounds 134 and 148

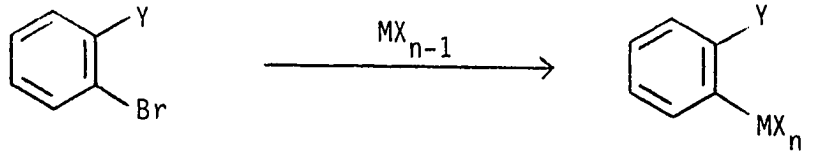
To a -78°C solution of 0.13 ml of 1.8 M n-butyllithium (0.24 mmol) in 5 ml of THF was added 0.2424 g (0.24 mmol) of diisopropylamine. The mixture was stirred at -78°C for 1 h. A mixture of 134 and 148 (0.436 g, 0.2 mmol) was added to the above lithium diisopropylamide solution at -78°C. The mixture was stirred at -78°C for 1 h and then at 25°C for 10 min. After being cooled back down to -78°C, 0.858 g (0.6 mmol) of methyl iodide was added to the above solution. The reaction mixture was allowed to slowly warm up to room temperature and kept at that temperature overnight. A small amount of water was added and THF was evaporated. The residue was extracted three times with ether. The ethereal extracts were combined and washed with 0.5 N HCl. The organic layer was separated, dried ($MgSO_4$) and concentrated to afford a mixture of 134, 148, 149 (contains two isomers 149a and 149b), and 150 (contains three

isomers 150a, 150b, and 150c). The ratio of (134 + 148):149:150 is 5:1:20. The mixture of 3 isomers of 150 has been isolated in 13% yield (57.6 mg). For compound 149a: GC/MS, m/z (relative intensity) 246 (17.45, $M^+$), 203 (5.62, prob. $M^+$-i-Pr), 187 (12.15, prob. $M^+$-O-i-Pr), 186 (58.38, prob. $M^+$-i-PrOH), 171 (4.12), 159 (26.72, prob. $M^+$-$CO_2$-i-Pr), 158 (100, prob. $M^+$-H-$CO_2$-i-Pr), 131 (16.02), 115 (12.37). For compound 149b : GC/MS, m/z (relative intensity) 246 (32.38, $M^+$), 218 (16.04), 204 (12.10), 203 (9.98, prob. $M^+$-i-Pr), 187 (13.09, prob. $M^+$-O-i-Pr), 186 (48.34, prob. $M^+$-i-PrOH), 176 (15.81), 171 (5.45), 159 (31.85, prob. $M^+$-$CO_2$-i-Pr), 158 (100, prob. $M^+$-H-$CO_2$-i-Pr), 131 (39.64). For compound 150a: GC/MS, m/z (relative intensity) 260 (17.67, $M^+$), 203 (7.05), 187 (14.41), 186 (80.96), 159 (27.59), 158 (100), 131 (16.44). For compound 150b: GC/MS, m/z (relative intensity) 260 (28.04), 232 (9.59), 204 (16.11), 187 (13.71), 186 (59.87), 176 (25.71), 159 (32.78), 158 (100), 131 (41.98). For compound 150c: GC/MS, m/z (relative intensity) 260 (2.86, $M^+$), 204 (0.55), 187 (15.91), 186 (100), 171 (3.28), 159 (21.85), 158 (73.25), 131 (6.27), 130 (12.01).

# V. HETEROCYCLIC SYNTHESIS VIA THALLATION-OLEFINATION OF ARENES

## A. Introduction

There has been considerable recent interest in the generation and utilization of ortho-metallated aromatic compounds in organic synthesis [142-146]. Three basic approaches to this class of compounds have been reported: (1) generation via ortho-haloaromatics (eq. 71), (2) ortho-lithiation in which a functional group is used to direct metallation (eq. 72), and (3) electrophilic metallation directed by a neighboring functional group (eq. 73).

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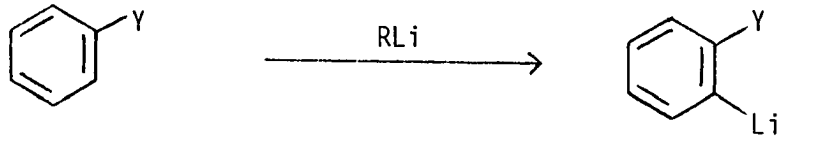


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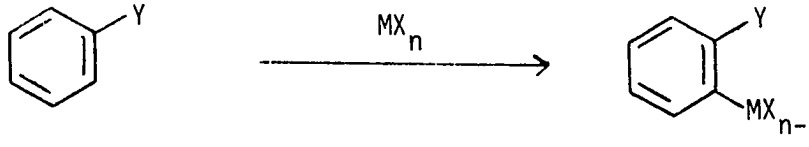
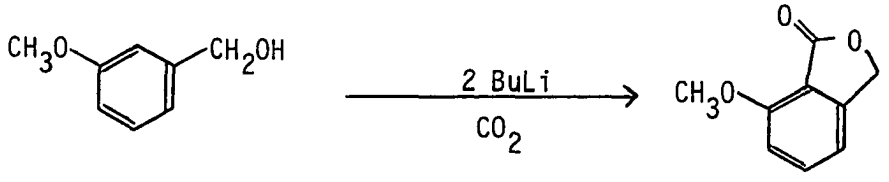



(73)

The first approach has been beautifully exploited by Mori, Ban and co-workers in the synthesis of indoles, quinolines [147,148], benzolactams [149-152] and benzolactones [153]. Unfortunately, this approach requires prior preparation of a specific ortho-haloaromatic.

The direct lithiation of aromatic compounds has been extensively studied [144]. A number of functional groups have been observed to

direct metallation exclusively ortho, including alcohol, alkoxy, and amide groups. Subsequent electrophilic reactions have afforded a variety of novel new heterocyclic syntheses, including phthalides (eq. 74) [154,155], isocoumarins (eq. 75) [156], anthraquinones [157], and

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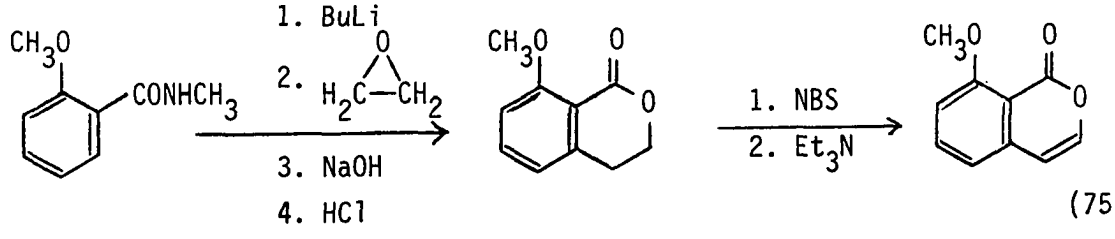


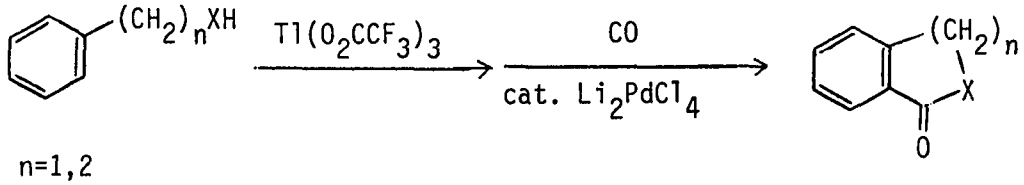

(75)

phthalideisoquinolines [158]. While these reactions are usually highly regioselective, they do not accommodate much functionality in the aromatic ring.

The direct electrophilic ortho-metallation of aromatic compounds is also now well-known, particularly with transition metals [142,145,146] such as palladium [143], but relatively few applications of these complexes in organic synthesis have been reported.

Larock and co-workers have recently taken advantage of the strong ortho-directing effect of a variety of oxygen- and nitrogen-containing functional groups in the electrophilic thallation of aromatic compounds [159,160], to develop novel new routes to a variety of heterocyclic

systems. The resulting arylthallium compounds can be readily carbonylated at room temperature and one atmosphere of carbon monoxide using catalytic amounts of palladium chloride (eq. 76) [161]. This thallation-carbonylation approach has proved applicable to the synthesis



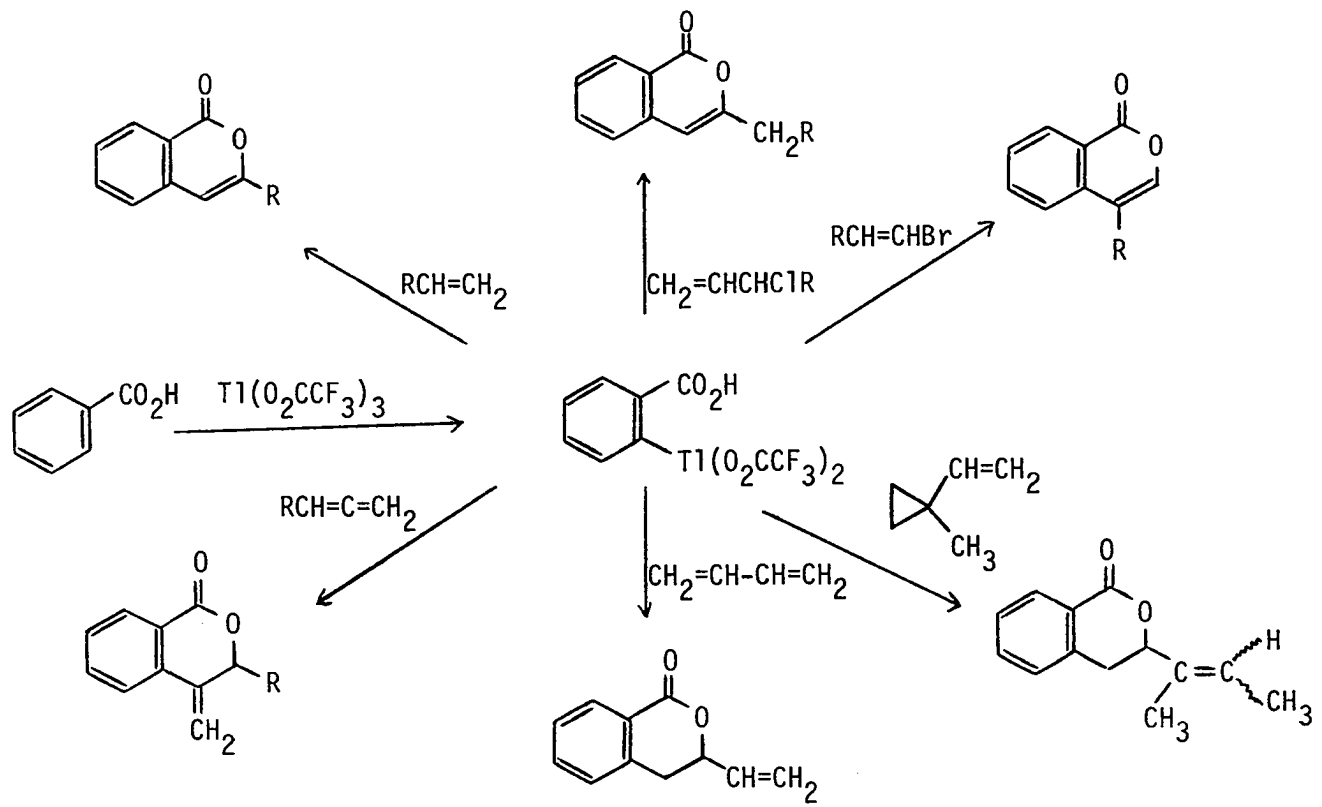

(76)

n=1,2
XH=OH, $CO_2H$, $CONH_2$

of phthalides, 3,4-dihydroisocoumarins, anhydrides, imides and a number of other ortho-substituted carbonyl compounds. These reactions can be effected in one pot, using readily available arenes, and they are highly regioselective.

Recent work has indicated that the palladium-promoted olefination of these same thallated arenes affords a highly convenient approach to a number of biologically important heterocyclic ring systems. Thus, the thallation reaction of benzoic acid with thallium(III) trifluoroacetate (TTFA) gives almost exclusively the ortho-thallated benzoic acid [160], which can be easily vinylated and cyclized to isocoumarins and 3,4-dihydroisocoumarins using palladium assisted reactions (Scheme XIV) [162]. This reaction sequence greatly simplifies the synthesis of these important ring systems [163]. We have also observed that a variety of arenes other than benzoic acid undergo analogous reactions. Here, we will report the thallation-olefination of p-tolylacetic acid,

Scheme XIV. Olefination-cyclization of thallated benzoic acid



N-methylbenzamide, benzamide, and acetanilide. The palladium-promoted olefination of these thallated arenes appears to be a general reaction for the synthesis of a wide variety of heterocylic ring systems.

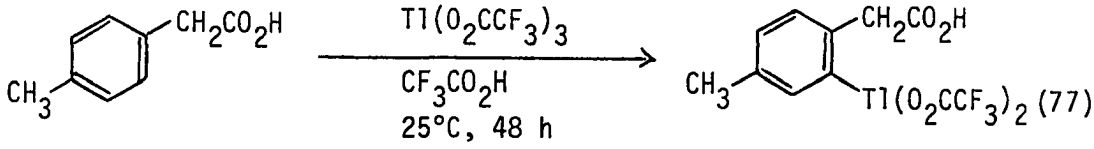
## B. Results and Discussion

### 1. Preparation and iodination of the thallated arenes

Aromatic thallation is known to be a reversible, electrophilic substitution reaction with a large steric requirement. The factors (kinetic, thermodynamic, and steric) which control the position of thallation have been systematically explored [160]. Meta substitution is achieved under conditions of thermodynamic control. Under conditions of kinetic control, ortho substitution results when chelation of the reagent [thallium(III) trifluoroacetate, TTFA] with the directing substituent permits intramolecular delivery of the electrophile, and para substitution results when such capabilities are absent.

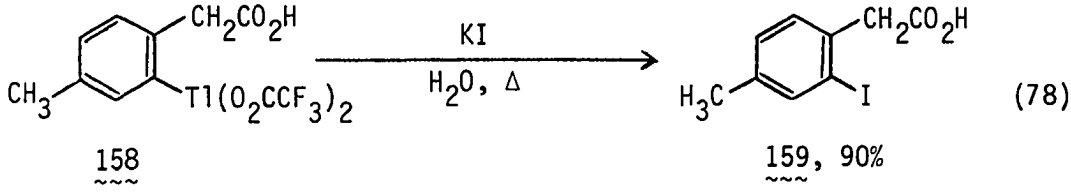
Inspection of the results obtained upon thallation and subsequent iodination of phenylacetic acid indicated that three isomers (92% ortho, 3% meta, and 5% para) were formed in 72% yield. In order to eliminate the complication of the formation of regioisomers, we decided to examine the thallation-olefination of p-tolylacetic acid. The thallated p-tolylacetic acid was prepared under conditions identical to those described for the preparation of thallated phenylacetic acid [160]. Thus, p-tolylacetic acid was treated with thallium(III) trifluoroacetate in trifluoroacetic acid and the mixture was stirred at room temperature for 48 h. The white precipitate formed was collected by filtration and

dried under vacuum to afford 71% of a stable white solid (158) (eq. 77). Elemental analysis of the crude product gave reasonably good




158

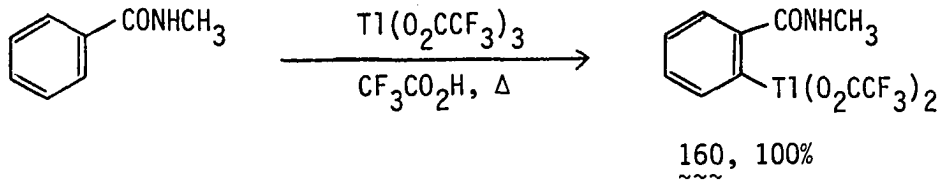
results. The distribution of regioisomers formed from the thallation of p-tolylacetic acid has been determined by converting the crude thallated compound 158 to the corresponding iodide according to the method reported by Taylor and co-workers [160] (eq. 78). The iodide (159) can be




158 159, 90% (78)

isolated in 90% yield and GLC (capillary column) analysis of compound 159 shows only one peak. We assumed that only ortho-thallated product is formed and this has been proved by the formation of cyclized product from olefination of compound 158 (to be discussed later). For our convenience, the crude product 158 was used directly without further purification in our studies on the olefination-cyclization reaction.

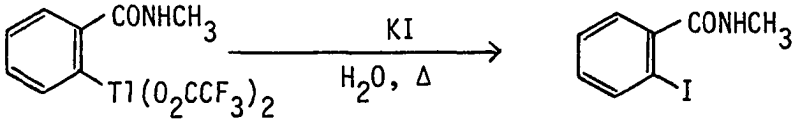
N-Methylbenzamide was thallated with thallium(III) trifluoroacetate in trifluoroacetic acid by heating under reflux for 24 h. After removal of the solvent, a quantitative yield of crude product was isolated (eq.




(79)

160, 100%

79). Iodination of the crude product 160 gave a quantitative yield of the corresponding iodide 161 (eq. 80). GLC (capillary column) analysis

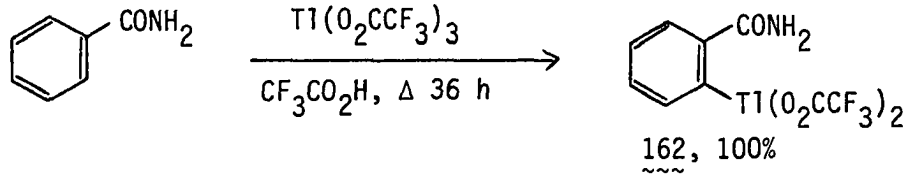



(80)

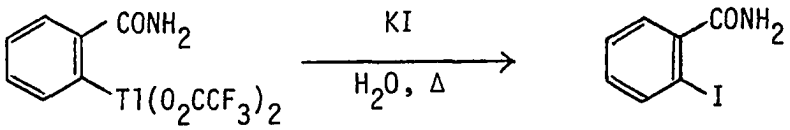
160 161, 100%

of the crude iodide showed only one peak. Again, the only isomer must come from ortho-thallated N-methylbenzamide and this can be proved by the products of olefination (to be discussed later).

Thallated benzamide can be obtained in quantitative yield by treating benzamide with thallium(III) trifluoroacetate in trifluoroacetic acid (eq. 81). Iodination of the crude product 162 gave only one iodo compound (analyzed by GC/MS) (eq. 82). We assumed again that compound 162 is the ortho thallated benzamide.

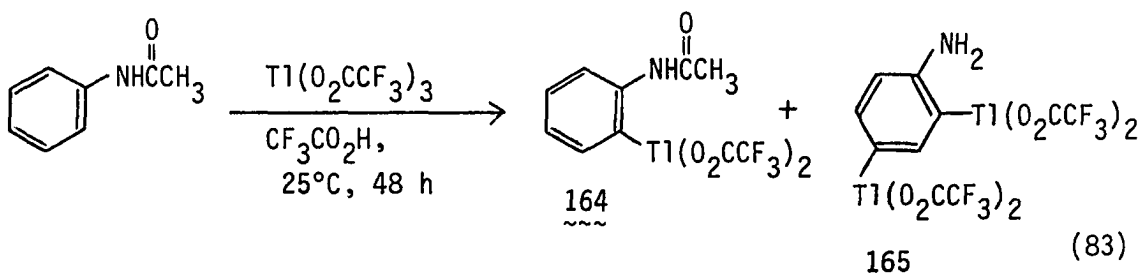



162, 100% (81)



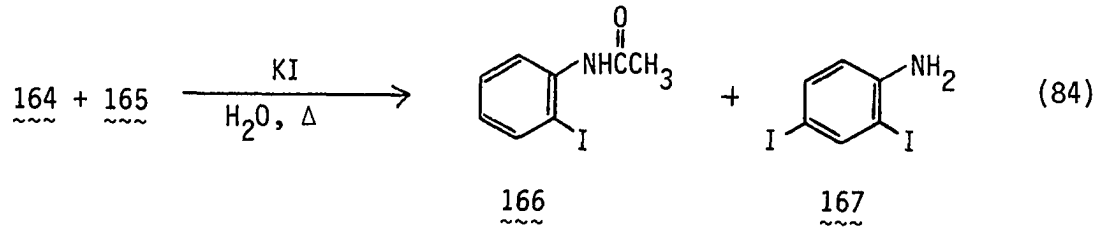

162 163, 100% (82)

Acetanilide can be thallated in 72% yield using thallium(III) trifluoroacetate at room temperature (eq. 83). The iodination of the crude thallated compound gave two products, 166 and 167, in ca. 77% (eq.



