1982

Organopalladium approaches to bicyclic heteraotom containing prostaglandin analogues

Douglas Robert Leach
Iowa State University

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ORGANOPALLADIUM APPROACHES TO BICYCLIC HETEROATOM CONTAINING PROSTAGLANDIN ANALOGUES

Iowa State University PH.D. 1982

Organopalladium approaches to bicyclic heteroatom containing prostaglandin analogues

by

Douglas Robert Leach

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Iowa State University
Ames, Iowa

1982

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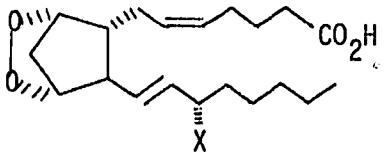
CHAPTER I. INTRODUCTION

The prostaglandins are a class of C-20 unsaturated hydroxy acids. Their wide range of activity includes involvement in such important physiological processes as smooth muscle contraction, blood platelet aggregation, chemotaxis and inflammation. It is thought they may have pharmacological use in the treatment of thrombosis, asthma, ulcers, hypertension and inflamation (1,2). They are also potentially useful in termination of pregnancy, induction of labor, and contraception (3).

However, their wide range of activity implies a corresponding lack of selectivity, which is a major drawback to any clinical use. Their very short lifetime under physiological conditions, due to rapid metabolic deactivation, also makes them impractical for such use. These problems have prompted the synthesis of a wide variety of structural analogues which hopefully would exhibit more selectivity and greater resistance to metabolic deactivation (4-6).

In 1965, in studies on the biosynthesis of $PGF_{2\alpha}$ and PGE_2 using labeled oxygen, Samuelsson postulated the presence of an endoperoxide intermediate (7). However, it was not until 1973 that Samuelsson actually isolated the endoperoxide PGH_2 1 (8). Later studies showed that PGH_2 and PGG_2, 2, were intermediates in the biosynthesis of $PGF_{2\alpha}$, PGE_2 and the thromboxanes, as shown in Scheme I (9,10).

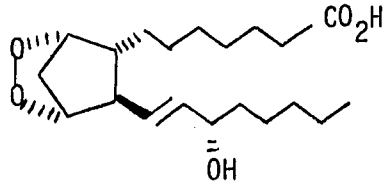


1 X = OH

2 X = OOH

PGH_2 and PGG_2 were found to induce rapid, irreversible blood platelet aggregation and were 100 - 450 and 50 - 200 times more active respectively than PGE_2 in stimulating contraction of rabbit aorta strip, a standard assay of prostaglandin activity. The half-lives of both PGH_2 and PGG_2 in aqueous media were found to be approximately 5 minutes (9).

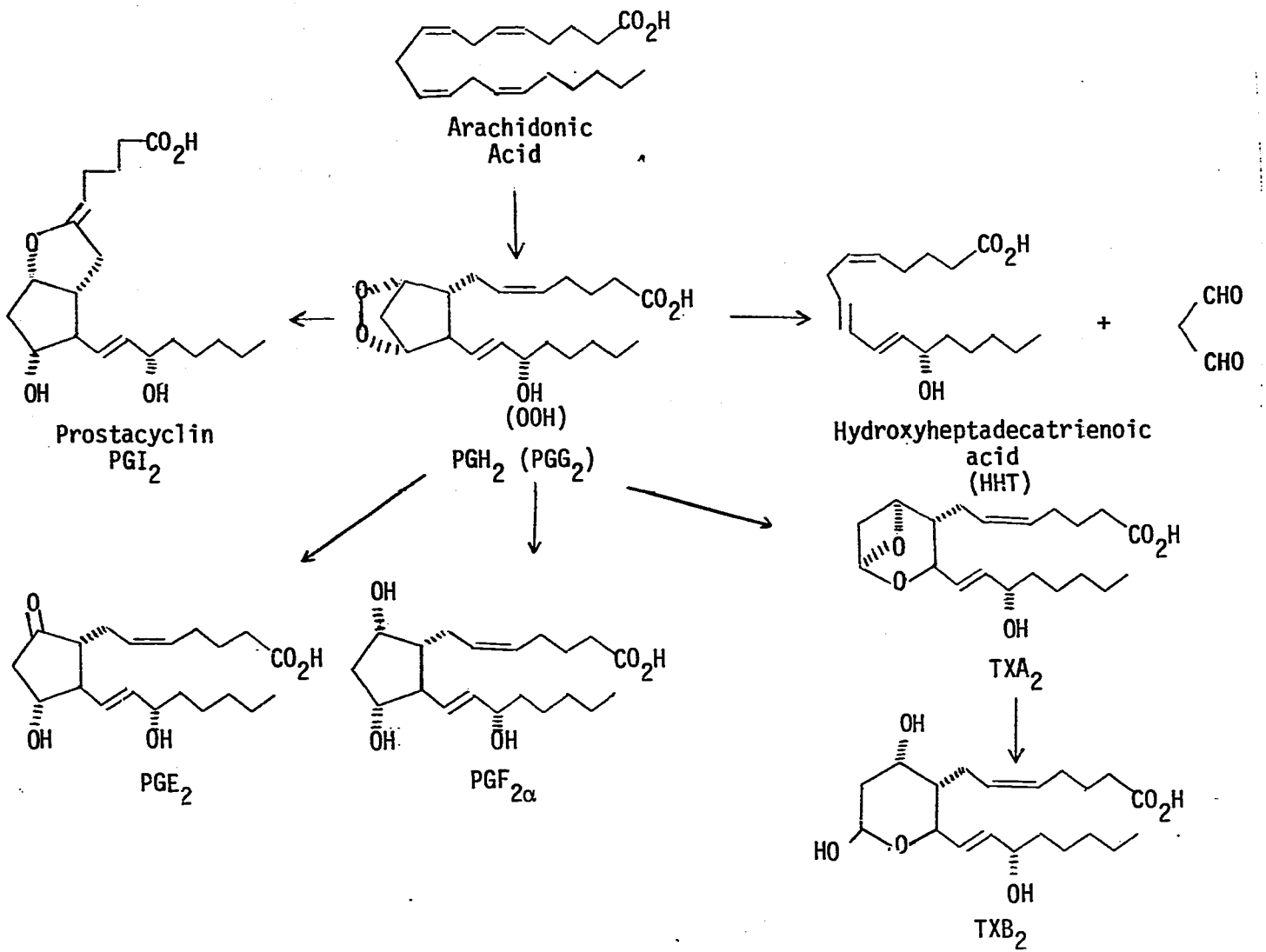
The combination of the high biological potency of PGG_2 and PGH_2 and their extreme instability made the synthesis of stable analogues a very desirable goal. Although one bicyclic analogue (of PGH_1, 3, at that time a proposed biosynthetic intermediate) was synthesized in 1971, it was

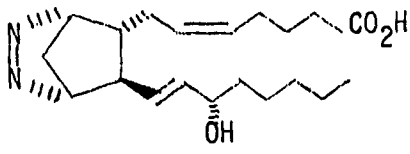


PGH_1, 3

not until 1975 that substantial progress toward this goal was reported. Since then there have been over thirty analogues synthesized. The structures of these analogues are shown below.

SCHEME I


Arachidonic Acid
Prostacyclin
PGI2
OH
(OOH)
PGH2 (PGG2)
Hydroxyheptadecatrienoic acid
(HHT)
CHO
CHO
PGE2
PGF2α
TXA2
TXB2
HO



4 (11)

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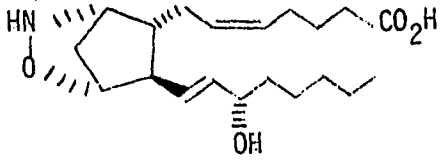

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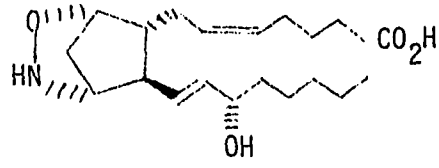

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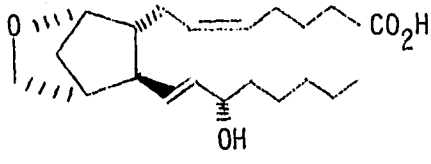

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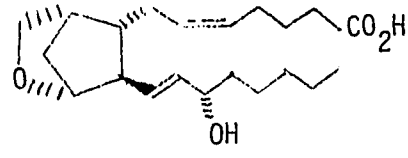

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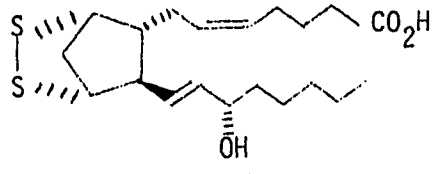

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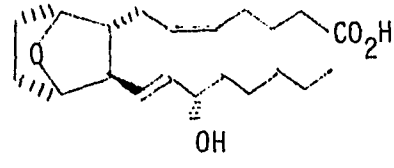

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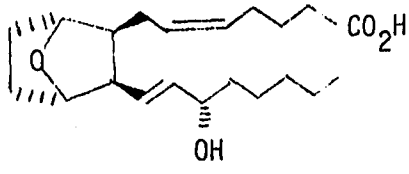

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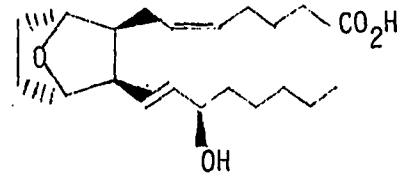

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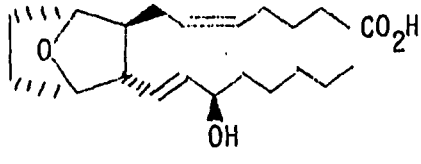

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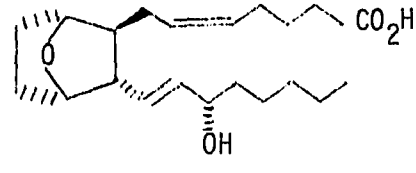

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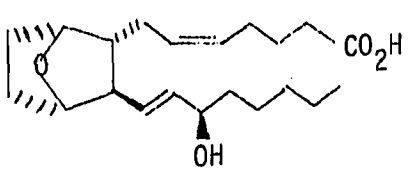

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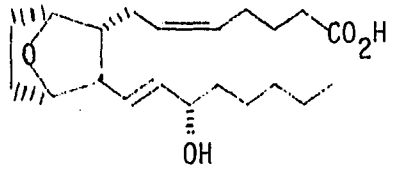

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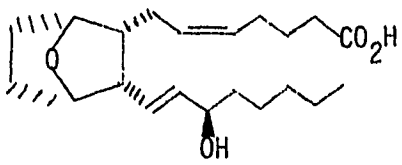

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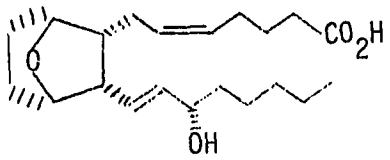

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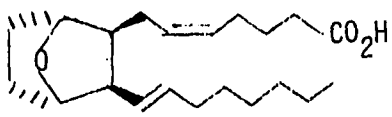

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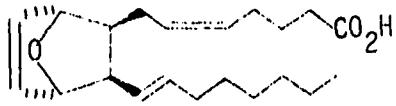

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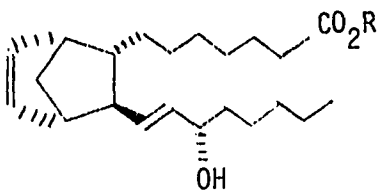
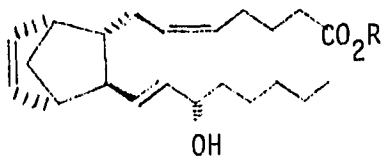
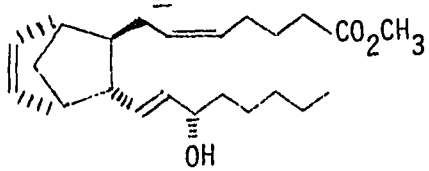


22 a : R=CH_3
b : R=H (23-25)



23 a : R=H
b : R=CH_3 (26-28)



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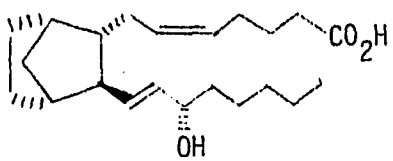

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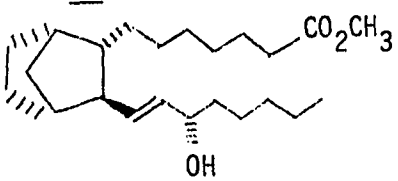

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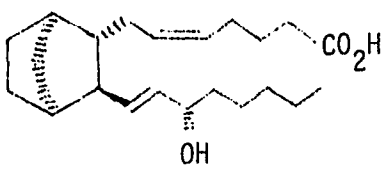

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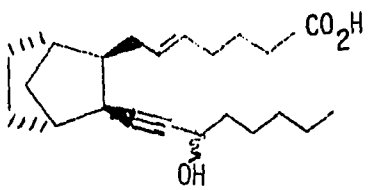

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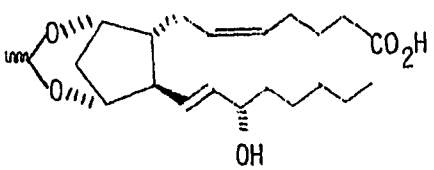

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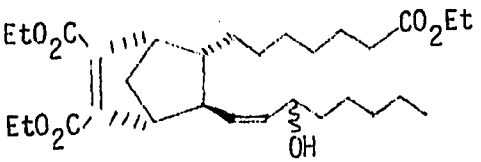

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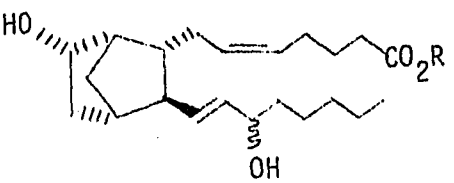


31 a : R=H
b : R=CH_3 (33)

As can be seen from the structures, a wide variety of different skeletons has been employed. Among the most common groups substituted for the 9,11-endoperoxide linkage are various heteroatoms, an ethylene bridge and an ethano-bridge. A variety of stereochemistries of the substituents on the bicyclo[2.2.1]heptane ring has also been produced, all of which possess substantial activity.

While a discussion of the synthesis of each of these compounds would be much too lengthy to present here, several general comments about the synthetic routes employed can be made. The syntheses of these analogues can be separated into two different basic approaches. Compounds 4 - 9 and 30 were synthesized by modifying natural prostaglandins. Generally PGA_2 or $PGF_{2\alpha}$, hardly readily available compounds, were used as starting material. The other analogues were generally constructed by an approach utilizing a Diels-Alder reaction, followed by a Michael addition or a series of Wittig reactions. Unfortunately, in many cases the initial Diels-Alder adduct from a trans dieneophile gives substantial amounts, sometimes up to 40% as in 22b, of the wrong exo-endo substitution pattern in the bicyclo[2.2.1]heptane ring system. Therefore, one can see that there are major problems inherent in both of the general approaches to the analogues studied to date.

The biological activities of these compounds are reported in Table 1. As can be seen from the results, the compounds exhibit a variety of activities. These range from acting as prostaglandin mimics in inducing blood platelet aggregation and stimulating smooth muscle contraction, to inhibition of prostaglandin activity and inhibition of the biosynthesis of prostaglandins and thromboxanes. Three of the analogues; 4, 12, and 30 were specifically reported to produce their effects for much longer periods of time than PGH_2 or PGG_2. Several of the analogues have been postulated to act to inhibit prostaglandin and thromboxane biosynthesis by competitive binding to the appropriate enzyme site.

The objective of this research has been to apply various aspects of organometallic chemistry towards the synthesis of bicyclic prostaglandin analogues. By using this approach it was hoped to develop several, rapid, stereospecific routes to a variety of analogues from readily available starting materials, thus overcoming several of the previously mentioned drawbacks in the prior syntheses of these compounds. It was thought that the addition of appropriate organometallic compounds to bicyclic olefins, such as norbornene and norbornadiene, would afford intermediates that could be readily elaborated to the desired prostaglandin analogues.

Table 1. Biological activities of known bicyclic prostaglandin analogues

Compound	Biological Activity
4	8 times as active as PGG_2 in stimulating blood platelet aggregation. 6 times as potent as PGG_2 in inducing seratonin release. 6.9 times as active as PGH_2 and 1450 times as active as PGE_2 in stimulating contraction of rabbit aorta strip.
5	Potent inhibitor of PGH_2 induced blood platelet aggregation. Thromboxane A_1 synthetase inhibitor.
6	Potent inhibitor of Thromboxane A_2 synthetase.
7	Potent inhibitor of Thromboxane A_2 synthetase.
8	Potent bronchoconstrictor. Inhibits artificially induced blood platelet aggregation.
9	Potent bronchoconstrictor. Antagonizes PGE_1-induced c-AMP formation.
10	24 times as active as PGH_2 and 5000 times as active as PGE_2 in stimulating contraction of rabbit aorta strip. Induces rapid irreversible blood platelet aggregation.
11	Not reported.
12	Induces rapid platelet aggregation. Functions as an agonist of Thromboxane A_2 receptors.

Table 1. continued

Compound	Biological Activity
13	Selective and potent Thromboxane A_2 receptor antagonist. Inhibits platelet aggregation induced by 3 and 11.
14	Inhibits arachidonic acid induced blood platelet aggregation.
15	Not reported.
16	Inhibits arachidonic acid induced blood platelet aggregation. Inhibits Thromboxane A_2 synthetase.
17	Inhibits platelet aggregation. Inhibits Thromboxane A_2 synthetase.
18	Inhibits platelet aggregation. Inhibits Thromboxane A_2 synthetase.
19	Not reported.
20	Not reported.
21	Not reported.
22a	Specific inhibitor of PGE_1 synthetase.
22b	Inhibits synthesis of PGE_1.
23a	1/10 as active as PGG_2 in inducing platelet aggregation. Induces seratonin release. Stimulates smooth muscle contraction. Potent inhibitor of PGE_2 biosynthesis.
23b	Stimulates PGE_2 biosynthesis.

Table 1. continued

Compound	Biological Activity
24	Potent inducer of blood platelet aggregation. Stimulates smooth muscle contraction.
25	Potent inhibitor of PGE_2 biosynthesis.
26	Not reported.
27	Weak inhibitor of ADP-induced platelet aggregation and Thromboxane A_2 synthetase.
28	Inhibits blood platelet aggregation.
29	Not reported.
30	1/40 as active as PGG_2 in inducing blood platelet aggregation. Potent venoconstrictor.
31	55 times as active as $PGF_{2\alpha}$ in inducing contraction of isolated guinea pig lung. Did not inhibit collagen-induced platelet aggregation.

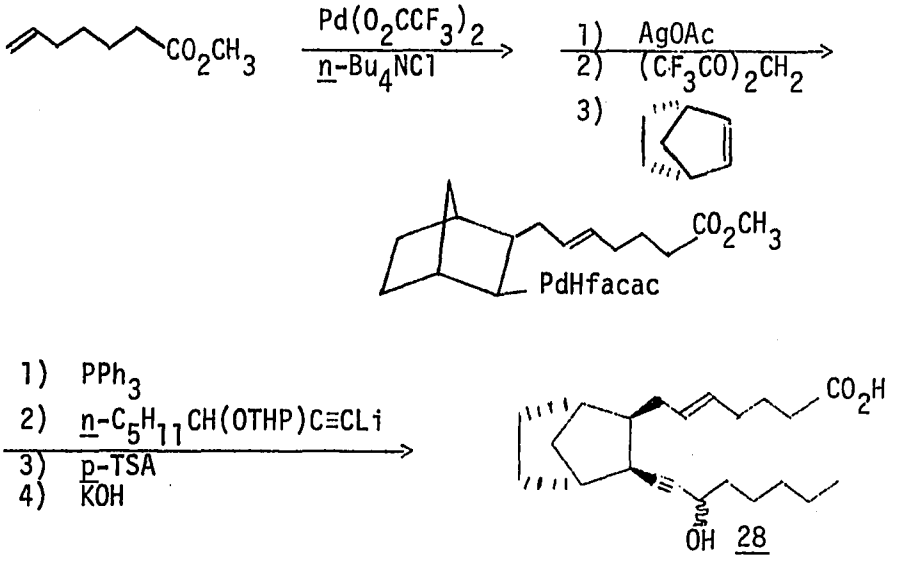
The following chapter describes the results of work directed towards the synthesis of thiophene - containing prostaglandin analogues. Chapter III describes the synthesis of several 7-oxa prostaglandin analogues. Chapter IV gives the results of the exploration of a new reaction for the alkylation of organomercurials with organocuprates, a reaction we hoped would be useful in several prostaglandin syntheses. Lastly, Chapter V briefly summarizes the results of this research and presents some suggestions for future work.

CHAPTER II. SYNTHESIS OF HETEROCYCLIC PROSTAGLANDIN ENDOPEROXIDE ANALOGOUS

Introduction

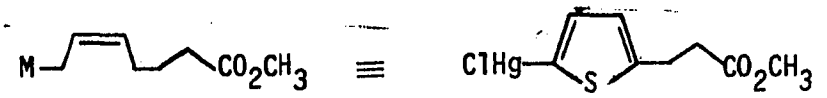
An initial approach to bicyclic prostaglandin analogues using organopalladium chemistry has been reported (30). This approach is outlined in Scheme II below. Using this approach, a number of analogues

Scheme II

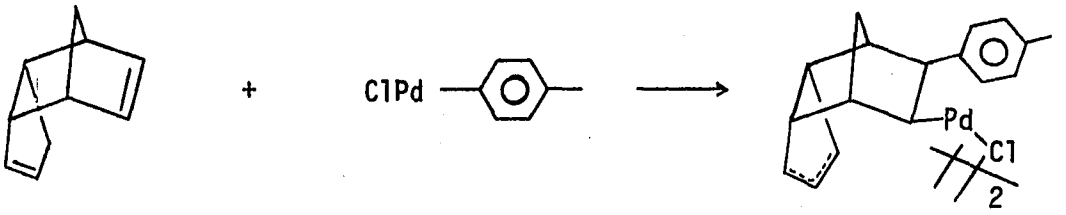


have been synthesized. Several of them, in particular compound 28, are extremely active in the inhibition of arachidonic acid-induced blood platelet aggregation. Based on these results, it was considered desirable to develop a route to prostaglandin analogues possessing a cis-5,6-double bond in the carboxylic acid side chain.

Since cis-σ-allylmetal complexes are generally unknown in acyclic cases, some sort of functional equivalent was required. It was thought that an appropriately substituted thiophene would be a good choice for several reasons. First, the addition of arylpalladium compounds to



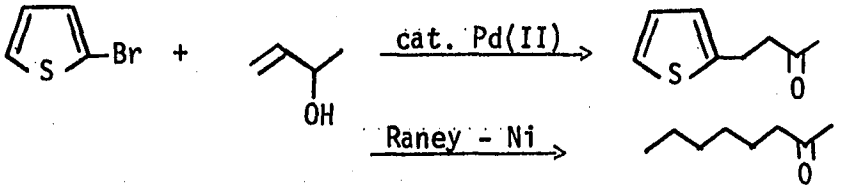
bicyclic olefins is a well-known reaction (eq. 1) (34-38). The transmetalation of organomercurials with palladium salts to produce



(1)

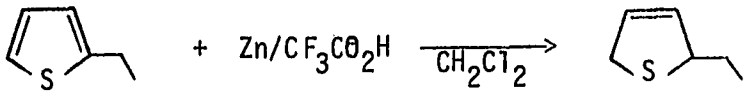
organopalladium compounds is also well-known (39-43).

There have been several reports in the literature demonstrating the use of a thiophene ring as the synthetic equivalent of a four carbon chain (eq. 2) (44, 45). Reductive desulfurization with



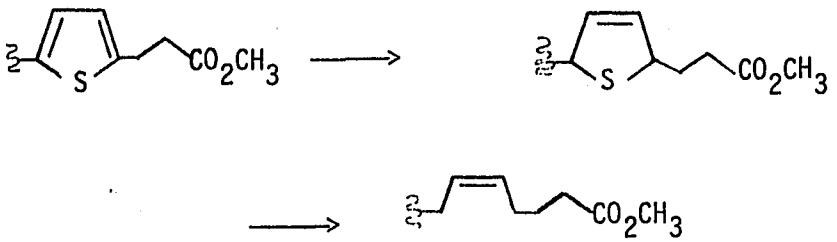
(2)

Raney-nickel afforded the final product. The reduction of thiophenes to 2,5-dihydrothiophenes has also been reported (eq. 3) (46). It was hoped that such a transformation, followed by selective desulfurization



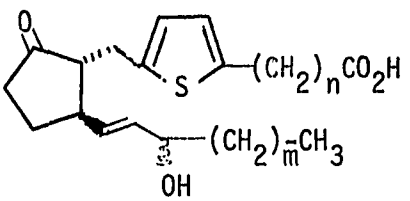
(3)

would allow introduction of the desired cis-5,6-double bond (eq. 4).



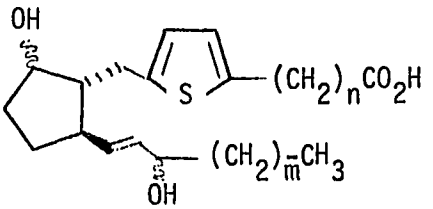
(4)

Lastly, there has been considerable interest in prostaglandin analogues containing aromatic rings in various positions in either side chain (47-51). In particular, a number of thiophene- and furan-containing prostaglandin analogues have been synthesized, several of which are shown below (52-54).



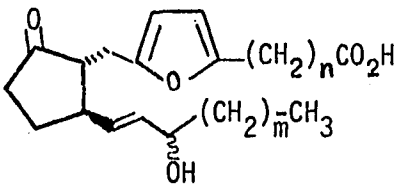
n = 0-3
m = 0-8

(52)



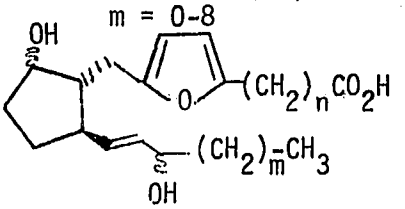
n = 0-3
m = 0-8

(52)



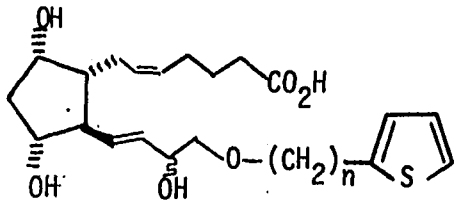
n = 0-3
m = 0-8

(52)

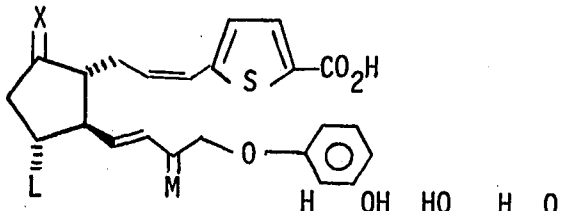


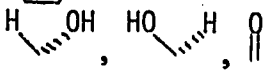
n = 0-3
m = 0-8

(52)



n = 0, 1 (53)

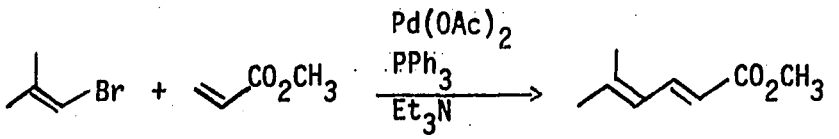


X and M are: 

L = H or OH (54)

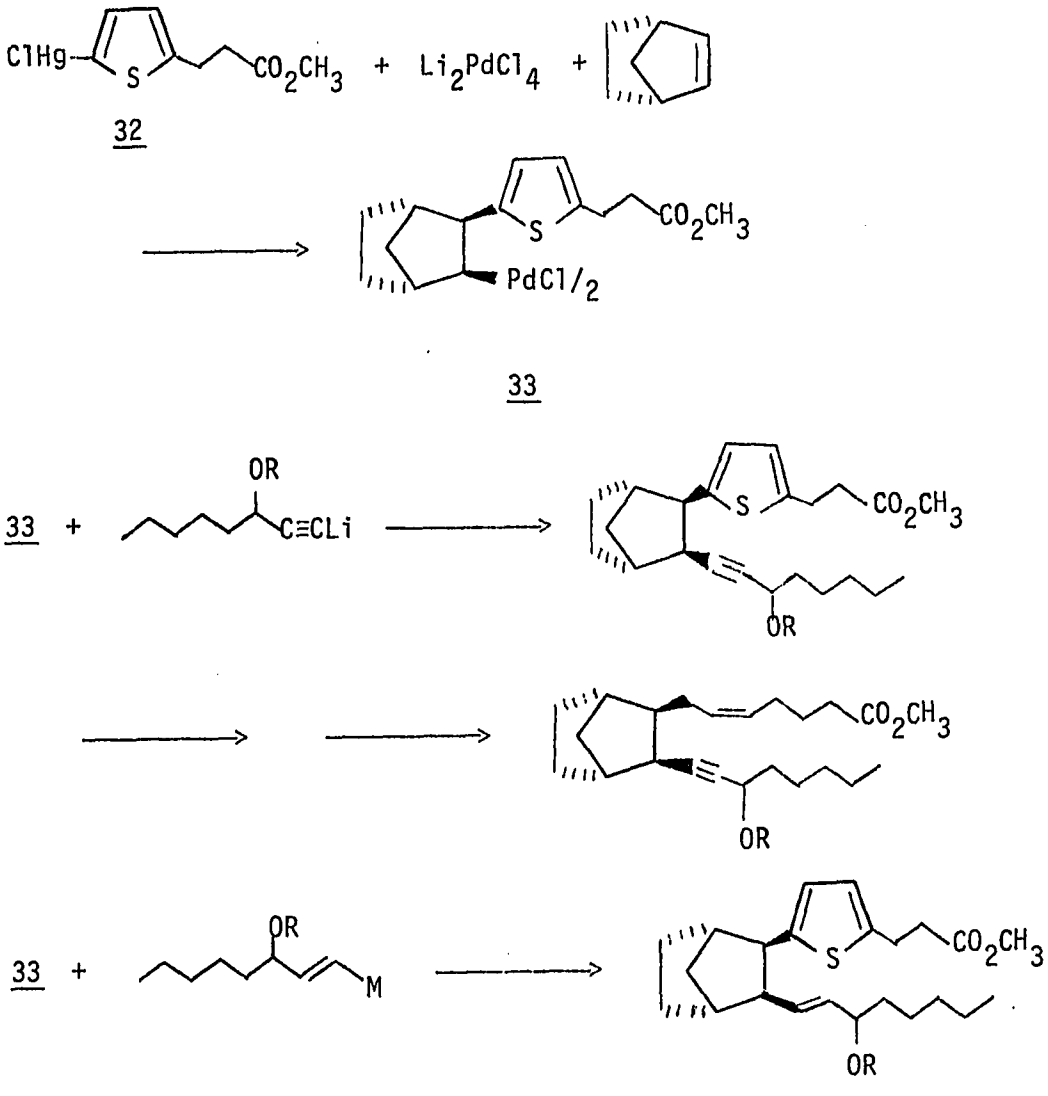
For these reasons then, it was desirable to synthesize a number of thiophene- and furan- containing bicyclic prostaglandin analogues.