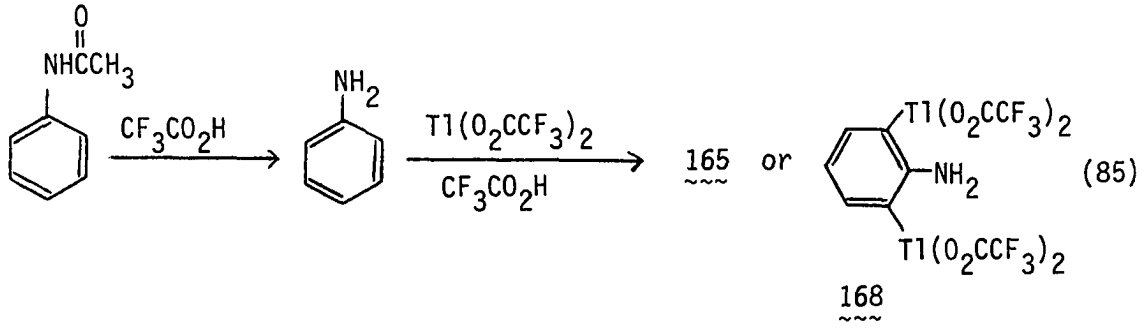

164 165 (83)

84). The ratio of 166:167 was 6:1 (analyzed by GLC and GC/MS). The structure of compound 167 is tentatively assigned as shown. The GC/mass spectrum of compound 167 shows m/z 345 ($M^+$), 218 ($M^+$-I), and 91 ($M^+$-




(84)

2I). The diiodo compound must come from 1,4-dithallated aniline which in turn comes from aniline as shown in Equation 85. Acetanilide is

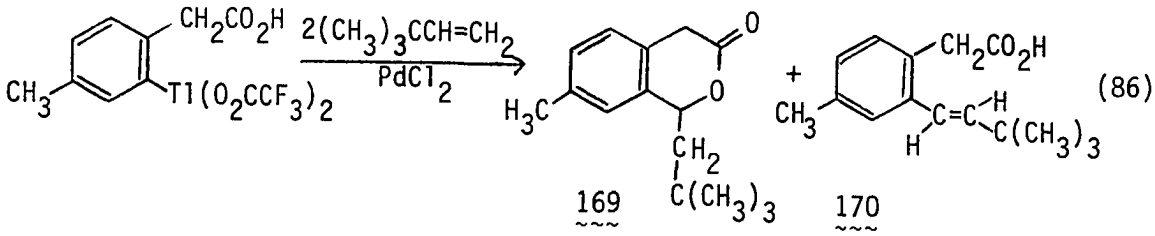



(85)

apparently first hydrolyzed to aniline which then undergoes electrophilic thallation to give either compound 165 or 168. For steric reasons, we assumed that compound 165 is the one we obtained. The formation of compound 165 might be eliminated by carrying out the thallation reaction at 0°C, although this was not done.

2. Vinylation-cyclization of thallated p-tolylacetic acid (158)

a. Vinylation of compound 158 with 3,3-dimethyl-1-butene The palladium-assisted vinylation of compound 158 with 3,3-dimethyl-1-butene gave both cyclized and uncyclized products (eq. 86). The results are




169 170 (86)

summarized in Table XVI. From the results, we found that adding a base is necessary in order to obtain a higher yield of compound 169. Triethylamine and sodium carbonate gave comparable yields of compound 169, but using both bases together seems to give still a cleaner reaction (i.e., fewer by-products could be detected by TCL analysis). The reaction temperature has no effect on the yield of compound 169, except that the reaction proceeds faster at a higher temperature. Lithium chloride has almost no effect on the yield of compound 169.

We assumed that compound 170 is the intermediate for the formation of compound 169. In order to understand the reaction mechanism, we have examined the possibility of converting compound 170 into 169. The results are summarized in Table XVII. We found that this conversion is

Table XVI. The palladium-promoted reaction of compound 158 and 3,3-dimethyl-1-butene (eq. 86)

| Solvent | Reagents and Reaction conditions | % Isolated yield 169 | 170 |
|---|---|---|---|
| $CH_3CN$ | $PdCl_2$, 25°C 16 h; then 2 $Et_3N$, 80° 5 h | 30 | 30 |
| | $PdCl_2$, 25°C 16 h; then 2 $Et_3N$, RT 24 h | 39 | 54 |
| | $PdCl_2$, 25°C 16 h; then 4 $Na_2CO_3$, RT 24 h | 38 | 52 |
| | $PdCl_2$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, RT 24 h | 43 | 47 |
| | $Li_2PdCl_4$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, RT 24 h | 15 | 51 |
| | $Li_2PdCl_4$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, 80° 5 h | 5 | 50 |
| $CH_2Cl_2$ | $PdCl_2$, 0°C 48 h | 39 | 56 |
| | $PdCl_2$, 25°C 48 h | 64 | 15 |
| | $PdCl_2$, 2 $Et_3N$, 25°C 48 h | 17 | 75 |
| | $PdCl_2$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, RT 24 h | 72 | 12 |
| | $Li_2PdCl_4$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, RT 24 h | 76 | 9 |
| | $Li_2PdCl_4$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, 50°C[a] 5 h | 77 | 5 |
| | $Li_2PdCl_4$, 25°C 16 h; then 2 $Et_3N$, 50°C[a] 5 h | 74 | trace |
| | $Li_2PdCl_4$, 25°C 16 h; then 1.5 NaH, 50°C[a] 5 h | 68 | 21 |

[a]Bath temperature.

Table XVII. Conversion of compound 170 into 169

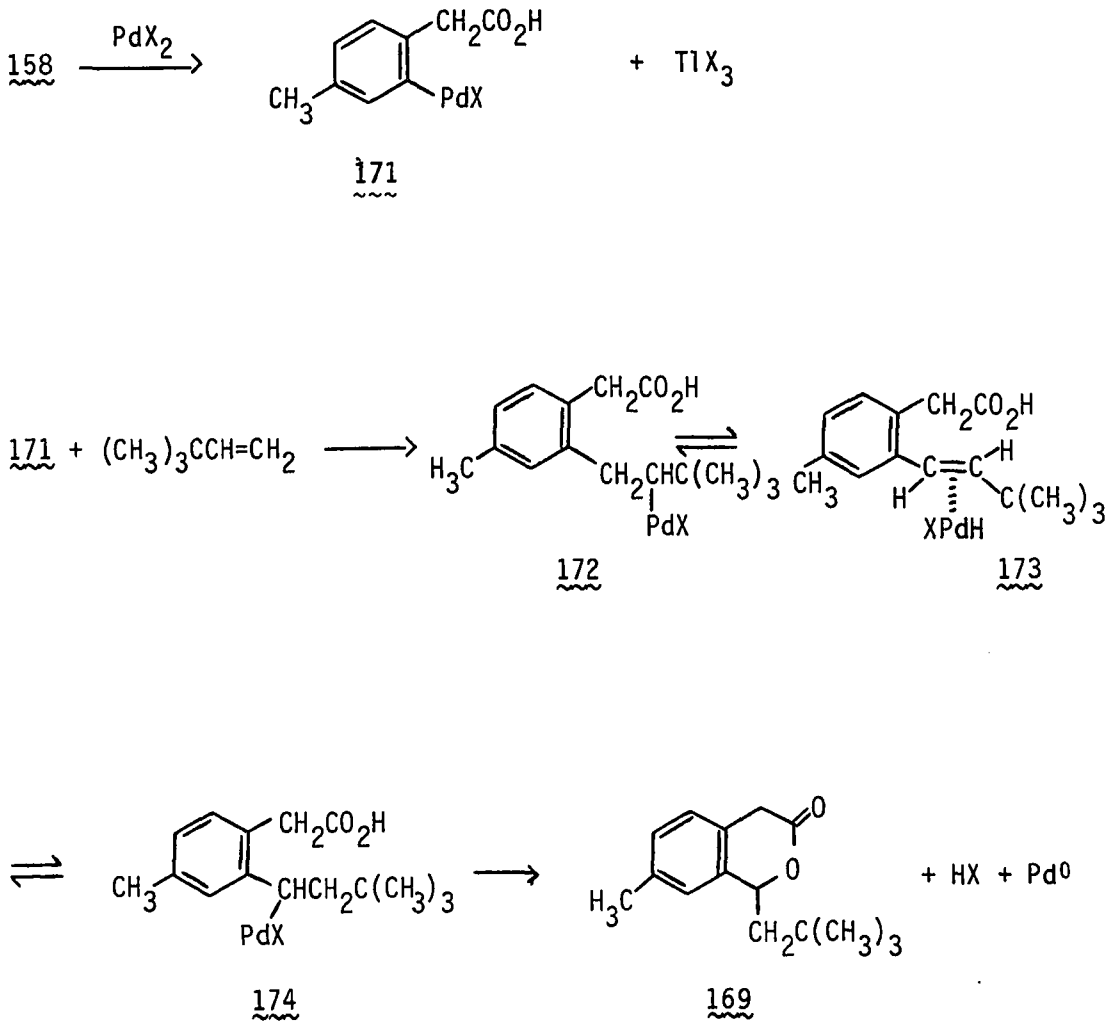
170 ⟶ 169

| Solvent | Reagents | Reaction Condition | % Isolated Yield of 169 | % Recovery of 170 |
|---|---|---|---|---|
| $CH_3CN$ | $PdCl_2$ | 25°C, 40 h | 0 | 94 |
| | $PdCl_2$ | 25°C, 16 h then 2 $Et_3N$, 2 $Na_2CO_3$, 25°C, 24 h | 0 | 81 |
| | $Pd(OAc)_2$ | 25°C, 48 h | 0 | 73 |
| $HCCl_3$ | 5% $H_2SO_4$ | 65°C | 0 | ~100 [164] |
| $CH_3CN$ | $HCl_{(g)}$ | 25°C, 30 h | ~5 | 70 |
| | $HCl_{(g)}$ and cat. $Pd(DBA)_2$ | 25°C, 36 h | 28 | 40 |

not assisted by Pd (II) salts. However, this reaction does occur when compound 170 was treated with HCl + Pd $(DBA)_2$, which presumably forms HPdCl. As reported by Tsuji, HPdCl can be generated *in situ* by passing dry HCl gas into a solution of a Pd(0) salt [165]. A stream of dry HCl gas was passed into a solution of compound 170 and 0.25 equiv. of $Pd(DBA)_2$ (DBA=dibenzylidene acetone, PhCH=COCH=CHPh) for 5 min and the mixture was stirred at room temperature for 36 h. This reaction afforded 28% of compound 169 together with 40% of the starting material 170. This result suggests that the ring-closure reaction is assisted by HPdCl. Based on the results we obtained, we propose a mechanism for the

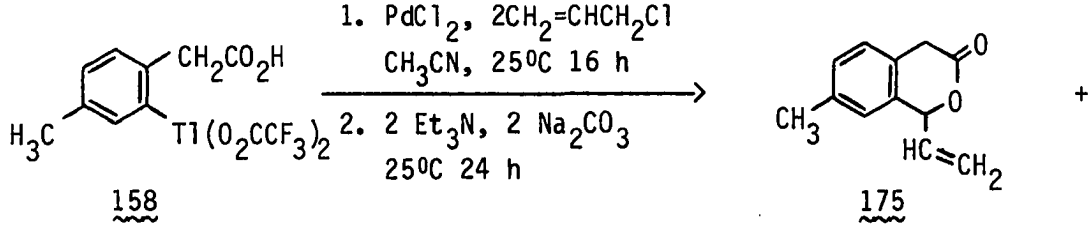
formation of compound 169 from 158 as shown in Scheme XV. The arylpalladium compound 171 formed by a transmetallation reaction can add

Scheme XV. Mechanism for the formation of compound 169

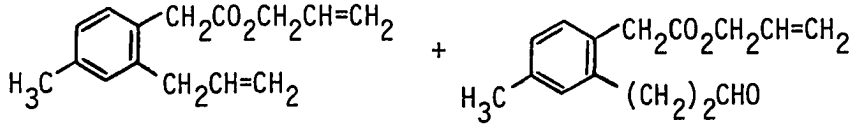


to the double bond of 3,3-dimethyl-1-butene to give organopalladium compound 172. Compound 172 undergoes β-hydride elimination (eliminates HPdCl) to give a π-complex 173 which then undergoes palladium hydride readdition in the opposite direction to afford compound 174. Intramolecular displacement of palladium by carboxylate then gives compound 169.

b. Vinylation of compound 158 with 3-chloro-1-propene The reaction of compound 158 and 3-chloro-1-propene is solvent dependent. When the reaction was carried out in acetonitrile using $PdCl_2$, three major products can be identified by GC/MS analysis (eq. 87). The ratio of 175:176:177 is 2.5:3.4:1. When examined in dichloromethane at room temperature, the reaction gave 3 major products 178, 176, and 175 in the ratio of 1:5.5:20 and compound 175 can be isolated in ca. 25% yield (eq.

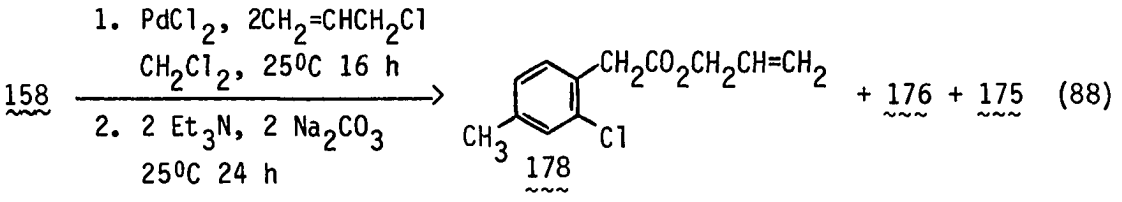


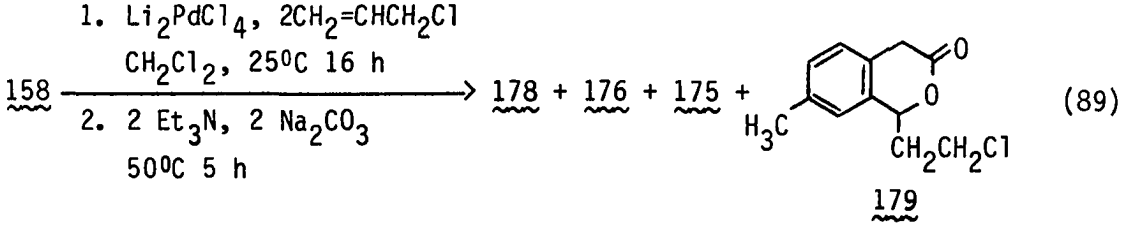

158 175




176 177

(87)

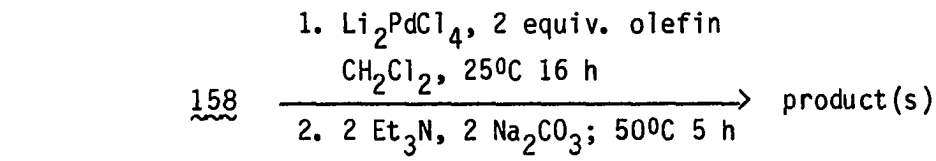


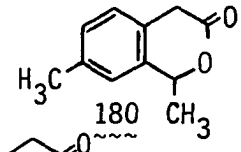
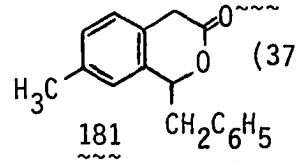
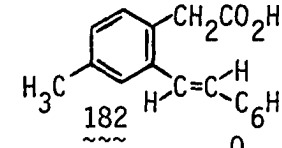
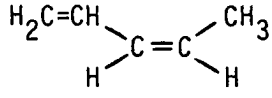
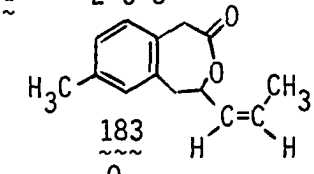
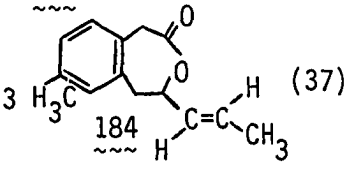
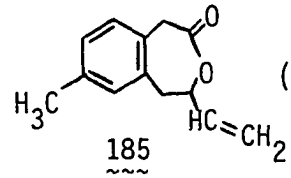
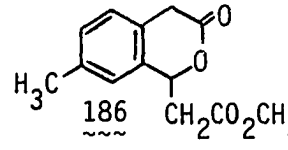
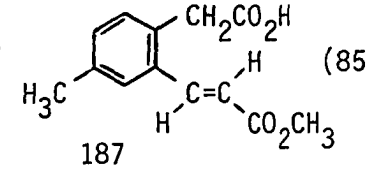




88). When 2 equiv. of lithium chloride was added and the reaction mixture was refluxed for 5 h, 4 major products (178, 176, 175, and 179) could be detected (eq. 89). The ratio of 178:176:175:179 is 1:4.1:2.1:4.4. It looks like the major complication in this reaction is the formation of an ester group between the carboxylic acid group and 3-chloro-1-propene. Since we have no control over this side reaction, this reaction has not been further studied.

c. Vinylation of compound 158 with other olefins The reactions of compound 158 with ethylene (excess), styrene, cis-1,3-pentadiene, 1,3-butadiene (excess), 3-methyl-1,2-butadiene, methyl acrylate, and 1-methyl-1-vinylcyclopropane have been examined. The results are summarized in Table XVIII. Vinylation of compound 158 gave low yields of cyclized products (except with 1,3-butadiene). In most of the cases, the uncyclized product could be detected in the NMR spectrum of the crude

Table XVIII. Reaction of 158 with olefins




| Olefin | Product(s) (% isolated yield) |
|---|---|
| $CH_2=CH_2$ |  (28)  |
| $C_6H_5CH=CH_2$ |  (37)   (~22)[a]  |
|  |    (37)[b]  |
| $CH_2=CH-CH=CH_2$ |  (69)  |
| $(CH_3)_2C=C=CH_2$ | ---[c] |
| $CH_2=CHCO_2CH_3$ |  (3.5)   (85)  |
| 1-methyl-1-vinyl-cyclopropane | ---[c] |

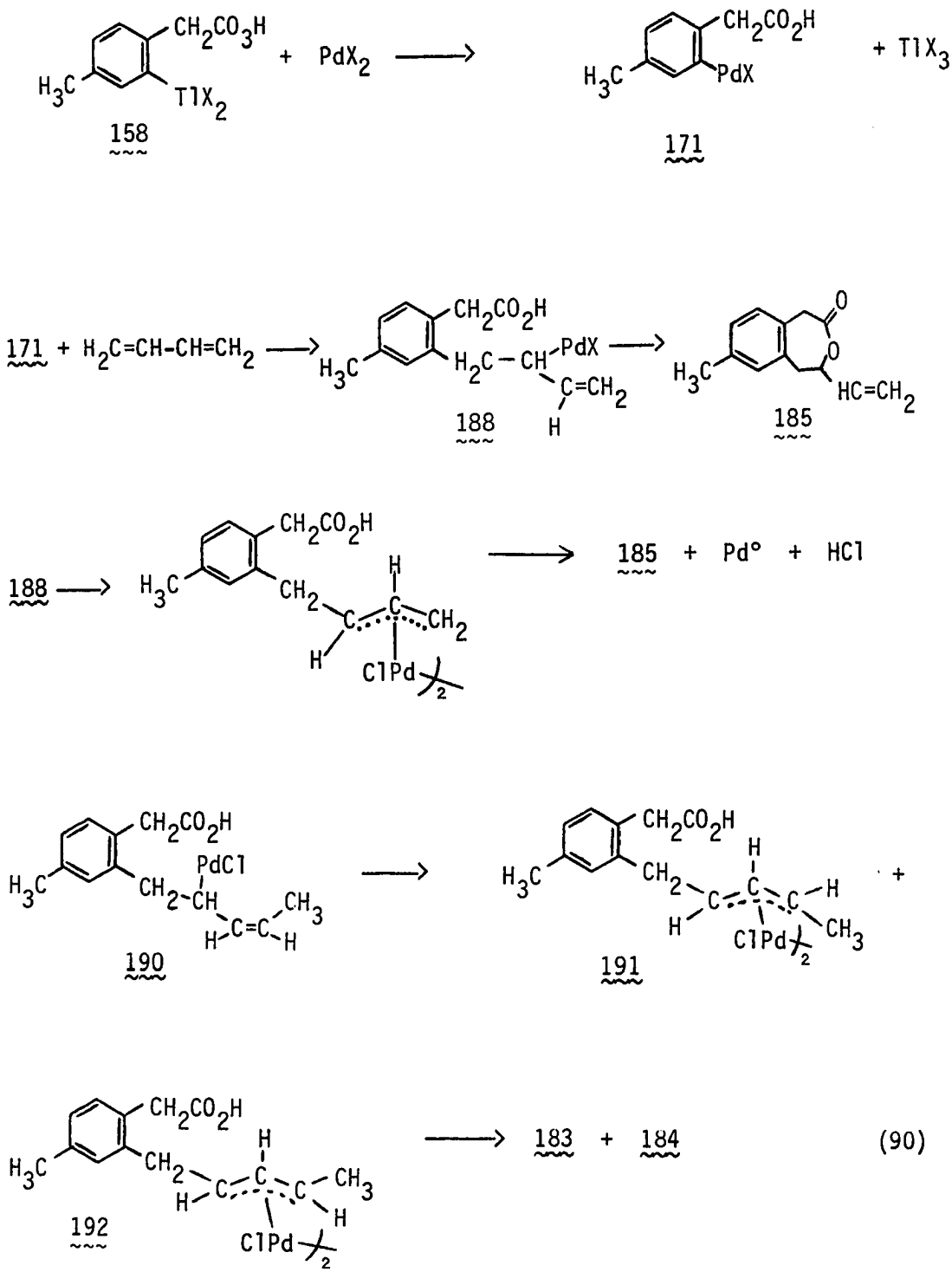
[a]This compound still contains a very small amount of impurities.

[b]Total yield. The ratio of 184:183 is 5.2:1 as judged by GLC analysis.

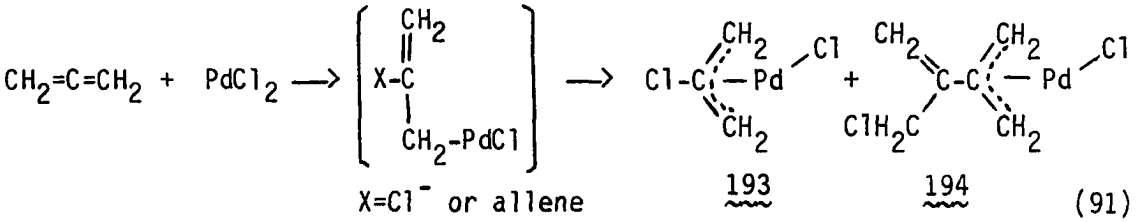
[c]No vinylation product could be detected.

reaction mixture, but could not be isolated by column chromatography. The reaction of 158 and ethylene in acetonitrile as opposed to methylene chloride gave a comparable yield (26%) of compound 180. The reaction of compound 158 and styrene in methylene chloride gave 37% of compound 181 together with ca. 22% of the uncyclized product (182). Unfortunately, we were unable to obtain a pure sample of compound 182 (it has been characterized by $^1$H NMR and IR analysis only). The vinylation of compound 158 with cis-1,3-pentadiene gave an inseparable mixture of 183 and 184 in 37% yield. The ratio of 183:184 could not be determined by 300 MHz NMR decoupling experiments. It could only be determined by GLC relative peak areas as cis/trans=1:5.2. The presence of regioisomers (isomers with a different position of the carbon-carbon double bond) was ruled out after we examined the reaction with 1,3-butadiene. Vinylation of compound 158 with 1,3-butadiene gave only one product 185 in 69% yield. The structure of compound 185 has been determined by 300 MHz NMR decoupling experiments. The mechanism for the formation of compound 185 is shown in Scheme XVI. The organopalladium intermediate 188 can either undergo direct displacement to yield compound 185 or isomerize to a $\pi$-allylpalladium complex (189) which then undergoes displacement to afford compound 185. Since the reaction with cis-1,3-pentadiene gave a mixture of E and Z isomers, we believe that the $\pi$-allylpalladium complexes analogous to 189 are the actual intermediates in the formation of 183 and 184 (eq. 90). In the reaction of compound 158 with 3-methyl-1,2-butadiene, no recognizable olefination product could be detected in

Scheme XVI.



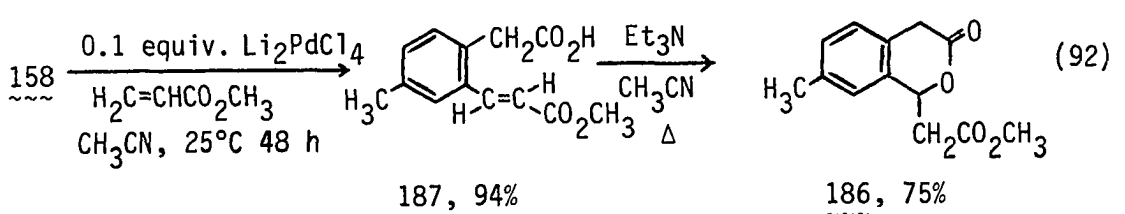
the reaction mixture. Only high molecular weight compound from the chlorinated 3-methyl-1,2-butadiene could be isolated. This result is not surprising. Since it has been reported that allenes can react with $PdCl_2$ to form π-allylpalladium complexes involving multiple insertions of the allene (eq. 91) [166-169]. Complexes 193 and 194 then decompose or




(91)

polymerize to give high molecular weight chlorinated products. This also indicates that the chloropalladation of allenes proceeds much faster than the transmetallation of compound 158 to the corresponding arylpalladium compound.

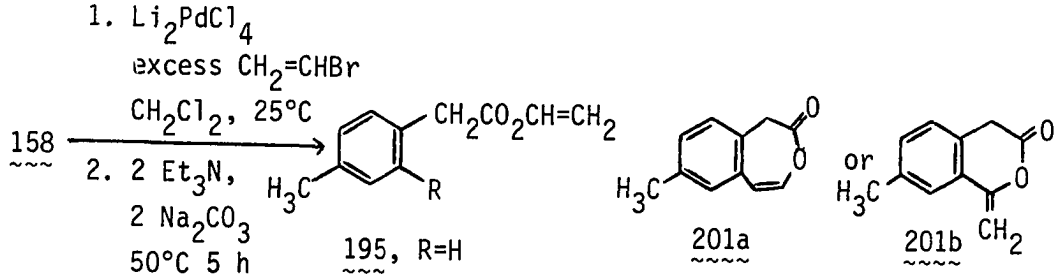
The reaction of compound 158 and methyl acrylate has been examined by Larock and Lau [164]. In a two-step process, compound 158 was converted to compound 186 in high yield (eq. 92). We have examined the




(92)

possibility of effecting the olefination-cyclization in one step. When the reaction was examined in $CH_2Cl_2$, only a 3.5% yield of the cyclized product 186 could be isolated. The major product was still the uncyclized product 187 obtained in 85% yield. Upon changing the solvent from $CH_2Cl_2$ to $CH_3CN$ and heated to 80°C for 5 h, the same reaction gave a 11% yield of compound 186 and an 81% yield of compound 187. Thus the best method to effect the conversion of 158 to 186 is the two-step process. At this stage, we have no explanation why we were unable to effect the vinylation and cyclization in one step. Finally, the reaction of compound 158 and 1-methyl-1-vinylcyclopropane gave no recognizable olefination product at all.

Since vinyl bromide has been shown to be an ethylene equivalent for the vinylation of thallated benzoic acid [163], we have examined the same reaction with thallated p-tolylacetic acid. Unfortunately, this reaction




195, R=H
196, R=Cl
197, R=CH=$CH_2$
198, R=Br
199, R=CH=CHCl
200, R=$CH_2CHO$

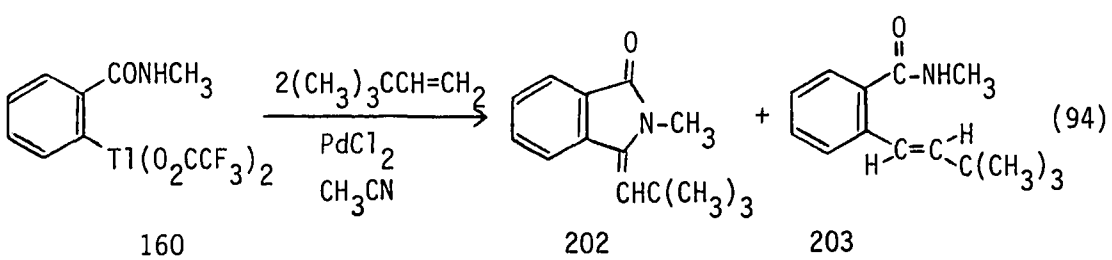
201a 201b

(93)

gave at least seven products (eq. 93). The ratio of 195:196:197:198:200:201a (or 201b) is 1:3.1:2.2:7.7:1.1:2:6.1 (determined by relative GLC peak areas). From the distribution of reaction products, we found that this reaction suffers the same difficulty as the reaction of 158 and 3-chloro-1-propene. The esterification of the acid functionality with vinyl bromide is apparently much faster than the reaction between vinyl bromide and the arylpalladium intermediate. This reaction has not been further studied.

3. Vinylation-cyclization of thallated N-methylbenzamide (160)

a. Vinylation of compound 160 with 3,3-dimethyl-1-butene The reaction of compound 160 and 3,3-dimethyl-1-butene gave only low yields of cyclized product (eq. 94), the results are summarized in Table XIX.



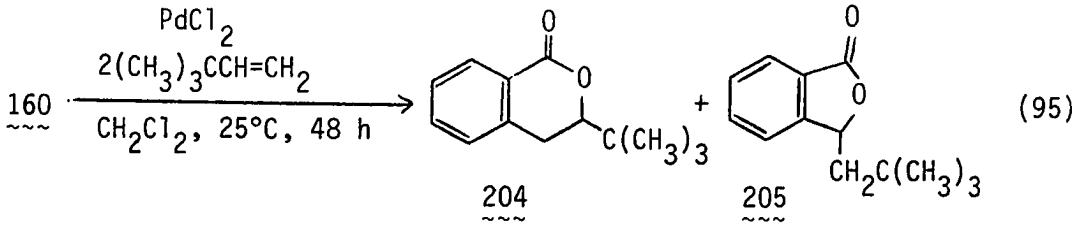

160 202 203

By adding base(s) (especially NaH) to the reaction mixture, the yield of cyclized product 202 increased slightly, but the total yield of 202 and 203 decreased drastically. The reaction temperature appears to have no effect on the yields of either product. Since the yields for compound 202 are so low for all of the conditions that have been examined, we cannot conclude which condition is the best one. When the reaction was

Table XIX. Reaction of compound 160 and 3,3-dimethyl-1-butene

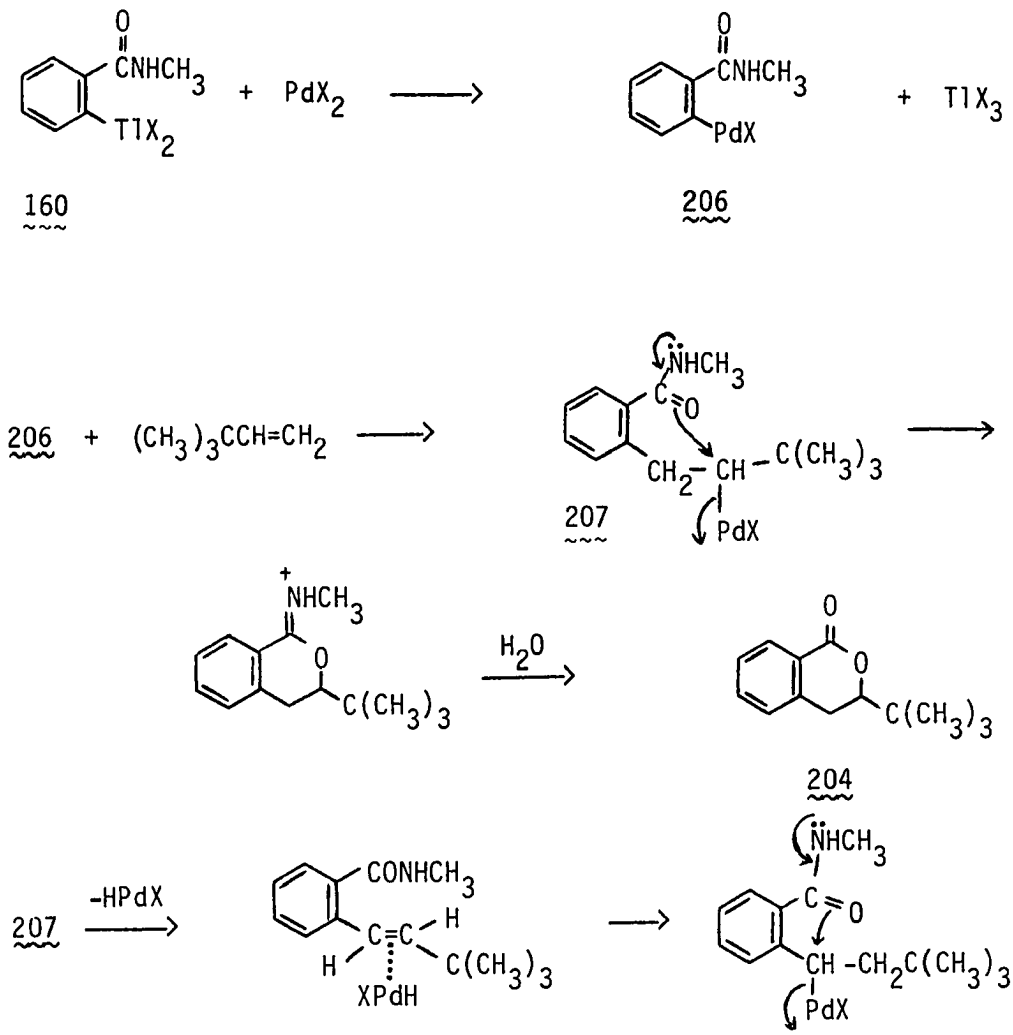
| Reagents and Reaction Conditions | % Isolated Yield 202 | 203 |
|---|---|---|
| $PdCl_2$, 25°C 48 h | 8 | 24 |
| $PdCl_2$, 25°C 16 h; then 0.75 equiv. NaH, 25°C 24 h | 12 | 9 |
| $PdCl_2$, 25°C 16 h; then 2 equiv. NaH, 25°C 24 h | 12 | 6 |
| $PdCl_2$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, 25°C 24 h | 7 | 4 |
| $PdCl_2$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, 80°C 5 h | 9 | 5 |
| $Li_2PdCl_4$, 25°C 16 h; then 2 $Et_3N$, 2 $Na_2CO_3$, 80°C 5 h | 5 | 19 |
| $Li_2PdCl_4$, 25°C 48 h | trace | 44 |
| $Li_2PdCl_4$, 25°C 48 h (in $CH_2Cl_2$) | trace | 9 |
| $Li_2PdCl_4$, 25°C 16 h; then 80°C 5 h | 5 | 48 |

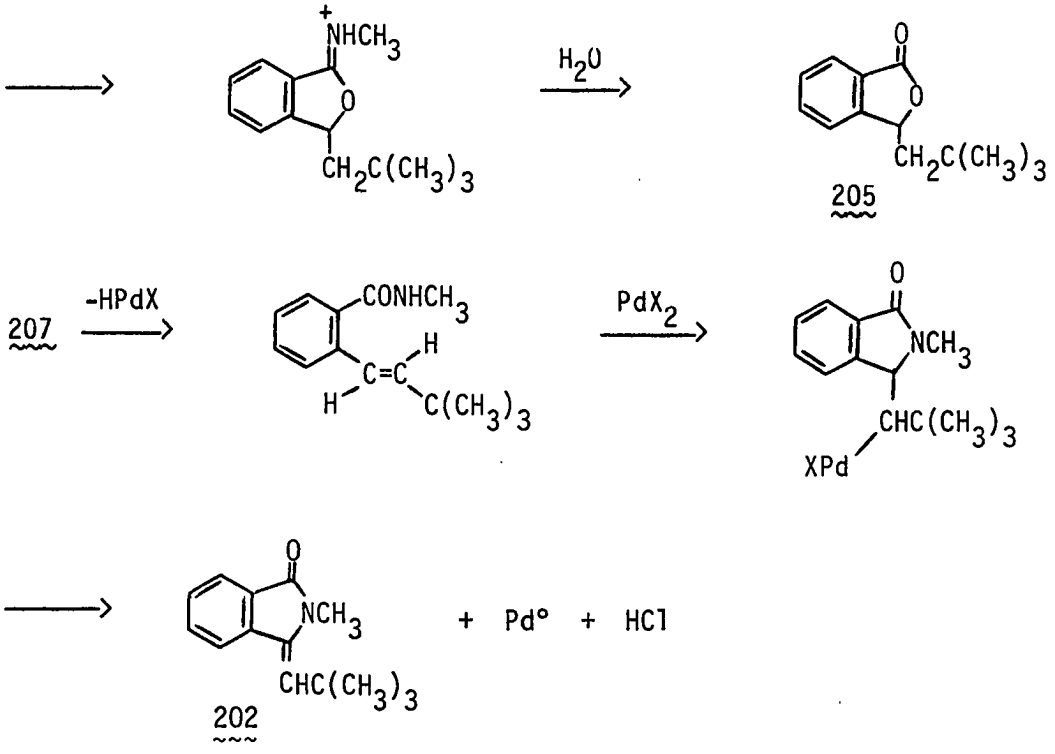
examined in dichloromethane and no lithium chloride was added, only lactones could be detected in the reaction mixture (eq. 95). The ratio of 204:205 has been determined by GLC relative peak areas as 3.7:1. When 1 equiv. of lithium chloride was added to the above reaction mixture, no lactones could be detected and we could isolate 9.2% of compound 203 but less than 5% of compound 202. A possible mechanism for the formation of lactones 204, 205 and lactam 202 is shown in Scheme XVII. The effect of lithium chloride is not clear at this stage.




(95)

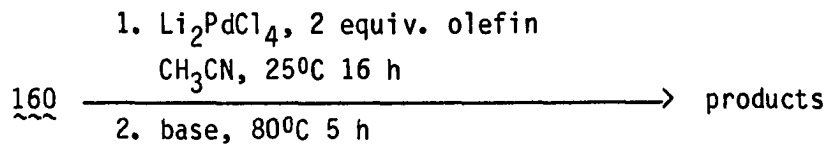
Scheme XVII. The mechanism for the formation of 202, 204, and 205

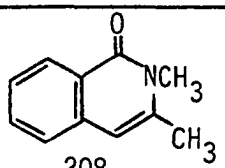
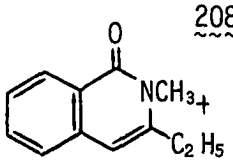
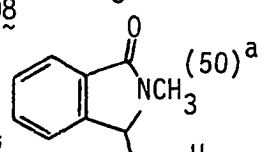
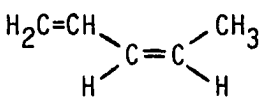
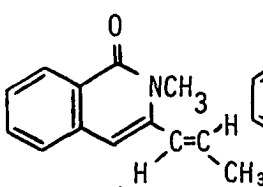
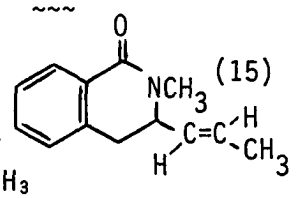
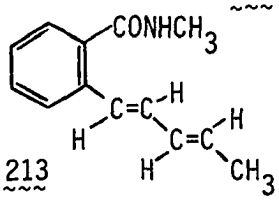
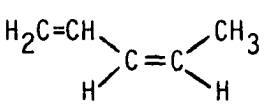




b. Reaction of compound 160 and other olefins Vinylations of compound 160 with 3-chloro-1-propene, 3-chloro-1-butene, cis-1,3-pentadiene, methyl acrylate, styrene, 3-methyl-1,2-butadiene, ethylene (excess), vinyl bromide (excess), and 1-methyl-1-vinylcyclopropane have been examined. The results are summarized in Table XX. For the reaction of compound 160 and 3-chloro-1-propene, we have also studied the effect of lithium chloride. We found that in the absence of lithium chloride the yield of compound 208 dropped from 61% to 50%. By adding 2 equiv. $Et_3N$ and 2 equiv. $Na_2CO_3$ to the reaction without lithium chloride, the yield of compound 208 decreased drastically to 21%. Lithium chloride has the same effect on the reaction of compound 160 and 3-chloro-1-butene.