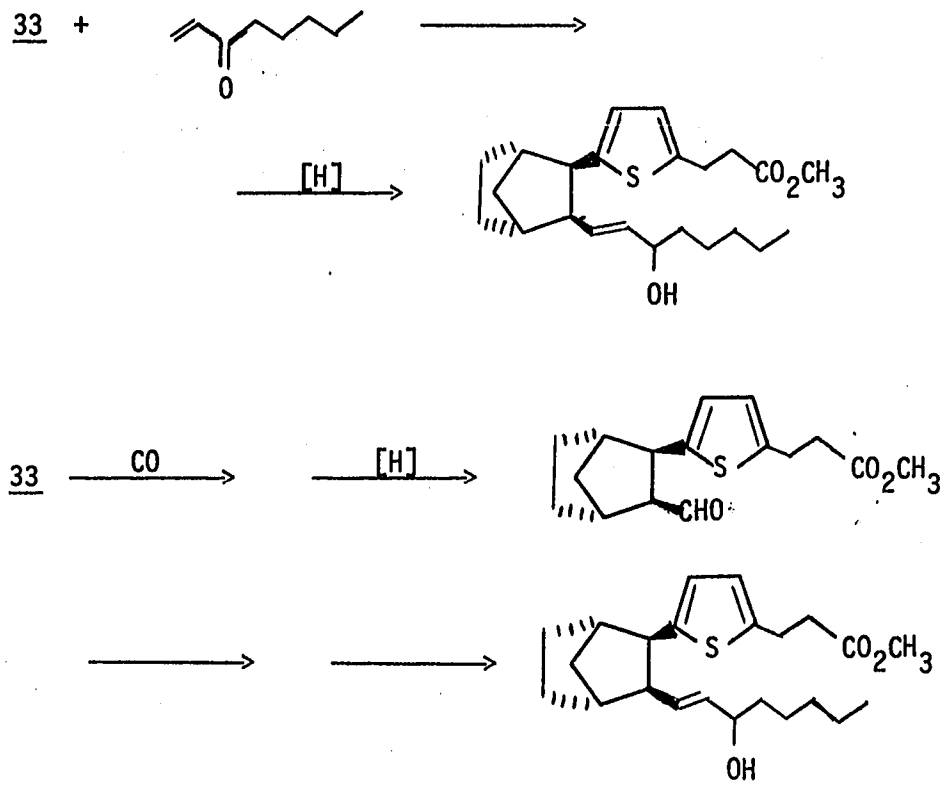
The basic synthetic approach that was envisioned is outlined in Scheme III. Initial addition of the organo mercurial to norbornene should give the σ-palladium adduct 33. From this point, several possibilities exist for introduction of the unsaturated alcohol side chain. Treatment of 33 with 1-lithio-3-(2-tetrahydropyranyloxy)-1-octyne should afford the acetylenic alcohol derivatives as in Scheme II. The trans-allylic alcohol chain could be introduced by one of several methods. Reaction of 33 with a vinyl metal reagent should introduce the alcohol chain in a process similar to that of the lithium acetylide method. A second possible method is a Heck olefination of 33 with 1-octen-3-one (39, 43, 55, 56). An example of this is shown in equation 5. Lastly, carbonylation of 33 and reduction to the aldehyde, followed by Wittig reaction and reduction of the resulting ketone would also provide the desired alcohol.



(5)

Scheme III


ClHg
S
CO_2CH_3
+ Li_2PdCl_4 +
32
S
CO_2CH_3
$PdCl/_2$
33
33 +
OR
C≡CLi
S
CO_2CH_3
OR
CO_2CH_3
OR
33 +
OR
M
S
CO_2CH_3
OR


33 +
O
[H]
S
CO2CH3
OH
33
CO
[H]
S
CO2CH3
CHO
S
CO2CH3
OH

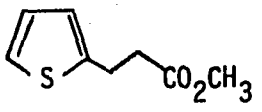
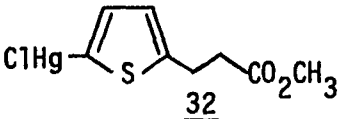
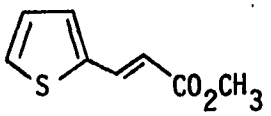
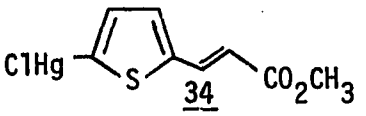
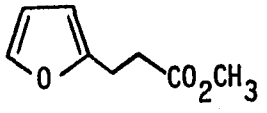
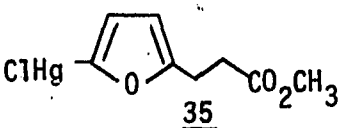
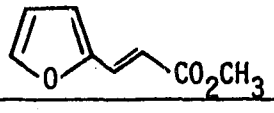
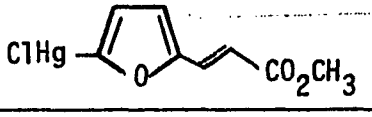
Results and Discussion

Synthesis of the organomercurials

Methyl trans-3-(2-thienyl)acrylate was prepared from the commercially available acid, by acid catalyzed esterification, in 88% yield. Methyl 3-(2-thienyl)propanoate was prepared by hydrogenation (57) of the unsaturated acid followed by esterification in 79% overall yield. The analogous furans were prepared similarly. Methyl 3-(2-furyl)acrylate was prepared from the corresponding acid in 70% yield. Methyl 3-(2-furyl)propanoate was prepared by hydrogenation of the ester with palladium on charcoal in basic methanol to avoid over-reduction (58).

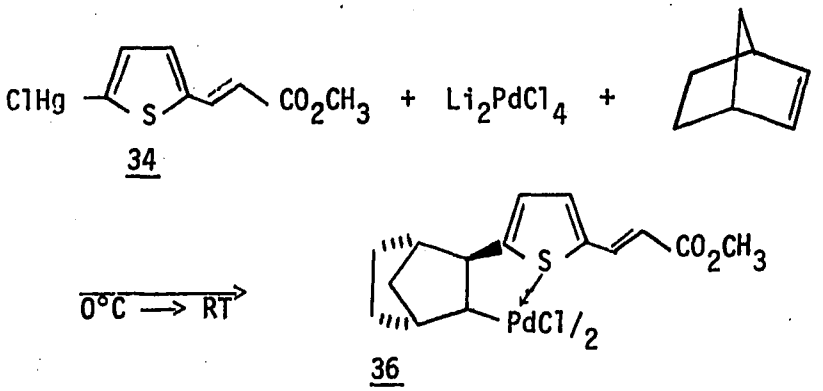
These heterocycles were then mercurated using a modification of Volhard's procedure (59) using two equivalents of $HgCl_2$ and ten equivalents of NaOAc in aqueous ethanol. The yields of the mercurials are given in Table II. All attempts to mercurate methyl 3-(2-furyl)acrylate under a variety of conditions proved unsuccessful. Several explanations for this are possible. Conjugation of the weakly aromatic furan ring with the unsaturated ester may remove sufficient electron density from the ring making it unreactive. Mercuration of the double bond may also be a possible difficulty.

Table 2. Synthesis of mercurials

Heterocycle	Mercurial	% Yield
	 32	83
	 34	86
	 35	84
		0

Additions to bicyclic olefins

The next step involves transmetalation of the mercurials with palladium salts and addition to bicyclic olefins. The addition of methyl 3-(5-chloromercuri-2-thienyl)acrylate, 34, to norbornene was studied first (eq. 6). An initial attempt using THF as the solvent



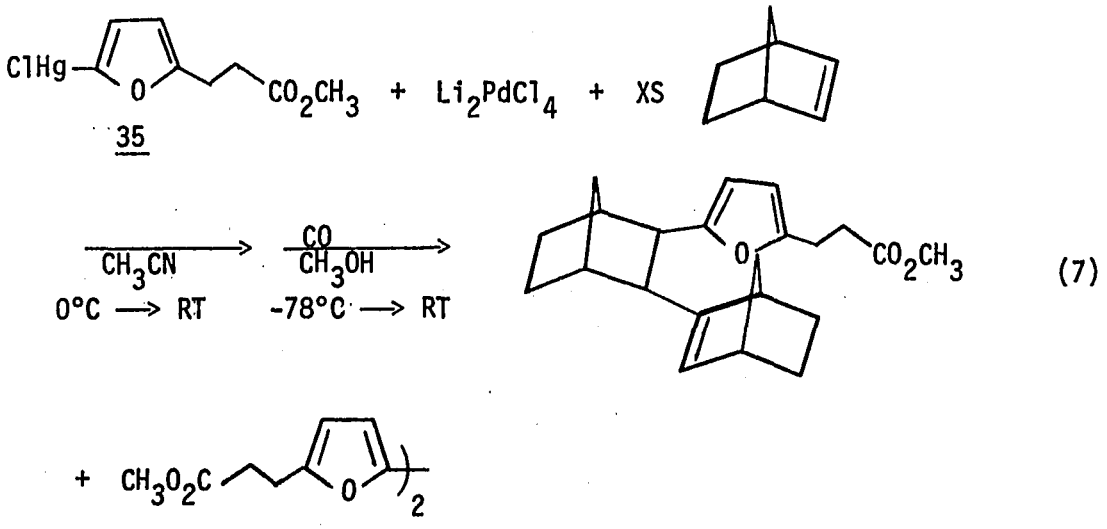
34 + Li_2PdCl_4 + (6)

$0°C \longrightarrow RT$

36

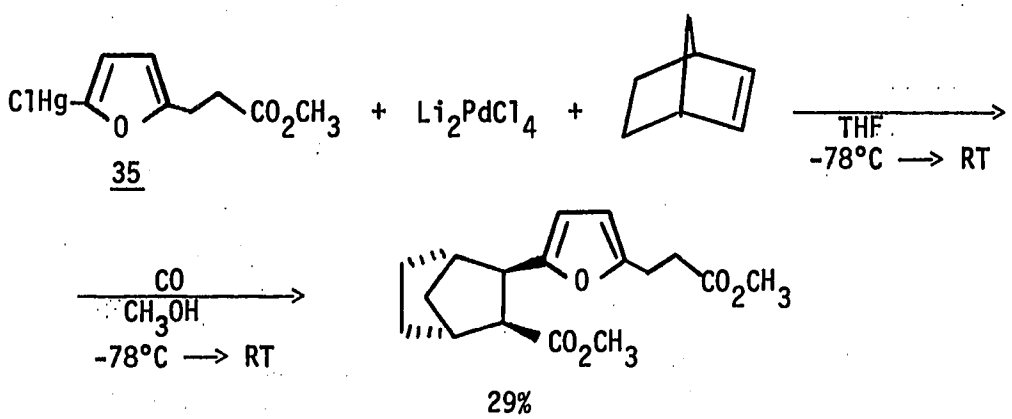
and an extractive work-up with ether afforded a low yield of product that was difficult to purify. However, addition of the mercurial to a 0°C solution of Li_2PdCl_4 and norbornene in acetonitrile and warming to room temperature gave the σ-palladium adduct in 67% yield after methylene chloride work-up. Addition of methyl 3-(5-chloromercuri-2-thienyl)propanoate, 32, to norbornene following the same procedure afforded the σ-palladium adduct in 78% yield.

The addition of methyl 3-(5-chloromercuri-2-furyl)propanoate, 35, proved to be much more difficult. Addition of the mercurial to a 0°C solution of Li_2PdCl_4 and norbornene (10 equivalents) in acetonitrile as before did not yield any isolable product on work-up. Attempted trapping of the σ-palladium adduct by carbonylation in methanol gave what apparently is the product of a double addition, and a bifuryl as products (eq. 7). These products were characterized only by mass



(7)

spectrometry and were not examined further. Substituting THF for acetonitrile as the solvent and cooling to -78°C before adding the organomercurial gave similar results. However, using only one equivalent of norbornene in THF did give the expected diester in 29% yield (eq. 8). Attempted isolation of the palladium complex from this

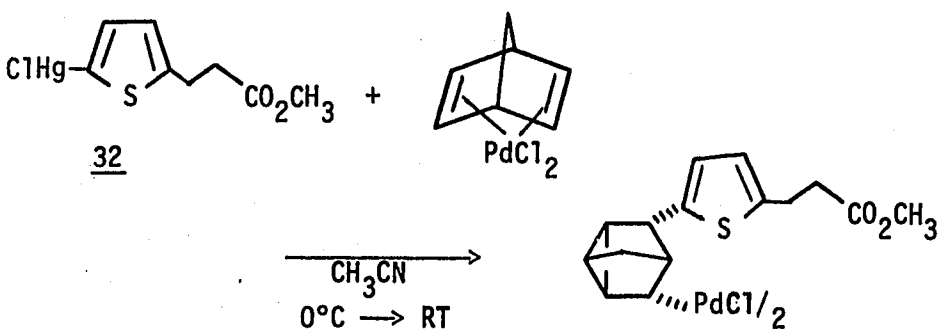


35

29%

(8)

reaction was unsuccessful, presumably due to decomposition, and this approach was discontinued at this point. The analogous reaction of methyl 3-(5-chloromercuri-2-thienyl)propanoate with norbornadiene-palladium dichloride gave the nortricyclo σ-palladium adduct in 74% yield (eq. 9). The structure of 37 was assigned based on the lack of



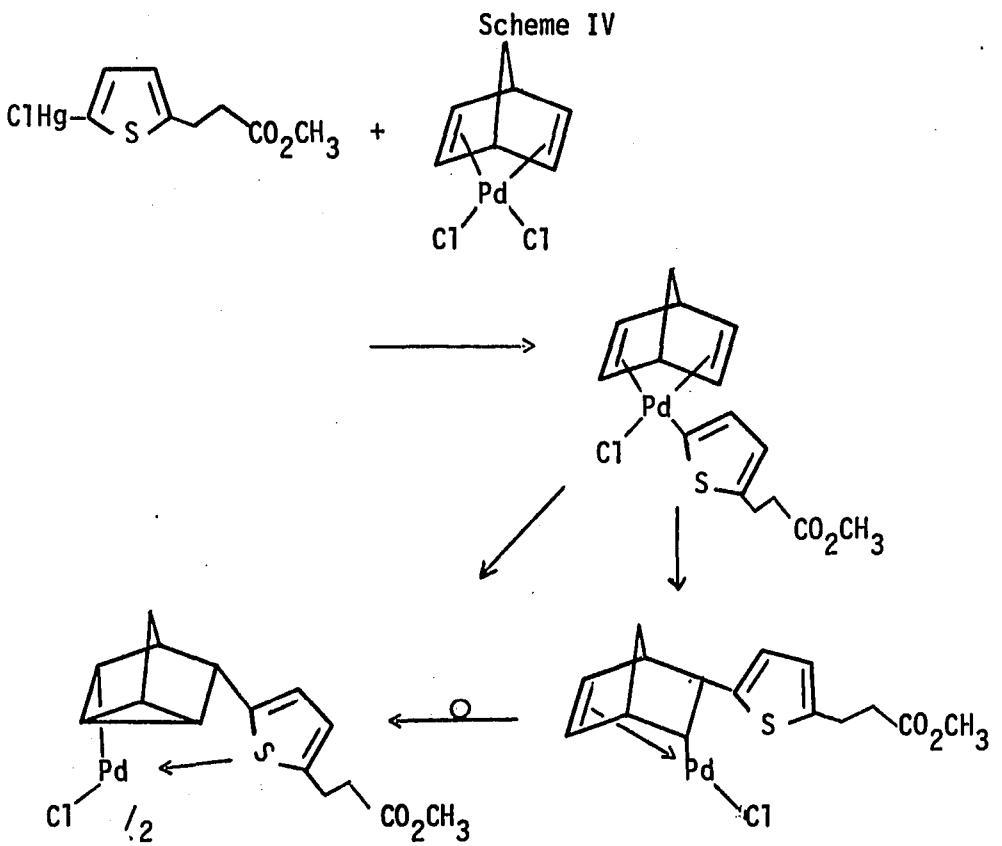
32

37

(9)

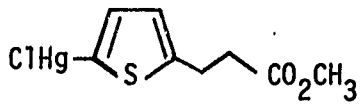
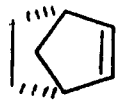
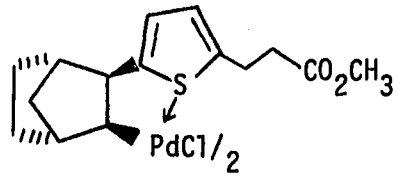
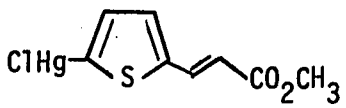
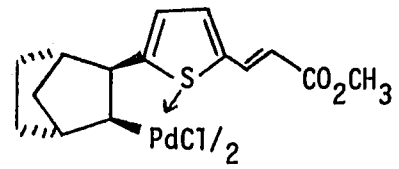
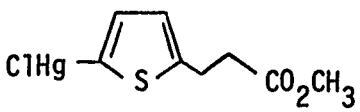
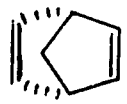
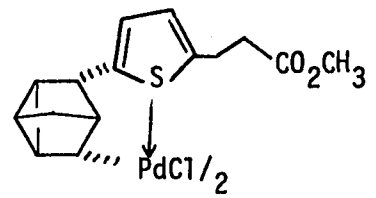
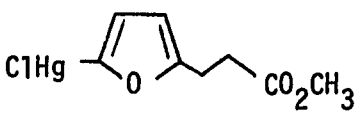
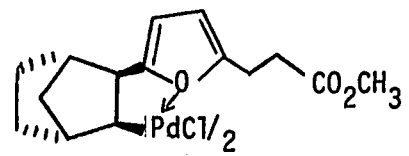
olefinic absorbances in its NMR spectrum, and the presence of a strong band at 810 cm^{-1} in the infrared spectrum, which is characteristic of nortricyclene ring systems (60). This was not surprising since the addition of vinylmercurials to this complex is reported to give the analogous vinyl adducts (61). This probably arises via an arylpalladium-diene complex, which then may either add directly in a homo-1,4 manner, or add to the endo side of one of the double bonds and then rearrange to give the product, as shown in Scheme IV.

Scheme IV



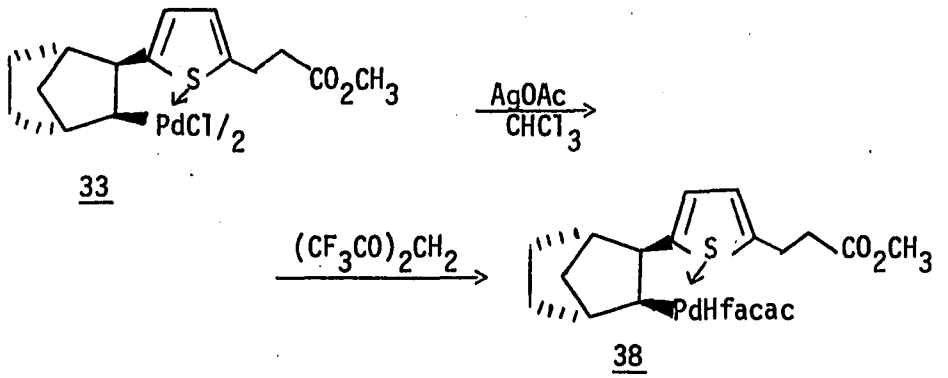
The results of these reactions are summarized in Table III.

Table 3. Addition to bicyclic olefins

Organomercurial	Olefin	σ-Palladium adduct	% Yield
			78
		33	
			67
		36	
			74
		37	
			0

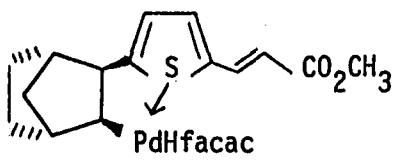
Reactions with 1-lithio-3-(2-tetrahydropyranyloxy)-1-octyne

Previous work has shown that reactions of bicyclic organopalladium compounds with lithium acetylides proceed more cleanly and in higher yield when the chloride anion on palladium is exchanged for hexafluoroacetylacetonate (30). This was accomplished by treating the palladium complex with 1 equivalent of AgOAc in chloroform followed by 1.5-2.0 equivalents of hexafluoroacetylacetone (eq. 10).

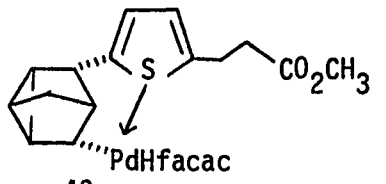


33 38 (10)

By this method 33 was converted to 38 in 100% yield. Compounds 39 and 40 were similarly prepared in 98% and 96% yield respectively.



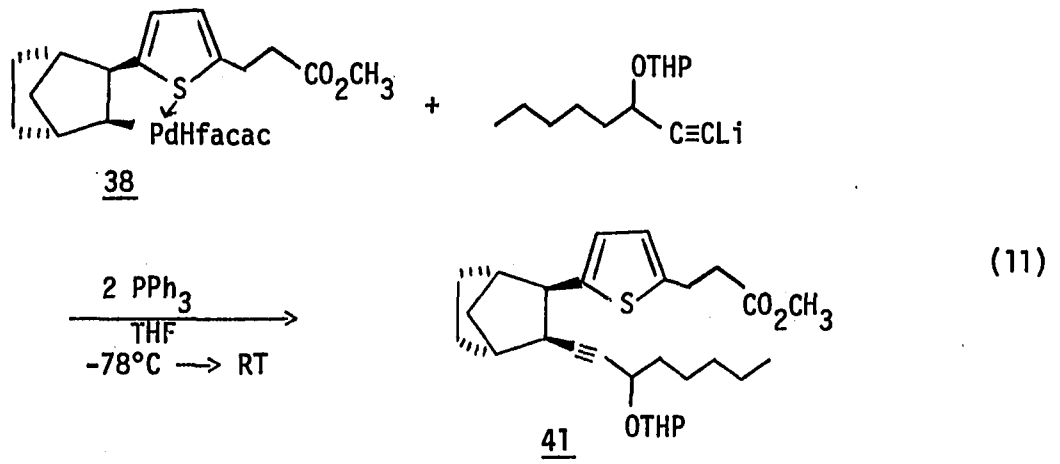
39



40

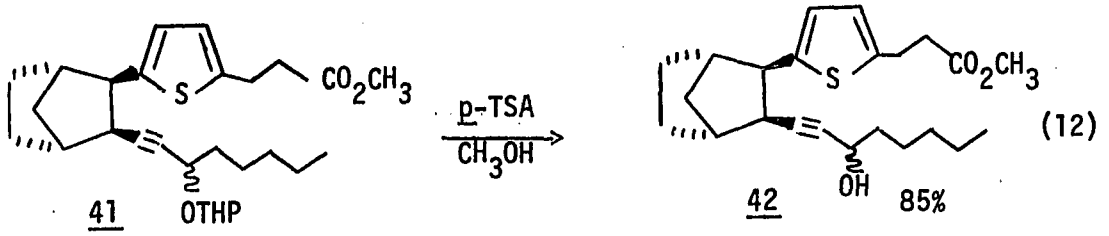
Treatment of 38 with two equivalents of triphenylphosphine followed by 1.05 equivalents of 1-lithio-3-(2-tetrahydropyranyloxy)-1-octyne at -78°C, stirring at -78°C for approximately 1 hour, and

warming slowly to room temperature afforded the coupled product in 68% yield (eq. 11). The tetrahydropyranyl ether, 41, was cleaved with



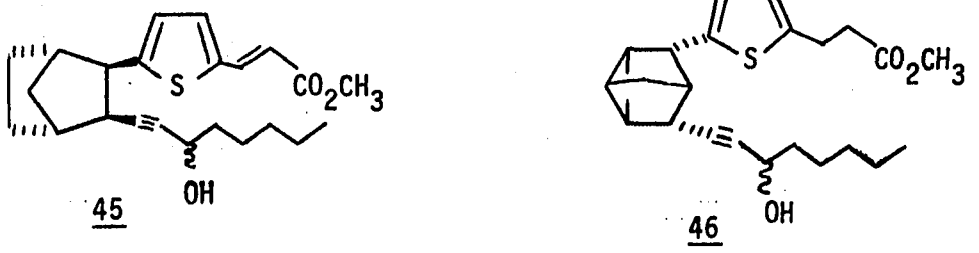
(11)

a catalytic amount of p-toluenesulfonic acid in methanol to give the propargylic alcohol in 58% overall yield from 38 (eq. 12).

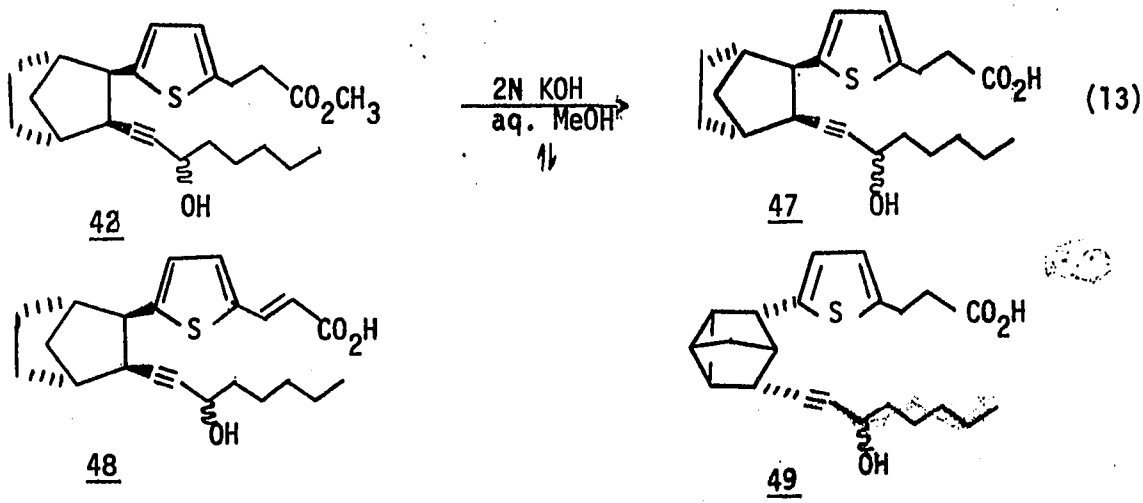


(12)

Compounds 39 and 40 were subjected to similar treatment and gave alcohols 45 and 46 in 64% and 62% yields, respectively, after hydrolysis of the tetrahydropyranyl ethers.



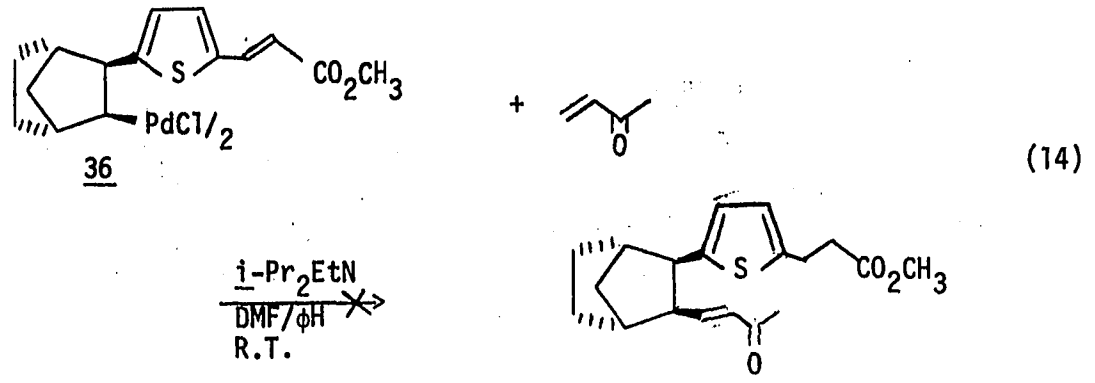
Hydrolysis of the methyl ester to afford the carboxylic acid was effected by refluxing for 30 minutes with 2N KOH in aqueous methanol. For example, ester 42 was converted to acid 47 in 82% yield by this procedure (eq. 13). Acids 48 and 49 were obtained similarly in 96% and 86% yields respectively.



42 47 48 49 (13)

Introduction of the trans-allylic alcohol side chain

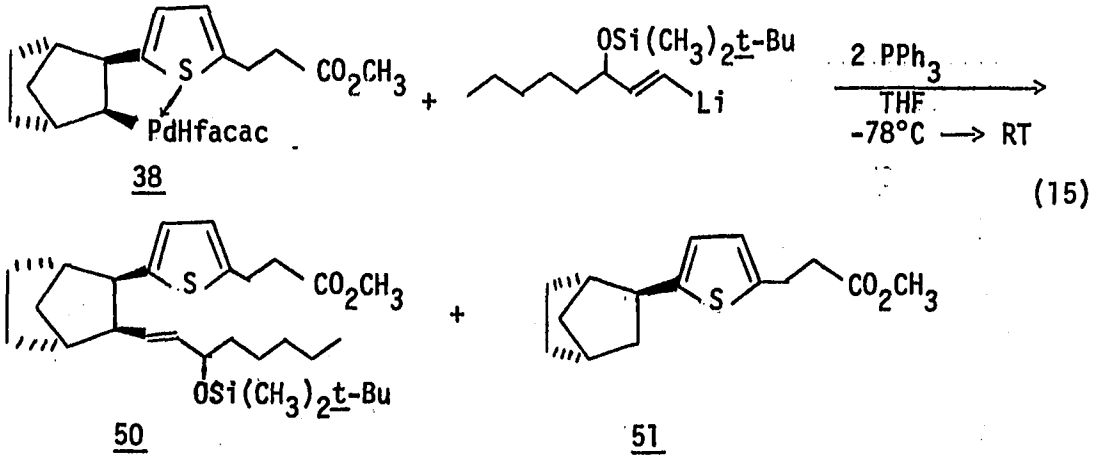
One potential method for introducing the trans-allylic alcohol side chain would appear to involve a Heck olefination of complexes 33, 36, and 37 with 1-octen-3-one. In order to study the potential usefulness of this method, the reaction of 36 with methyl vinyl ketone was chosen as a model system (eq. 14). Stirring 36 with eight equivalents of methyl vinyl ketone and an excess of tertiary amine in a mixture of DMF and benzene for one day gave only starting material plus a small amount of decomposition.



36 (14)

A second possible method for introducing the trans-allylic alcohol side chain involves treatment of 38-40 with a vinylmetallic to produce an alkyl-vinyl palladium species that would be expected to undergo reductive elimination to give the desired product. Palladium complexes have been coupled with organolithium (61-65), -zinc (66), and -aluminum (67) reagents in this manner.

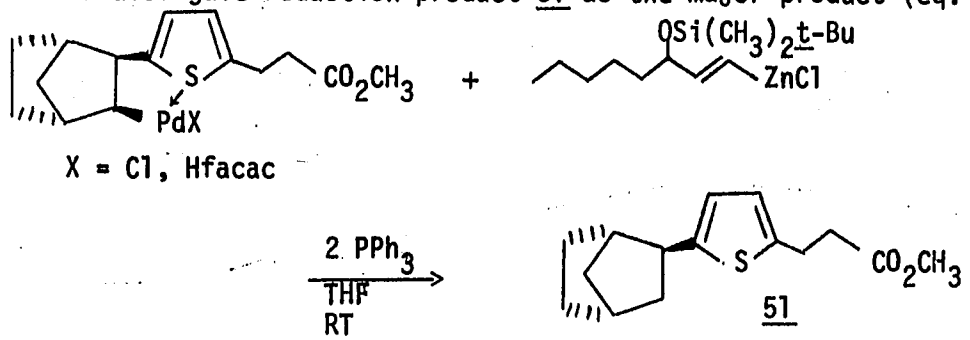
Reaction of 38 with 1.05 equivalents of 3-t-butyldimethylsilyoxy-trans-1-octenyllithium in the presence of 2 equivalents of triphenylphosphine in THF gave only a trace of the desired product, 50, and reduction product 51 (eq. 15).



38 (15)

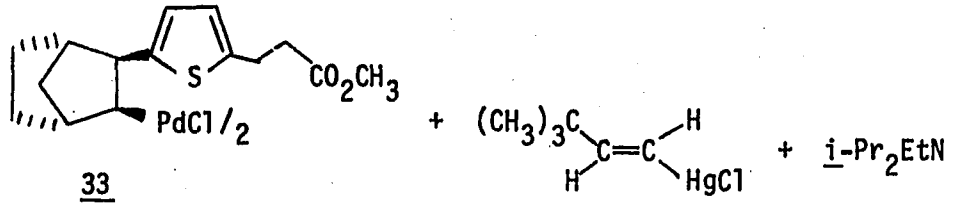
50 51

Treatment of either 33 or 38 with 2 equivalents of triphenylphosphine and 3-t-butyldimethylsilyloxy-trans-1-octenylzinc chloride in THF also gave reduction product 51 as the major product (eq. 16).



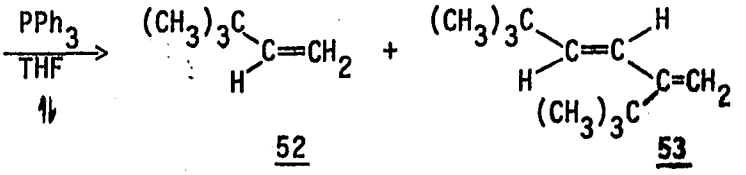
(16)

As an alternative to the use of strongly nucleophilic vinylmetallics in this reaction, one could envision the use of nonnucleophilic vinylmetallics that would undergo a facile transmetalation reaction with organopalladium complexes 33, 36, and 37 to give the desired alkyl-vinyl palladium species. With this in mind, compound 33 was refluxed with two equivalents of trans-3,3-dimethyl-1-butenylmercuric chloride, two equivalents of triphenylphosphine and two and one-half equivalents of di-iso-propylethylamine in THF (eq. 17). After work-up, extraction of the residue with hexanes afforded a mixture of 3,3-dimethyl-1-butene, 52, and 1,3-di-tert-butylbutadiene, 53. The yellow solid remaining after extraction was assumed to be the bis-phosphine complex of 33.



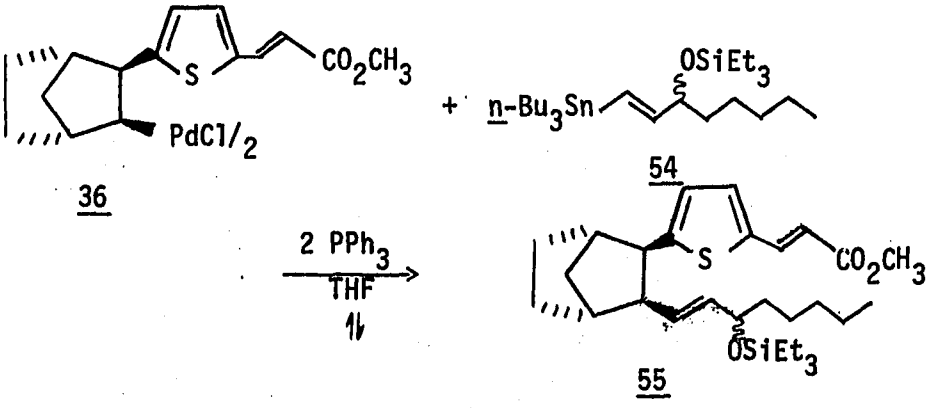
33

(17)



52 53

Another possible way to effect this exchange involved the use of the known vinyltin compound trans-1-tributylstannyl-3-triethylsilyloxy-1-octene, 54 (68). Refluxing palladium compound 36 with 54 and two equivalents of triphenylphosphine in THF for one day gave the desired product, 55, but in only 34% yield (eq. 18). Substitution

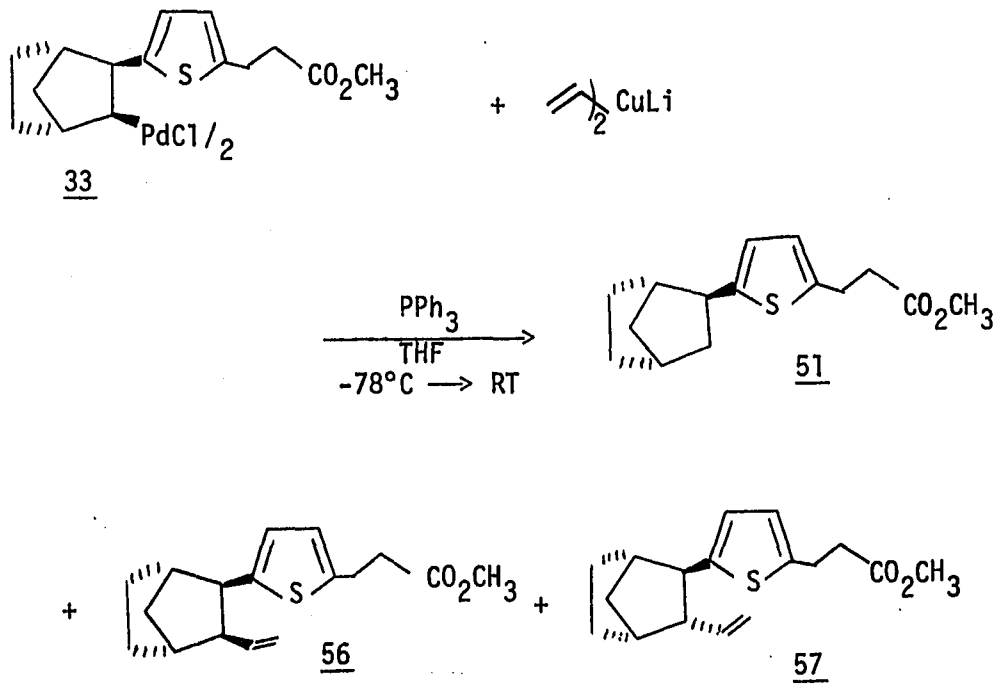


36 54 55

(18)

of HMPA for THF also gave the desired product, but in only 24% yield. Although this allows us to reach our goal, the yield is quite low. Vinyltin compounds are also difficult to prepare and are toxic. Therefore, we sought another method.

Organocuprates have been used several times for the introduction of the allylic alcohol chain in prostaglandins (69-72). Since organocuprates are less nucleophilic, and in general less reactive than their lithium counterparts, it was thought they might provide a solution. Towards this end, 1.3 equivalents of lithium divinylcuprate was added to a -78°C solution of 33, and 2.0 equivalents of triphenylphosphine in THF. After work-up and column chromatography, analysis by gas chromatography revealed the presence of three products: reduction product 51, and the isomeric vinylated products 56 and 57, in a ratio of 7:3:2 (eq. 19). These products were identified by gas

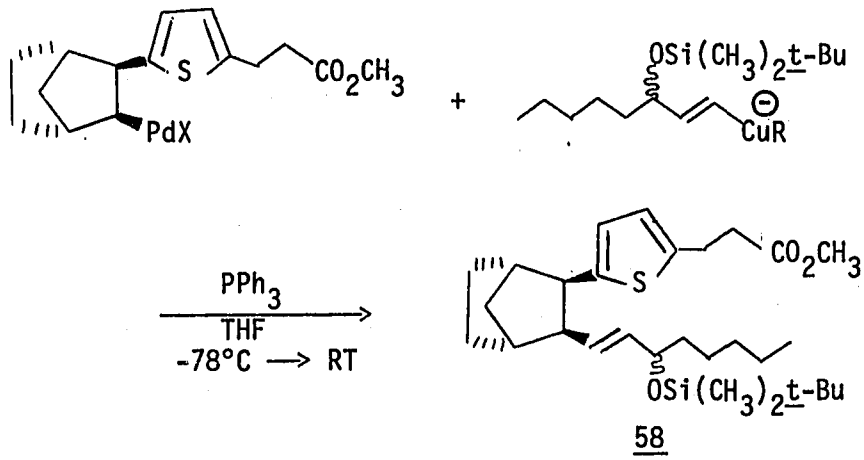


(19)

chromatography - mass spectrometry. With the hexafluoroacetylacetonate complex 38 in the same reaction, the products were the reduction product 51 and the exo-vinylated product, 56, in a ration of 2:3,

with only a trace of 57. The combined yield in both cases was approximately 40%. The presence of the endo-product, 57, was totally unexpected, and unexplainable on the basis of currently accepted mechanisms for similar reactions.

The introduction of the allylic alcohol chain using various mixed and divinyl cuprates was investigated next using known cuprate reagents (eq. 20) (73, 74).



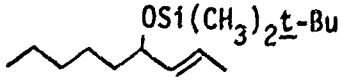
(20)

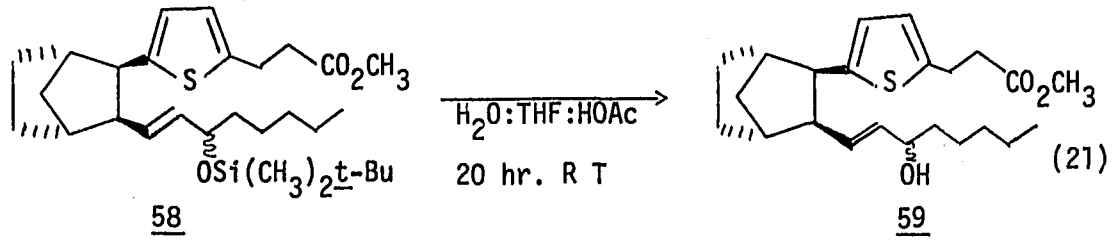
58

These results are summarized in Table IV below. From these data, it can be seen that the best results are obtained when X=Hfacac (entries 3 and 4). Furthermore, even though a large amount of reduction product is obtained, the conditions for entry 3 are preferred since separation of the product of acetylene transfer from 58 in entry 4 was rather difficult.

Cleavage of the t-butyldimethylsilyl ether of 58 with tetra-n-butylammonium fluoride in THF was unsuccessful. However, hydrolysis of the silyl ether was effected with 3:1:1 acetic acid: water: THF in 77% yield (eq. 21) (75).

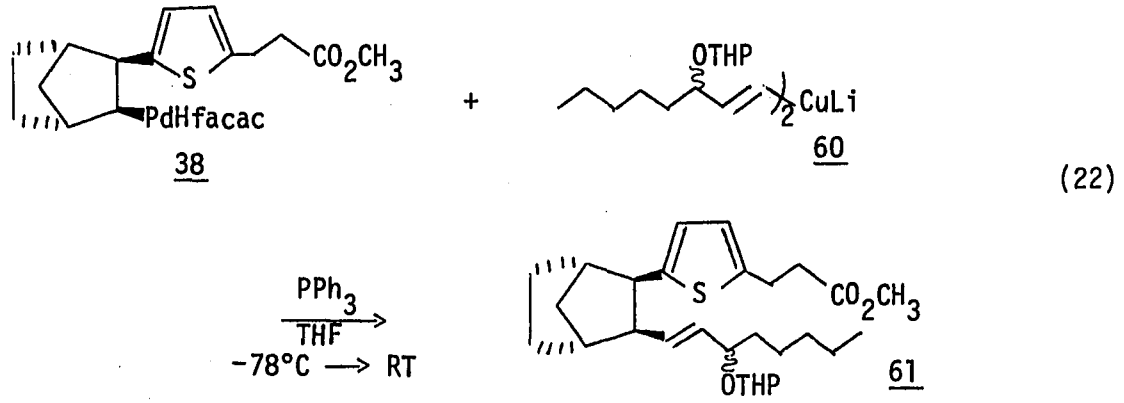
Table 4. Reactions with vinylcuprates

Entry	X	R	% Yield of 51	% Yield of 50	% Yield from transfer of R
1	Cl	$\underline{n}$-$C_3H_7C{\equiv}C$	trace	26	29
2	Cl		~20	17	--
3	Hfacac		58	31	--
4	Hfacac	$CH_3O(CH_3)_2CC{\equiv}C$	37	30	9



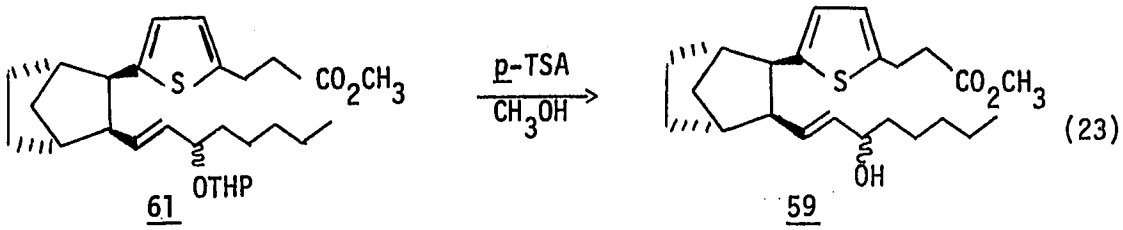
58 59 (21)

In view of the difficulty of removing the t-butyldimethylsilyl protecting group, the use of the more easily removed tetrahydropyranyl ether was investigated. Treatment of palladium compound 38 with 1.05 equivalents of the THP-protected cuprate (76), 60, in the presence of triphenylphosphine in THF afforded the desired product, 61, in 55% yield (eq. 22). Cleavage of the THP ether with 5%



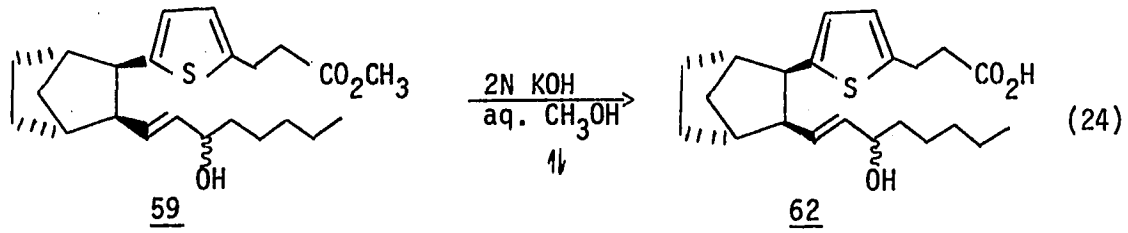
38 60 (22) 61

p-toluenesulfonic acid in methanol gave the desired alcohol, 59, in 60% yield for an overall yield of 33% (eq. 23). This compares favorably to the 24% yield obtained from the silyl-protected cuprate.



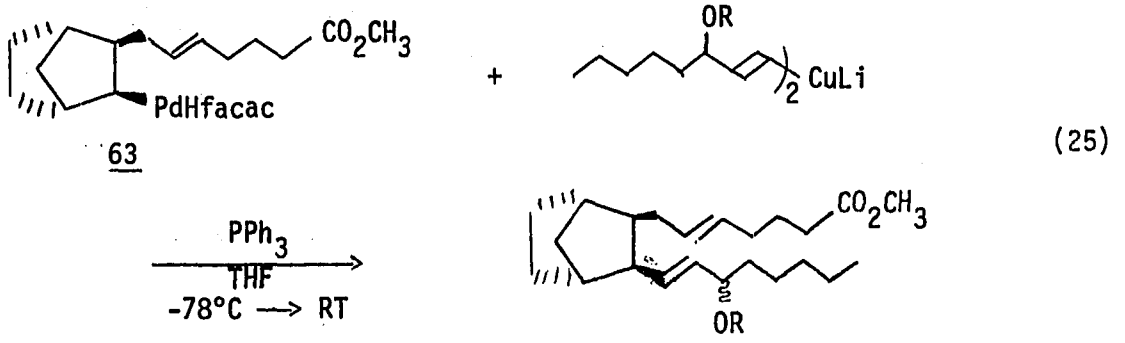
61 59 (23)

Hydrolysis of the methyl ester was accomplished by refluxing 59 with 2N KOH in aqueous methanol for 30 minutes. This provided the hydroxy acid in 79% yield (eq. 24).



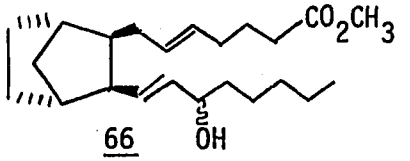
59 62 (24)

The extension of this method to the synthesis of the allyl alcohol analogue of 28 was investigated. Addition of palladium compound 63 to a solution of either vinylcuprate in THF at -78°C afforded the protected allyl alcohols 64 or 65 (eq. 25). The yield of the silyl-protected alcohol 64 was 50% while the yield of the

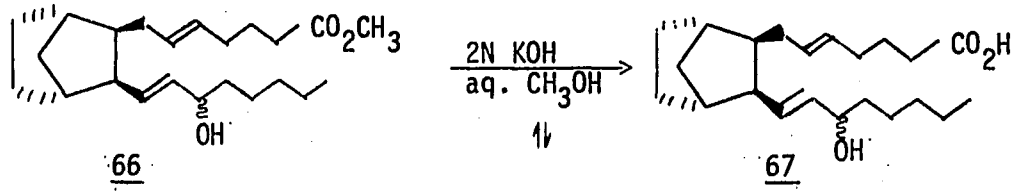


(25)

THP-protected product 65 was 65%. Removal of the protecting group was accomplished as described previously (eqs. 21, 23) to give the allylic alcohol 66. The overall yield with either cuprate was 30%. Hydrolysis



of this ester with 2N KOH provided the hydroxy acid in 93% yield (eq. 26).



(26)

At this point, some discussion of the mechanism of these reactions seems appropriate. The coupling reaction of σ-organopalladium compounds with a wide variety of nucleophiles has been described (30, 62-67). The generally accepted mechanism for such reactions is shown in Scheme V.

Scheme V

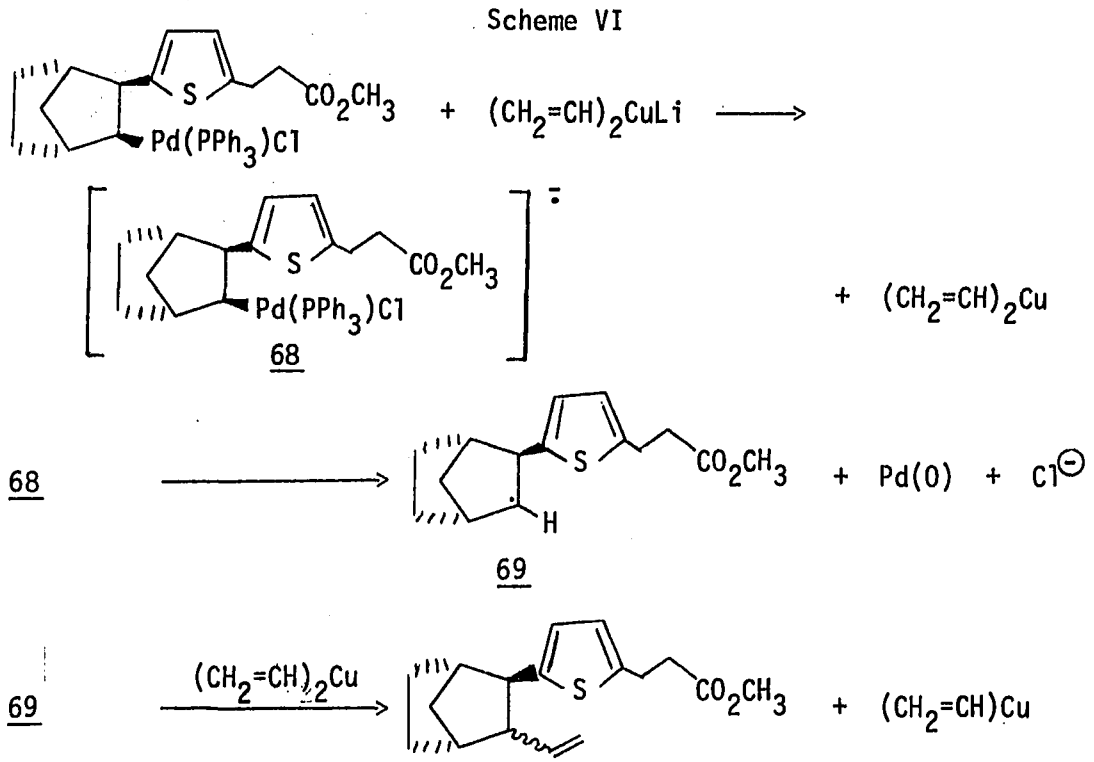
$$R\text{-}PdCl + R'M \longrightarrow R\text{-}Pd\text{-}R' + MX$$

$$R\text{-}Pd\text{-}R' \longrightarrow R\text{-}R' + Pd(0)$$

The organopalladium compound undergoes a metathesis reaction with the nucleophile in an SN2 process to give a diorganopalladium(II) species. This then undergoes a concerted 1,1-reductive elimination to give the coupled product and palladium(0). However, the presence of the endo-vinylated product 57, from the reaction of lithium divinylcuprate with 33 (eq. 19), cannot be explained by this mechanism, since a concerted reductive elimination should afford only the exo-isomer.

An alternative mechanism is shown below in Scheme VI. Initial single electron transfer from the cuprate to the organopalladium compound generates a radical anion, 68. This decomposes with loss of Pd metal and Cl^- to give a carbon radical, 69, which couples, possibly with divinylcopper(II), to give the vinylated isomers. This mechanism

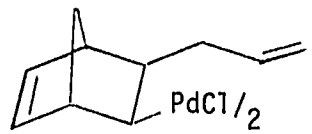
Scheme VI



is attractive for a number of reasons. The intermediacy of 69 certainly explains the formation of exo- and endo-isomers, since coupling could occur from either side of the radical, with exo- collapse predominating. The differences in product composition with different X groups on the palladium moiety are also explained. From the work of Larock and Burkhart outlined in Scheme II, organopalladium hexafluoroacetylacetonates were found to give higher yields and cleaner reactions, with lithium acetylides, than the corresponding chlorides (30), possibly because Hfacac was more easily displaced by the acetylide anion. In the coupling reaction of 38 (X=Hfacac) with lithium divinylcuprate, displacement probably occurs readily enough that very little of the

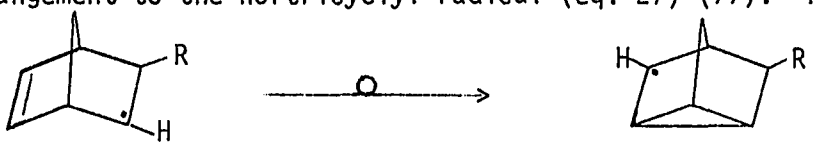
reaction proceeds via the electron transfer pathway. However with 33 (X=Cl), this displacement must be slow enough to allow electron transfer to compete favorably.