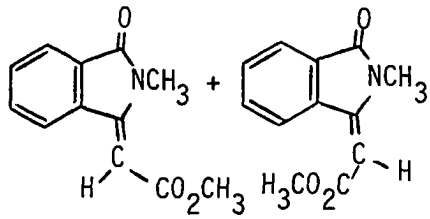
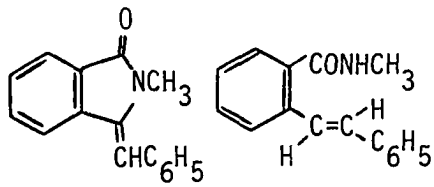
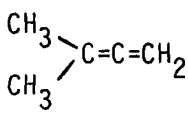
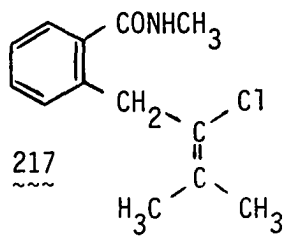
Table XX. Vinylation of compound 160




| Entry | Olefin used | Base added | Product(s) (% isolated yield) |
|---|---|---|---|
| 1 | $H_2C{=}CHCH_2Cl$ | --- |  (61) <br> 208 |
| 2 | $H_2C{=}CHCH(Cl)CH_3$ | --- |   (50)[a] <br> 209 210 |
| 3 |  | --- |   (15) <br> 211 (12) 212 <br>  (35) <br> 213 |
| 4 |  | 1.5 equiv. NaH | 212 (4.5), 213 (9) |

[a]Total yield of 209 + 210; the ratio of 209:210 judged by GLC analysis is 96:4.

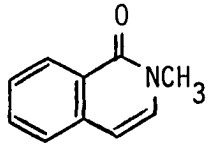
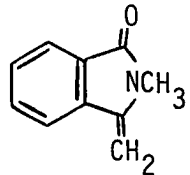
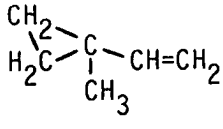
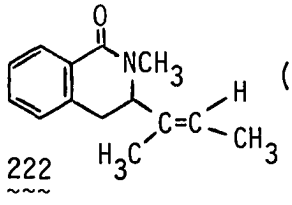
Table XX. (continued)

| Entry | Olefin used | Base added | Product(s) % Isolated yield) |
|---|---|---|---|
| 5 | $H_2C{=}CHCO_2CH_3$ | 1.5 equiv. NaH |  214a (52)[b] 214b |
| 6 | $H_2C{=}CHCO_2CH_3$ | | 214a + 214b (5.5)[c] |
| 7 | $C_6H_5CH{=}CH_2$ | --- |  215 (37) 216 (28) |
| 8 | $C_6H_5CH{=}CH_2$ | 1.5 equiv. NaH | 215 (20) 216 (22) |
| 9 |  | 1.5 equiv. NaH |  217 |

[b]Total yield of 214a + 214b; the ratio of 214a:214b judged by $^1H$ NMR spectral analysis is 1:3.8.

[c]Total yield of 214a + 214b; the ratio of 214a:214b judged by $^1H$ NMR spectral analysis is 1:11.8.

Table XX. (continued)

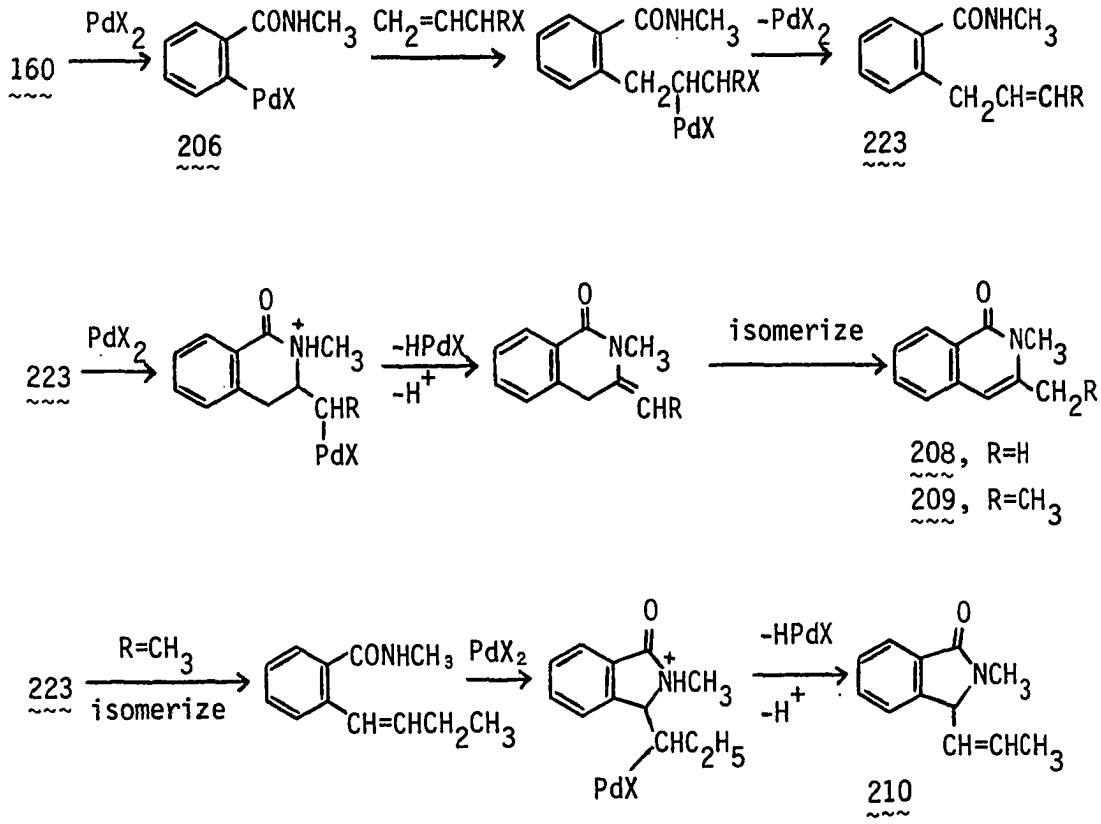
| Entry | Olefin Used | Base added | Product(s) (% isolated yield) |
|---|---|---|---|
| 10 | $CH_2=CH_2$ | --- |  218 (39)  219 (∿20)[d] |
| 11 | $CH_2=CH_2$ | 1.5 equiv. NaH | 218 (10) |
| 12 | $CH_2CHBr$ | --- | 218 (36) |
| 13 | $CH_2=CHBr$ | 1.5 equiv. NaH | 218 (21) |
| 14 |  | --- |  222 (8.4) |

[d]It still contains two other compounds 220 and 221. Please see text for discussion.

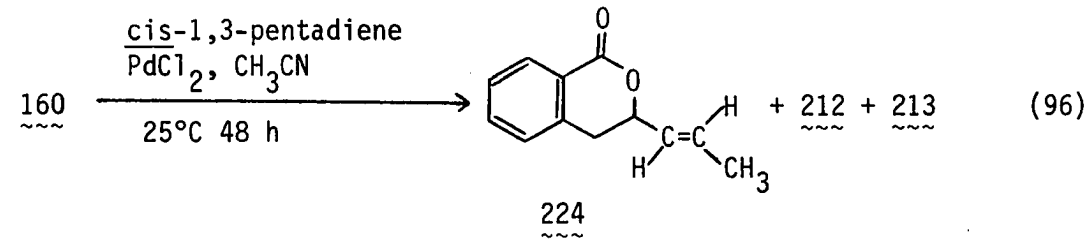
In the absence of lithium chloride, the reaction of compound 160 with 3-chloro-1-butene gave only a 40% yield of compound 209 + 210 with the ratio 209:210 = 93:7. The effect of lithium chloride may simply be to increase the solubility of the palladium salt in acetonitrile. The formation of a soluble complex of $LiPdCl_3$ in acetonitrile [probably exists as $LiPdCl_3(CH_3CN)$] [170] may enhance the rate of the

transmetallation step which might give a higher yield of olefination product. In the absence of lithium chloride, an insoluble complex, $PdCl_2(CH_3CN)_2$, is formed which is less effective in the palladium-assisted olefination reaction than $LiPdCl_3$. A possible mechanism for the reaction of compound 160 and allylic chlorides is shown in Scheme XVIII.

Scheme XVIII. Possible mechanism for the reaction of compound 160 and allylic chlorides



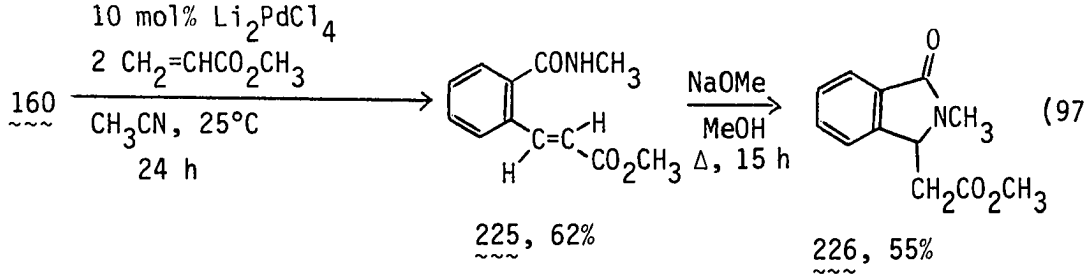
The reaction of compound 160 with cis-1,3-pentadiene and palladium chloride gave 6 major products, 224, 212, 213, and 3 unidentified compounds (with molecular weights of 220, 159, and 210) (eq. 96). The




(96)

ratio of 224:212:213:3 unidentified products is 2:2:1:4 as judged by their GLC peak areas. The same reaction with 2 equiv. LiCl added gave compound 224 in 9.6% isolated yield. The addition of sodium hydride only reduced the yield of vinylation products (see entry 4, Table XX). The mechanism for the reaction of compound 160 with cis-1,3-pentadiene may be the same as that shown for the reaction of compound 158 with 1,3-butadiene (see Scheme XVI).

The olefination of compound 160 with methyl acrylate and $Li_2PdCl_4$ has been examined earlier by Larock and Lau [164]. With 10 mol% of $Li_2PdCl_4$, the uncyclized product 225 could be obtained in 62% yield which could then be cyclized using sodium methoxide in methanol (eq. 97). With



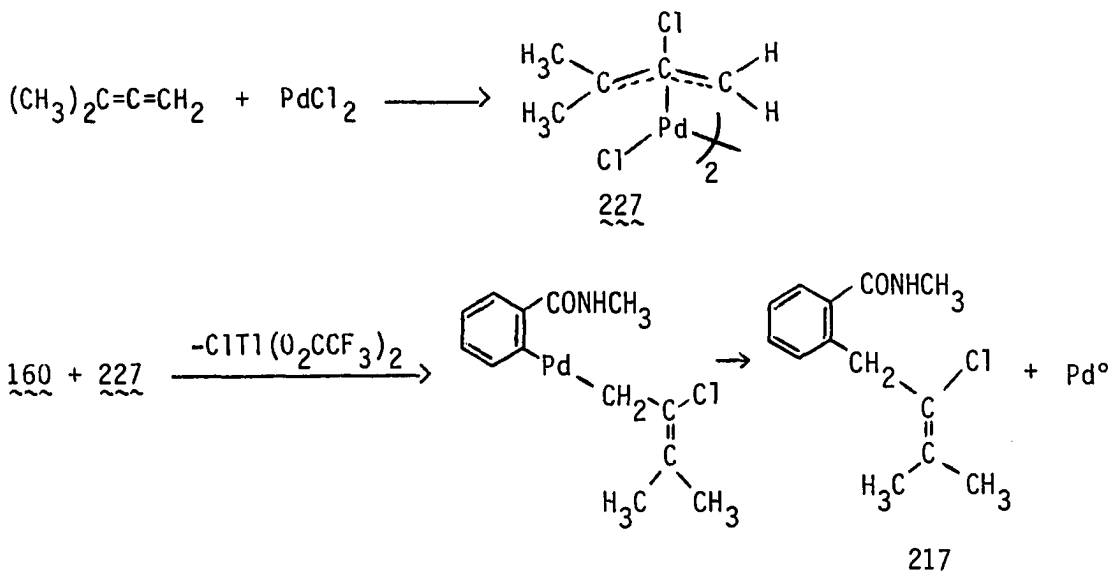

(97)

only a slight modification, we were able to obtain different cyclization products in 52% yield (see entry 5, Table XX). The $^1H$ NMR spectrum of the mixture showed two singlets for the $OCH_3$ groups and two singlets for the olefinic protons. According to literature examples, the chemical shift for an olefinic proton cis to an aryl group is found further downfield than one trans to an aryl group. Based on this observation, we tentatively assigned the structure with the olefinic proton peak appearing further downfield as compound 214a and calculated the ratio of 214a:214b as 1:3.8. In order to prove that base (NaH) is really needed, we have also examined the same reaction without adding sodium hydride. The reaction gave only 5.5% of the mixture 214a and 214b in the ratio of 1:11.8 and the major product was the uncyclized product 225 (see entry 6, Table XX). On the other hand, the reaction of compound 160 and styrene gave a lower yield of cyclized product 215 (a single isomer, not a mixture of E, Z isomer as judged by 300 MHz NMR) when sodium hydride was added (see entries 7 and 8, Table XX). The reason for the effect of sodium hydride is still not clear.

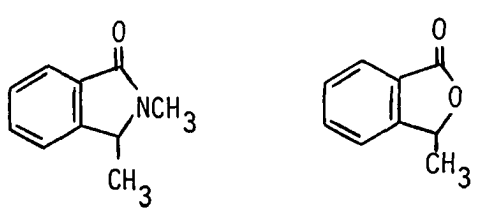
The reaction of compound 160 and 3-methyl-1,2-butadiene gave lots of high molecular weight compounds from chloropalladated 3-methyl-1,2-butadiene. The only vinylation product which could be isolated is compound 217 (see entry 9, Table XX). It has been reported that arylthallium compounds can react with $\pi$-allylpalladium complexes to give coupling products [171]. From the reaction product, we assume that the formation of a $\pi$-allylpalladium complex between palladium chloride and 3-methyl-1,2-butadiene is much faster than the transmetallation reaction.

One possible mechanism for the formation of compound 217 is shown in Scheme XIX.

Scheme XIX. Mechanism for the formation of 217



The vinylation of compound 160 with ethylene gave compound 218 as the major product alongside a mixture of 219, 220, and 221. GLC analysis

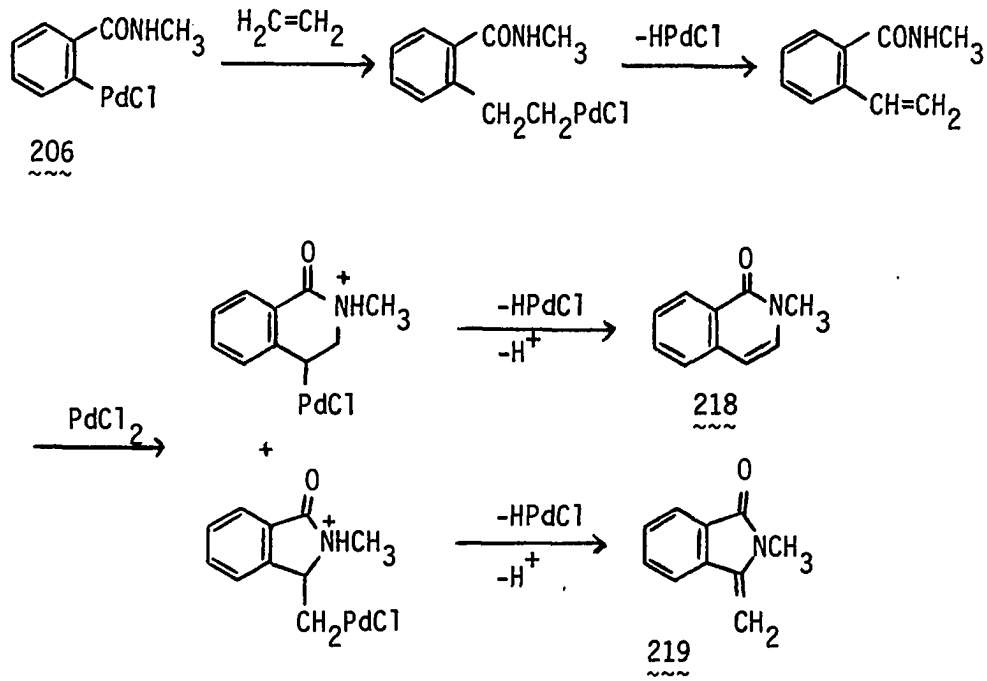


220 221

of the mixture shows 3 peaks in the ratio 219:220:221=6:3:1. The proton NMR spectrum of the mixture shows two products 219 and 220 present in the ratio 2.6:1. When the solution of the mixture was kept in the freezer

for one week to wait for GC/mass spectral analysis, one of the peaks corresponding to compound 219 disappeared. Presumably, compound 219 decomposed on standing in solution. Thus we could only obtain GC/mass spectra for compounds 220 and 221. A possible mechanism for the formation of compounds 218 and 219 is shown in Scheme XX. The vinylation of compound 160 with vinyl bromide gave compound 218 (36%) as the only isolable product.

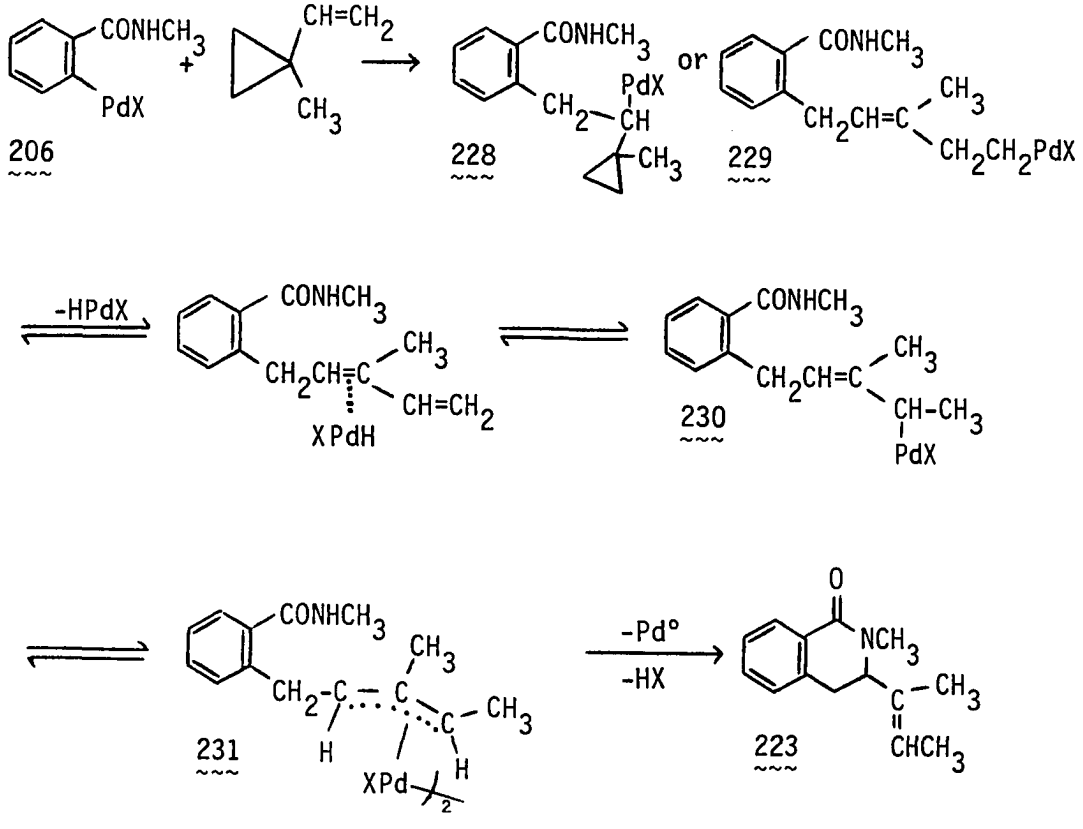
Scheme XX. Possible mechanism for the formation of 218 and 219




Vinylcyclopropanes have been shown to be a 1,3-diene equivalent when reacted with thallated benzoic acid [162]. We also examined the reaction of compound 160 and 1-methyl-1-vinylcyclopropane and found that only a

very small amount of vinylation product could be isolated (see entry 14, Table XX). Scheme XXI provides a possible mechanism for the formation of compound 223 from 160.