To obtain further evidence for the proposed mechanism, we sought to demonstrate the existence of the alkyl radical 69. Trapping the intermediate radical via a characteristic intramolecular rearrangement is a particularly useful technique for doing this. A variety of alkyl radicals which give diagnostic rearrangements have been studied and their rates determined (77). The palladium compounds corresponding to several of these radicals are readily available. In particular, compound 70, which is readily available from allylpalladium addition to norbornadiene (78), appeared to be an ideal starting



70

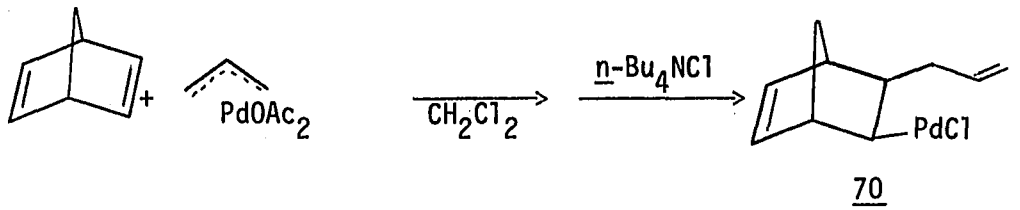
material. The radical derived from 70 undergoes a well-known rearrangement to the nortricyclyl radical (eq. 27) (77). The rate



(27)

constant for this rearrangement has been determined to be $1 \times 10^5\ s^{-1}$ at -78°C (79). This is quite fast and therefore might be expected to trap the intermediate radical if it is present.

Addition of allylpalladium acetate to an excess of norbornadiene in methylene chloride, followed by 1.0 equivalent of n-Bu_4NCl afforded compound 70 in 76% yield (eq. 28). Treatment of 70 with



(28)

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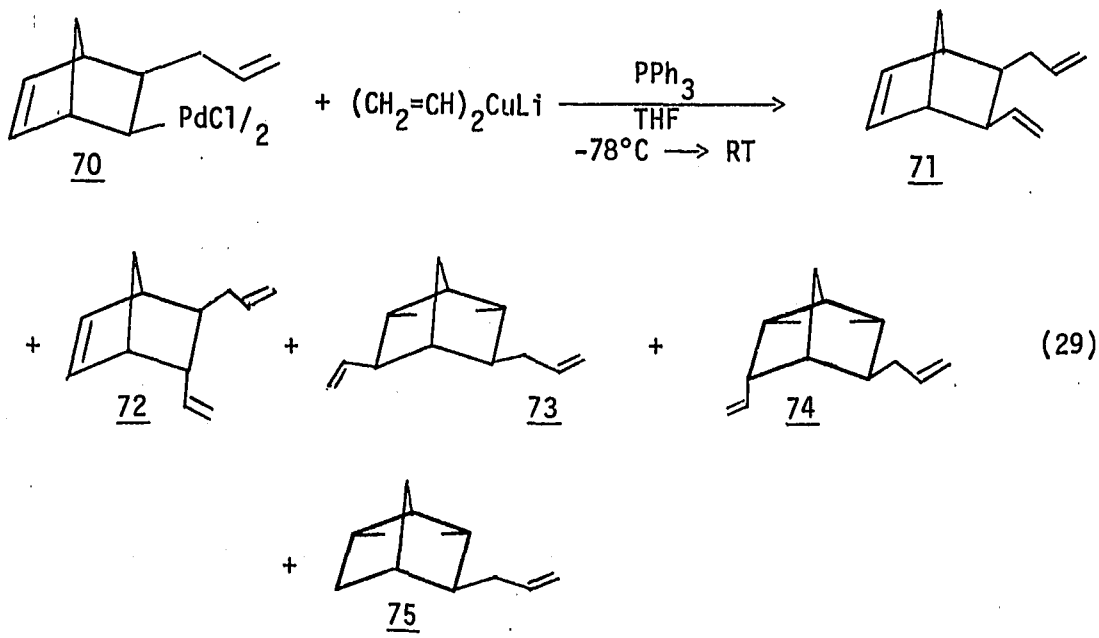
1.1 equivalents of lithium divinylcuprate in THF at -78°C and warming to room temperature gave a mixture of products after purification by column chromatography (eq. 29). The major products of the reaction were separated by glass capillary gas chromatography and identified as



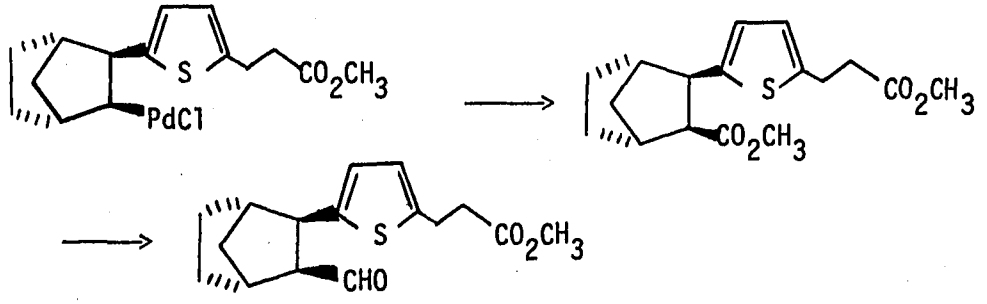
70 71 72 73 74 75

(29)

exo-isomer 71 (50%), endo-isomer 72 (16%), rearranged products 73 (5%) and 74 (5%), and 75 (trace). The products were identified, and structures assigned on the basis of their mass spectra. These are

shown for compounds 71-74 in Figures 1-4. Structures for 71 and 72 are assigned based upon their ready fragmentation via a retro Diels-Alder reaction to afford an ion of mass 66 (C_5H_6) as the base peak. Compounds 73 and 74 on the other hand cannot undergo this fragmentation and therefore give only a minor peak at m/z 66. The base peak for both 73 and 74 has a mass of 91, characteristic of the nortricyclo skeleton. The exo- and endo- configurations were assigned based on the relative retention times of exo- and endo- isomers 56 and 57 (56 eluting before 57). The presence of products 73-75, presumably arising from rearrangement of the 3-allyl-5-norbornen-2-yl radical, suggests that the electron transfer mechanism outlined in Scheme VI may be correct.

Since the overall yield for the introduction of the allyl alcohol side chain using organocuprates is only 33%, a more efficient method to accomplish this transformation was sought. One potential approach involves carbonylation of the palladium compound to an ester and selective reduction to the aldehyde so that the rest of the side chain can be introduced by a Wittig reaction (eq. 30). However, this introduces the problem of having to selectively reduce or hydrolyze one of two methyl esters, and is therefore not very attractive.



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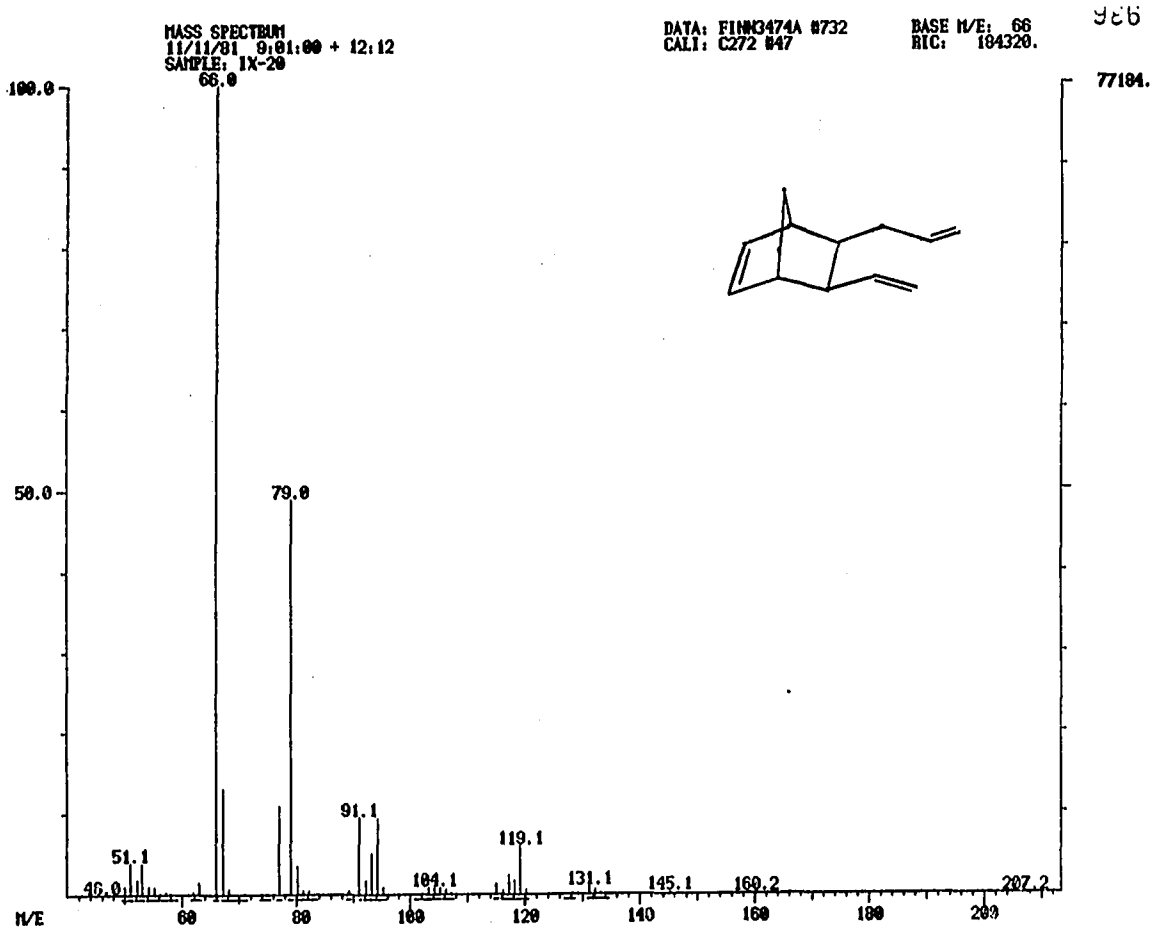


Figure 1. Mass spectrum of compound 71

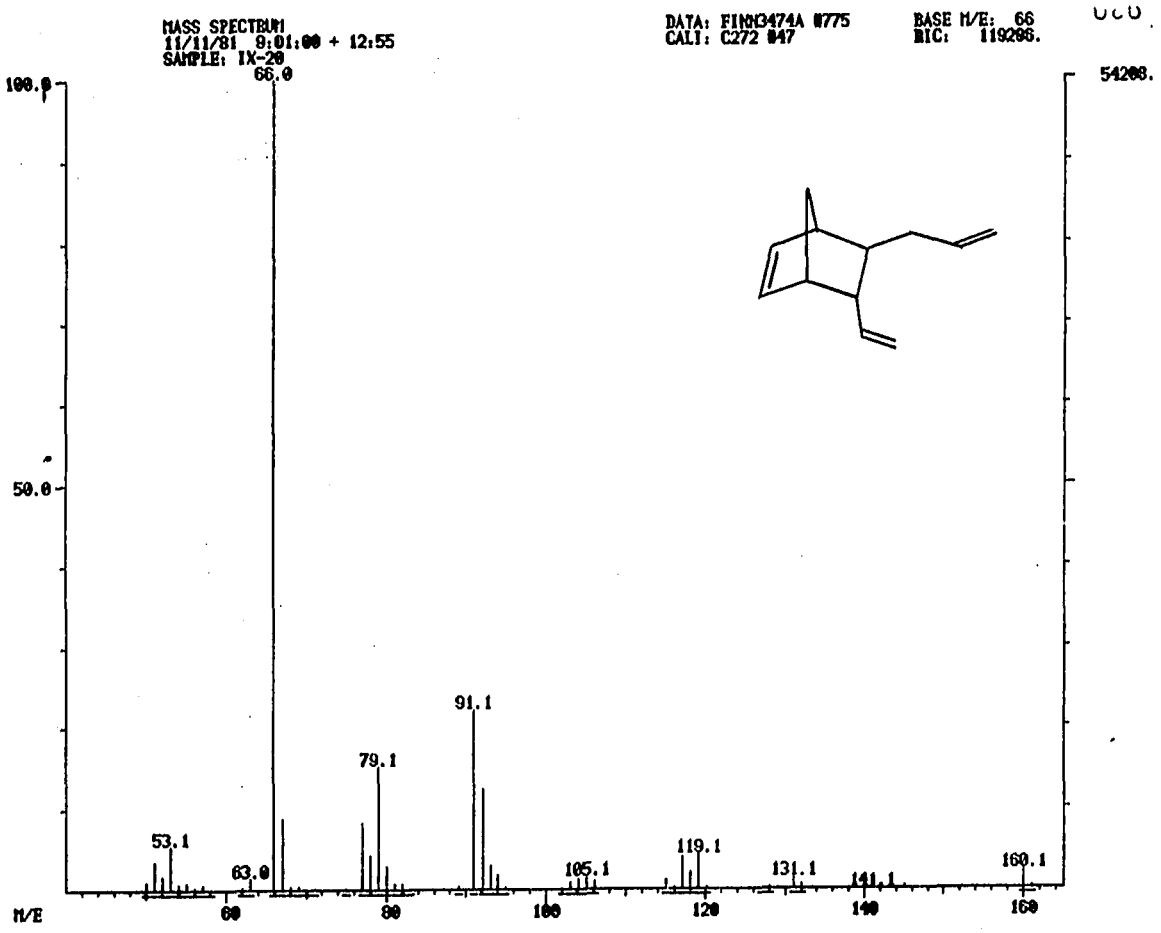


Figure 2. Mass spectrum of compound 72

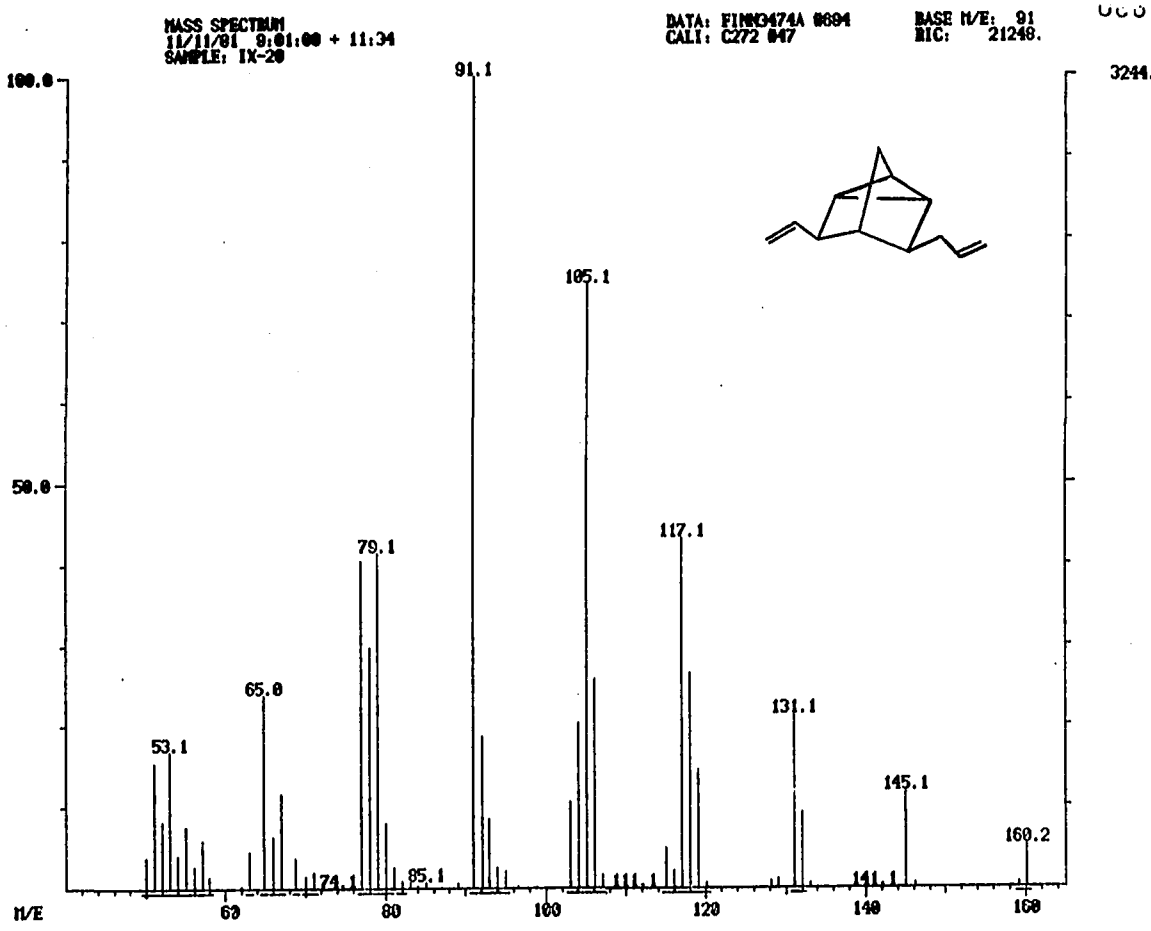


Figure 3. Mass spectrum of compound 73

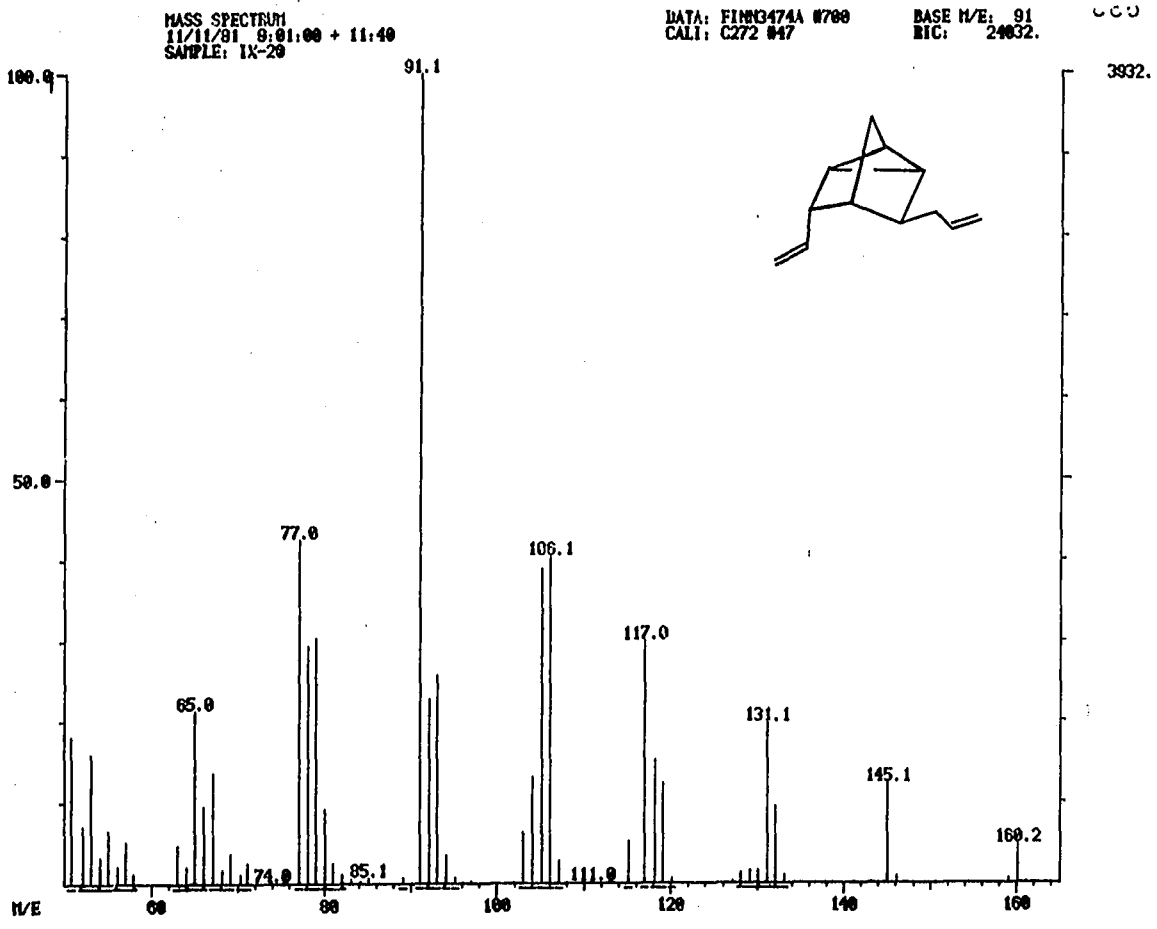
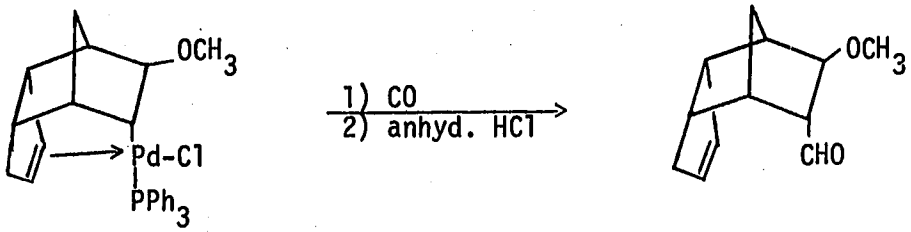


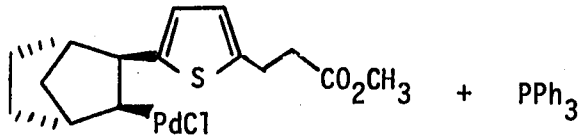
Figure 4. Mass spectrum of compound 74

Graziani has reported the carbonylation of an organopalladium compound to an aldehyde (eq. 31) (80). No yield for the aldehyde



(31)

was reported. This reaction would allow introduction of the desired aldehyde in one step without having to differentiate between two esters. Palladium compound 33 and one equivalent of triphenylphosphine were stirred under an atmosphere of carbon monoxide, followed by anhydrous HCL (eq. 32). However, after work-up, NMR analysis of the crude



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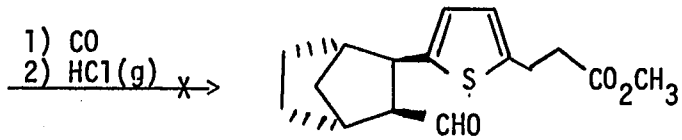
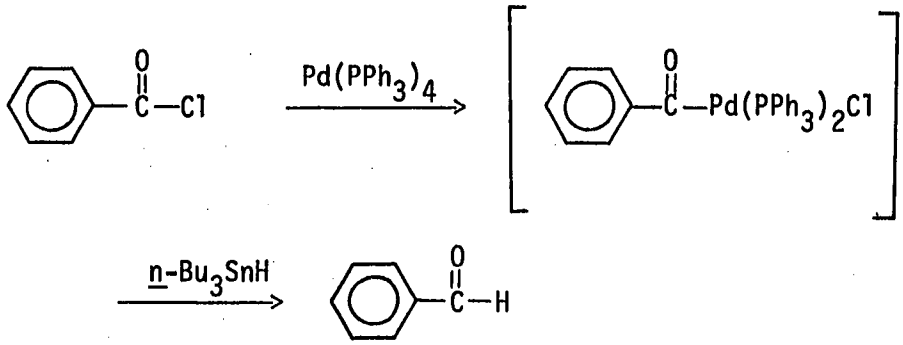
(32)



76

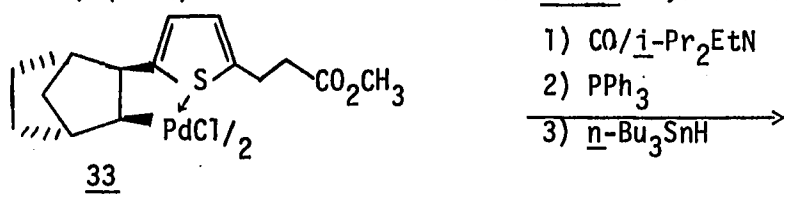
product showed that no aldehyde had been formed.

Guibe has recently reported the palladium-catalyzed reduction of acid chlorides to aldehydes using tri-n-butyltin hydride (81). This reaction is reported to go through an acylpalladium intermediate (eq. 33).



(33)

This should then provide a method for the carbonylation of organopalladium compounds to aldehydes. Indeed, sequential treatment of 33 with di-iso-propylethylamine and carbon monoxide, triphenyl phosphine, and tri-n-butyltin hydride afforded the desired aldehyde in 100% yield (eq. 34). Introduction of the trans-13,14-double bond and the



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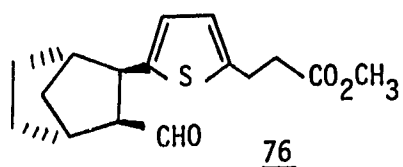
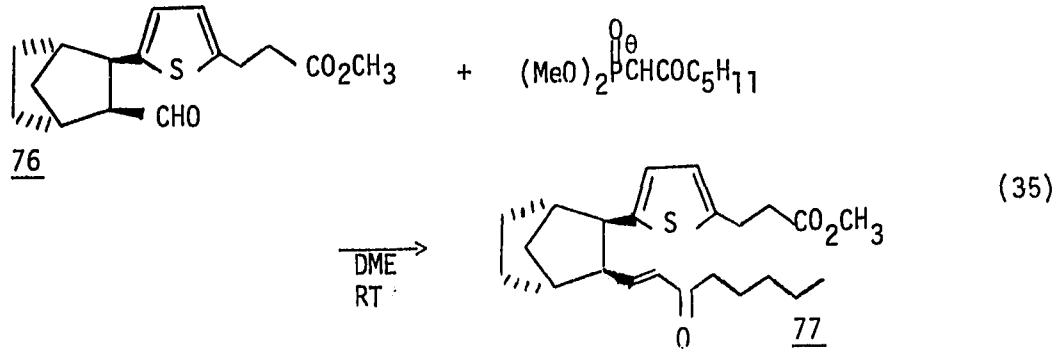
(34)



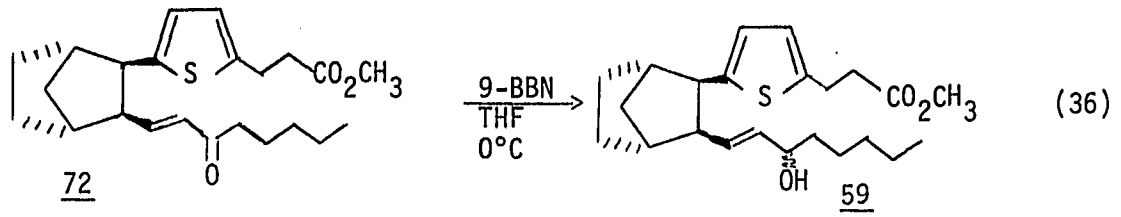
76

remainder of the alcohol side chain of several prostaglandins has been accomplished using the Wadsworth-Emmons' modification of the Wittig reaction (82). Addition of 76 to the sodium anion of dimethyl 2-oxoheptylphosphonate in dimethoxyethane (DME) gave the trans-enone 77 in 86% yield, along with 10% of the cis-isomer (eq. 35).



76 77 (35)

Reduction of the enone to the allylic alcohol was accomplished in 95% yield with 9-borabicyclononane(9-BBN) in THF at 0°C (eq. 36) (83).

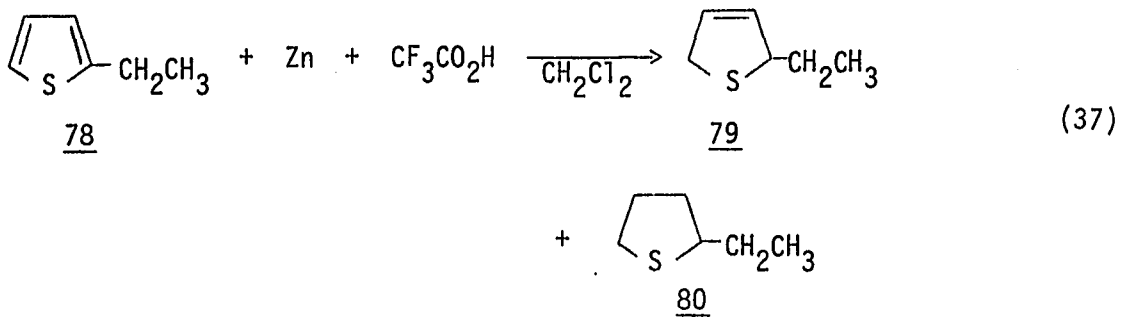


72 59 (36)

The overall yield of 59 from the starting palladium compound was 82%, a significant improvement on the vinylcuprate method.

Reduction of thiophenes

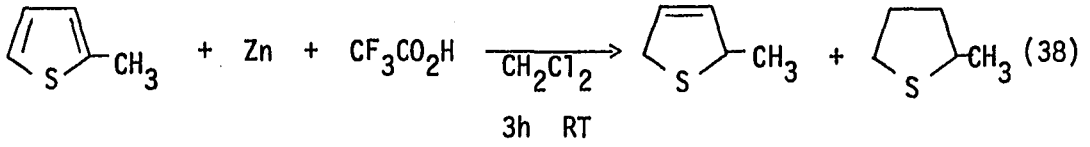
The reduction of thiophenes to 2,5-dihydrothiophenes by ionic hydrogenation has been reported (eq. 37) (46). The yield of 79 was



78 79 80 (37)

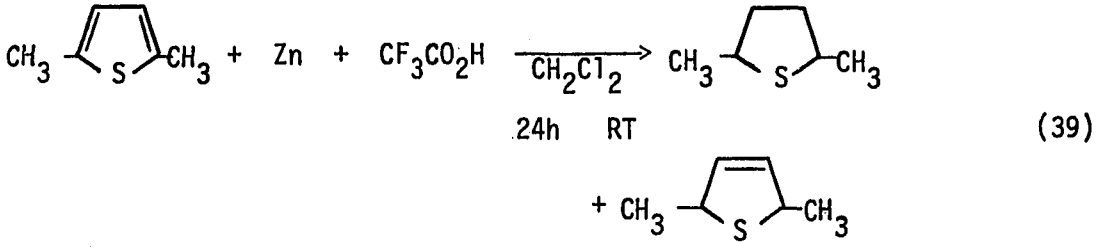
70%, accompanied by 6% of 80.

The reductions of 2-methylthiophene and 2,5-dimethylthiophene were examined as model systems for the reduction of our thiophene-containing prostaglandin analogues. Reduction of 2-methylthiophene under conditions similar to those in eq. 37 gave a mixture of 2-methyl-2,5-dihydrothiophene in 60% yield and 2-methyltetrahydrothiophene in 15% yield (eq. 38). Optimal yields were obtained after 3 hours.



(38)

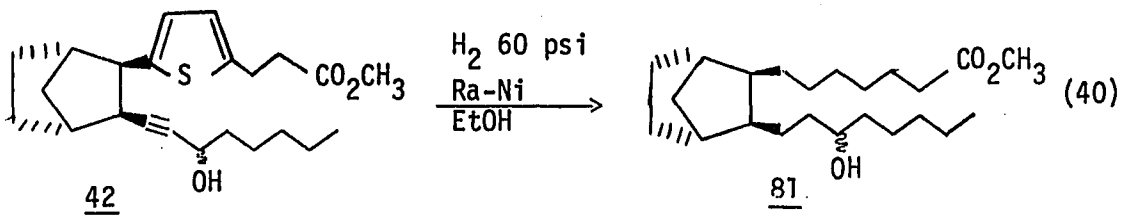
The reduction of 2,5-dimethylthiophene was much slower. Reduction for 24 hours gave a mixture of 50% of 2,5-dimethyltetrahydrothiophene and 18% of the desired product, 2,5-dimethyl-2,5-dihydrothiophene (eq. 39). Using higher or lower concentrations of reducing agent and



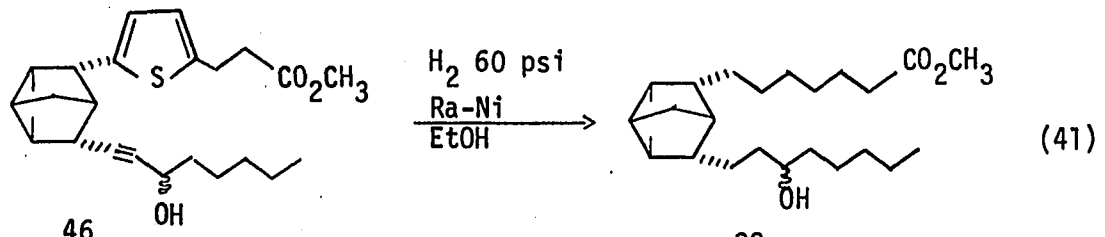
(39)

higher or lower temperatures all failed to improve the yield. In view of the low yields of dihydrothiophenes obtained on model systems, analogous reductions on our thiophene containing prostaglandin analogues were not pursued.

However, the Raney nickel hydrogenation of the thiophene-containing prostaglandin analogues 42 and 46 to afford the corresponding saturated prostanoic acid analogues has been studied. The reductive desulfurization of substituted thiophenes to alkanes is a well-studied reaction (84). Hydrogenation of 42 and 46 over Raney nickel W-7 under hydrogen in ethanol afforded the saturated analogues 81 and 82 in 82% and 87% yield respectively (eqs. 40, 41). Hydrogenation of

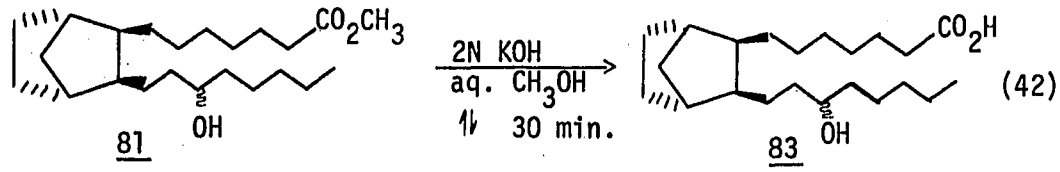


42 81 (40)

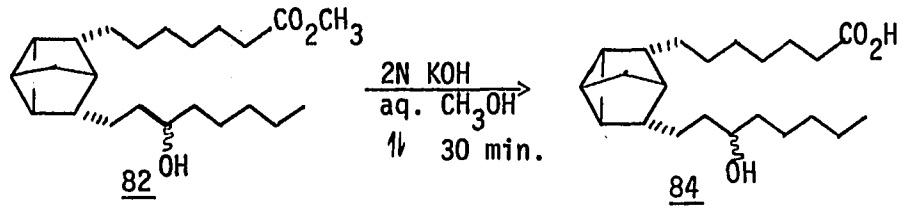


46 82 (41)

the methyl esters instead of the acids was preferred due to the ease of their subsequent purification by chromatography. Hydrolysis of the methyl esters to the corresponding acids was accomplished by refluxing with 2N KOH in aqueous methanol (eqs. 42, 43). Acids 83 and 84 were isolated in 86% and 95% yield respectively.



81 83 (42)



82 84 (43)

Biological results

The biological activity of these new prostaglandin analogues has been examined by Bristol Laboratories of Syracuse, New York. The compounds were evaluated for in vivo inhibition of arachidonic acid induced platelet aggregation in rabbit platelet rich plasma. The EC_{50} for a compound is the effective concentration necessary to reduce the induced blood platelet aggregation by 50%. These results are summarized in Table V. For comparison, the EC_{50}'s of PGE_1 and PGI_2 are 18ng/mL and 4ng/mL respectively. The EC_{50} for compound 28 was 45ng/mL.

Table 5. Biological activity

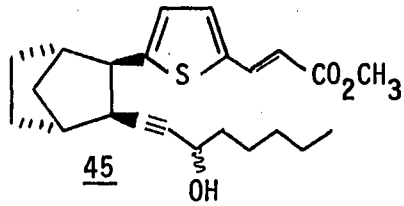
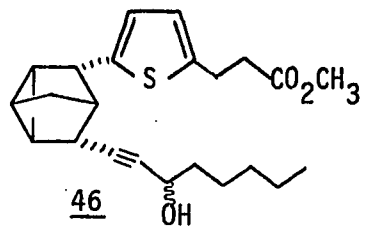
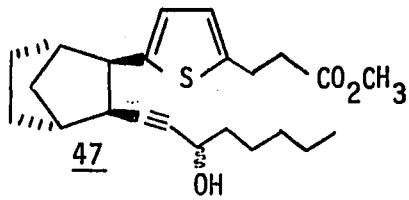
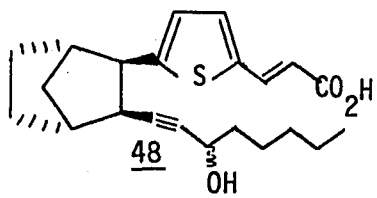
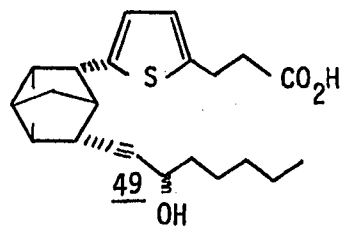
Compound	EC_{50} (ng/mL)
 45	970
 46	1,300
 47	1,500
 48	29,000
 49	24,000

Table 5. continued

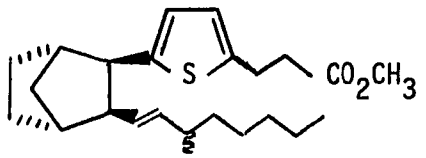
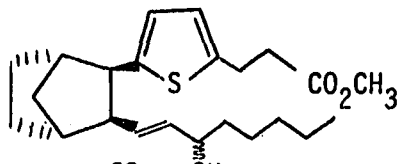
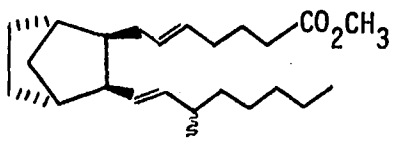
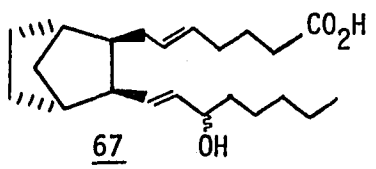
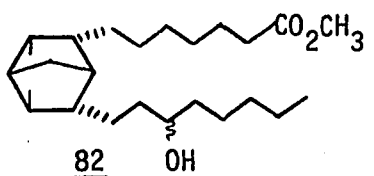
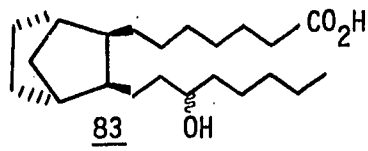
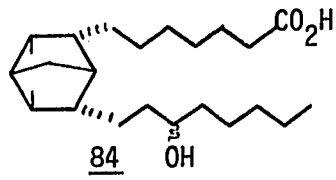
Compound	EC_{50} (ng/mL)
 59	10,800
 62	40,000
 66	2,200
 67	143,000
 82	>256,000

Table 5. continued

Compound	EC_{50} (ng/mL)
 83	6,100
 84	76,000

From these results it can be seen that these new prostaglandin analogues are considerably less active in the inhibition of blood platelet aggregation than other previously synthesized analogues and several natural prostaglandins. Particularly interesting are compounds 66 and 67 which are 30 and 300 times less active respectively than the corresponding propargyl alcohol analogues.

Conclusion

An approach to the synthesis of thiophene-containing bicyclic prostaglandin analogues via thienylpalladation of bicyclic olefins has been developed. Unfortunately, application of this approach to the synthesis of the analogous furans was unsuccessful. An approach has also been developed for the introduction of the trans-allylic alcohol side chain in a number of bicyclic prostaglandin analogues. The thiophene-containing bicyclic prostaglandin analogues could also be hydrogenated to the completely saturated prostanoic acid analogues.

Experimental

Equipment

Proton NMR spectra were recorded on either a Varian EM-360, or HA-100 spectrometer. ^{13}C NMR spectra were recorded on a JEOL-FX90Q spectrometer. Infrared spectra were recorded on a Beckman IR-4250 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 30 m SE-30 capillary column from J. W. Scientific and a Varian CDS-111 chromatography data system was used for gas chromatographic analyses. HPLC analyses of all bicyclic prostaglandin analogues were performed on a Varian model 5060 HPLC equipped with a variable wavelength detector and a Varian MCH-10 30 cm reverse-phase column. Analyses were carried out using gradient elution at the rate of 10%/minute (initial solvents: methyl esters; 50% acetonitrile in water; carboxylic acids; 20% acetonitrile in water) while monitoring at 254 nm.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. THF and diethyl ether were distilled from calcium hydride. HMPA was refluxed over calcium hydride and distilled under reduced pressure. Dimethoxyethane was distilled from lithium aluminum hydride. n-Butyllithium and t-Butyllithium were obtained from Alfa and titrated before use with 2,5-dimethoxybenzyl alcohol (85). Vinyllithium was obtained from Org-Met and titrated by the method of Watson and Eastham (86). Copper(I) iodide was obtained from Alfa

and purified by a literature procedure (87). Zinc(II) chloride was dried by refluxing with excess thionyl chloride followed by removal of thionyl chloride and drying under high vacuum. 1-Buten-3-one was distilled immediately prior to use. Di-iso-propylethylamine was distilled from calcium hydride.

(E)-3-t-Butyldimethylsilyloxy-1-iodo-1-octene (73), (E)-1-tri-n-butylstannyl-3-triethylsilyloxy-1-octene (68), norbornadiene-palladium dichloride (88), (E)-3,3-dimethyl-1-butenylmercuric chloride (89), and 3-(2-tetrahydropyranyloxy)-1-octyne (90) were prepared using literature procedures. Raney nickel W-7 was prepared by a literature procedure using Raney nickel-aluminum alloy from W. R. Grace (91).

Syntheses of thiophenes and furans

Methyl trans-3-(2-thienyl)acrylate: trans-3-(2-Thienyl)acrylic acid (10.0 g, 65 mmol) was refluxed in 100 mL of methanol with 3 drops concd H_2SO_4 for 8 hours. The mixture was then diluted with ether, washed twice with 10% $NaHCO_3$, and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo and recrystallization from hexane gave 9.35 g (55.6 mmol, 86%) of methyl trans-3-(2-thienyl)acrylate: mp 42°C, lit. mp 40-42.2°C (39).

Methyl 3-(2-thienyl)propionate: 3-(2-Thienyl)propanoic acid (2.30 g, 14.7 mmol), prepared by hydrogenation of 3-(2-thienyl)acrylic acid according to a literature procedure (57), was treated as above to afford 2.35 g (95%) of methyl 3-(2-thienyl)propionate: ^{1}H NMR($CDCl_3$) δ 2.4-2.8 (2H, m, CH_2CO), 2.9-3.35 (2H, m, thienyl-CH_2), 3.60 (3H, s, OCH_3), 6.5-7.2 (3H, m, thienyl).

Methyl trans-3-(2-furyl)acrylate: trans-3-(2-furyl)acrylic acid (10.0 g, 72.4 mmol) was esterified as above to give 7.18 g (70%) of methyl 3-(2-furyl)acrylate: mp 35-36°, ^{1}H NMR($CDCl_3$) δ 3.80 (3H, s, OCH_3), 6.27 (1H, d, J=16Hz, $CHCO_2Me$), 6.3-6.7 (2H, m, furyl), 7.43 (1H, d, J=16Hz, $HC{=}CCO_2Me$), 7.50 (1H, brs, furyl).

Methyl 3-(2-furyl)propionate: Methyl trans-3-(2-furyl)acrylate (1.66 g, 10.9 mmol) was dissolved in 50 mL of methanol and .8 mL (11 mmol) of concd NH_4OH. 10% Palladium on charcoal (.50 g) was then added and the flask was flushed with hydrogen. The mixture was stirred under hydrogen for 6 hours after which it was filtered and the catalyst washed with diethyl ether. The filtrate was diluted with ether and benzene, washed with water, and dried over anhydrous magnesium sulfate. Distillation via Kugelrohr [90°C (14 torr)] afforded 1.30 g (78%) of methyl 3-(2-furyl)propionate: ^{1}H NMR($CDCl_3$) δ 2.35-3.15 (4H, m, CH_2), 3.65 (3H, s, OCH_3), 5.95 (1H, m, furyl), 6.20 (1H, m, furyl), 7.25 (1H, m, furyl).

Syntheses of the organomercurials

The synthesis of methyl 3-(5-chloromercuri-2-thienyl)propionate, 32, is representative. Methyl 3-(2-thienyl)propionate (2.0 g, 11.8 mmol) in 5 mL of ethanol was added to a solution of 6.4 g (23.6 mmol) of $HgCl_2$ and 6.7 g NaOAc in 35 mL of 30% ethanol. This was allowed to stand for two days after which time the product was isolated by filtration and recrystallized to give 3.77 g (83%) of methyl 3-(5-chloromercuri-2-thienyl)propanoate, 32: mp 155-157°C; ^1H NMR (DMSO-d^6) δ 2.68 (2H, d, J=6Hz, CH_2CO), 3.04 (2H, d, J=6Hz, thienyl-CH_2), 3.59 (3H, s, OCH_3), 6.8-7.1 (2H, m, thienyl). Anal. Calcd for $C_8H_9O_2SHgCl$: C, 23.71; H, 2.24; O, 7.90; S, 7.91. Found: C, 23.65; H, 2.31; O, 8.02; S, 8.06.

Methyl 3-(5-chloromercuri-2-thienyl)acrylate, 34: 86% yield; mp 243-245°C; ^1H NMR(acetone-d^6) δ 3.75 (3H, s, -OCH_3), 6.24 (1H, d, J=16Hz, =CHCO), 7.18 (2H, d, J=4Hz, thienyl), 7.73 (1H, d, J=16Hz, CH=CCO). Anal. Calcd for $C_8H_7O_2SHgCl$: C, 23.83; H, 1.75; O, 7.94; S, 7.95. Found: C, 23.87; H, 1.63; O, 7.76; S, 7.61.

Methyl 3-(5-chloromercuri-2-furyl)propionate, 35: 84% yield; mp 100-105°C(d); ^1H NMR(DMSO-d^6) δ 2.4-3.25 (4H, m, CH_2), 3.68 (3H, s, -OCH_3), 5.8-6.1 (2H, m, furyl). Anal. Calcd for $C_8H_9O_3HgCl$: C, 24.69; H, 2.33; Hg, 51.54. Found: C, 24.20; H, 2.59; Hg, 53.14.

Synthesis of compounds 33 and 36

The synthesis of compound 33 is representative. Norbornene (1.88 g, 20.0 mmol), 0.35 g palladium chloride (2.0 mmol), and 0.18 g lithium chloride (4.1 mmol) were dissolved in 15 mL of acetonitrile and cooled to 0°C. To this was added 0.81 g (2.0 mmol) of methyl 3-(5-chloromercuri-2-thienyl)propionate while backflushing with nitrogen. The reaction was then allowed to warm slowly to room temperature and stirred for 24 hours. The reaction was then cooled to 0°C and filtered. The green solid obtained was dissolved in CH_2Cl_2, filtered through Celite to remove palladium metal, washed with saturated NH_4Cl, and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded 1.58 g (78%) of 33: mp 155-157°C(d); ^1H NMR($CDCl_3$) δ .8-1.8 (6H, m), 2.35-3.2 (8H, m), 3.68 (3H, s, $-OCH_3$), 6.62 (1H, d, J=3.5Hz, thienyl), 6.98 (1H, d, J=3.5Hz, thienyl); IR(KBr) 1740 (ester C=O), 1170 (C-O)cm^{-1}. Anal. Calcd for $C_{15}H_{19}O_2SPdCl$: C, 44.46; H, 4.73; O, 7.90; S, 7.91. Found: C, 44.65; H, 4.82; O, 8.15; S, 8.04.

Compound 36: 67% yield; mp 165°C(d); ^1H NMR($CDCl_3$) δ 1.1-1.6 (6H, m), 1.9-2.15 (1H, m), 2.6 (2H, m), 3.05 (1H, d, J=8Hz), 3.75 (3H, s, OCH_3), 6.25 (1H, d, J=16Hz, =CHCO), 6.75 (1H, d, J=7Hz, thienyl), 7.2 (1H, d, J=7Hz, thienyl), 7.6 (1H, d, J=16Hz, HC=CCO); IR(KBr) 1720 (C=O), 1160 (C-O), 980 [(E)-C=C]cm^{-1}. Anal. Calcd for $C_{15}H_{17}O_2SPdCl$: C, 44.68; H, 4.25; O, 7.96; S, 7.94. Found: C, 44.90; H, 4.32; O, 8.02; S, 8.03.

Synthesis of compound 37

Norbornadienepalladium dichloride (1.51 g, 5.61 mmol) was stirred in 40 mL of acetonitrile and cooled to 0°C under nitrogen. Methyl 3-(5-chloromercuri-2-thienyl)propionate (2.27 g, 5.60 mmol) was added while backflushing with nitrogen. The reaction was allowed to slowly warm to room temperature and stirred for 8 hours. The reaction was then cooled to 0°C and filtered. The green solid was dissolved in methylene chloride, treated with charcoal, filtered through Celite, and evaporated in vacuo to afford 1.67 g (74%) of 37: mp 181-182°C (d); ^{1}H NMR($CDCl_3$) δ 1.45 (2H, br s), 1.6-1.9 (2H, m), 1.9-2.1 (2H, m), 2.2-2.5 (2H, m), 2.5-3.2 (4H, m, CH_2CH_2), 3.72 (3H, s, OCH_3), 6.73 (2H, s, thienyl); IR(KBr) 1740 (C=O), 1170 (C-O), 810 (nortricyclene ring system)cm^{-1}. Anal. Calcd for $C_{15}H_{17}O_2SPdCl$: C, 44.69; H, 4.25. Found: C, 44.56; H, 4.53.

Synthesis of 38, 39, and 40

The synthesis of 39 is representative. Compound 36 (406 mg, 1.008 mmol) and 176 mg silver acetate (1.06 mmol) were stirred for 1 hour in 10 mL of chloroform. The suspension was then filtered through Celite to remove AgCl. Hexafluoroacetylacetone (.27 g, 1.3 mmol) was added and the yellow solution was stirred for 30 minutes. The solvent was then removed in vacuo to afford 568 mg (98%) of 39 as a yellow brown oil.

Reaction of 38, 39, and 40 with 1-lithio-3-(2-tetrahydropyranyloxy)-1-octyne

The reaction of compound 39 is representative. 3-(2-Tetrahydropyranyloxy)-1-octyne (196.6 mg, .9348 mmol) was dissolved in 5 mL of THF and cooled to -78°C under nitrogen. The acetylene was deprotonated by adding .40 mL (.908 mmol) of 2.27 N n-butyllithium and stirring for 1 hour at -78°C. Compound 39 (499 mg, .868 mmol) and 456 mg (1.738 mmol) of triphenylphosphine were stirred for 30 minutes in 8 mL of THF at room temperature under nitrogen and then cooled to -78°C. The solution of the lithium acetylide was then transferred via stainless steel cannula to the cold solution of the palladium complex. This was stirred at -78°C for 1 hour and then allowed to slowly warm to room temperature overnite. The reaction was then quenched with 1 mL of CH_3OH. The solvent was then removed in vacuo and the residue extracted with 3 25 mL portions of hexanes. The extract was filtered through Celite, concentrated, and purified by chromatography on silica gel using benzene: ethyl acetate (29:1) as eluent to afford 311 mg (77%) of 43: Rf .29; ^1H NMR($CDCl_3$) δ .8-2.2 (23H, m), 2.3-3.6 (6H, m), 3.72 (3H, s, $-OCH_3$), 4.08 (1H, m, C≡C-CHOR), 4.51 (1H, br s, -OCHO-), 6.04 (1H, d, J=16Hz, (E)-C=CHCO), 6.69 (1H, d, J=3.5Hz, thienyl), 7.00 (1H, d, J=3.5Hz, thienyl), 7.65 (1H, d, J=16Hz, (E)-CH=CCO).

Compound 41: 68% yield; Rf .51, benzene: ethyl acetate (9:1); ^{1}H NMR($CDCl_3$) δ .7-2.3 (23H, m), 2.35-3.6 (8H, m), 3.68 (3H, s, OCH_3), 4.0 (1H, m, C≡CHOR), 4.55 (1H, m, -OCHO-), 6.51 (2H, s).

Compound 44: 75% yield; Rf .28, hexanes: ethyl acetate (7:1); ^{1}H NMR($CDCl_3$) δ .6-1.7 (25H, m), 2.1-2.8 (4H, m), 2.9-3.15 (2H, m), 3.68 (3H, s, $-OCH_3$), 3.75-4.0 (1H, m, C≡CHOR), 4.6-4.7 (1H, m, -OCHO-), 6.45-6.75 (2H, m).

Synthesis of 42, 45, and 46

The synthesis of 45 from 43 is representative. Compound 43 (230 mg, .489 mmol) and 5 mg p-TsOH were stirred in 10 mL of CH_3OH for 6 hours. The solution was diluted with benzene, washed with 2N $KHCO_3$ and water, and dried over sodium sulfate. Chromatography on silica gel using benzene: ethyl acetate (9:1) as eluent afforded 45 (148 mg, 83%): Rf .27; ^{1}H NMR($CDCl_3$) δ .7-2.2 (16H, m), 2.45 (2H, br s), 2.75 (1H, dt, J=2, 8Hz), 3.12 (1H, d, J=9Hz), 3.73 (3H, s, OCH_3), 4.00 (1H, br s, C≡C-CHO), 6.00 (1H, d, J=16Hz, (E)-C=CHCO), 6.66 (1H, d, J=4Hz, thienyl), 6.97 (1H, d, J=4Hz), 7.60 (1H, d, J=16Hz, (E)-CH=CCO); IR($CHCl_3$) 3600 (OH), 1710 (C=O), 1620 (C=C), 1160 (C-O)cm^{-1}; ^{13}C NMR($CDCl_3$) 167.32, 151.46, 137.54, 136.96, 130.65, 125.77, 115.04, 85.50, 62.43, 51.50, 48.06, 44.35, 43.38, 42.21, 37.78, 36.09, 31.54, 30.30, 27.90, 24.65, 22.57, 19.98; m/z 386.19013 (calcd for $C_{23}H_{30}O_3S$, 386.19157).

Compound 42: 85% yield; Rf .34, benzene: ethyl acetate (9:1), ^{1}H NMR($CDCl_3$) δ .7-2.2 (18H, m), 2.3-3.5 (8H, m), 3.68 (3H, s, $-OCH_3$), 4.05 (1H, m, C≡CCHO), 6.55 (2H, s, thienyl); IR($CHCl_3$) 3600 (OH), 2240 (C≡C), 1740 (C=O), 1175 (C-O)cm^{-1}; ^{13}C NMR($CDCl_3$) 172.72, 145.41, 140.21, 123.95, 123.36, 85.97, 85.45, 62.23, 51.57, 47.73, 44.29, 43.38, 42.21, 37.72, 35.90, 31.48, 30.30, 27.90, 25.30, 24.71, 22.57, 13.98; m/z 388.20905 (calcd for $C_{23}H_{32}O_3S$, 388.20722).

Compound 46: 83% yield; Rf .32, hexanes: ethyl acetate (3.4:1); ^{1}H NMR($CDCl_3$) δ .9-1.02 (3H, t, J=4Hz, $-CH_3$), 1.1-1.8 (17H, m), 2.25-2.8 (4H, m), 3.0-3.25 (3H, m), 3.70 (3H, s, $-OCH_3$), 3.9 (1H, br s, C≡CCHO), 6.62 (1H, d, J=4Hz, thienyl), 6.73 (1H, dd, J=1, 4Hz, thienyl); IR($CHCl_3$) 1730 (C=O)cm^{-1}; ^{13}C NMR($CDCl_3$) 172.72, 145.08, 141.44, 124.34, 123.43, 84.34, 62.10, 51.63, 45.52, 41.68, 41.55, 37.59, 35.77, 34.66, 34.53, 31.54, 25.43, 24.91, 22.63, 16.06, 14.83, 14.05, 11.58; m/z 386.19258 (calcd for $C_{23}H_{30}O_3S$, 386.19157).

Synthesis of 47, 48, and 49

The procedure for 48 is representative. Hydroxyester 45 (112 mg, .290 mmol) was stirred for 2 hours in 5 mL of methanol and 1 mL of 2N KOH and then refluxed for 30 minutes. After cooling the reaction was diluted with ether, washed with 2N H_2SO_4 and water, and dried over sodium sulfate. After evaporation of the solvent in vacuo, the residue was chromatographed on silica gel [hexanes: ethyl acetate (1:1), Rf .15-.37] to afford 104 mg (96%) of 48: ^{1}H NMR($CDCl_3$) δ

.8-2.2 (19H, m), 2.3-2.66 (2H, br s), 2.8 (1H, d, J=9Hz), 3.2 (1H, d, J=9Hz), 4.08 (1H, m, C≡CCHO-), 6.07 (1H, d, J=16Hz, (E)-C=CHCO), 6.6-7.2 (4H, m, thienyl, OH), 7.75 (1H, d, J=16Hz, CH=CCO); IR($CHCl_3$) 1670 (C=O), 1615 (C=C), 1205 (C-O)cm^{-1}; ^{13}C NMR($CDCl_3$) 172.06, 152.39, 139.50, 136.79, 131.37, 126.01, 114.63, 85.65, 62.52, 48.11, 44.42, 43.45, 42.26, 37.76, 36.13, 31.53, 30.28, 27.90, 24.70, 22.59, 14.03; m/z 372.17406 (calcd for $C_{22}H_{28}O_3S$, 372.17593).