Scheme XXI. Mechanism for the formation of 223



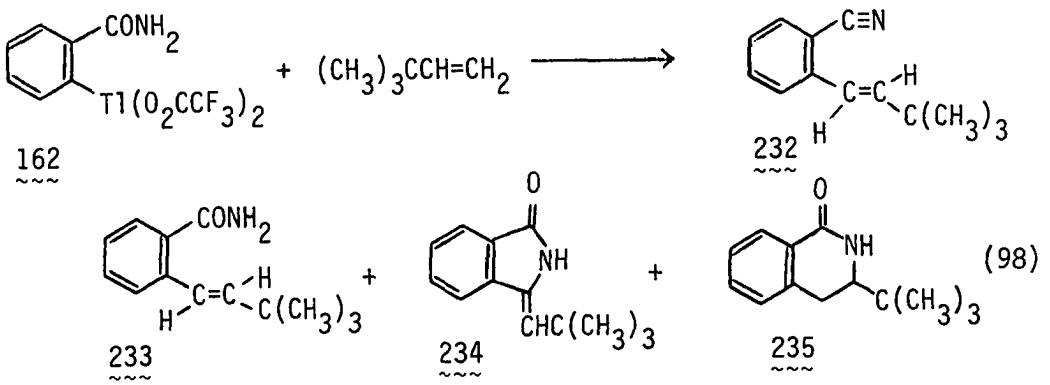

4. Vinylation-cyclization of thallated benzamide (162)

a. Olefination of compound 162 with 3,3-dimethyl-1-butene The reaction of compound 162 with 3,3-dimethyl-1-butene and palladium chloride gave several products (eq. 98). The results are summarized in Table XXI. When the reaction was carried out in acetonitrile, both

Table XXI. Reaction of 162 with 3,3-dimethyl-1-butene

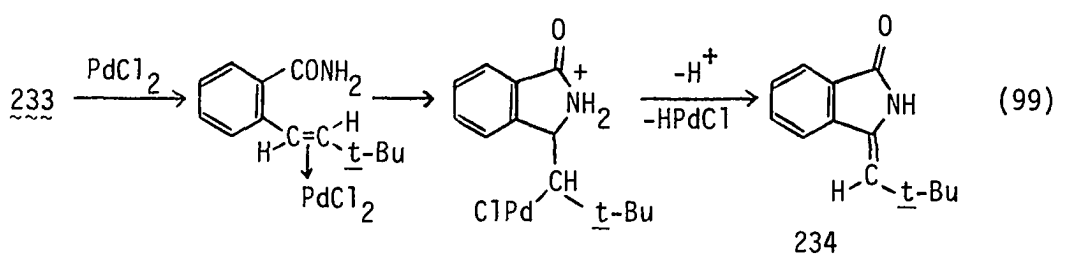
| Entry | Solvent | Pd salt and Reaction Conditions | % Isolated Yield 232 | 233 | 234 | 235 |
|---|---|---|---|---|---|---|
| 1 | $CH_3CN$ | $PdCl_2$, 25°C 16 h, then 80°C 5 h | 26 | 5 | 0 | 0 |
| 2 | | $PdCl_2$, 25°C 48 h | 42.4 | 0 | 0 | 0 |
| 3 | | $PdCl_2$, 2 equiv. $H_2O$, 25°C 48 h | 41 | 0 | 0 | 0 |
| 4 | | $Li_2PdCl_4$, 25°C 48 h | 8 | 44 | 0 | 0 |
| 5 | | $Li_2PdCl_4$, 25°C 16 h, then 1.5 equiv NaH 80°C 5 h | 32 | 0 | 35 | 0 |
| 6 | $CH_2Cl_2$ | $PdCl_2$, 25°C 33 h | 0 | 0 | 26 | 0 |
| 7 | $CH_2Cl_2$ | $PdCl_2$, 25°C 16 h, then 1.5 equiv. NaH 50°C 5 h | 0 | 5 | 26 | 0 |
| 8 | | $Li_2PdCl_4$, 25°C 48 h | 0 | 28.3 | 0 | 17 |
| 9 | | $Li_2PdCl_4$, 25°C 16 h then 50°C 5 h | 0 | 41 | 22 | 0 |
| 10 | | $Li_2PdCl_4$, 25°C 16 h, then 1.5 equiv. NaH 50°C 5 h | 0 | 39 | 26 | 0 |
| 11 | | $Li_2PdCl_4$, 25°C 16 h, then 2 equiv. $Et_3N$ 50°C 5 h | 0 | 5.1 | 24 | 0 |
| 12 | | $Li_2PdCl_4$, 25°C 16 h, then 2 equiv. $Et_3N$, 1.5 equiv. NaH, 50°C 5 h | 0 | 24 | 25 | 0 |
| 13 | | 2 equiv. $Li_2PdCl_4$, 25°C 16 h then 1.5 equiv. NaH, 50° 5 h | 0 | 6 | 16.2 | 0 |

ortho-vinylated benzamide and ortho-vinylated benzonitrile were formed. The addition of 2 equiv. of $H_2O$ to the reaction mixture in acetonitrile



(98)

failed to prevent the formation of dehydration product 232 (entry 3, Table XXI). The vinylation of thallated benzonitrile with 3,3-dimethyl-1-butene has been examined by Larock and Lau [164]. Starting from thallated benzonitrile, one gets both products 232 and 233. The mechanism for the formation of the benzonitrile derivative from thallated benzamide is still not clear. No vinylated benzonitrile could be detected when the reaction was carried out in dichloromethane. In dichloromethane, neither the base(s) employed nor lithium chloride, nor the reaction temperature appeared to have any effect on the yield of the cyclized product 234. Since compound 233 is believed to be the intermediate in the formation of compound 234 (eq. 99), we studied the

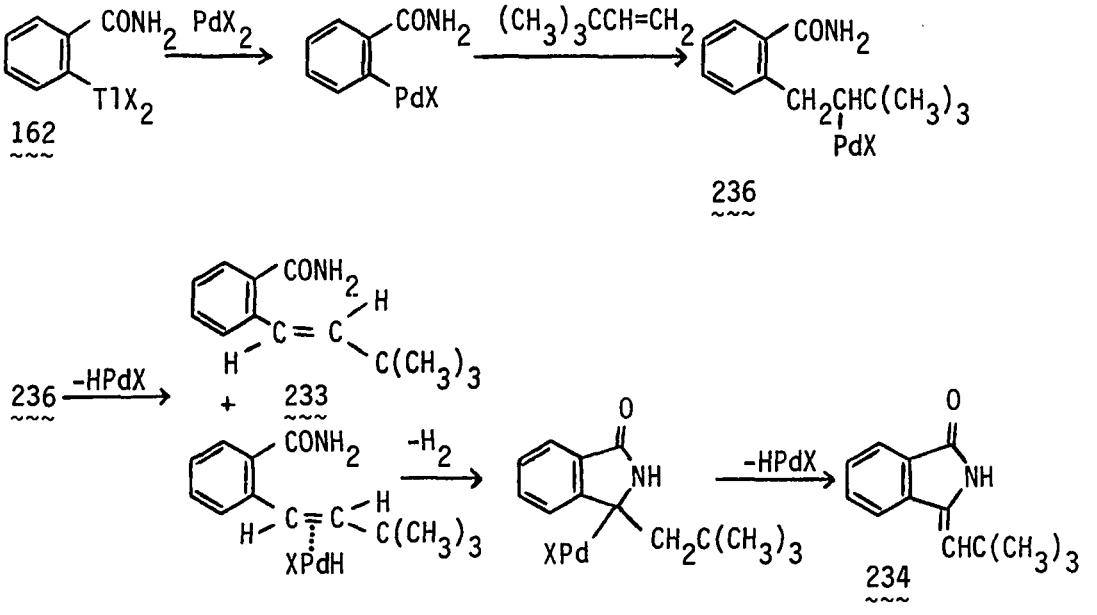


(99)

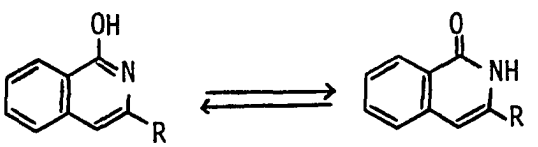
effect of using 2 equiv. $Li_2PdCl_4$ in the olefination reaction and found that it caused a decrease in the formation of both products 233 and

234 (entry 13, Table XXI). The conversion of compound 233 to 234 has been examined by Larock and Lau [164]. When compound 233 was treated with $Li_2PdCl_4$ and $Et_3N$ in acetonitrile and heated under reflux for 6 h, three products 232 (37%), 233 (31%), and 234 (29%), could be isolated. Since the formation of compound 232 is solvent dependent, we have also studied the same conversion in dichloromethane ($Li_2PdCl_4$, 2 equiv. $Et_3N$ or 1.5 equiv. NaH, 50°C 6 h), and found no cyclized product 234 was formed. Thus the formation of compound 234 does not apparently involve compound 233 as the intermediate. A possible mechanism for the formation of compounds 233 and 234 is shown in Scheme XXII.

Scheme XXII. Possible mechanism for the formation of 233 and 234



b. Olefination of compound 162 with other olefins Olefinations of compound 162 with 3-chloro-1-propene, 3-chloro-1-butene, styrene, methyl acrylate, ethylene (excess), vinyl bromide (excess), cis-1,3-pentadiene, 3-methyl-1,2-butadiene, and 1-methyl-1-vinylcyclopropane have been examined. Only the reaction with allylic chlorides gave good results. Several olefins did not give any apparent olefination product. The results are summarized in Table XXII. Isocarbostyrils



247 248

(247), a class of compounds structurally similar to the valuable isoquinoline system (248), which possess marked antidepressant, tranquilizing, analgesic, and sedative activities [172] could be synthesized efficiently by our new approach (entries 1, 2, and 10, Table XXII).

The olefination of compound 162 with ethylene has also been examined in dichloromethane (eq. 100). Unfortunately, both lactones and lactams

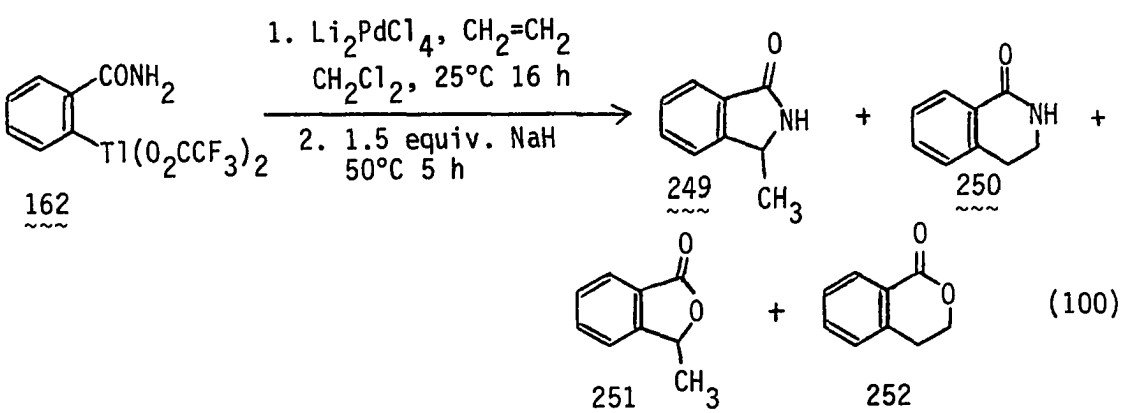
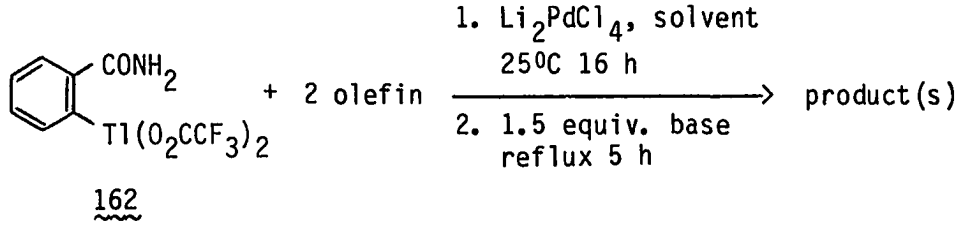
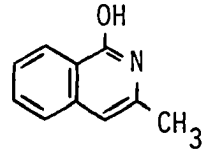
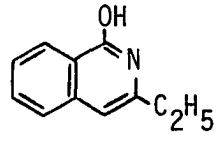
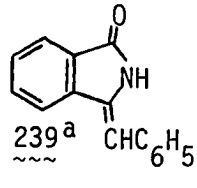
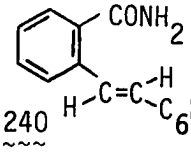


Table XXII. Olefination of compound 162

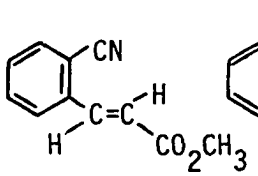
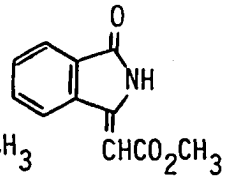
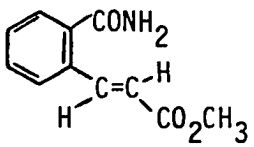
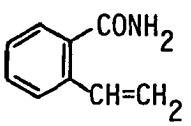
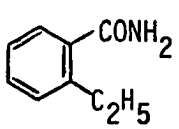
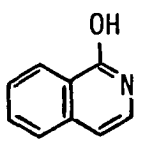
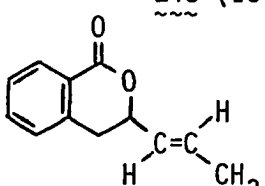



162

| Entry | Olefin | Solvent Added | Base | Product (% isolated yield) |
|---|---|---|---|---|
| 1 | $CH_2$=CH$CH_2Cl$ | $CH_3CN$ | --- |  237 (60) |
| 2 | $CH_2$=CHCH(Cl)$CH_3$ | $CH_3CN$ | --- |  238 (44) |
| 3 | $C_6H_5CH$=$CH_2$ | $CH_2Cl_2$ | NaH |  239[a] (17)  240 (17) |
| 4 | $C_6H_5CH$=$CH_2$ | $CH_3CN$ | NaH | 239 (43) 240 (6) |
| 5 | $C_6H_5CH$=$CH_2$ | $CH_3CN$ | --- | 239 (4) 240 (10) |
| 6 | $CH_2CHCO_2CH_3$ | $CH_2Cl_2$ | NaH | no olefination product |

[a]Single isomer, not a mixture of E,Z isomers.

Table XXII. (continued)

| Entry | Olefin | Solvent | Base Added | Product (% isolated yield) |
|---|---|---|---|---|
| 7 | $CH_2=CHCO_2CH_3$ | $CH_3CN$ | NaH |  241 (11)  242 (25)  243 (10) |
| 8 | $CH_2=CH_2$ | $CH_3CN$ | --- |  244[b]  245[b] |
| 9 | $CH_2=CH_2$ | $CH_3CN$ | NaH | 244[G] 245[C] |
| 10 | $CH_2=CHBr$ | $CH_3CN$ | --- | 244 (23)  246 (15) |
| 11 | cis-1,3-pentadiene | $CH_2Cl_2$ | NaH |  224 (7.5) |

[b]Total yield of 244 + 245 is 37% and the ratio of 244:245 as judged by $^1H$ NMR spectral analysis is 1:1.4.

[c]Total yield of 244 + 245 is 21% and the ratio of 244:245 as judged by $^1H$ NMR spectral analysis is 1:2.

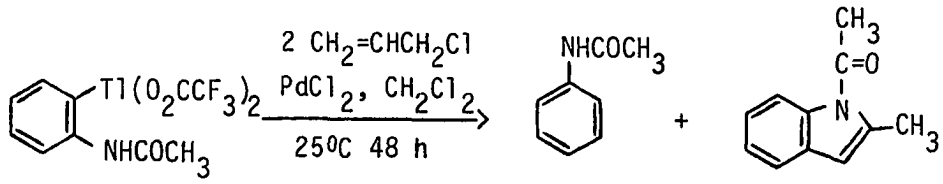
were formed and the ratio of 249:250:251:252 was 1.5:1:1.2:10.4. The possible mechanism for the formation of compounds 249-252 is very similar to that shown in Scheme XVII. The same reaction in acetonitrile gave a very low yield of a mixture of 244 and 245 . The reaction of compound 162 with vinyl bromide in either dichloromethane or acetonitrile in the presence of sodium hydride gave no olefination product at all. The reaction in acetonitrile without added base gave compounds 244, 246 and some unidentified products (entry 10, Table XXII).

The reaction of compound 162 with cis-1,3-pentadiene has also been studied in acetonitrile. Unfortunately, TLC analysis of the reaction mixture (with or without added NaH) showed a smear all the way up the plate and therefore no isolation has been attempted. Finally, the olefination of compound 162 with either 3-methyl-1,2-butadiene or 1-methyl-1-vinylcyclopropane gave no olefination product at all.

5. Vinylation-cyclization of thallated acetanilide (164)

Since we were unable to separate compound 164 from 165, a mixture of 164 and 165 has been used for all of the following studies.

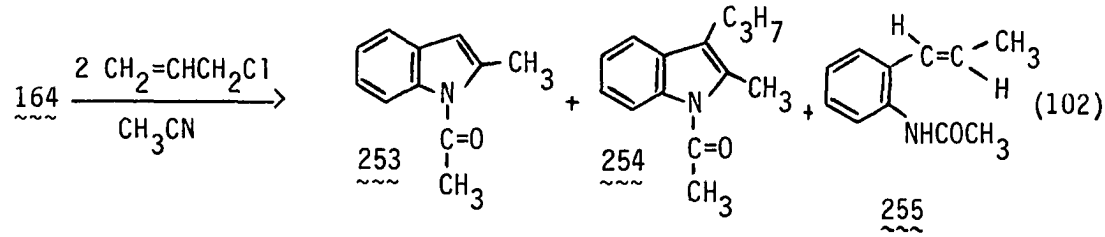
a. Olefination of compound 164 with allylic chlorides The reaction of compound 164 with 3-chloro-1-propene and palladium chloride in dichloromethane gave 10% of acetanilide and 5.8% of indole derivative 253 (eq. 101). The formation of acetanilide in dichloromethane indicates that the thallated acetanilide was probably reduced by HPdCl in some fashion. The same reaction in acetonitrile has also been examined (eq.




(101)

164 10% 253, 5.8%

102). The results are summarized in Table XXIII. We found that both lithium chloride and sodium hydride are needed in order to get the highest yield of indole derivative 253.




(102)

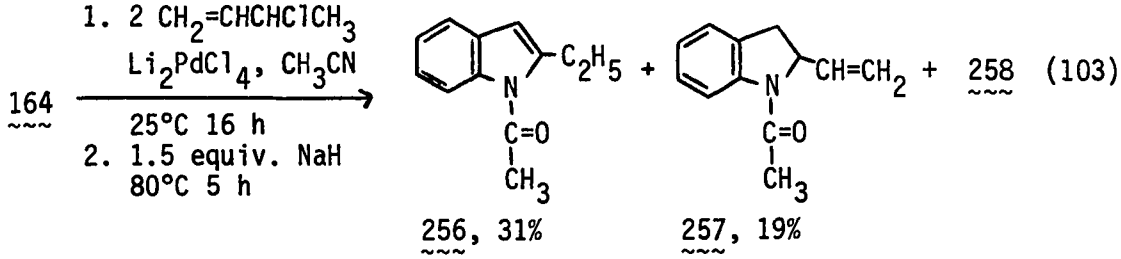
253 254 255

Table XXIII. Reaction of compound 164 with 3-chloro-1-propene

| Reaction Conditions | % Isolated Yield 253 | 254 | 255 |
|---|---|---|---|
| $PdCl_2$, 25°C 33 h | 10 | 0 | < 5%[a] |
| $PdCl_2$, 25°C 16 h, then 80°C 5 h | 0 | 0 | 0 |
| $Li_2PdCl_4$, 25°C 16 h, then 80°C 5 h | 25 | 10 | < 5%[a] |
| $Li_2PdCl_4$, 25°C 16 h, then 2 equiv. $Et_3N$, 80°C 5 h | 32 | 0 | < 5%[a] |
| $Li_2PdCl_4$, 25°C 16 h, then 1.5 equiv. NaH, 80°C 5 h | 45 | 0 | < 5%[a] |
| $Li_2PdCl_4$, 25°C 16 h, then 2 equiv. $Et_3N$, 1.5 equiv. NaH, 80°C, 5 h | 43 | 0 | < 5%[a] |

[a]This compound can be detected in the reaction mixture by NMR analysis but could not be isolated.