Compound 47: 82% yield; Rf .18-.34, hexanes: ethyl acetate (1:1); ^1H NMR($CDCl_3$) δ .85 (3H, t, J=4Hz, $-CH_3$), 1.05-2.2 (14H, m), 2.3-3.5 (8H, m), 4.10 (1H, m, C≡CCHO), 6.38 (2H, s, OH), 6.60 (2H, s, thienyl); IR($CHCl_3$) 3580 (OH), 1720 (C=O), 1120 (C-O)cm^{-1}; ^{13}C NMR($CDCl_3$) 177.27, 145.41, 140.14, 124.01, 123.49, 86.43, 84.93, 62.49, 47.73, 44.35, 43.44, 42.27, 37.59, 36.03, 35.83, 31.48, 30.30, 27.96, 25.10, 24.71, 22.57, 13.98; m/z 374.19307 (calcd for $C_{22}H_{30}O_3S$, 374.19157).

Compound 49: 86% yield; Rf .37, hexanes: ethyl acetate (1:1); ^1H NMR($CDCl_3$) δ .9 (3H, t, J=4Hz, $-CH_3$), 1.1-1.9 (14H, m), 2.2-3.1 (6H, m), 3.9 (1H, m, C≡CCHO), 6.5-6.8 (4H, m, thienyl, OH); IR (neat) 3400 (br) (OH), 2240 (C≡C), 1740 (C=O)cm^{-1}; ^{13}C NMR($CDCl_3$) 177.40, 145.02, 141.18, 124.34, 123.49, 96.18, 84.54, 62.23, 45.52, 41.62, 41.49, 37.46, 35.64, 34.73, 34.53, 31.54, 25.17, 24.84, 22.63, 16.06, 14.83, 14.05, 11.51; m/z 354.16579 (calcd for $C_{22}H_{26}O_2S(M^{\cdot+}-H_2O)$, 354.16535).

Attempted reaction of 36 and methyl vinyl ketone

Compound 36 (202 mg, .500 mmol), .28 g (4.0 mmol) methyl vinyl ketone and .32 g (2.5 mmol) di-iso-propylethylamine were stirred under nitrogen in 9 mL of DMF:benzene (2:1) for 24 hours. The reaction was diluted with methylene chloride and the organic layer was washed twice with water and twice with saturated NH_4Cl. After drying over sodium sulfate, removal of the solvent in vacuo gave only unreacted starting material contaminated with a small amount of decomposition product.

Reaction of 36 with 54 in THF

Compound 36 (143.3 mg, .3557 mmol) was stirred under nitrogen with 191 mg (.7274 mmol) of triphenylphosphine in 6 mL THF for 30 minutes. To this was added a solution of 199.8 mg (.3759 mmol) of 54 in 1 mL of THF. After 24 hours at room temperature, there had been essentially no change in the reaction, as determined by TLC analysis, so the reaction was refluxed for 24 hours. After cooling, the reaction was diluted with ether, washed with saturated NH_4Cl, and concentrated on a rotary evaporator. Chromatography afforded 58 mg (34%) of 55 as a mixture of diastereomers which were not separable. Rf .32, .27, benzene; ^1H NMR($CDCl_3$) δ .8-2.5 (48H, m), 3.80 (3H, s, OCH_3), 4.05 (1H, m, $-CH(OSiEt_3)$), 5.5-7.1 (3H, m, vinyl, =CHCO), 7.35 (2H, s, thienyl), 7.7 (1H, d, J=16Hz, CH=CCO).

Reaction of 33 and 38 with lithium divinyl cuprate

The reaction of 33 is representative. Copper(I) iodide (191.7 mg, 1.007 mmol) was suspended in 5 mL of THF under nitrogen and cooled to -78°C. Vinyllithium (1.06 mL, 2.01 mmol) was then added dropwise by syringe as a solution in THF. This was then stirred for 30 minutes at -78°C. Compound 33 (302.8 mg, .7472 mmol) and 393.2 mg (1.499 mmol) of triphenylphosphine were dissolved in 8 mL of THF under nitrogen and stirred for 30 minutes at room temperature and then cooled to -78°C. The solution of the divinylcuprate was then added to the palladium complex via stainless steel cannula. This mixture was then allowed to slowly warm to room temperature and then to stir at room temperature for 12 hours. The mixture was quenched by adding 1 mL of methanol and diluted with 100 mL of hexanes. This was filtered through Celite and concentrated on a rotary evaporator. The gummy residue was extracted with two 100 mL portions of hexanes, filtered through Celite, and concentrated to afford 300 mg of an oily residue. Purification by flash chromatography (92) gave 75 mg of a mixture of 51, 56 and 57 in a ratio of 7:3:2 as identified by gas chromatography-mass spectrometry [Rf .35, hexanes: ethyl acetate (9:1)].

Syntheses of 58 and 64

The synthesis of 58 is representative. trans-1-Lithio-3-t-butyldimethylsilyloxy-1-octene was prepared from the iodide using Corey's method (72). Copper(I) iodide (108.2 mg, .5687) was suspended in 5 mL of THF under nitrogen and cooled to -78°C whereupon 1.13 mmol of

the lithium compound at -78°C was added via cannula. The resulting solution was stirred for 1 hour at -78°C. Compound 38 (293.0 mg, .5080 mmol) and 134.6 mg (.5132 mmol) of triphenylphosphine were stirred under nitrogen in 10 mL of THF. After 30 minutes the palladium complex was cooled to -78°C and the -78°C solution of the cuprate was added via cannula. The reaction was then allowed to slowly warm to room temperature overnite. The reaction was then quenched with 1 mL of methanol and the solvent removed in vacuo. The black residue that remained was extracted with 3 25 mL portions of hexanes. These were then filtered through Celite and concentrated to give 270 mg of a yellow oil. Purification by flash chromatography using hexanes: ethyl acetate (14:1) as eluent afforded 80.0 mg (31%) of 58 and 78.0 mg of (51%) of reduction product 51 (Rf .27). Compound 58: Rf .37; ^{1}H NMR($CDCl_3$) δ .12 (6H, s, $SiCH_3$), .8-2.0 (27H, m), 2.1-3.4 (8H, m), 3.80 (3H, s, $-OCH_3$), 3.90 (1H, m, CHOSi), 5.1-5.25 (2H, m, vinyl), 6.6 (2H, br s, thienyl).

Compound 51: ^{1}H NMR($CDCl_3$) δ .9-1.8 (10H, m), 2.1-3.1 (5H, m), 3.52 (3H, s, OCH_3), 6.40 (2H, s, thienyl).

Compound 64: 50% yield; Rf .33, hexanes: ethyl acetate (15:1); ^{1}H NMR($CDCl_3$) δ .05 (6H, s, $Si(CH_3)_2$), .9 (9H, s, $SiC(CH_3)_3$), .95-2.3 (29H, m), 3.60 (3H, s, $-OCH_3$), 3.85-4.1 (1H, m, CHOSi), 5.2-5.4 (4H, m, vinyl).

Synthesis of 59 and 66

The synthesis of 59 from 58 is representative. Compound 58 (152.1 mg, .301 mmol) was stirred for 12 hours in 5 mL of a 3:1:1 mixture of acetic acid: THF: water. The reaction was then diluted with ether, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After concentration the residue was purified by flash chromatography using hexanes: ethyl acetate (3.4:1) as the eluent to afford 91 mg (77%) of 59: Rf .35; ^{1}H NMR($CDCl_3$) δ .8-2.2 (18H, m), 2.3-3.2 (8H, m), 3.67 (3H, s, $-OCH_3$), 3.7-3.85 (1H, m, CHO), 5.1-5.3 (2H, m, vinyl), 6.4-6.6 (2H, m, thienyl); IR($CHCl_3$) 1730 (C=O), 1190 (C-O)cm^{-1}; ^{13}C NMR($CDCl_3$) 172.70, 145.28, 140.14, 133.19, 132.86, 123.62, 72.77, 51.76, 51.57, 48.71, 43.70, 43.38, 42.73, 37.00, 36.74, 35.96, 35.31, 31.80, 30.37, 28.81, 28.68, 25.30, 25.04, 24.84, 22.50, 13.98; m/z 390.22283 (calcd for $C_{23}H_{34}O_3S$, 390.22288).

Compound 66: 60% yield; Rf .35, hexanes: ethyl acetate (4:1); ^{1}H NMR($CDCl_3$) δ .8-1.1 (3H, t, J=8Hz, $-CH_3$), 1.2-2.2 (25H, m), 2.35 (2H, t, J=7Hz, CH_2CO), 3.70 (3H, s, OCH_3), 4.0-4.15 (1H, m, CHOH), 5.3-5.5 (4H, m, vinyl); IR(neat) 1740 (C=O), 965 (trans-C=C)cm^{-1}; ^{13}C NMR($CDCl_3$) 174.22, 133.44, 133.18, 131.82, 129.48, 73.29, 73.16, 51.44, 49.81, 49.62, 47.21, 43.38, 40.06, 39.80, 37.46, 34.66, 33.69, 33.43, 33.10, 32.00, 31.80, 29.91, 29.72, 29.26, 25.23, 24.84, 22.63, 14.05.

Synthesis of 3-(2-tetrahydropyranyloxy)-trans-1-iodo-1-octene

Dihydropyran (1.30 g, 19.1 mmol) and 4.70 g (18.5 mmol) of trans-1-iodo-1-octen-3-ol were stirred for 20 hours with 2 drops of concd HCl. The reaction was then diluted with ether, washed twice with saturated $NaHCO_3$, and dried over $MgSO_4$. Purification by flash chromatography with hexanes: ethyl acetate (14:1) afforded 3.95 g (63%) of 3-(2-tetrahydropyranyloxy)-trans-1-iodo-1-octene: Rf .42; ^1H NMR($CDCl_3$) δ .8-1.8 (17H, m), 3.2-4.1 (4H, m), 4.6 (1H, br s, -OCHO-), 6.2-6.5 (2H, m, vinyl).

Synthesis of 61 and 65

The synthesis of 61 is representative. 3-(2-Tetrahydropyranyloxy)-trans-1-iodo-1-octene (1.573 g, 4.650 mmol) was lithiated with 9.03 mmol of t-butyllithium in 18 mL of ether at -78°C for 3 hours. This was added to a -78°C suspension of copper(I) iodide (419 mg, 2.2021 mmol) in 20 mL of THF and stirred for 1 hour to form the cuprate. Compound 38 (1.165 g, 2.02 mmol) and 1.053 g (4.014 mmol) of triphenylphosphine were stirred in 20 mL of THF for 30 minutes and then cooled to -78°C. The solution of the cuprate was then added and the mixture allowed to slowly warm to room temperature overnight. After quenching with 1 mL of methanol, the THF was removed in vacuo and the product extracted with 3 25 mL portions of hexanes. The hexane extract was filtered and concentrated to afford 1.26 gm of residue. This was purified by chromatography to give 440 mg (55%)

of 61: Rf. 28, hexanes: ethyl acetate (8:1); ^{1}H NMR($CDCl_3$) δ .9 (3H, t, J=5Hz, $-CH_3$), 1.0-2.2 (22H, m), 2.3-2.7 (3H, m), 2.8-3.2 (3H, m), 3.3-3.6 (2H, m, $-CH_2-O-$), 3.65 (4H, s, $-OCH_3$, -CH(OTHP)), 4.5-4.7 (1H, br, -OCHO-), 5.0-5.3 (2H, m, vinyl), 6.3-6.5 (2H, m, thienyl).

Compound 65: 65% yield; Rf .34, hexanes: ethyl acetate (8:1); ^{1}H NMR($CDCl_3$) δ .9 (3H, t, J=8Hz, $-CH_3$), 1.2-2.2 (30H, m), 2.35 (2H, t, J=7Hz, CH_2CO), 3.4-4.3 (3H, m), 3.70 (3H, s, $-OCH_3$), 4.7 (1H, br s), 5.2-5.6 (4H, m, vinyl).

Synthesis of 59 and 66 from 61 and 65

The preparation of 59 from 61 is representative. Compound 61 (304 mg, .640 mmol) and 5 mg p-TSA were stirred in 10 mL of methanol for 14 hours. The mixture was then diluted with ether, washed with brine, and dried over $MgSO_4$. The residue was purified by flash chromatography to give 151 mg (61%) of 59.

Synthesis of 62 and 67

The synthesis of 67 is representative. Compound 66 (95.1 mg, .262 mmol) was refluxed for 30 minutes in 8 mL of methanol and 2 mL of 2N KOH. After cooling, the reaction was diluted with ether, acidified with 50 mL of 2N H_2SO_4, washed with brine and dried over $MgSO_4$. Purification by chromatography with hexanes: ethyl acetate: glacial acetic acid (30:15:1) afforded 85.0 mg (93%) of 67: Rf .28;

^{1}H NMR($CDCl_3$) δ .9 (3H, t, J=5Hz, $-CH_3$), 1.1-2.6 (26H, m), 4.1 (1H, br, CH(OH)), 5.4 (4H, m, vinyl), 7.2 (2H, br s, -OH, CO_2H); IR(neat) 1720 (C=O), 970 (trans-C=C-), 730 (cis-C=C-); ^{13}C NMR($CDCl_3$) 178.83, 133.57, 133.38, 132.73, 131.88, 129.34, 73.29, 49.75, 49.62, 47.15, 43.38, 39.99 39.86, 37.26, 34.60, 33.04, 31.73, 29.91, 29.20, 25.17, 24.58, 22.63, 13.98; m/z 330.25483 (calcd for $C_{22}H_{34}O_2$, M^+-H_2O, 330.25589).

Compound 62: 79% yield; Rf .31, hexanes: ethyl acetate: acetic acid (30:15:1); ^{1}H NMR($CDCl_3$) δ .9 (3H, t, J=5Hz, $-CH_3$), 1.1-2.3 (19H, m), 2.3-2.85 (2H, m), 3.05 (2H, t, J=9Hz, CH_2CO), 3.7-3.9 (1H, m, CHOH), 5.1-5.3 (2H, m, vinyl), 6.4-6.8 (4H, m, aryl, -OH, $-CO_2H$); IR(neat) 1720 (C=O), 965 (-C=C-); ^{13}C NMR($CDCl_3$) 176.88, 145.28, 140.08, 133.77, 133.12, 132.60, 132.21, 123.69, 72.96, 51.83, 48.64, 43.83, 43.25, 43.12, 42.60, 36.87, 36.68, 36.03, 35.38, 34.73, 31.80, 30.43, 28.88, 25.17, 24.84, 22.57, 14.11; m/z 376.20584 (calcd for $C_{23}H_{32}O_3S$, 376.20722).

Synthesis of 70

Silver acetate (1.84 g, 11.0 mmol) and 1.86 g (10.2 mmol) π-allylpalladium chloride were stirred in 60 mL of chloroform for 1 hour. After filtering through Celite the chloroform was removed on a rotary evaporator and the product was dissolved in 100 mL of CH_2Cl_2. This was added dropwise via an addition funnel over 30 minutes to a solution of 23.5 g (255 mmol) of norbornadiene in 200 mL of CH_2Cl_2.

After stirring for 12 hours, 3.43 g (10.5 mmol) of n-Bu_4NCl was added and the reaction was stirred for an additional 30 minutes. After filtration to remove metallic palladium, the mixture was washed with water and dried over $MgSO_4$. Filtration through a Florisil column with CH_2Cl_2 gave 2.18 g (76%) of 70: mp 160-165°C (d); ^1H NMR($CDCl_3$) δ 1.3-1.7 (2H, m), 1.88 (1H, d, J=8Hz), 2.3-2.6 (3H, m), 2.9 (1H, d, J=6Hz), 3.3 (1H, br), 4.2-4.6 (2H, m, $C=CH_2$), 5.7-6.1 (3H, m, -CH=C, -CH=CH-); ^{13}C NMR($CDCl_3$) 135.89, 134.65, 106.31, 79.99, 62.00, 48,35, 46.40, 43.47, 39.03, 37.46. Anal. Calcd for $C_{10}H_{13}PdCl$: C, 43.67, H, 4.76. Found: C, 43.95; H, 4.87.

Reaction of 70 with lithium divinylcuprate

Compound 70 (550.5 mg, 2.001 mmol) and 534.0 mg (2.036 mmol) of triphenylphosphine were stirred in 15 mL of THF for 30 minutes and then cooled to -78°C. Vinyllithium (4.37 mmol) was added to a suspension of 417.9 mg (2.194 mmol) of copper(I) iodide in 10 mL of THF at -78°C. After stirring for 30 minutes at -78°C, this was added to the solution of the palladium compound and the resulting solution was allowed to slowly warm to room temperature. After quenching with methanol, the mixture was diluted with hexanes, filtered and concentrated to provide 400 mg of residue. This was chromatographed with hexanes to provide a mixture (one spot, Rf .52) of compounds

71-75 as determined by glass capillary GC-MS. Structural assignments were made on the basis of the compounds' fragmentation patterns in the mass spectrometer. Compounds 71 and 72 undergo a facile retro-Diels-Alder fragmentation to give an ion of m/z=66 as the base peak. Compounds 73-75 cannot undergo this fragmentation.

Attempted carbonylation of 33 with CO and HCl

A solution of 405 mg (1.00 mmol) of 33 and 260 mg (1.00 mmol) of triphenylphosphine in 15 mL of dry benzene was degassed by bubbling with nitrogen for 30 minutes. The flask was then flushed with CO and stirred for 14 hours. The flask was then flushed with HCl gas for 1 hour and the reaction mixture was concentrated, diluted with hexanes, filtered and concentrated again. NMR analysis of the residue showed that no aldehyde was present.

Synthesis of 76

Compound 33 (1.2821 g, 3.163 mmol) and 0.83 g (6.4 mmol) of di-iso-propylethylamine were dissolved in 30 mL of THF and stirred under nitrogen for 10 minutes. The flask was then flushed with CO and stirred for 40 minutes. Triphenylphosphine (1.66 g, 6.33 mmol) was added and the reaction was stirred for 30 minutes. Tri-n-butyltin hydride (1.10 g, 3.78 mmol) was then added and the reaction was stirred for 1 hour. THF was removed in vacuo and the product was extracted with 200 mL of hexanes. Filtration through Celite and removal of

the solvent with a rotary evaporator gave 1.9 g of residue that was purified by flash chromatography to afford 0.97 g (100%) of 76: Rf .30, hexanes: ethyl acetate (4:1); ^{1}H NMR($CDCl_3$) δ .8-2.0 (7H, m), 2.2-2.6 (4H, m), 2.7-3.35 (3H, m), 3.65 (3H, s, $-OCH_3$), 6.53 (2H, s, thienyl), 9.13 (1H, d, J=3Hz, -CHO); IR(neat) 2710 (CHO), 1740 (CO_2CH_3), 1720 (CHO)cm^{-1}; m/z 292.11362 (calcd for $C_{16}H_{20}O_3S$, 292.11320).

Synthesis of 77

Sodium hydride (170 mg, 4.77 mmol) (67% dispersion in mineral oil) was washed with 3 5 mL portions of hexanes under nitrogen and then suspended in 45 mL of DME. Dimethyl 2-oxoheptylphosphonate (1.15 g, 5.18 mmol) in 5 mL of DME was added via syringe and stirred for 1 hour. Compound 76 (923.9 mg, 3.163 mmol) in 5 mL of DME was added and the reaction was stirred for 3 hours at room temperature. After quenching with .5 mL of acetic acid, the solvent was removed in vacuo. The product was extracted with 100 mL of hexanes and filtered through Celite. Flash chromatography of the residue gave 1.05 g (86%) of 77: Rf .29, hexanes: ethyl acetate (6:1); ^{1}H NMR($CDCl_3$) δ .83 (3H, t, J=5Hz, $-CH_3$), 1.0-1.9 (12H, m), 1.9-2.8 (7H, m), 2.8-3.3 (3H, m), 3.60 (3H, s, $-OCH_3$), 5.67 (1H, d, J=16Hz, (E)-C=CHC=O), 6.18 (1H, dd, J=7, 16Hz, (E)-CH=CC=O), 6.37 (2H, s thienyl); IR(neat) 1740 (CO_2CH_3), 1680 (C=O), 1630 (trans-C=C), 980 (trans-C=C)cm^{-1}.

Reduction of 77 to 59

Compound 77 (190.3 mg, .4897 mmol) was dissolved in 10 mL of THF under nitrogen and cooled to 0°C. 9-BBN (65.0 mg, .533 mmol) was added and the reaction was stirred for 3 hours at 0°C. Methanol (.5 mL) was added to hydrolyze excess hydride and the solvent was removed in vacuo. The residue was taken up in 25 mL of pentane and treated with 34 mg (.56 mmol) of ethanolamine to complex the boron. After filtration the solution was then washed with 3 25 mL portions of water and 3 25 mL portions of brine. Purification by flash chromatography afforded 181.7 mg (95%) of 59, identical in all respects with that prepared previously.

Reduction of thiophenes by ionic hydrogenation

The procedure for 2-methylthiophene is representative. Trifluoroacetic acid (11.40 g, 100 mmol) and 0.20 g (2.0 mmol) of 2-methylthiophene were dissolved in 80 mL of CH_2Cl_2. Zinc dust (12.03 g, 184 mmol) was then added and the suspension was stirred for 3 hours at room temperature. After that time, the zinc was filtered off and the CH_2Cl_2 solution was washed with water. After drying over $MgSO_4$, removal of the solvent in vacuo afforded 150 mg of a yellow oil which was determined to be a 4:1 mixture of 2-methyl-2,5-dihydrothiophene and 2-methyl-2,5-dihydrothiophene by GC and GC-MS.

Synthesis of 81 and 82 by Raney nickel hydrogenation

The procedure for the synthesis of 82 is representative. Compound 46 (180 mg, .466 mmol) and Raney nickel W-7, prepared (89) from 2.5 g of alloy, were shaken in 40 mL of absolute ethanol in a Parr shaker under 60 psi of hydrogen for 48 hours. The mixture was then diluted with ether, filtered, washed twice with brine, and dried over $MgSO_4$. Flash chromatography afforded 141 mg (83%) of 82: Rf .35, hexanes: ethyl acetate (4:1); ^1H NMR($CDCl_3$) δ .88 (3H, t, J=5Hz, $-CH_3$), 1.2-1.9 (31H, m), 2.3 (2H, t, J=7Hz, CH_2CO), 3.7 (4H, s, overlapping peaks, $-OCH_3$, CHOH); IR(neat) 3430 (-OH), 1740 (C=O)cm^{-1}; ^{13}C NMR($CDCl_3$) 174.14, 72.02, 71.06, 51.27, 46.34, 37.68, 36.81, 36.21, 33.99, 31.88, 30.69, 29.60, 29.33, 29.06, 26.73, 26.62, 25.27, 24.84, 22.56, 15.30, 13.95, 11.40; m/z 364.29664 (calcd for $C_{23}H_{40}O_3$, 364.29775).

Compound 81: 82% yield; Rf .37, hexanes: ethyl acetate (4:1); ^1H NMR($CDCl_3$) δ .9 (3H, t, J=6Hz, $-CH_3$), 1.1-1.9 (30H, m), 1.9-2.1 (3H, br s), 2.3 (2H, t, J=7Hz, CH_2CO), 3.7 (4H, s, overlapping peaks, $-OCH_3$, -CH(OH)); IR(neat) 3420 (OH), 1740 (C=O)cm^{-1}; ^{13}C NMR($CDCl_3$) 174.22, 72.38, 72.05, 51.31, 46.82, 46.56, 40.77, 37.78, 37.52, 37.39, 34.01, 32.65, 31.86, 29.91, 29.52, 29.13, 25.75, 25.56, 25.30, 24.91, 22.57, 13.98; m/z 366.31398 (calcd for $C_{23}H_{42}O_3$, 366.31340).

Synthesis of 83 and 84

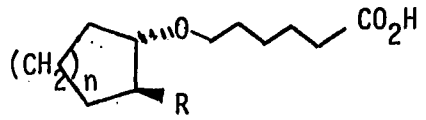
The synthesis of 83 is representative. Compound 81 (125.5 mg, .3423 mmol) was refluxed for 30 minutes in 10 mL of a 4:1 mixture of methanol and 2N KOH. After cooling, the reaction was diluted with ether, acidified with 10 drops of concentrated HCl, washed with brine, and dried over $MgSO_4$. Purification by chromatography afforded 104 mg (86%) of 83: Rf .43, hexanes: ethyl acetate (1:1); ^1H NMR($CDCl_3$) δ .95 (3H, t, J=7hz, $-CH_3$), 1.2-1.8 (30H, m), 2.0 (2H, br s), 2.37 (2H, t, J=7Hz, $CH_2CO_2CH_3$). 3.7 (1H, m, CH(OH)), 6.35 (2H, br s, -OH, $-CO_2H$); IR(neat) 3410 (OH), 1720 (C=O)cm^{-1}; ^{13}C NMR($CDCl_3$) 179.16, 72.77, 72.38, 46.95, 46.63, 40.90, 37.78, 37.46, 34.08, 32.78, 31.93, 30.04, 29.52, 29.00, 25.95, 25.56, 25.36, 24.71, 22.70, 14.05; m/z 334.28753 (calcd for $C_{22}H_{38}O_2$ ($M^{+\cdot}-H_2O$), 334.28718).

Compound 84: 95% yield; Rf .39, hexanes: ethyl acetate (1:1); ^1H NMR($CDCl_3$) δ .8-1.1 (3H, t, J=7Hz, $-CH_3$), 1.2-2.1 (30H, m), 2.3 (2H, t, J=6Hz, $CH_2CO_2CH_3$), 3.5-3.7 (1H, m, CH(OH)), 6.5 (2H, br s, -OH, $-CO_2H$); IR(neat) 3400 (OH), 1730 (C=O)cm^{-1}; ^{13}C NMR($CDCl_3$) 178.90, 72.31, 46.50, 37.59, 37.33, 37.07, 36.35, 34.08, 32.00, 30.63, 29.59, 29.26, 28.81, 26.79, 25.36, 24.65, 22.70, 15.41, 15.22, 14.05, 11.51; m/z 332.27232 (calcd for $C_{22}H_{36}O_2$ ($M^{+\cdot}-H_2O$), 332.27153).

CHAPTER III. SYNTHESIS OF 7-OXA PROSTAGLANDIN ENDOPEROXIDE ANALOGUES

Introduction

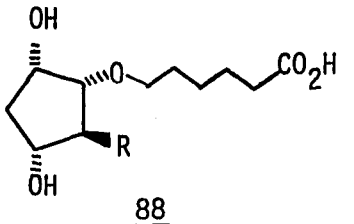
One group of prostaglandin analogues that has been widely studied is that in which the C-7 methylene has been replaced by oxygen. Fried has synthesized a wide variety of these compounds, the structures of which are shown below (93-97). These compounds were generally



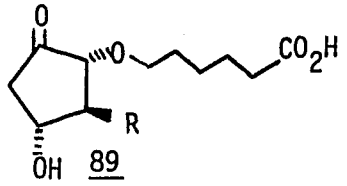
85, n=0

86, n=1

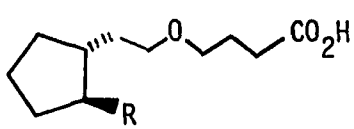
87, n=2



88

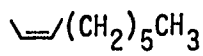


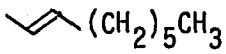
89

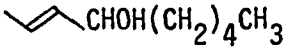


90

a, R = n-C_8H_{17}

b, R = 

c, R = 

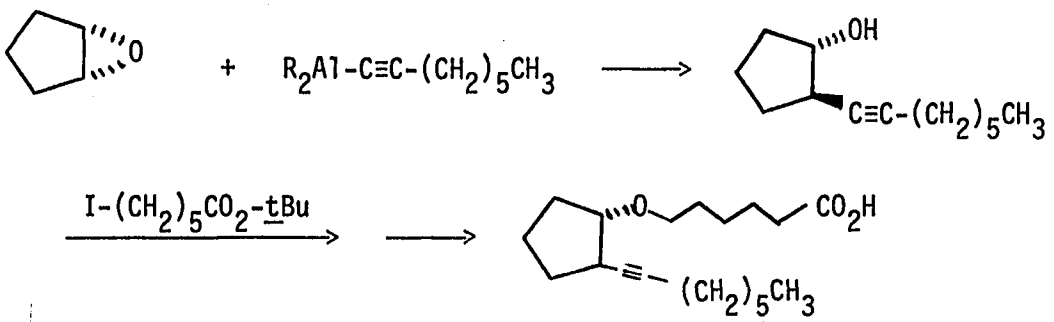
d, R = 

e, R = $-C{\equiv}C-(CH_2)_5CH_3$

f, R = $-C{\equiv}CCHOH(CH_2)_4CH_3$

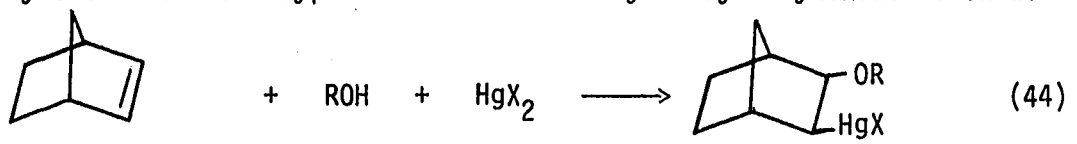
synthesized by the route shown in Scheme VII for 86 e. The dialkylalkynylalane opens the epoxide to form the acetylenic alcohol. This is then treated with the t-butyl ester of 6-iodohexanoic acid to add the carboxylic acid chain.