The olefination of compound 164 with 3-chloro-1-butene in acetonitrile gave 7 products (eq. 103). Five isomers with a molecular

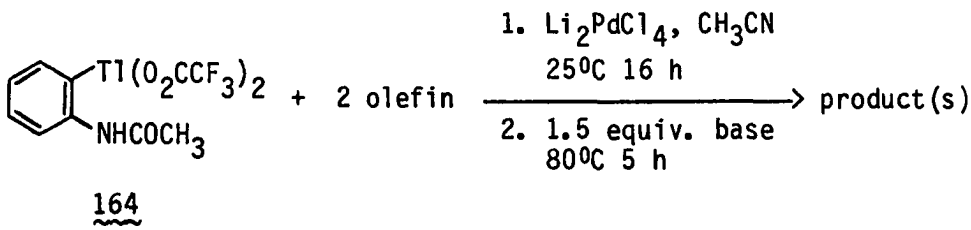



258 (103)

weight of 189 (characterized by GC/MS only) were isolated as a mixture (258) in 14% yield. When changing the base from sodium hydride to triethylamine, the reaction still gave 7 products--256 (26%), 257 (30%), and 258 (30%). The formation of a significant amount of compound 257 suggests that the isomerization of the terminal double bond into the ring is difficult.

b. Olefination of compound 164 with other olefins Olefinations of compound 164 with 3,3-dimethyl-1-butene, methyl acrylate, styrene, ethylene (excess), vinyl bromide, cis-1,3-pentadiene, trans-1,3-pentadiene, 3-methyl-1,2-butadiene, and 1-methyl-1-vinylcyclopropane have been examined. The results are summarized in Table XXIV. For those reactions that gave only uncyclized products, base is not necessary for the reaction. Compound 260 has been cyclized with conc. HCl (eq. 104) [173].

Table XXIV. Olefination of compound 164




164

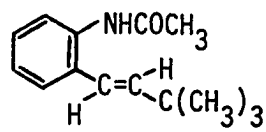
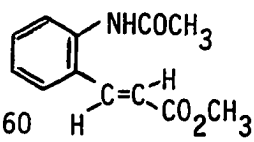
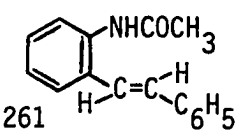
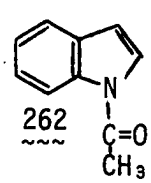
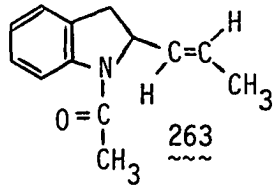
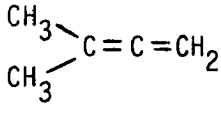
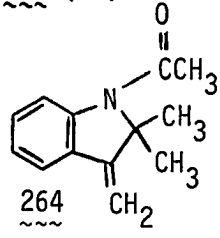
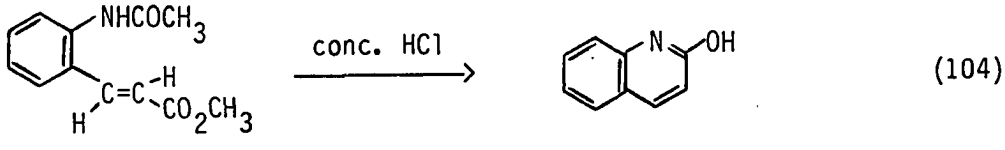
| Entry | Olefin | Base Added | Product (% isolated yield) |
|---|---|---|---|
| 1 | $(CH_3)_3CCH=CH_2$ | NaH |  259 (49) |
| 2 | $(CH_3)_3CCH=CH_2$ | --- | 259 (55) |
| 3 | $CH_2=CHCO_2CH_3$ | NaH |  260 (60) |
| 4 | $CH_2=CHCO_2CH_3$ | --- | 260 (63) |
| 5 | $C_6H_5CH=CH_2$ | NaH |  261 (45) |
| 6 | $C_6H_5CH=CH_2$ | | 261 (60) |
| 7 | $CH_2=CH_2$ | NaH |  262 (13) |

Table XXIV. (continued)

| Entry | Olefin | Base added | Product (% isolated yield) |
|---|---|---|---|
| 8 | $CH_2$=CHBr | NaH | 262 (45) |
| 9 | cis-1,3-pentadiene | NaH |  263 (25) |
| 10 | trans-1,3-pentadiene[a] | NaH | 263 (13) |
| 11 |  | NaH |  264 (20) |

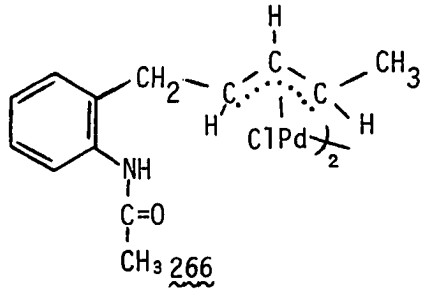
[a]Only 1 equiv. of diene was used.




260 265, 54.5% (104)

For the reaction of compound 164 with cis-1,3-pentadiene, using a large excess (5 equiv.) of diene had no effect on the yield of compound 263 (28% compared to 25%). The olefinic carbon-carbon double bond in compound 263 has the E configuration as determined by its 300 MHz proton NMR spectrum and decoupling experiments. Reaction of compound 164 with trans-1,3-pentadiene gave the same product 263 in 13% yield. The low yield is due to the fact that there was only 1 equiv. of trans-1,3,-

pentadiene available in our laboratory at the time. Since both cis- and trans-1,3-pentadiene gave the same product, we conclude that the intermediate for both reactions must be the more stable syn-π-allylpalladium complex 266.




266

The reaction of compound 164 with 1-methyl-1-vinylcyclopropane gave no olefination product.

## C. Conclusion

p-Tolylacetic acid, N-methylbenzamide, benzamide, and acetanilide were thallated regiospecifically in the ortho position, and the resulting arylthallium compounds were olefinated under mild conditions by stirring with one equivalent of palladium chloride, two equivalents lithium chloride, and two equivalents of olefin in acetonitrile or dichloromethane. For most cases, the cyclization of the vinylated aryl compound is promoted by palladium chloride already present in the reaction mixture.

3-Methyl-N-methylisoquinolone [174], 3-methylisocarbostyril [174], and 2-methylindoles [175] have been prepared recently by the palladium-assisted cyclization of ortho-substituted allylarenes. Unfortunately, these methods require properly substituted aryl halides as starting

materials, which are not always readily available. The halide is subsequently replaced by an allyl group using π-allylnickel halides, compounds very difficult to handle due to their extreme sensitivity to air and moisture. As discussed in this Chapter, N-methylisoquinolones and isocarbostyrils can be prepared efficiently from thallated N-methylbenzamide and benzamide respectfully and N-acetylindoles can be prepared from thallated acetanilide.

This thallation-olefination reaction sequence provides a new, general route to the synthesis of a number of oxygen- and nitrogen-containing heterocycles.

## D. Experimental Section

### 1. Equipment

The infrared spectra were recorded on a Beckman AccuLab 2 infrared spectrophotometer, and the GC/IR spectra were recorded on an IBM IR/98 FT-IR spectrophotometer. $^1$H NMR spectra were recorded on a Varian EM 360A NMR spectrometer and the high resolution $^1$H NMR spectra were recorded on 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. A Varian 3700 gas chromatograph equipped with a 30 m SE-30 capillary column from J. W. Scientific and a Varian CDS-111 chromatography data system was used for gas chromatographic analyses. Silica gel (230-400 mesh) for column chromatography was purchased from MCB Manufacturing Chemists, Inc. Elemental analyses were performed by Galbraith Laboratories, Inc.

## 2. Reagents

All chemicals were used directly as obtained commercially unless otherwise indicated. Acetanilide and anhydrous sodium carbonate were purchased from Fisher; lithium chloride came from Mallinckrodt; 3-chloro-1-propene came from Eastman Kodak; cis-1,3-pentadiene came from Chem Samples Co.; trans-1,3-pentadiene came from Fluka Chemical Co.; and sodium hydride came from J. T. Baker. Ethylene and 1,3-butadiene were purchased from Matheson Gas Products, and thallic oxide came from Asarco (American Smelting and Refining Company). Reagents purchased from Aldrich include p-tolylacetic acid, benzamide, N-methylbenzamide, vinyl bromide, 3,3-dimethyl-1-butene, styrene, methyl acrylate, and 3-chloro-1-butene. Acetonitrile and dichloromethane were distilled from phosphorus pentoxide, and triethylamine was distilled from barium oxide before using. Palladium chloride was generously supplied by Johnson Matthey, Inc., and Engelhard Industries. 3-Methyl-1,2-butadiene and 3-methyl-1-vinylcyclopropane were generously supplied by Dr. Sudarsanan Varaprath.

## 3. Preparation and use of thallium(III) trifluoroacetate

Thallium(III) trifluoroacetate was prepared according to the method of McKillop et al. [159] with only slight modification [176]. Thallium(III) oxide (25 g) was weighed into a 250 ml round bottom flask and trifluoroacetic acid (100 ml) was then added and the mixture was stirred vigorously. A reflux condenser was attached, and water (12 ml) was added through the top of the condenser. The flask was wrapped with aluminum foil and the mixture was refluxed overnight (12-19 h).

Filtration of the reaction mixture while still hot through a coarse sintered-glass Büchner funnel into a weighed 250 ml round bottom flask removed any residual brown or yellow solid. The colorless solution was concentrated as much as possible on a rotary evaporator. Usually, white solid could be observed in the flask at this stage. The last traces of solvent were removed on a vacuum pump. The thallium(III) trifluoroacetate thus produced was a white solid. Yields ranged from 95-99%. The reagent was stored under $N_2$ in a stoppered round bottom flask wrapped in aluminum foil. Exposure to warm, moist air caused the white solid to become brown and sticky.

The reagent was transferred in a glove bag under $N_2$ to a preweighed flask and then dissolved in the appropriate amount of trifluoroacetic acid prior to each experiment.

4. Thallation of arenes

a. Thallation of p-tolylacetic acid To a solution of 19.77 g (37 mmol) of thallium(III) trifluoroacetate in 74 ml of trifluoroacetic acid was added 5.56 g (37 mmol) of p-tolylacetic acid. The mixture was stirred at room temperature, protected from light, for 48 h. The white solid that precipitated from the reaction mixture was collected by filtration, washed with hexanes, and dried under vacuum to afford 13.44 g of compound 158. The filtrate was concentrated to afford further white solid (1.72 g). The total yield of compound 158 is 71%. Anal. Calcd for $C_{13}H_9O_6F_6Tl$: C, 26.94; H, 1.57. Found: C, 27.37; H, 1.63.

b. Thallation of N-methylbenzamide To a solution of 16.0 g (29.4 mmol) of thallium(III) trifluoroacetate in 58 ml of trifluoroacetic acid was added 3.97 g (29.4 mmol) of N-methylbenzamide. The mixture was heated to reflux and kept refluxing for 36 h. The mixture was cooled and the solvent was evaporated to afford 17.1 g of compound 160: yield 100%.

c. Thallation of benzamide To a solution of 13.73 g (25.27 mmol) of thallium(III) trifluoroacetate in 60 ml of trifluoroacetic acid was added 3.06 g of benzamide (25.27 mmol). The reaction mixture was heated to reflux and kept refluxing for 24 h. The mixture was cooled to room temperature and trifluoroacetic acid was removed under reduced pressure. The last trace amount of trifluoroacetic acid was removed by coevaporation with 1,2-dichloroethane twice to afford 14.0 g of compound 160: yield 100%.

d. Thallation of acetanilide To a solution of 15.86 g (29.19 mmol) of thallium(III) trifluoroacetate in 70 ml of trifluoroacetic acid was added 3.95 g (29.19 mmol) of acetanilide. The reaction mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure and the last trace of trifluoroacetic acid was removed by coevaporation twice with 1,2-dichloroethane to afford 11.9 g of a mixture of 164 and 165.

5. Iodination of thallated arenes

All iodination reactions were carried out under conditions identical to those described by Taylor and co-workers [160]. The iodination of thallated p-tolylacetic acid (158) is representative. To a suspension of

0.5796 g (1 mmol) of crude compound 158 in 30 ml of water was added 0.83 g (5 mmol) of potassium iodide. The mixture was heated under reflux for 5 h, and sodium matabisulfite ($Na_2S_2O_5$) (0.1 g, 0.53 mmol) was then added to reduce any iodine which had been formed during the reaction. Heating was continued for another 30 min, and the precipitated thallium(I) iodide filtered off (without prior cooling). The collected inorganic material was thoroughly washed with acetone, and the filtrate and washings were evaporated to afford 0.2484 g of compound 159: yield 90%. GLC analysis of the crude product shows only one peak. The crude product was recrystallized from hexanes to yield 0.232 g (84%) of compound 159: mp 137-139°C; $^1H$ NMR ($CDCl_3$) δ 2.30 (s, 3 H, $CH_3$), 3.80 (s, 2 H, $CH_2$), 7.0-7.35 (m, 2 H, ArH), 7.72 (br s, 1 H, ArH), 11.48 (br s, 1 H, OH); IR (Nujol) 2400-3200 (OH), 1695 (C=O) $cm^{-1}$; mass spectrum, m/z calcd for $C_9H_9IO_2$ 275.96473, obsd 275.96553.

The iodination of compounds 160, 162 and a mixture of 164 and 165 was carried out in identical fashion. Iodination of thallated N-methylbenzamide: yield of compound 161 100%; GLC analysis on a capillary column shows one peak; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.956 (d, J = 4.92 Hz, 3 H, $NCH_3$), 6.179 (br s, 1 H, NH), 7.040-7.097 (m, 1 H, ArH), 7.285-7.364 (m, 2 H, ArH), 7.822 (d, J = 8.09 Hz, ArH); IR ($HCCl_3$) 3440 (NH), 1650 (C=O and amide II) $cm^{-1}$. Iodination of thallated benzamide: yield of compound 163 100%; GLC analysis on a capillary column shows one peak; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.145 (br s, 2 H, $NH_2$), 7.023-7.491 (m, 3 H, ArH), 7.710-7.833 (m, 1 H, ArH); IR ($HCCl_3$) 3400 and 3518 (NH), 1670 (C=O) $cm^{-1}$; GC/MS (relative intensity, assignment) 247 (100, $M^+$), 231 (40.85,

$M^+-NH_2$), 120 (29.18, $M^+-I$). The iodination of thallated acetanilide gave ca. 70% of a mixture of compound 166 and 167 in a ratio of 6:1. For compound 166: GC/MS (relative intensity, assignment) 261 (11.44, $M^+$), 219 (25.55, $M^+-CH_2CO$), 134 (100, $M^+-I$), 92 (7.25, $M^+-CH_2CO-I$). For compound 167: GC/MS (relative intensity, assignment) 345 (100, $M^+$), 218 (54.59, $M^+-I$), 91 (65.48, $M^+-2I$).

6. Olefination of thallated p-tolylacetic acid (158)

The following is the general procedure used for olefination of compound 158. To a solution of 0.2898 g (0.5 mmol) of compound 158, 0.0887 g (0.5 mmol) of palladium chloride, and 0.0425 g (1 mmol) of lithium chloride in 6 ml of dry solvent was added the appropriate olefin (1 mmol). The mixture was stirred at room temperature for 16-18 h. Triethylamine (0.101 g, 1 mmol) and sodium carbonate (0.106 g, 1 mmol) were added and the mixture was heated under reflux for 5 h. After being cooled to room temperature, the reaction mixture was filtered through Celite. The Celite pad was washed with 100 ml of ether. The filtrate and washing were combined and washed twice with saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$), and concentrated. The reaction products were isolated by flash chromatography on a silica gel (230-400 mesh) column.

Olefination of 158 with 3,3-dimethyl-1-butene in dichloromethane gave products 169 and 170. For compound 169: yield 77%; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.075 (s, 9 H, $CH_3$), 1.717 (dd, J = 15.03 Hz, J = 2.67 Hz, 1 H, $CH_2$-t-Bu), 1.837 (dd, J = 15.03 Hz, J = 10.32 Hz, $CH_2$-t-Bu), 2.332 (s,

3 H, $ArCH_3$), 3.600 (d, J = 18.80 Hz, 1 H, $ArCH_2$), 3.678 (d, J = 18.80 Hz, 1 H, $ArCH_2$), 5.423 (dd, J = 10.32 Hz, J = 2.67 Hz, 1 H, CH), 6.976-7.082 (m, 3 H, ArH); IR ($HCCl_3$) 1739 (C=O) $cm^{-1}$. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.41; H, 8.80. For compound 170: yield 5%; $^1H$ NMR ($CDCl_3$) δ 1.08 (s, 9 H, $CH_3$), 2.30 (s, 3 H, $ArCH_3$), 3.65 (s, 2 H, $ArCH_2$), 6.0 (d, J = 16 Hz, 1 H, ArCH=C), 6.47 (d, J = 16 Hz, 1 H, C=CH-t-Bu), 7.01 (d, J = 2 Hz, 2 H, ArH), 7.21 (d, J = 2 Hz, 1 H, ArH), 9.15 (br s, 1 H, OH); IR ($HCCl_3$) 2400-3200 (OH), 1705 (C=O), 1610 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{15}H_{20}O_2$ 232.14633, obsd 232.14704.

The olefination of compound 158 with 3-chloro-1-propene in acetonitrile (without lithium chloride added) gave compounds 175, 176, and 177 the ratio of 2.5:3.4:1. The reaction in dichloromethane (without lithium chloride added) gave compounds 178, 176, and 175 in the ratio of 1:5.5:20. The same reaction in dichloromethane (with lithium chloride added) gave compounds 178, 176, 175, and 179 in the ratio of 1:4.1:2.1:4.4. For compound 175: GC/MS, m/z (relative intensity, assignment) 188 (57.73, $M^+$), 173 (2.16, $M^+-CH_3$), 161 (13.96, $M^+-CH=CH_2$), 160 (100, $M^+-CH=CH_2-H^+$), 144 (49.57, $M^+-CO_2$), 133 (19.14, $M^+-OCHCH=CH_2$ + H), 129 (99.48, $M^+-CH_2COO$). For compound 176: GC/MS, m/z (relative intensity, assignment) 230 (13.91, $M^+$), 189 (17.49, $M^+-CH_2CH=CH_2$), 161 (15.21, $M^+-CH_2CH=CH_2$ - $CH=CH_2$ - H), 143 (100, $M^+-CO_2CH_2CH=CH_2$ - 2H). For compound 177: GC/MS, m/z (relative intensity, assignment) 246 (21.93, $M^+$), 217 (19.71, $M^+-CHO$), 205 (18.50, $M^+-CH_2CH=CH_2$), 189 (65.72, $M^+-OCH_2CH=CH_2$), 188 (100, $M^+-OCH_2CH=CH_2$ - H), 161 (40.60, $M^+-CO_2CH_2CH=CH_2$), 160 (96.22, $M^+-CHO$ - $OCH_2CH=CH_2$). For compound 178: GC/MS, m/z (relative

intensity, assignment) 226 (2.58, $M^+$+2), 224 (8.10, $M^+$), 189 (39.14, $M^+$-Cl), 167 (0.39, $M^+$-$OCH_2CH{=}CH_2$), 148 (11.19, $M^+$-Cl-$CH_2CH{=}CH_2$), 141 (31.99, $M^+$+2-$CO_2CH_2CH{=}CH_2$), 139 (100, $M^+$-$CO_2CH_2CH{=}CH_2$). For compound 179: GC/MS, m/z (relative intensity, assignment) 226 (5.39, $M^+$+2), 224 (16.73, $M^+$), 182 (0.64, $M^+$+2-$CO_2$), 180 (1.93, $M^+$-$CO_2$), 175 (0.36, $M^+$-$CH_2Cl$), 167 (1.34, $M^+$+2-$CH_2CO_2$-H), 165 (4.12, $M^+$-$CH_2CO_2$-H), 145 (25.50, $M^+$-$CO_2$-Cl), 132 (3.44, $M^+$-$OCHCH_2CH_2CH_2Cl$), 131 (33.74, $M^+$-$OCHCH_2CH_2CH_2Cl$ - H), 118 (100, $M^+$-$CO_2$ - $CH_2CH_2Cl$ + H).

The olefination of compound 158 with ethylene gave one isolable product 180: yield 28%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.730 (d, J = 6.65 Hz, 3 H, $CH_3$), 2.373 (s, 3 H, $ArCH_3$), 3.640 (d, J = 18.30 Hz, 1 H, $ArCH_2$), 3.726 (d, J = 18.30 Hz, 1 H, $ArCH_2$), 5.441 (q, J = 6.65 Hz, 1 H, CH), 7.058-7.150 (m, 3 H, ArH); IR ($HCCl_3$) 1740 (C=O) $cm^{-1}$; mass spectrum, m/z calcd for $C_{11}H_{12}O_2$ 176.08373, obsd 176.08308.

The olefination of compound 158 with styrene gave products 181 and 182. For compound 181: yield 37%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.266 (s, 3 H, $CH_3$), 3.263 (d, J = 18 Hz, 1 H, $PhCH_2$), 3.451 (dd, J = 18 Hz, J = 11.62 Hz, 1 H, $PhCH_2$), 3.606 (d, J = 15.11 Hz, 1 H, $CH_2C{=}O$), 4.482 (d, J = 15.11 Hz, 1 H, $CH_2C{=}O$), 5.880 (d, J = 11.62 Hz, 1 H, ArCH), 6.858-7.466 (m, 8 H, ArH); IR($HCCl_3$) 1740 (C=O) $cm^{-1}$; mass spectrum, m/z calcd for $C_{17}H_{16}O_2$ 252.11503, obsd 252.11565. For compound 182: yield ca. 22% (it still contains small amounts of impurities); $^1H$ NMR ($CDCl_3$) δ 2.32 (s, 3 H, $CH_3$), 3.73 (s, 2 H, $ArCH_2$), 6.6-7.7 (m, 8 H, ArH), 10.0 (br s, 1 H, OH); IR ($HCCl_3$) 2800-3400 (OH), 1700 (C=O) $cm^{-1}$.

The olefination of compound 158 with cis-1,3-pentadiene gave a mixture of compounds 183 and 184 in 37% yield. For compound 183: GC/MS, m/z (relative intensity, assignment) 216 (3.52, $M^+$), 174 (1.57, $M^+$-$CH{=}CHCH_3$-H), 172 (0.42, $M^+$-$CO_2$), 157 (5.61, $M^+$-$CH_2CO_2$-H), 146 (100, $M^+$-$OCHCH{=}CHCH_3$), 118 (72.71, $M^+$-$CO_2CHCH{=}CHCH_3$). For compound 184: GC/MS, m/z (relative intensity, assignment) 216 (3.47, $M^+$), 174 (0.87, $M^+$-$CH{=}CHCH_3$-H), 172 (0.69, $M^+$-$CO_2$), 157 (3.76, $M^+$-$CH_2CO_2$-H), 146 (100, $M^+$-$OCHCH{=}CHCH_3$), 118 (77.49, $M^+$-$CO_2CHCH{=}CHCH_3$).

The olefination of compound 158 with 1,3-butadiene gave only one product 185: yield 69%; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.288 (s, 3 H, $CH_3$), 3.132-3.297 (m, 2 H, $ArCH_2$), 3.603 (d, J = 15.1 Hz, 1 H, $CH_2C{=}O$), 4.392 (d, J = 15.1 Hz, 1 H, $CH_2C{=}O$), 5.30 (d, J = 10.52 Hz, 1 H, $C{=}CH_2$), 5.335-5.369 (m, 1 H, CH-O-), 5.465 (dd, J = 17.16 Hz, J = 0.83 Hz, 1 H, $C{=}CH_2$), 5.934-6.046 (m, 1 H, $HC{=}CH_2$), 6.912-7.010 (m, 3 H, ArH); IR ($HCCl_3$) 1740 (C=O), 1616 (C=C), 1276 (C-O) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{14}O_2$ 202.09938, obsd 202.09970.

The olefination of compound 158 with methyl acrylate gave two products 186 and 187. For compound 186: yield 3.5%; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.365 (s, 3 H, $CH_3$), 2.949-3.103 (m, 2 H, $CH_2C{=}O$), 3.690 (s, 1 H, $ArCH_2$), 3.694 (s, 1 H, $ArCH_2$), 3.762 (s, 3 H, $OCH_3$), 5.813 (dd, J = 7.44 Hz, J = 6.00 Hz, 1 H, CH-O-), 7.011-7.172 (m, 3 H, ArH); IR ($HCCl_3$) 1742 (C=O, lactone and ester) $cm^{-1}$. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.64; H, 6.02. Found: C, 66.61; H, 6.18. For compound 187: yield 81%; $^1$H NMR ($CDCl_3$) $\delta$ 2.33 (s, 3 H, $CH_3$), 3.73 (s, 2 H, $CH_2$), 3.80 (s, 3 H, $OCH_3$), 6.38 (d, J = 16 Hz, 1 H, C=CH), 7.18 (S, 2 H, ArH), 7.42 (S, 1 H, ArH),

7.96 (d, J = 16 Hz, 1 H, C=CH); IR ($CCl_4$) 3200-3600 (OH), 1750 (C=O), 1630 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{14}O_4$ 234.08921, obsd 234.08979.

The vinylation of compound 158 with excess vinyl bromide gave compounds 195-201. The ratio of 195:196:197:198:199:200:201 is 1:3.1:2.2:7.7:1.1:2:6.1 as judged by GLC peak areas. For compound 195: GC/MS, m/z (relative intensity, assignment) 176 (34.08, $M^+$), 133 (61.16, $M^+$-$OCH=CH_2$), 105 (100, $M^+$-$CO_2CH=CH_2$). For compound 196: GC/MS, m/s (relative intensity, assignment) 212 (9.51, $M^+$+2), 210 (22.77, $M^+$), 169 (23.24, $M^+$+2-$OCH=CH_2$), 167 (73.65, $M^+$-$OCH=CH_2$), 141 (29.90, $M^+$+2-$CO_2CH=CH_2$), 139 (100, $M^+$-$CO_2CH=CH_2$). For compound 197: GC/MS, m/z (relative intensity, assignment) 202 (51.05, $M^+$), 174 (1.06, $M^+$-$H_2C=CH_2$), 159 (100, $M^+$-$OCH=CH_2$), 131 (83.68, $M^+$-$CO_2CH=CH_2$). For compound 198: GC/MS, m/z (relative intensity, assignment) 256 (11.38, $M^+$+2), 254 (11.93, $M^+$), 213 (58.62, $M^+$+2-$OCH=CH_2$), 211 (55.53, $M^+$-$OCH=CH_2$), 185 (100 $M^+$+2-$CO_2CH=CH_2$), 183 (94.34, $M^+$-$CO_2CH=CH_2$), 175 (66.29, $M^+$-Br). For compound 199: GC/MS, m/z (relative intensity, assignment) 238 (9.73, $M^+$+2), 236 (20.98, $M^+$), 195 (16.35, $M^+$+2-$OCH=CH_2$), 193 (49.83, $M^+$-$OCH=CH_2$), 167 (31.38, $M^+$+2-$CO_2CH=CH_2$), 165 (100, $M^+$-$CO_2CH=CH_2$), 129 (19.31, $M^+$-$CO_2CH=CH_2$-HCl). For compound 200: GC/MS, m/z (relative intensity, assignment) 218 (1.64, $M^+$), 91 (1.59, $M^+$-$CH=CH_2$), 190 (15.30, $M^+$-$H_2C=CH_2$), 175 (55.22, $M^+$-$OCH=CH_2$ or $M^+$-$CH_2CHO$), 174 (46.62, $M^+$-$OCH=CH_2$ - H), 147 (100, $M^+$-$CO_2CH=CH_2$), 119 (76.60, $M^+$-$CO_2CH=CH_2$-CHO + 1); GC/IR 1800 (C=O of ester), 1745 (C=O of aldehyde), 1645 (C=C) $cm^{-1}$. For compound 201 (either 201a or 201b): GC/MS, m/z (relative intensity,

assignment) 174 (100, $M^+$), 161 (33.16, $M^+$-CH), 146 (42.15, $M^+$-CO), 133 (12.34, $M^+$-$CH_2CO$ + 1 or $M^+$-OCH=CH + 1 or $M^+$-$OC=CH_2$ + 1); GC/IR 1800 (C=O), 1641 (C=C) $cm^{-1}$.

7. Olefination of thallated N-methylbenzamide (160)

The following is the general procedure used for olefination of compound 160. To a solution of 0.2823 g (0.5 mmol) of compound 160, 0.0887 g (0.5 mmol) of palladium chloride, and 0.0425 g (1 mmol) of lithium chloride is 6 ml of dry acetonitrile was added the appropriate olefin (1 mmol; except for ethylene and vinyl bromide, they were used in large excess). The mixture was stirred at room temperature for 16-18 h and then heated under reflux for 5 h. After being cooled to room temperature, the reaction mixture was filtered through Celite. The Celite pad was washed with 100 ml of ether. The filtrate and washing were combined and washed twice with saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$), and concentrated. The reaction products were isolated by flash chromatography on a silica gel (230-400 mesh) column.

The olefination of compound 160 with 3,3-dimethyl-1-butene in acetonitrile gave two products 202 and 203. For compound 202: yield 5%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.43 (s, 9 H, $CH_3$), 3.23 (s, 3 H, $NCH_3$), 5.56 (s, 1 H, C=CH), 7.33-8.07 (m, 4 H, ArH); IR ($HCCl_3$) 1687 (C=O), 1625 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{14}H_{17}NO$ 215.13102, obsd 215.13070. For compound 203: yield 19%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.13 (s, 9 H, $CH_3$), 2.98 (d, J = 5.2 Hz, 3 H, $NCH_3$), 6.13 (d, J = 16 Hz, 1 H, ArCH=C), 6.57 (d, J = 16

Hz, 1 H, ArC=CH), 7.12-7.65 (m, 4 H, ArH); IR ($HCCl_3$) 3458 (NH), 1659 (C=O), 1602 (C=C), 1520 (NH) $cm^{-1}$; mass spectrum, m/z calcd for $C_{14}H_{19}NO$ 217.14667, obsd 217. 14693.

The olefination of compound 160 with 3,3-dimethyl-1-butene in dichloromethane (no lithium chloride was used) gave products 204 and 205 in the ratio of 3.7:1. For compound 204: GC/MS, m/z (relative intensity, assignment) 204 (11.34, $M^+$), 189 (1.36, $M^+-CH_3$), 147 (100, $M^+$-t-Bu), 119 (54.64, $M^+$-CO-t-Bu). For compound 205: GC/MS, m/z (relative intensity, assignment) 204 (15.62, $M^+$), 189 (1.19, $M^+-CH_3$), 148 (29.57, $M^+$-t-BuH), 133 (100, $M^+-CH_2$-t-Bu), 120 (3.91, $M^+-CHCH_2$-t-Bu), 105 (70.43, $M^+$-CO-$CH_2$-t-Bu).

The vinylation of compound 160 with 3-chloro-1-propene gave only one isolable product 208: yield 61%; $^1H$ NMR ($CDCl_3$) $\delta$ 2.37 (s, 3 H, $CH_3$), 3.55 (s, 3 H, $NCH_3$), 6.30 (s, 1 H, C=CH), 7.18-7.74 (m, 3 H, ArH), 8.24-8.47 (m, 1 H, ArH); IR ($HCCl_3$) 1650 (C=O), 1620 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{11}H_{11}NO$ 173.08407, obsd 173.08366.

The vinylation of compound 160 with 3-chloro-1-butene gave two products 209 and 210 in the ratio 96:4. For compound 209: $^1H$ NMR ($CDCl_3$) $\delta$ 1.30 (t, J = 7.5 Hz, 3 H, $CH_3$), 2.68 (q, J = 7.5 Hz, 2 H, $CH_2$), 3.60 (s, 3 H, $NCH_3$), 6.35 (s, 1 H, C=CH), 7.17-7.97 (m, 3 H, ArH), 8.28-8.57 (m, 1 H, ArH); IR ($HCCl_3$) 1635 (C=O), 1610 (C=C) $cm^{-1}$; GC/MS, m/z (relative intensity, assignment) 187 (100, $M^+$), 172 (14.88, $M^+-CH_3$), 142 (22.93, $M^+-C_2H_5-CH_4$); mass spectrum, m/z calcd for $C_{12}H_{13}NO$ 187.9972, obsd 187.09915. For compound 210: GC/MS, m/z (relative intensity,

assignment) 187 (66.51, $M^+$), 172 (62.22, $M^+-CH_3$), 146 (100, $M^+-CH{=}CHCH_3$).

The reaction of compound 160 and cis-1,3-pentadiene ($Li_2PdCl_4$, RT for 16 h and then 80°C for 5 h) gave products 211, 212, and 213. For compound 211: yield 12%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.945 (dd, J = 5.45 Hz, J = 0.9 Hz, 3 H, $CH_3$), 3.607 (s, 3 H, $NCH_3$), 6.222-6.294 (m, 1 H, C=CHMe), 6.369-6.551 (m, 1 H, HC=CMe), 6.551 (s, 1 H, ArCH), 7.389-7.612 (m, 3 H, ArH), 8.376 (d, J = 7.95 Hz, 1 H, ArH); IR ($HCCl_3$) 1631 (C=O), 1608 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{13}NO$ 199.09972, obsd 199.09899. For compound 212: yield 15%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.607 (dd, J = 6.24 Hz, J = 1.04 Hz, 3 H, $CH_3$), 2.789 (dd, J = 15.67 Hz, J = 2.82 Hz, 1 H, $ArCH_2$), 3.083 (s, 3 H, $NCH_3$), 3.388 (dd, J = 15.67 Hz, J = 6.24 Hz), 4.008-4.018 (m, 1 H, NCH), 5.297-5.378 (m, 1 H, HC=CMe), 5.543-5.614 (m, 1 H, MeCH=C), 7.125 (d, J = 7.31 Hz, 1 H, ArH), 7.291-7.424 (m, 2 H, ArH), 8.059 (dd, J = 7.55 Hz, J = 1.22 Hz, 1 H, ArH); IR ($HCCl_3$) 1630 (C=O), 1600 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{15}NO$ 201.11537, obsd 201.11458. For compound 213: yield 35%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.818 (dd, J = 6.81 Hz, J = 1.51 Hz, 3 H, $CH_3$), 2.969 (d, J = 4.89 Hz, 3 H, $NCH_3$), 5.815-5.911 (m, 2 H, NH + MeHC=C), 6.190-6.272 (m, 1 H, MeC=CH), 6.690-6.835 (m, 2 H, ArCH=CH), 7.169-7.589 (m, 4 H, ArH); IR ($HCCl_3$) 3450 (NH), 1654 (C=O) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{15}NO$ 201.11537, obsd 201.11491.

The reaction of 160 with cis-1,3-pentadiene and lithium tetrachloropalladate in acetonitrile (25°C, 48 h) gave one product 224: yield 10%; $^1H$ NMR ($CDCl_3$) δ 1.75 (d, J = 5 Hz, 3 H, $CH_3$), 3.03 (d, J =

6.2 Hz, 2 H, $ArCH_2$), 4.80-5.30 (m, 1 H, OCH), 5.40-6.30 (m, 2 H, HC=CH), 7.10-7.78 (m, 3 H, ArH), 7.97-8.33 (m, 1 H, ArH); IR ($CCl_4$) 1725 (C=O), 1610 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{12}H_{12}O_2$ 188.08373, obsd 188.08415.

The reaction of compound 160 and methyl acrylate (with 1.5 equiv. of NaH added) gave products 214a and 214b in the ratio of 1:3.8. For the mixture of 214a and 214b: yield 52%; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 3.275 (s, 3 H, $NCH_3$ of 214b), 3.584 (s, 3 H, $NCH_3$ of 214a), 3.802 (s, 3 H, $OCH_3$ of 214a), 3.831 (s, 3 H, $OCH_3$ of 214b) 5.704 (s, 1 H, C=CH of 214b), 5.877 (s, 1 H, C=CH of 214a), 7.574-7.661 (m, 2 H, ArH), 7.849 (d, J = 7.39, 1 H, ArH), 9.045 (d, J = 7.76 Hz, 1 H, ArH); IR ($HCCl_3$) 1704 (C=O of ester), 1620 (C=O of amide), 1582 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{12}H_{11}NO_3$ 217.07390, obsd 217.07418.

Reaction of compound 160 and styrene gave both cyclized (215) and uncyclized (216) products. For compound 215: yield 37%; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 3.417 (s, 3 H, $NCH_3$), 6.452 (s, 1 H, C=CH), 7.380-7.624 (m, 8 H, ArH), 8.442 (d, J = 7.85 Hz, 1 H, ArH); IR ($HCCl_3$) 1632 (C=O), 1610 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{16}H_{13}NO$ 235.09972, obsd 235.10022. For compound 216: yield 28%; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.976 (d, J = 4.89 Hz, 3 H, $NCH_3$), 5.952 (br s, 1 H, NH), 7.033 (d, J = 16.26 Hz, 1 H, C=CH), 7.230-7.682 (m, 10 H, C=CH + ArH); IR ($HCCl_3$) 3442 (NH), 1650 (C=O), 1591 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{16}H_{15}NO$ 237.11537, obsd 237.11543.

The reaction of compound 160 with 3-methyl-1,2-butadiene gave one olefination product 217: yield 13%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.90 (s, 6 H, $CH_3$),

2.94 (d, J = 5 Hz, $NCH_3$), 3.93 (s, 2 H, $ArCH_2$), 6.0 (br s, 1 H, NH), 7.10-7.85 (m, 4 H, ArH); IR ($HCCl_3$) 3450 (NH), 1650 (C=O and C=C) $cm^{-1}$; MS (18 ev), m/z (relative intensity, assignment) 237 (13.1, $M^+$), 222 (11.8, $M^+-CH_3$), 202 (100, $M^+-Cl$), 186 (98.3; $M^+-Cl-CH_3-H$); mass spectrum ($M^+-Cl$), m/z calcd for $C_{13}H_{16}NO$ 202.12320, obsd 202.12275.

The vinylation of compound 160 with ethylene gave 4 products: 218 (39%), 219, 220, and 221 (total yield of 219 + 220 + 221 is ca. 20%). For compound 218: $^1H$ NMR ($CDCl_3$) δ 3.60 (s, 3 H, $NCH_3$), 6.47 (d, J = 7 Hz, 1 H, C=CHAr), 7.08 (d, J = 7 Hz, 1 H, HC=CAr), 7.39-7.86 (m, 3 H, ArH), 8.32-8.63 (m, 1 H, ArH); IR ($HCCl_3$) 1640 (C=O), 1620 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{10}H_9NO$ 159.06842, obsd 159.06816. For compound 219: $^1H$ NMR ($CDCl_3$, 300 MHz, identified from the spectrum of the mixture) δ 3.283 (s, 3 H, $NCH_3$), 4.853 (d, J = 2.24 Hz, 1 H, $C=CH_2$), 5.183 (d, J = 2.24 Hz, 1 H, $C=CH_2$), 7.427-7.859 (m, 4 H, ArH). For compound 220: $^1H$ NMR ($CDCl_3$, 300 MHz, identified from the spectrum of the mixture) δ 1.644 (d, J = 6.70 Hz, 3 H, $CH_3$), 3.184 (s, 3 H, $NCH_3$), 5.575 (q, J = 6.70 Hz, 1 H, CH), 7.427-7.859 (m, 4 H, ArH); GC/MS, m/z (relative intensity, assignment) 161 (100, $M^+$), 132 (20.03, $M^+-NCH_3$), 117 (29.97, $M^+-NCH_3-CH_3$), 104 (61.75, $M^+-CONCH_3$), 76 (57.70, $M^+-CONCH_3CHCH_3$). For compound 221: 148 (18.14, $M^+$), 133 (59.42, $M^+-CH_3$), 105 (100, $M^+-CO_2$ + 1 or $M^+-OCHCH_3$ + 1).

The reaction of compound 160 and 1-methyl-1-vinylcyclopropane gave one olefination product 222: yield 8.4%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.480 (s, 3 H, $CH_3$), 1.528 (d, J = 6.68 Hz, 3 H, $CH_3$), 2.929 (dd, J = 15.97 Hz, J = 3.46 Hz, 1 H, $ArCH_2$), 3.050 (s, 3 H, $NCH_3$), 3.316 (dd, J = 15.97 Hz,

J = 6.95 Hz, 1 H, $ArCH_2$), 4.003-4.035 (m, 1 H, N-CH), 5.225-5.272 (m, 1 H, C=CH), 7.082 (d, J = 7.37 Hz, 1 H, ArH), 7.268-7.403 (m, 2 H, ArH), 8.059 (dd, J = 7.44 Hz, J = 1.09 Hz, 1 H, ArH); IR ($HCCl_3$) 3020 (C=C-H), 1636 (C=O), 1605 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{14}H_{17}NO$ 215.13102, obsd 215.13025.