Scheme VII

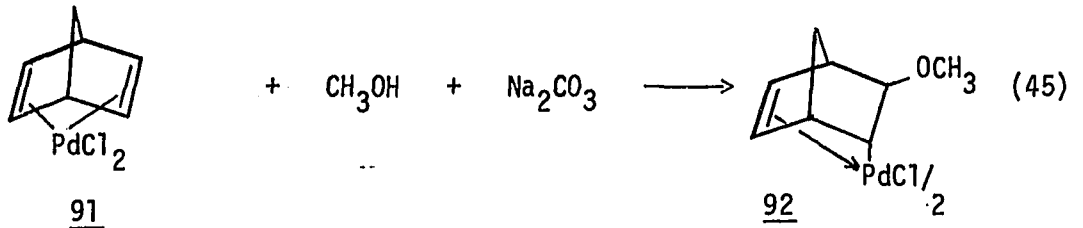


A number of these compounds show substantial biological activity. Compounds 85 e, 86 a-f and 87 a-f all inhibit PGE_1-induced smooth muscle contraction at various concentrations, but do not themselves exhibit smooth muscle contracting ability (93). This was postulated to occur via competitive inhibition at the appropriate receptor sites. Compounds 85 e, 86 e and 90 c were also found to completely inhibit PGE_2 biosynthesis. 7-oxa $PGF_{1\alpha}$, 88 d, and 7-oxa PGE_1, 89 d, on the other hand, were agonists of the natural prostaglandins, possessing 5×10^{-2} and 4×10^{-4} times the activity of the natural materials respectively. Compounds 86 f, 89 f and to a lesser extent 89 e, were found to activate PGE_2 biosynthesis (97). In view of the variety of activity of these compounds, the synthesis of bicyclic analogues of 7-oxa PGH_2 seemed a desirable goal.

The oxymercuration of norbornene (98) and methoxypalladation of norbornadiene (99) are well-known reactions (eqs. 44, 45). Either oxymercuration or oxypalladation with methyl 6-hydroxyhexanoate should



(44)



(45)

91 92

provide intermediates that would be elaborated to 7-oxa bicyclic prostaglandin analogues using chemistry similar to that described in Chapter 2.

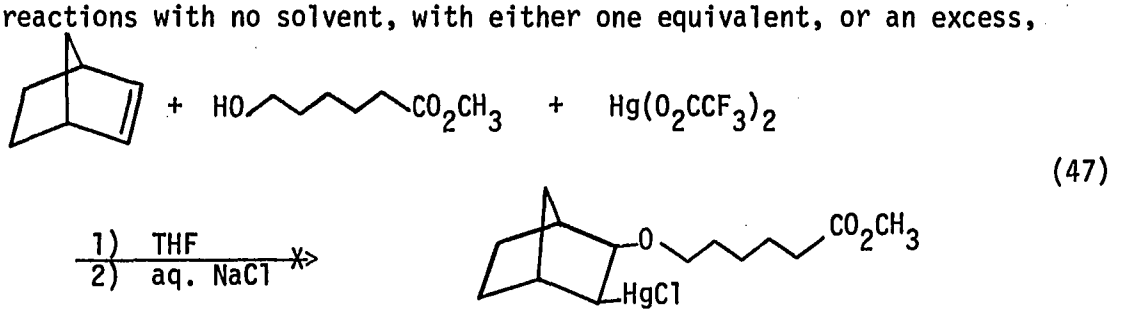
Results and Discussion

Oxymercuration with methyl 6-hydroxyhexanoate

The oxymercuration of olefins, followed by demercuration with sodium borohydride, is a well-known reaction for the synthesis of unsymmetrical ethers. Addition of either mercuric acetate or, preferably, mercuric trifluoroacetate to one equivalent of the olefin and an excess of the alcohol, usually the reaction solvent, results in a rapid reaction to provide the intermediate β-alkoxymercurial which is reduced in situ (eq. 46). This reaction is quite general,

$$CH_2{=}CH_2 + Hg(O_2CCF_3)_2 + ROH \longrightarrow R\text{-}O\text{-}CH_2CH_2\text{-}HgO_2CCF_3 \longrightarrow R\text{-}O\text{-}CH_2CH_3 \quad (46)$$

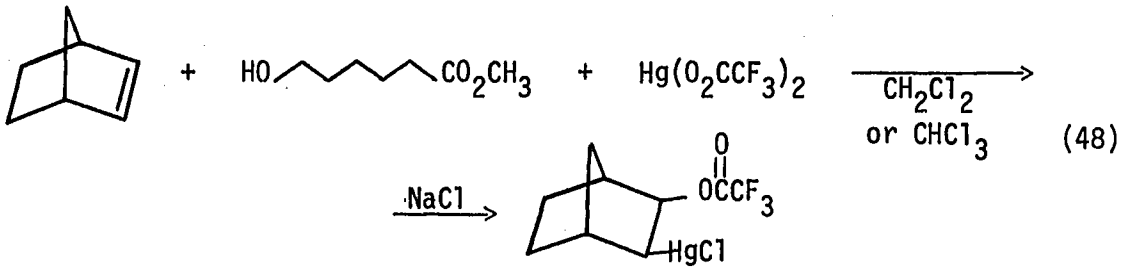
proceeding in high yield with a variety of olefins, including norbornene, and a number of simple alcohols. The oxymercuration of norbornene with methyl 6-hydroxyhexanoate and mercuric trifluoroacetate was attempted under a wide range of conditions. Initial attempts involved the reaction of norbornene with mercuric trifluoroacetate and either one equivalent, or an excess, of alcohol in THF for times ranging from 10 minutes to 12 hours. None of these attempts produced any of the desired organomercurial after addition of the reaction mixture to an aqueous sodium chloride solution (eq. 47). Running the reactions with no solvent, with either one equivalent, or an excess,



(47)

of alcohol also gave none of the desired mercurial after addition to aqueous sodium chloride. Running the reaction in solvents other than THF was also unsuccessful. The use of a 2:1 mixture of THF and DMSO did not afford any isolable product. The use of chloroform or methylene

chloride provided what was later found to be the product of mercuric trifluoroacetate addition to norbornene (eq. 48). At this point, work on this approach was discontinued.

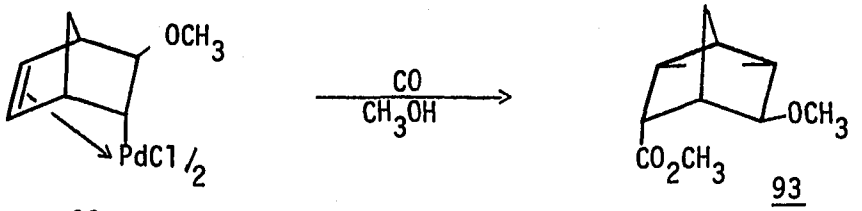


(48)

Oxypalladation of norbornadiene

The methoxypalladation of norbornadienepalladium dichloride in methanol with sodium carbonate affords the methoxy complex, 92, in high yield (eq. 45) (99). In order to determine the potential usefulness of complexes such as 92 in the synthesis of 7-oxa bicyclic prostaglandin analogues, compound 92 was chosen as a model system to explore methods of introducing the allylic alcohol chain common to prostaglandins.

Carbonylation of 92 by treatment with carbon monoxide in methanol has been reported to yield the nortricyclo ester 3-endo-carbomethoxy-5-exo-methoxynortricyclene, 93, in 73% yield (eq. 49) (60). The rearrangement of 92 to the nortricyclo structure was postulated as being induced by the coordination of carbon monoxide with palladium.

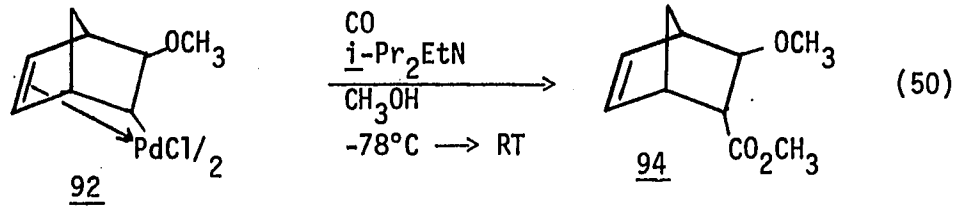


92 93

(49)

This rearrangement has also been reported upon complexation with bis(diphenylphosphino)ethane (100) and pyridine (101).

We have found, however, that the carbonylation of 92 in the presence of an excess of di-iso-propylethylamine affords only the bicyclic ester 94 in 87% yield (eq. 50). A possible explanation for



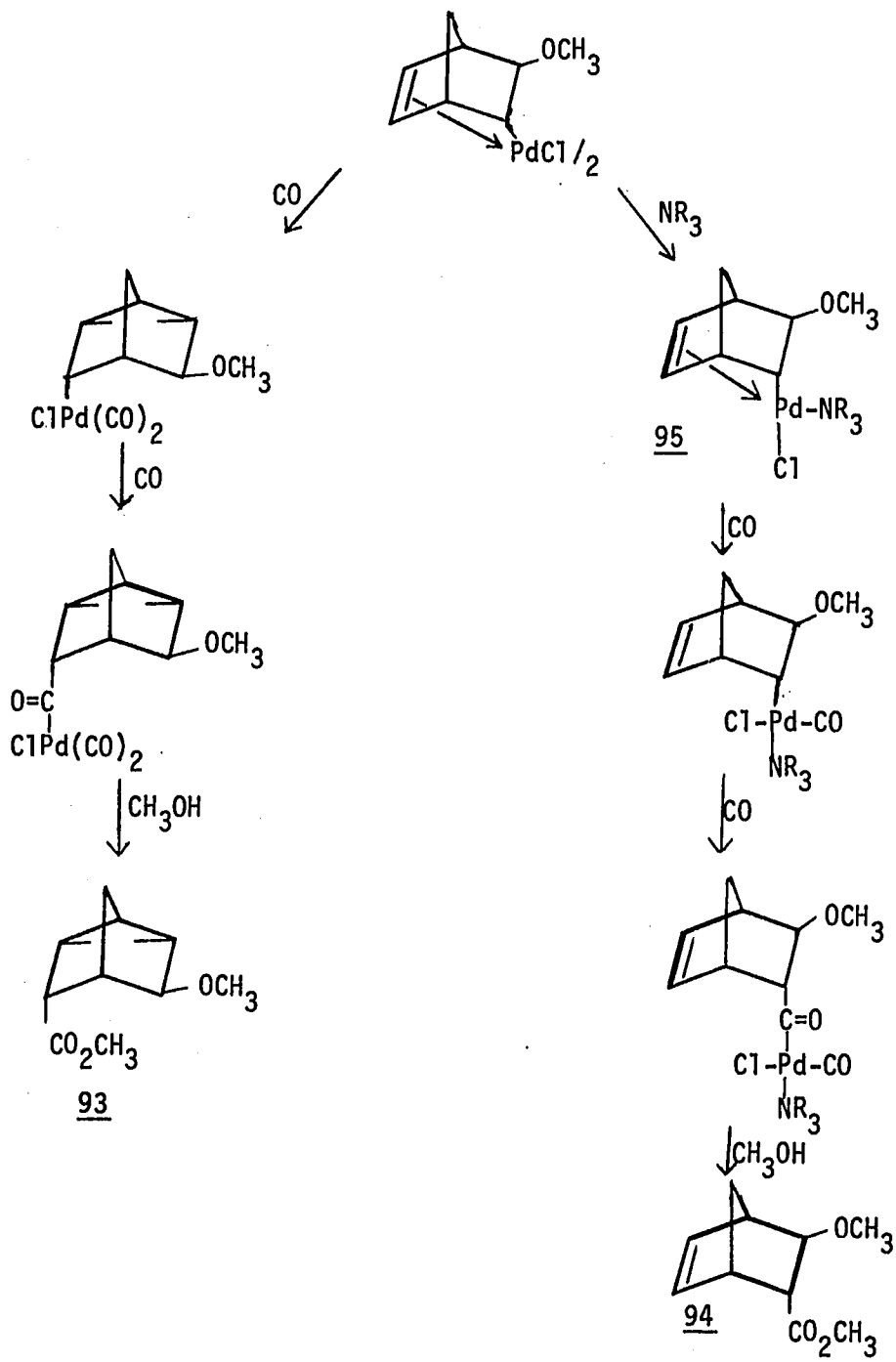
(50)

the difference in structure of the products may be found in the proposed mechanism in Scheme VIII. Coordination of di-iso-propylethylamine may provide the monoamine complex, 95, which then reacts with CO to displace the olefin ligand, followed by insertion into the C-Pd bond. The reason that the amine seems to facilitate CO coordination via olefin displacement instead of rearrangement is unknown.

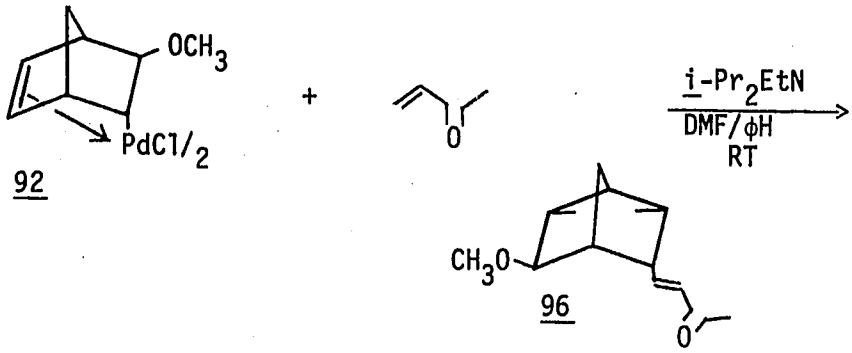
Reaction of 92 with methyl vinyl ketone

Attempted Heck olefination of 92 with methyl vinyl ketone in the presence of di-iso-propylethylamine, under conditions similar to those employed by Holton in the synthesis of $PGF_{2\alpha}$ (102), provided the nortricyclo enone in 57% yield (eq. 51). In this case, the

Scheme VIII


OCH3
PdCl2
CO
NR3
ClPd(CO)2
CO
O=C
ClPd(CO)2
CH3OH
CO2CH3
93
Pd-NR3
Cl
95
Cl-Pd-CO
NR3
C=O
Cl-Pd-CO
NR3
CH3OH
94
CO2CH3

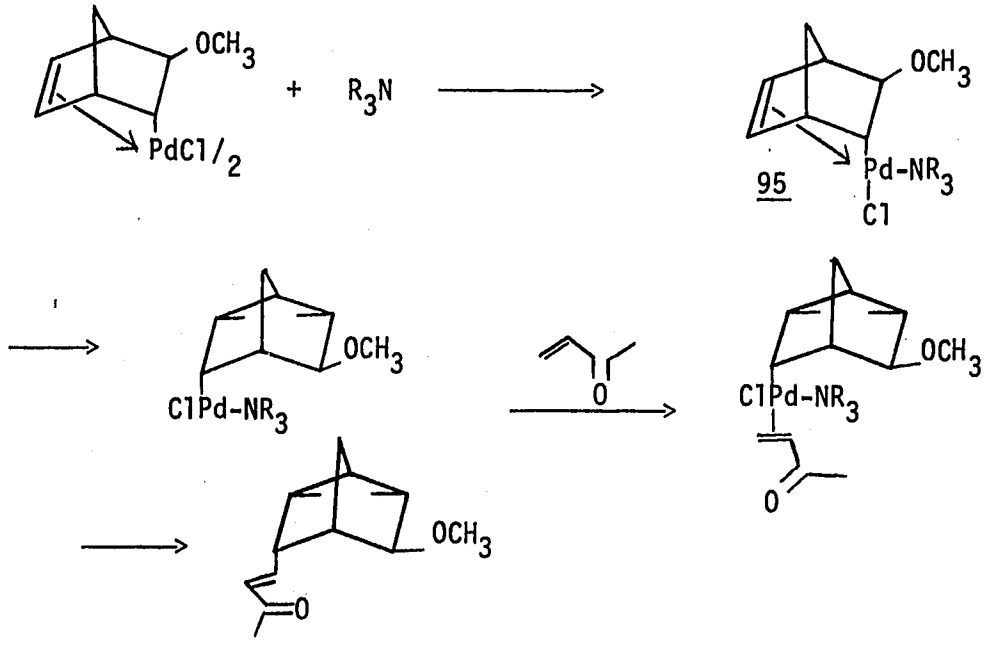
rearranged product is probably formed, even in the presence of amine,



(51)

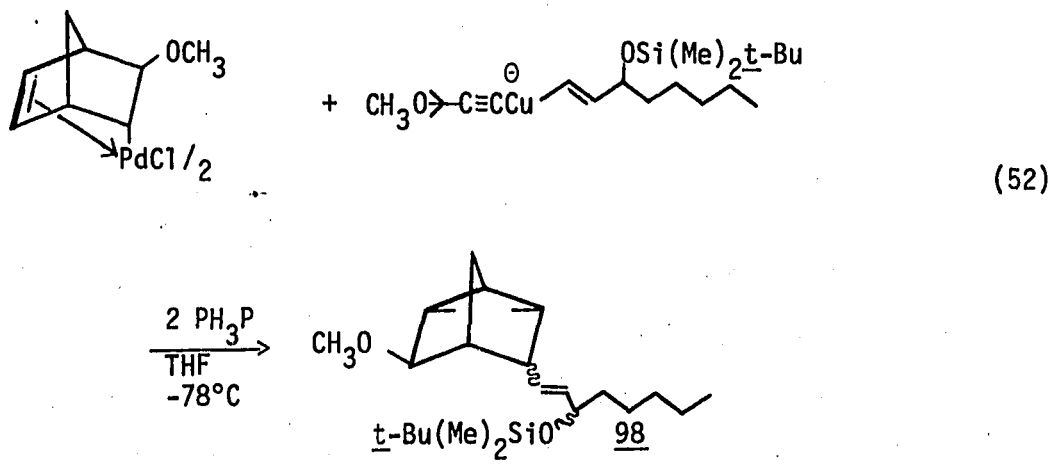
due to the fact that methyl vinyl ketone should not be a strongly coordinating ligand and therefore is unable to displace the intramolecular olefin coordination. Coordination probably occurs instead via the generation of an open coordination site through rearrangement as shown in Scheme IX.

Scheme IX



Reaction of 92 with nucleophiles

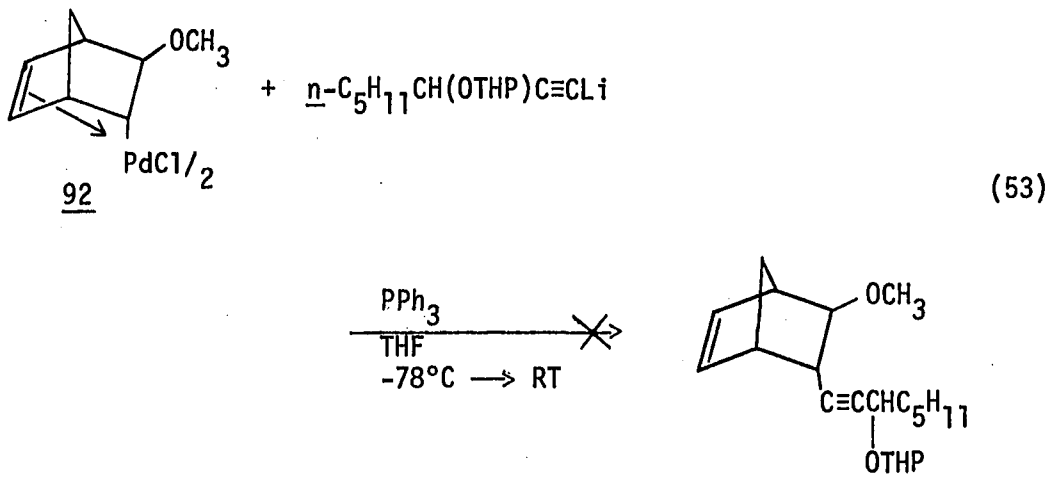
As discussed in chapter 2, a common method for the coupling of organopalladium compounds involves their reaction with various types of nucleophiles. The reaction of vinyl cuprates with organopalladium compounds was used successfully to introduce the allylic alcohol chain in several prostaglandin analogues. The reaction of 92 with a mixed vinyl cuprate was studied to determine its usefulness in the synthesis of 7-oxa bicyclic prostaglandin analogues. Compound 92 was treated with 1.05 equivalents of mixed cuprate 97 in THF for 1 hour at -78°C, affording the nortricyclo coupling product, 98, in 28% yield (eq. 52). There was no trace of the product from acetylene



(52)

transfer of the cuprate. Analysis of the product by ^{13}C NMR spectroscopy indicates that the product is a mixture of isomers, similar to the results obtained in chapter 2 from the reaction of organopalladium halides with vinyl cuprates.

In order to introduce the acetylenic alcohol side chain, compound 92 was converted to the hexafluoroacetylacetonate and then complexed with two equivalents of triphenylphosphine. Cooling this to -78°C in THF and addition of 1·1 equivalents of a -78°C solution of 1-lithio-3-(2-tetrahydropyranyloxy)-1-octyne and warming to room temperature did not give any isolable product after TLC analysis and chromatography (eq. 53). Analysis of the fractions resulting from



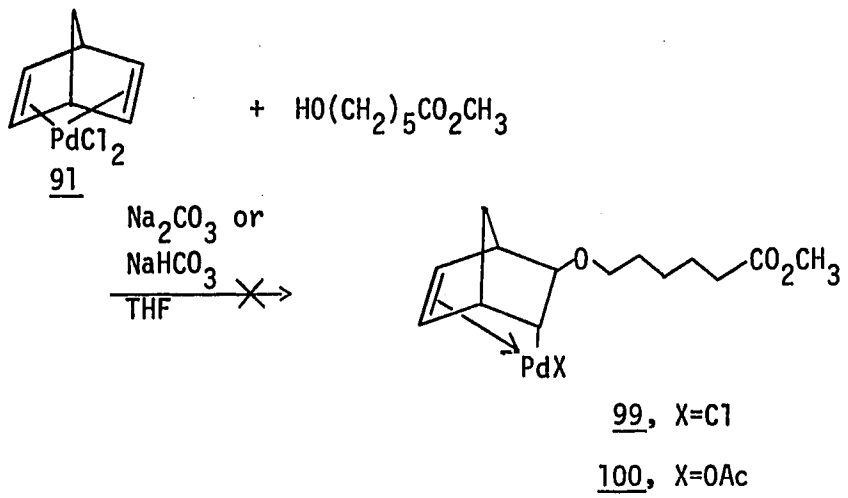
(53)

chromatography of the reaction mixture did not indicate the presence of any identifiable product.

Oxypalladation with methyl 6-hydroxyhexanoate

A major problem to be overcome in the oxypalladation of norbornadienepalladium dichloride is that of the solubility of both the diene complex and the inorganic base. Norbornadienepalladium dichloride is only slightly soluble, if at all, in most organic solvents. Oxypalladation of 91 with methyl 6-methoxyhexanoate and

either sodium carbonate or sodium bicarbonate in THF was unsuccessful (eq. 54). Substitution of acetonitrile, or a mixture of DMF and acetone,



(54)

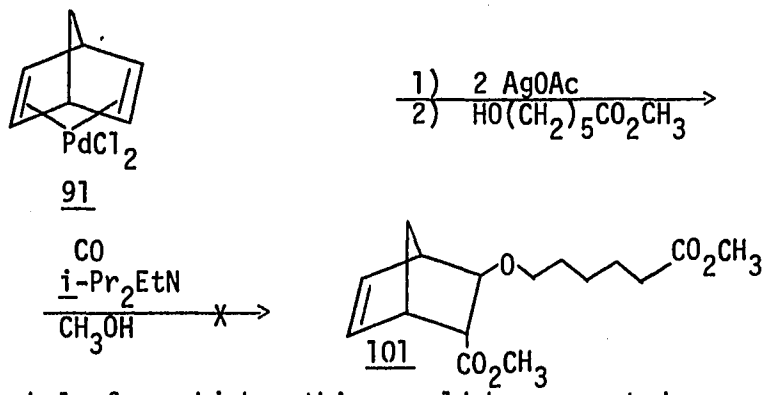
99, X=Cl

100, X=OAc

for THF did not afford any of the desired product. Use of DMSO as the solvent resulted in dissociation of the diene complex with no oxypalladation. Running the reaction in methyl 6-hydroxyhexanoate with or without base was also unsuccessful. Attempted oxypalladation after formation of the sodium alkoxide of methyl 6-hydroxyhexanoate with sodium hydride in THF also failed to give any of the desired product.

One way to increase the solubility of the starting palladium compound would be to exchange acetate for one or both chlorides, since organopalladium acetates are generally more soluble than the corresponding chlorides. Treatment of 91 with two equivalents of silver acetate in chloroform, followed by either 1 equivalent or an

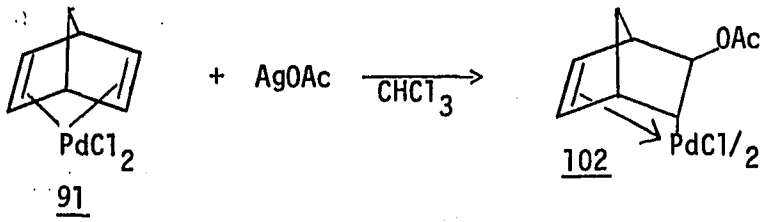
excess of methyl 6-hydroxyhexanoate in either THF, CH_2Cl_2 or $CHCl_3$, with or without di-iso-propylethylamine, did not afford any of the desired palladium complex, 100, or, after carbonylation in methanol with an excess of amine, the desired ester, 101 (eq. 55). These reactions generally produced complex mixtures of products, including



(55)

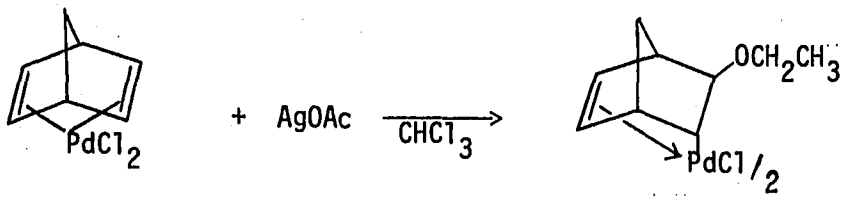
the starting alcohol, from which nothing could be separated or identified by thin layer or column chromatography.