8. Olefination of thallated benzamide (162)

The following is the general procedure used for olefination of compound 162. To a solution of 0.2753 g (0.5 mmol) of compound 162, 0.0887 g (0.5 mmol) of palladium chloride, and 0.0425 g (1 mmol) of lithium chloride in 6 ml of the appropriate dry solvent (acetonitrile or dichloromethane) was added the appropriate olefin (1 mmol). The mixture was stirred at room temperature for 16-18 h. Base (1.5 equiv. NaH or 2 equiv. $Et_3N$) was added (if base was used in the reaction) and the reaction mixture was heated under reflux for 5 h. After being cooled to room temperature, the reaction mixture was filtered through Celite. The Celite pad was washed with 100 ml of ether. The filtrate and washing were combined and washed twice with saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$), and concentrated. The reaction products were isolated by flash chromatography on silica gel (230-400 mesh) column.

The olefination of compound 162 with 3,3-dimethyl-1-butene in acetonitrile gave two products 232 and 233. For compound 232: yield 8%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.18 (s, 9 H, $CH_3$), 6.50 (d, J = 16. Hz, 1 H, ArCH=C), 6.78 (d, J = 16 Hz, 1 H, ArC=CH), 7.13-7.87 (m, 4 H, ArH); IR ($HCCl_3$)

2220 (C≡N), 1640 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{15}N$ 185.12045, obsd 185.12103. For compound 233: yield 44%; $^1H$ NMR ($CDCl_3$) δ 1.13 (s, 9 H, $CH_3$), 5.50-7.0 (br s, 2 H, $NH_2$), 6.20 (d, J = 16 Hz, 1 H, ArCH=C), 6.80 (d, J = 16 Hz, ArC=CH), 7.05-7.90 (m, 4 H, ArH); IR ($HCCl_3$) 3537 and 3420 (NH), 3020 (olefinic C-H), 1670 (C=O), 1600 (NH, amide II), 1585 (C=C) $cm^{-1}$. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.71; H, 8.41. The olefination of compound 162 with $Li_2PdCl_4$ and 3,3-dimethyl-1-butene in dichloromethane at room temperature for 48 h gave products 235, 233, and 234. For compound 235 (still contains small amounts of impurities): yield ca. 17%; GC/MS, m/z (relative intensity, assignment) 203 (4.44, $M^+$), 188 (1.39, $M^+-CH_3$), 146 (100, $M^+$-t-Bu), 118 (9.72, $M^+$-CO-t-Bu); GC/IR 1660.6 (C=O) $cm^{-1}$. For compound 234: yield 19%; $^1H$ NMR ($CDCl_3$) δ 1.32 (s, 9 H, $CH_3$), 5.61 (s, 1 H, C=CH), 7.35-8.31 (m, 5 H, NH + ArH); IR ($HCCl_3$) 3464 (NH), 1670 (C=O), 1628 (NH, amide II; C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{15}NO$ 201.11537, obsd 201.11568. For compound 233: yield 28%.

The reaction of compound 162 with $Li_2PdCl_4$ and 3-chloro-1-propene in acetonitrile gave one product 237: yield 60%; $^1H$ NMR ($CDCl_3$) δ 2.45 (s, 3 H, $CH_3$), 6.32 (s, 1 H, CH), 7.23-7.83 (m, 3 H, ArH), 8.40 (d, J = 8 Hz, 1 H, ArH), 11.55 (br s, 1 H, OH); IR ($HCCl_3$) 3392 (OH), 3175 (olefinic C-H), 1650 and 1640 (C=N and C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{10}H_{10}NO$ 159.06842, obsd 159.06898. Reaction of compound 162 with $Li_2PdCl_4$ and 3-chloro-1-butene in acetonitrile gave compound 238: yield 44%; $^1H$ NMR ($CDCl_3$) δ 1.35 (t, J= 7 Hz, 3 H, $CH_3$), 2.72 (q, J = 7 Hz, 2 H, $CH_2$), 6.30 (s, 1 H, CH), 7.26-7.80 (m, 3 H, ArH), 8.24-8.57 (m, 1 H,

ArH), 11.44 (br s, 1 H, OH); IR ($HCCl_3$) 3339 (OH), 3159 (olefinic C-H), 1650 and 1640 (C=N and C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{11}H_{11}NO$ 173.08407, obsd 173.08442.

The reaction of compound 162 with styrene in acetonitrile gave products 239 and 240. For compound 239: yield 43%; $^1H$ NMR ($CDCl_3$) $\delta$ 6.54 (s, 1 H, C=CH), 7.0-8.50 (m, 10 H, NH + ArH); IR ($HCCl_3$) 3460 (NH), 1710 (C=O) $cm^{-1}$; mass spectrum, m/z calcd for $C_{15}H_{11}NO$ 221.08407, obsd 221.08430. For compound 240: yield 6%; $^1H$ NMR ($CDCl_3$) $\delta$ 7.00-7.85 (m, $NH_2$ + ArH + HC=CH); IR ($HCCl_3$) 3360-3480 (NH), 1700 (C=O), 1660 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{15}H_{13}NO$ 223.09972, obsd 223.09952.

The reaction of compound 162 with methyl acrylate in acetonitrile gave products 241, 242, and 243. For compound 241: yield 11%; $^1H$ NMR ($CDCl_3$) $\delta$ 3.83 (s, 3 H, $OCH_3$), 6.64 (d, J = 16 Hz, 1 H, ArCH=C), 7.36-8.01 (m, 4 H, ArH), 8.03 (d, J = 16 Hz, 1 H, ArC=CH); IR ($HCCl_3$) 2220 (C≡N), 1711 (C=O), 1640 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{11}H_9NO_2$ 187.06333, obsd 187.06272. For compound 242: yield 25%; $^1H$ NMR ($CDCl_3$) $\delta$ 3.85 (s, 3 H, $OCH_3$), 5.80 (s, 1 H, C=CH), 7.44-8.05 (m, 4 H, ArH), 9.35-10.0 (br s, 1 H, NH); IR ($HCCl_3$) 3400 (NH), 1720 (C=O of ester), 1685 (C=O of amide), 1640 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{11}H_9NO_3$ 203.05825, obsd 203.05802. For compound 243: yield 10%; $^1H$ NMR (acetone-$d_6$) $\delta$ 3.75 (s, 3 H, $OCH_3$), 6.47 (d, J = 16 Hz, 1 H, ArCH=C), 7.32-8.00 (m, 6 H, $NH_2$ + ArH), 8.22 (d, J = 16 Hz, 1 H, ArC=CH); IR ($HCCl_3$) 3510 and 3380 (NH), 1700 (C=O of ester), 1670 (C=O of amide), 1630 (C=C), 1574 (NH, amide) II $cm^{-1}$; mass spectrum, m/z calcd for $C_{11}H_{11}NO_3$ 205.07390, obsd 205.07425.

The reaction of compound 162 with excess ethylene in acetonitrile (without adding base) gave a mixture of 244 and 245: yield 37%; $^1$H NMR ($CDCl_3$, 300 MHz) of compound 245 (identified from the NMR spectrum of the mixture of 244 + 245): δ 1.249 (t, J = 7.55 Hz, 3 H, $CH_3$), 2.850 (q, J = 7.55 Hz, 2 H, $ArCH_2$), 5.957 (br s, 2 H, $NH_2$), 7.278-7.831 (m, 4 H, ArH). The olefination of compound 162 with excess ethylene in dichloromethane (with 1.5 equiv. of NaH added) gave 4 products: 249, 250, 251, and 252. The ratio of 249:250:251:252 as judged by GLC peak area analysis is 1.5:1:1.2:10.4. For compound 249: GC/MS, m/z (relative intensity, assignment) 147 (4.59, $M^+$), 132 (4.78, $M^+$-$CH_3$), 121 (100, $M^+$-$C_2H_2$ or $M^+$-CN), 105 (79.85, $M^+$-CON or $M^+$-$C_2H_4N$). For compound 250: GC/MS, m/z (relative intensity, assignment) 147 (100, $M^+$), 117 (82.40, $M^+$-$CH_2NH$-H), 105 (76.48, $M^+$-$C_2H_4N$ or $M^+$-CON). For compound 251: GC/MS, m/z (relative intensity, assignment) 148 (36.07, $M^+$), 133 (41.95, $M^+$-$CH_3$), 105 (100, $M^+$-$CH_3$-CO). For compound 252: GC/MS, m/z (relative intensity, assignment) 148 (81.71, $M^+$), 118 (100, $M^+$-$OCH_2$), 90 (19.79, $M^+$-$COOCH_2$).

The olefination of compound 162 with excess vinyl bromide in acetonitrile gave two isolable products 244 and 246. For compound 244: yield 23%; $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.377 (dd, J = 10.97 Hz, J = 0.99 Hz, 1 H, ArC=CH), 5.735 (dd, J = 17.46 Hz, J = 0.99 Hz, 1 H, ArC=CH), 6.304 (br s, 2 H, $NH_2$), 7.147 (dd, J = 17.46 Hz, J = 10.97 Hz, 1 H, ArCH=C), 7.282-7.801 (m, 4 H, ArH); IR ($HCCl_3$) 3401 and 3520 (NH), 1670 (C=O), 1580 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_9H_9NO$ 147.06842, obsd 147.06881. For compound 246: yield 15%; $^1$H NMR ($CDCl_3$, 300 MHz) δ

6.560 (d, J = 7.12 Hz, 1 H, ArCH=C), 7.158 (d, J = 7.12 Hz, 1 H, ArC=CH), 7.422-7.897 (m, 3 H, ArH), 8.412 (d, J = 8.12 Hz, 1 H, ArH), 11.132 (br s, 1 H, OH); IR ($HCCl_3$) 3400-3700 (OH), 1640 (C=N and C=C) $cm^{-1}$. The spectral data for compound 246 are identical with those of authentic material obtained from Aldrich.

The reaction of compound 162 with cis-1,3-pentadiene in dichloromethane gave compound 224 in 7.5% yield.

9. Olefination of thallated acetanilide (164)

The following is the general procedure used for olefination of compoud 164. To a solution of 0.2823 g (0.5 mmol) of compound 164 (contains a small amount of 165), 0.0887 g (0.5 mmol) of palladium chloride, and 0.0425 g (1 mmol) of lithium chloride in 6 ml of dry acetonitrile was added the appropriate olefin (1 mmol). The mixture was stirred at room temperature for 16-18 h. Base (1.5 equiv. of NaH) was added (if base was used in the reaction) and the reaction mixture was heated under reflux for 5 h. After being cooled to room temperature, the reaction mixture was filtered through Celite and the Celite pad was washed with 100 ml of ether. The filtrate and washing were combined and washed twice with saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$), and concentrated. The reaction products were isolated by flash chromatography on silica gel (230-400 mesh) column.

The olefination of compound 164 with 3-chloro-1-propene (without adding base) gave 3 products: 253, 254, and 255. For compound 253: yield

25%; mp 42-42.5°C (lit. [177] mp 42-42.5°C); $^1$H NMR ($CDCl_3$) δ 2.53 (d, J = 0.8 Hz, 3 H, $CH_3$), 2.62 (s, 3 H, $CH_3CO$), 6.14 (br m, 1 H, CH), 6.86-7.90 (m, 4 H, ArH); IR ($HCCl_3$) 1688 (C=O) $cm^{-1}$. The NMR and IR spectral data for compound 253 are identical to those reported in the literature [175]. For compound 254: yield 10%; $^1$H NMR ($CDCl_3$) δ 1.15 (t, J = 6 Hz, 3 H, $CH_3$), 1.67-2.15 (m, 2 H, $CH_2Me$), 2.30-2.80 (m, 2 H, $CH_2$-C=C), 2.43 (s, 3 H, $CH_3$-C≡C), 2.55 (s, 3 H, $CH_3CO$), 6.82-7.33 (m, 2 H, ArH), 7.34-7.64 (m, 1 H, ArH), 7.65-7.98 (m, 1 H, ArH); IR ($HCCl_3$) 1689 (C=O) $cm^{-1}$; GC/MS, m/z (relative intensity, assignment) 215 (92.88, $M^+$), 173 (100, $M^+$-$C_3H_6$), 158 (66.46, $M^+$-$CH_3CO$-N). Compound 255 could not be isolated. The same reaction with the addition of 1.5 equiv. NaH gave compounds 253 (45%) and 255 (< 5%).

The olefination of compound 164 with 3-chloro-1-butene gave 3 products 256, 257, and 258. For compound 256: yield 31%; $^1$H NMR ($CDCl_3$) δ 1.35 (t, J = 7 Hz, 3 H, $CH_3$), 2.73 (s, 3 H, $CH_3CO$), 3.04 (qd, J = 7 Hz, J = 2 Hz, 2 H, $CH_2$), 6.41 (br t, J = 1.7 Hz, 1 H, CH), 7.1-7.6 (m, 3 H, ArH), 7.7-8.02 (m, 1 H, ArH); IR ($HCCl_3$) 1694 (C=O), 1590 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{12}H_{13}NO$ 187.09972, obsd 187.09980. For compound 257: yield 19%; $^1$H NMR ($CDCl_3$) δ 2.22 (s, 3 H, $CH_3CO$), 2.82 (br d, J = 16 Hz, 1 H, $ArCH_2$), 3.52 (dd, J = 16 Hz, J = 8 Hz, 1 H, $ArCH_2$), 4.75-5.10 (br m, 1 H, CH-N), 5.15 (d, J = 9 Hz, 1 H, C=$CH_2$), 5.20 (d, J = 16 Hz, 1 H, C=$CH_2$), 5.61-6.03 (m, 1 H, CH=C), 6.92-7.50 (m, 3 H, ArH), 7.90-8.36 (br m, 1 H, ArH); IR ($HCCl_3$) 1650 (C=O), 1597 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{12}H_{13}NO$ 187.09972, obsd 187.09907. For the

mixture of 5 isomers (258): yield 30%; GC/MS, m/z 189 (for all 5 isomers).

The vinylation of compound 164 with 3,3-dimethyl-1-butene (without adding NaH) gave compound 259: yield 55%; $^1$H NMR ($CDCl_3$) δ 1.13 (s, 9 H, $CH_3$), 2.13 (s, 3 H, $CH_3CO$), 6.10 (d, J = 15 Hz, 1 H, ArCH=C), 6.37 (d, J = 15 Hz, 1 H, ArC=CH), 6.95-7.60 (m, 4 H, ArH), 7.60-7.98 (br s, 1 H, NH); IR ($HCCl_3$) 3437 (NH), 1685 (C=O), 1581 (C=C), 1514 (NH, amide II) $cm^{-1}$. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.36; H, 9.00.

The vinylation of compound 164 with methyl acrylate (without adding NaH) gave compound 260: yield 63%; $^1$H NMR ($CDCl_3$) δ 2.17 (s, 3 H, $CH_3CO$), 3.80 (S, 3 H, $OCH_3$), 6.37 (d, J = 16 Hz, 1 H, ArCH=C), 6.95-8.26 (m, 5 H, ArH + NH), 7.80 (d, J = 16 Hz, ArC=CH); IR ($HCCl_3$) 3430 and 3200-3500 (NH), 1700 (ester and amide I), 1630 (amide II and C=C) $cm^{-1}$. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98. Found: C, 65.78; H, 6.02.

The vinylation of compound 164 with styrene (without adding base) gave compound 261: yield 60%; $^1$H NMR ($CDCl_3$) δ 2.11 (S, 3 H, $CH_3CO$), 6.70-8.30 (m, 12 H, NH + HC=CH + ArH); IR ($HCCl_3$) 3430 and 3160-3500 (NH), 1675 (C=O), 1630 (C=C), 1574 (NH, amide II) $cm^{-1}$; mass spectrum, m/z calcd for $C_{16}H_{15}NO$ 237.11537, obsd 237.11523.

The vinylation of compound 164 with excess ethylene gave compound 262 (13%); the same reaction with vinyl bromide gave compound 262 in 45%. For compound 262: $^1$H NMR ($CDCl_3$) δ 2.62 (s, 3 H, $CH_3$), 6.63 (d, J = 4 Hz, 1 H, ArCH=C), 7.28 (d, J = 4 Hz, 1 H, C=CHN), 7.20-7.95 (m, 3 H, ArH), 8.28-8.67 (m, 1 H, ArH); IR ($HCCl_3$) 1706 (C=O) $cm^{-1}$. All NMR and

IR spectral data for compound 262 were identical to those reported in the literature [178].

The olefination of compound 164 with either cis-1,3-pentadiene (25% yield) or trans-1,3-pentadiene (13% yield) gave the same product 263: $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.656 (d, J = 5.67 Hz, 3 H, $CH_3$), 2.211 (s, 3 H, $CH_3CO$), 2.782 (d, J = 15.82 Hz, 1 H, $ArCH_2$), 3.454 (dd, J = 15.82 Hz, J = 8.5 Hz, 1 H, $ArCH_2$), 4.735 (m, 1 H, CH-C=C), 5.465 (dd, J = 15.61 Hz, J = 6.69 Hz, 1 H, CH=CMe), 5.548-5.639 (m, 1 H, C=CHMe), 6.975-7.211 (m, 3 H, ArH), 8.185 (d, J = 7.76 Hz, 1 H, ArH); IR ($HCCl_3$) 1640 (C=O), 1594 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{15}NO$ 201.11537, obsd 201.11479.

Reaction of compound 164 with 3-methyl-1,2-butadiene gave compound 264: yield 20%; $^1$H NMR ($CDCl_3$) δ 1.66 (s, 6 H, $CH_3$), 2.42 (s, 3 H, $CH_3CO$), 4.90 (s, 1 H, C=CH), 5.41 (s, 1 H, C=CH), 7.00-7.88 (m, 4 H, ArH); IR ($HCCl_3$) 1650 (C=O), 1600 (C=C) $cm^{-1}$; mass spectrum, m/z calcd for $C_{13}H_{15}NO$ 201.11537, obsd 201.11516.

# VI. CONCLUSION

In this work, we have investigated the preparation of a number of oxygen- and nitrogen-containing heterocycles. These heterocycles have all been made by employing organopalladium intermediates. In Chapter II, the preparation of furans from 4-hydroxy-2-alkyn-1-ones via mercuration and palladium-assisted carbonylation was discussed. Mercuration of 4-hydroxy-2-alkyn-1-ones provides the first examples of syn addition of mercuric chloride to a carbon-carbon triple bond. The resulting vinylmercurial or furylmercurial can be converted to furans by palladium-assisted carbonylation.

In Chapter III, the mercuration of allenic acids and esters has been examined. Low yields of β-substituted $\Delta^{\alpha,\beta}$-butenolides could be obtained from mercuration and palladium-assisted carbonylation or acetoxylation of the allenic acid.

The results shown in Chapter IV were somewhat disappointing, the tetrasubstituted double bond of 2,3-dimethylnorbornadiene-palladium dichloride failed to participate in the cyclization to a tetracyclic product. Although vinyl-carbonylation of 2-methylnorbornadiene-palladium dichloride did give the desired tetracyclic products, we were unable to introduce the second methyl group into the tetracyclic ring system.

Finally, oxygen- and nitrogen-containing heterocycles have been prepared from thallated arenes as discussed in Chapter V. Unfortunately, these reactions require a stoichiometric amount of palladium chloride, and interfering side reactions such as the formation of uncyclized

products and ring closure to heterocycles of unexpected ring sizes have been observed. However, we have been able to obtain isoquinolones, isocarbostyrils, and indoles in moderate to good yields. This results suggests that thallation and palladium-assisted olefination of arenes should provide an efficient new route to these biologically important compounds.

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# VIII. ACKNOWLEDGEMENTS

The author wishes to express his gratitude and appreciation to Professor Richard C. Larock for his knowledgeable and patient guidance, counseling and stimulating encouragement throughout the course of this investigation.

I am greatly indebted to my colleagues who have rendered assistance in various ways. Among these are: Dr. Sudarsanan Varaprath for his valuable discussions and generous supply of 3-methyl-1,2-butadiene and 1-methyl-1-vinylcyclopropane; L. Wayne Harrison and Randall K. Carlson for their assistance and discussions. I also want to thank Professor Robert A. Jacobson and his research group for performing the x-ray crystallographic studies for two of my compounds.

I wish to especially thank my parents, wife, sister, and brothers for their support and encouragement throughout my education.

Finally, the author wishes to thank his typist, Elaine Wedeking, for her excellent work in the preparation of this dissertation.