The reaction of 91 with silver acetate in chloroform has been reported to afford the product of acetoxypalladation in high yield (eq. 56) (101). Since this product was not observed in the previous reactions, as judged by the NMR spectrum of the crude product mixture, this reaction was repeated. Treatment of 91 with 1 equivalent of



(56)

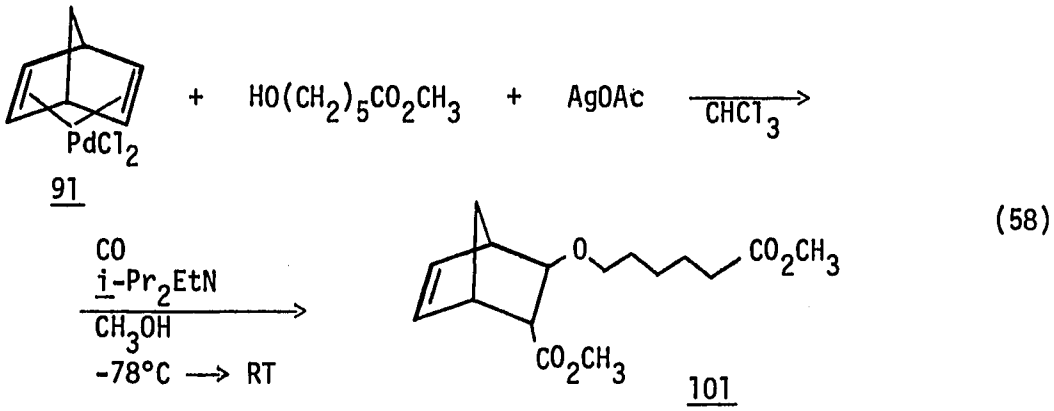
silver acetate in commercial chloroform did not provide the acetoxy compound, but instead produced the ethoxy complex 103 (eq. 57).



(57)

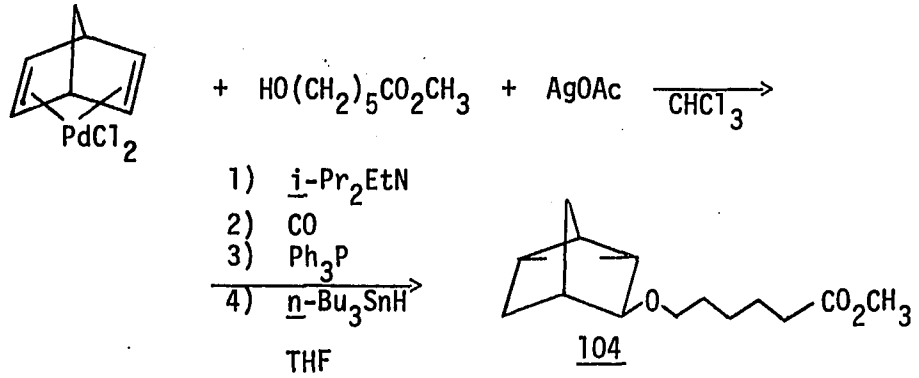
91 103

Analysis of commercial chloroform revealed that for reactions run at a concentration of 0.1 M, approximately 1 equivalent of ethanol, added as a stabilizer, was present. If the presence of one equivalent of ethanol was sufficient to provide for the exclusive formation of ethoxy complex 103 and the complete exclusion of acetoxy complex 102, then addition of 1 equivalent of methyl 6-hydroxyhexanoate should similarly afford the desired product, 99. Accordingly, 91 was treated with 1 equivalent of silver acetate and 1.02 equivalents of methyl 6-hydroxyhexanoate in ethanol-free chloroform for 1 hour. All attempts to isolate the product, after filtering through celite to remove silver chloride, either by recrystallization or precipitation with hexanes, were unsuccessful. However, carbonylation of the crude product in methanol in the presence of an excess of di-iso-propylethylamine provided the diester, 101, in 76% yield (eq. 58).



(58)

The successful synthesis of diester 101, and therefore of palladium compound 99, leaves only the introduction of the unsaturated alcohol chain to complete the synthesis of a 7-oxa PGH_2 analogue. From the previously described work on the methoxy model system, 92, the most attractive way to approach this seemed to be the three step approach involving carbonylation, a Wittig reaction, and enone reduction described in chapter two. Therefore, palladium compound 99 was synthesized as in equation 58, and then treated successively with 1.0 equivalent of di-iso-propylethylamine in THF, carbon monoxide, 2.0 equivalents of triphenylphosphine, and 1.2 equivalents of tri-n-butyltin hydride. Analysis of the crude product showed that the desired aldehyde had not been formed, but that the product instead was the reduced product, 104 (eq. 59). Since 104 must result from

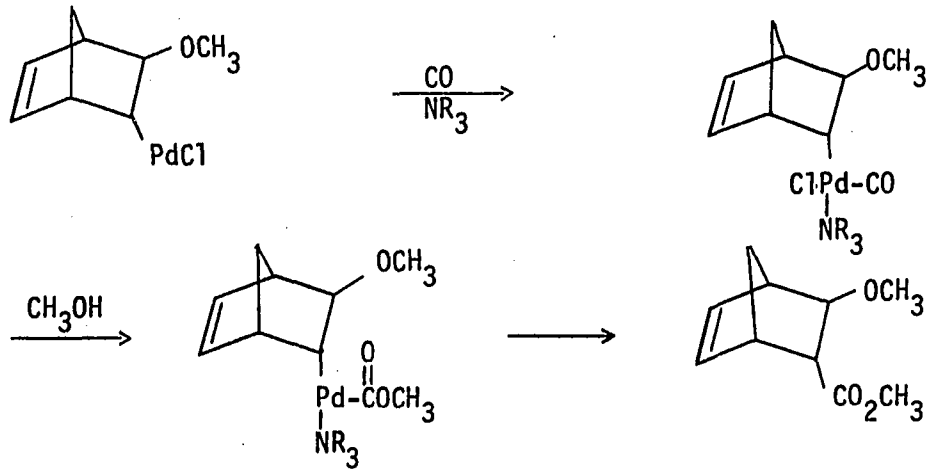


(59)

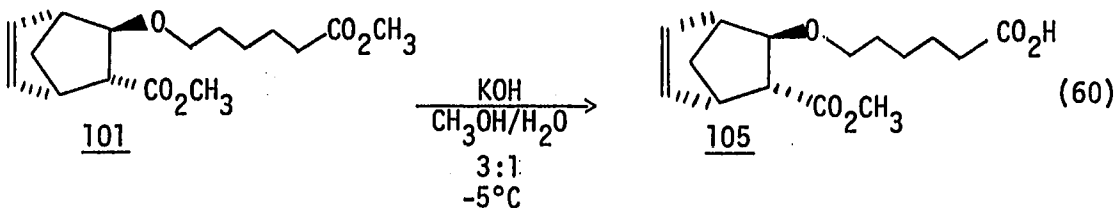
104

reduction of the palladium compound without carbon monoxide insertion, this raises the question of why this carbonylation can be accomplished in methanol but not in other solvents (102). One possible explanation is that, as a consequence of the unusual chemistry displayed by the methoxy complex, 92, carbonylation proceeds via a carbomethoxy organopalladium complex as outlined in Scheme X and not via insertion of carbon monoxide at all (103, 104).

Scheme X

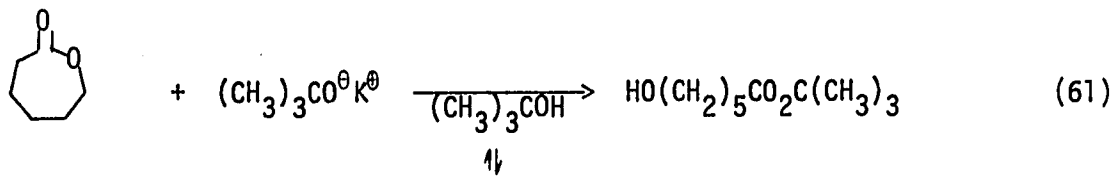


Since the carbonylation seemingly must be run in methanol, it now becomes necessary to alter the synthetic scheme in some way to allow differentiation of the two esters. Attempted saponification of the methyl ester at C-13 (prostaglandin numbering) of 101 with 4-5 equivalents of KOH in 3:1 CH_3OH-H_2O at -5°C for 12 hours resulted only in saponification of the C-1 ester (Eq. 60). Changing the C-1



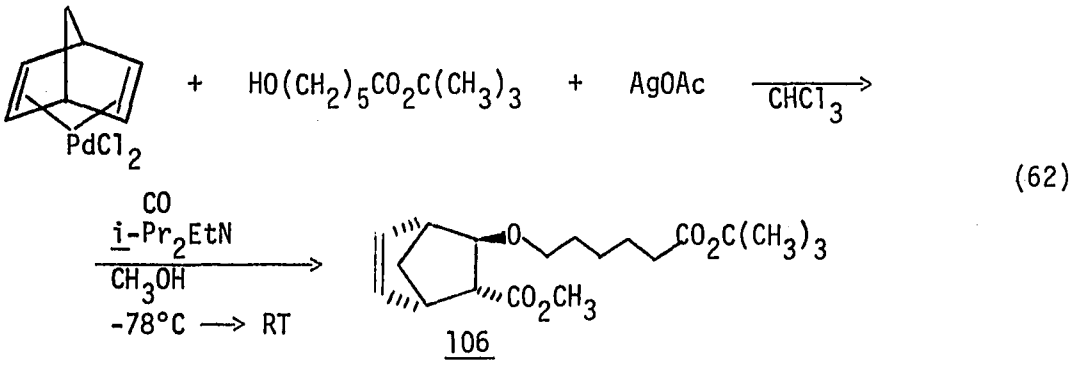
(60)

ester from methyl to tert-butyl through the use of t-butyl 6-hydroxyhexanoate seemed a logical course. The t-butyl ester was prepared from ε-caprolactone by refluxing with potassium t-butoxide in t-butanol in 68% yield (eq. 61). Oxypalladation with t-butyl



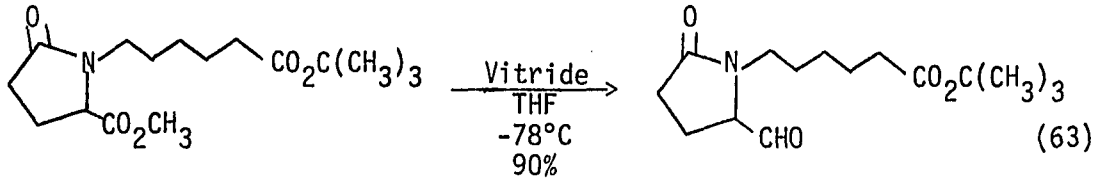
(61)

6-hydroxyhexanoate as before afforded the diester, 106 in 53% yield (eq. 62). Substitution of methylene chloride for chloroform increased the yield to 68%.



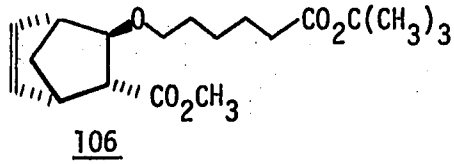
106 (62)

The most direct route to the desired aldehyde is the selective reduction of the methyl ester to an aldehyde. Di-iso-butylaluminum hydride has been found to be a general reagent for the reduction of esters to aldehydes (105), and sodium bis-(2-methoxyethoxy)aluminum hydride (vitride) has been used to reduce a methyl ester to an aldehyde in the presence of a t-butyl ester (eq. 63) (106). Attempted reduction



(63)

of 106 with either di-iso-butylaluminum hydride or sodium bis-(2-methoxyethoxy)aluminum hydride (1.1-1.2 equivalents) in THF at -78°C and warming to room temperature resulted in almost quantitative recovery of unchanged 106 (eq. 64). There was no obvious reason why the methyl ester should be so difficult to reduce although some sort of steric hindrance may be involved.

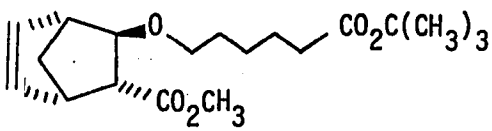


106

Dibal or Vitride
THF
-78°C ⟶ RT

recovered starting material (64)

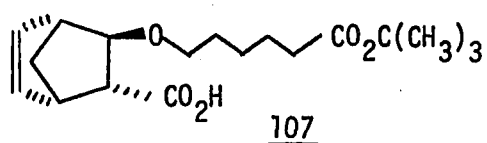
A second route to the desired aldehyde would be to selectively hydrolyze the methyl ester and then reduce the carboxylic acid in the presence of the t-butyl ester. Hydrolysis of the methyl ester was accomplished by heating 106 with 3.1 equivalents of KOH in aqueous methanol for 30 minutes at 60°C (eq. 65). The yield of 107 was 71%,



106

KOH
$CH_3OH:H_2O$
5:1
60°C 30 min.

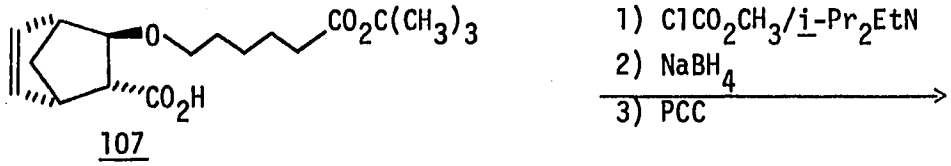
HCl



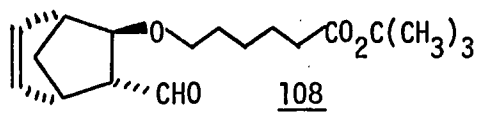
107

(65)

along with about 10% of the diacid. The carboxylic acid was reduced to the aldehyde using a three step sequence developed by Corey (11b). Sequential treatment of 107 with methyl chloroformate-di-iso-propylethylamine (4 equivalents each) in THF at 0°C, sodium borohydride (6 equivalents) in aqueous THF at 0°C, and pyridinium chlorochromate (107) (1.5 equivalents) in methylene chloride afforded the desired aldehyde, 108, in 76% overall yield (eq. 66).

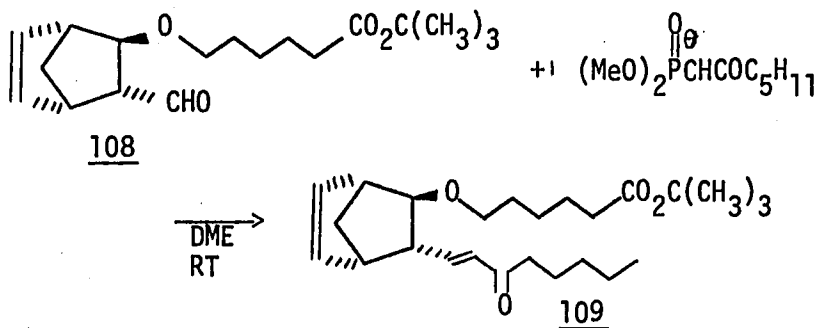


107 (66)



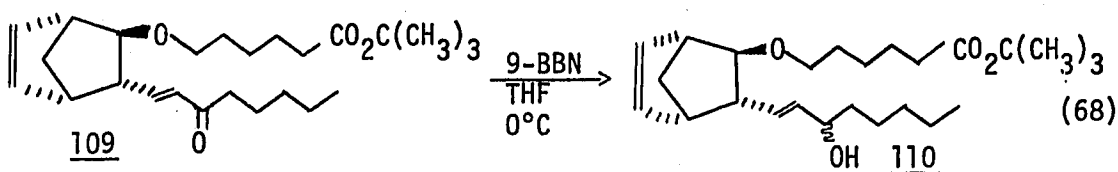
108

Wittig olefination of 108 with 1.6 equivalents of sodio dimethyl 2-oxoheptylphosphonate in dimethoxyethane gave the enone, 109, in 76% yield (eq. 67). Reduction of the enone was accomplished with



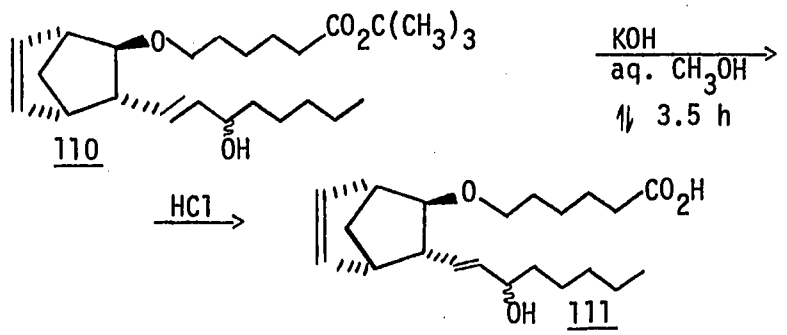
108 109 (67)

9-BBN in THF at 0°C, providing the allylic alcohol, 110, in 98% yield (eq. 68). Hydrolysis of the t-butyl ester by refluxing with



109 110 (68)

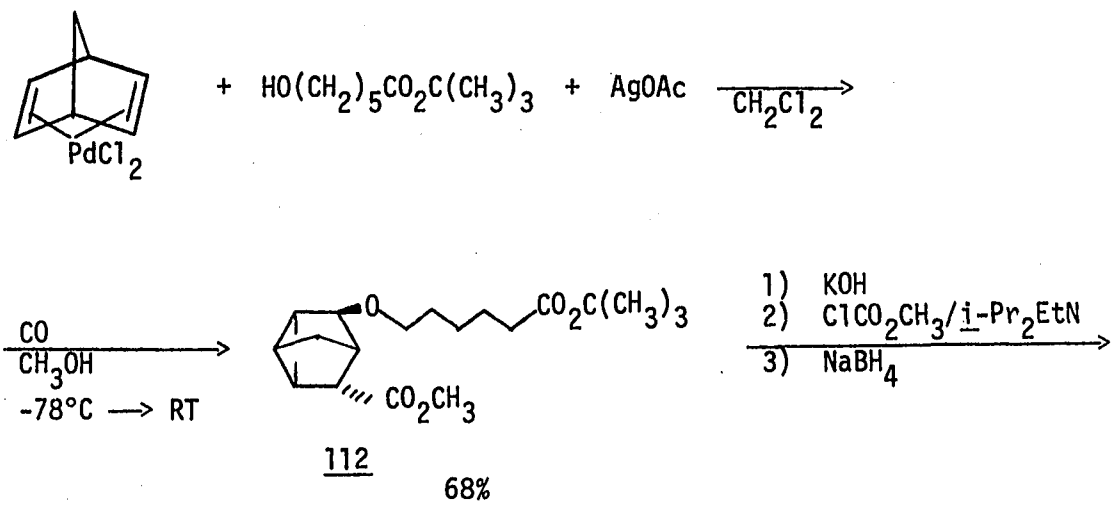
KOH (10 equivalents) in aqueous methanol for 3.5 hours and subsequent acidification afforded the 7-oxa bicyclic prostaglandin analogue 111 in 82% yield (eq. 69).



(69)

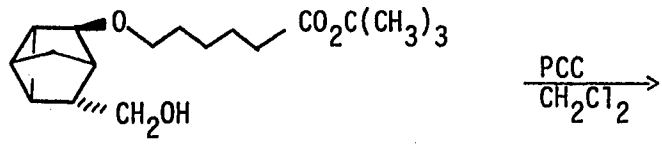
In order to study the effects on the biological activity of these compounds with various bicyclic skeletons, the nortricyclo isomer of 111 was synthesized using the same synthetic sequence just described, except that the carbonylation of the oxypalladation adduct was run in the absence of amine. This sequence, and the yield for each step, are outlined in Scheme XI.

Scheme XI

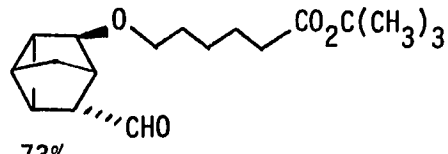


112

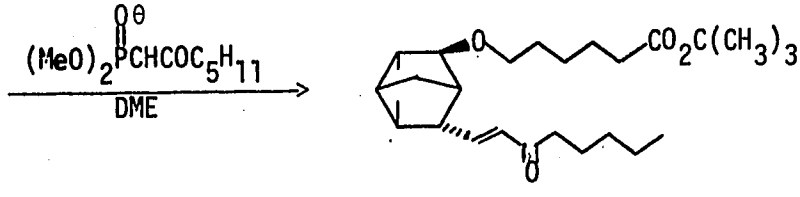
68%



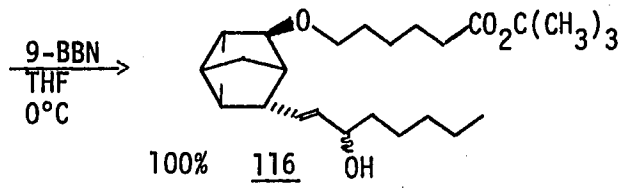
64% 113



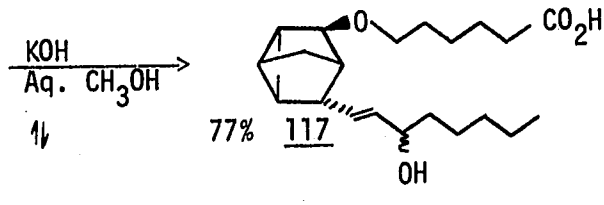
73% 114



99% 115



100% 116



77% 117

The biological profiles of both 111 and 117 are currently under study.

Conclusion

A method has been developed for the synthesis of 7-oxa bicyclic prostaglandin analogues. Silver acetate assisted alkoxypalladation of norbornadienepalladium dichloride by t-butyl 6-hydroxyhexanoate affords an alkoxypalladium complex. Although this cannot be isolated, it can be carbonylated in methanol to afford either one of two diesters, which are useful intermediates in the synthesis of 7-oxa bicyclic and tricyclic prostaglandin analogues. These syntheses were completed via a sequence involving selective ester hydrolysis, carboxylic acid reduction, Wittig olefination, and enone reduction. The synthesis of similar analogues through the reaction of an alkoxypalladium complex with a substituted lithium acetylide was unsuccessful.

Experimental

Equipment

Proton NMR spectra were recorded on either a Varian EM-360, or HA-100 spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer. Infrared spectra were recorded on a Beckman IR-4250 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. Many of the compounds studied in this chapter however, did not give measurable molecular ions.

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 all gas chromatographic analyses.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. THF, diethyl ether and dimethylsulfoxide were distilled from calcium hydride. Dimethoxyethane was distilled from lithium aluminum hydride. Commercial chloroform was purified by washing repeatedly with water, drying over magnesium sulfate, and distilling from 4A molecular sieves. n-Butyllithium and t-butyllithium were obtained from Alfa and titrated before use with 2,5-dimethoxybenzyl alcohol (85). Copper(I) iodide was obtained from Alfa and purified by a literature procedure (87). 1-Buten-3-one was distilled immediately prior to use. Di-iso-propylethylamine was distilled from calcium hydride.

(E)-3-t-Butyldimethylsilyloxy-1-iodo-1-octene (73), norbornadiene-palladium dichloride (88), 3-(2-tetrahydropyranyloxy)-1-octyne (90), and methyl 6-hydroxyhexanoate (108) were prepared using literature procedures.

Attempted oxymercuration with methyl 6-hydroxyhexanoate

Norbornene (.28 g, 3.0 mmol), 0.44 g (3.0 mmol) of methyl 6-hydroxyhexanoate, and 1.28 g (3.0 mmol) of mercuric trifluoroacetate were stirred in 20 mL of methylene chloride for 5 minutes. The mixture was then shaken for several minutes with a saturated solution of sodium chloride. The organic layer was separated, dried over sodium sulfate and concentrated in vacuo. The residue was taken up in 5 to 10 mL of chloroform, to which hexanes were added until the solution became cloudy. The solution was then cooled in the freezer for several hours. The product was isolated by filtration and washed with hexanes to afford 1.28 g (96%) of 3-exo-chloromercuri-2-exo-norbornyl trifluoroacetate:mp 111-112.5°C, ^{1}H NMR($CDCl_3$) δ 1.0-1.9 (6H, m), 2.69 (3H, dd, J=2,7Hz), 5.13 (1H, d, J=7Hz, $CH\text{-}O_2CCF_3$); IR($CHCl_3$) 2980 (C-H), 1785 (C=O), 1150 (C-O)cm^{-1}.

Synthesis of 94

Compound 92 (185 mg, .698 mmol) and 0.70 g (5.4 mmol) of di-iso-propylethylamine were dissolved in 8 mL of CH_3OH and cooled to -78°C. The flask was then flushed with carbon monoxide and allowed to slowly warm to room temperature overnight. The reaction mixture was then diluted with ether, filtered to remove palladium metal, washed with water and saturated ammonium chloride, and dried over sodium sulfate. After removal of the solvent, the product was distilled via Kugelrohr [bp, 110°C (.2 torr)] to afford 110 mg (87%) of 94: ^1H NMR($CDCl_3$) δ 1.4-1.9 (3H, m), 2.68 (1H, t, J=2.5Hz), 2.96 (1H, br s), 3.10 (1H, br s), 3.42 (3H, s, OCH_3), 3.69 (3H, s, CO_2CH_3), 6.13 (2H, m, -CH=CH); IR($CHCl_3$) 1740 (C=O), 1630 (C=C)cm^{-1}; m/z (rel intensity) 182 (1), 151 (3), 117 (63), 85 (63), 66 (100).

Synthesis of 96

Compound 92 (132.5 mg, 0.50 mmol), 0.18 g (2.6 mmol) of methyl vinyl ketone and 0.52 g (4.0 mmol) of di-iso-propylethylamine were stirred at room temperature in 7 mL of DMF and 3 mL of benzene for 36 hours. The reaction mixture was then diluted with ether, filtered, washed with water and saturated ammonium chloride, and dried over sodium sulfate. After removal of the solvent, the product was distilled via Kugelrohr [bp, 140°C (.02 torr)] to provide 51 mg (53%) of 96: ^1H NMR($CDCl_3$) δ 1.0-2.5 (8H, m), 2.27 (3H, s, $COCH_3$), 3.23

(3H, s, OCH_3), 6.03 (1H, d, J=16Hz, C=CHCO), 6.72 (1H, d, J=16Hz, CH=C-CO); IR($CHCl_3$) 1670 (C=O), 1620 (C=C), 1105 (C-O)cm^{-1}; m/z (rel intensity) 192 (9), 177 (12), 160 (12), 149 (58), 117 (100), 91 (66).

Synthesis of 98

Compound 92 (264 mg, 1.00 mmol) and 529 mg (2.02 mmol) of triphenylphosphine were stirred in 8 mL of THF for 30 minutes at room temperature and then cooled to -78°C. To this was added a -78°C solution of 1.05 mmol of mixed cuprate 97 in 3 mL of THF. This mixture was stirred for 1 hour at -78°C and then quenched by the addition of 1 mL of methanol. The reaction mixture was diluted with hexanes and washed repeatedly with saturated ammonium chloride buffer (pH 8) until the washes were colorless. The organic layer was then dried over sodium sulfate and concentrated. Chromatography on silica gel afforded 100 mg (28%) of 98: Rf. 29, benzene: ethyl acetate (9:1); ^1H NMR($CDCl_3$) δ .15 (6H, s, $SiCH_3$), 1.0 [12H, s, $-CH_3$ and $SiC(CH_3)_3$], 1.2-1.7 (12H, m), 1.8-2.1 (3H, m), 2.4 (1H, br s), 3.35 (3H, s, OCH_3), 3.7 (1H, br s, CHOMe), 4.2 (1H, br, CHOSi), 5.5-5.7 (2H, m, vinyl); ^{13}C NMR($CDCl_3$) 134.05, 132,53, 131.88, 130.86, 130.48, 83.62, 82.97, 73.00, 63.30, 56.42, 46.29, 46.02, 38.71, 37.30, 37.03, 36.59, 35.18, 31.72, 31.12, 30.80, 28.52, 27.92, 26.19, 25.59, 25.05, 22.40, 17.90, 17.04, 13.90, 13.52, 12.60, -4.80.

Reaction of 92 with 3-(2-tetrahydropyranyloxy)-1-lithio-1-octyne

Compound 92 (270.9 mg, 1.022 mmol) and 171.0 mg (1.024 mmol) of silver acetate were stirred for 1 hour in 10 mL of chloroform. The suspension was then filtered through Celite, treated with 0.34 g (1.6 mmol) of hexafluoroacetylacetone, and stirred for an additional hour. The solvent and excess hexafluoroacetylacetone were then removed with a rotary evaporator after which the product was dried under high vacuum overnight. This was then stirred with 541.9 mg (2.066 mmol) of triphenylphosphine in 10 mL of THF for 30 minutes, and then cooled to -78°C. 3-(2-Tetrahydropyranyloxy)-1-octyne (241.1 mg, 1.146 mmol) in 10 mL of THF was deprotonated at -78°C by adding 0.51 mL (1.08 mmol) of 2.11 N n-butyllithium and stirring for 1 hour. The solution of the lithium acetylide was then transferred via stainless steel cannula to the cold solution of the palladium complex. This was stirred at -78°C for 1 hour and then allowed to slowly warm to room temperature. The reaction was quenched with 1 mL of CH_3OH. The solvent was then removed in vacuo and the residue was extracted with 3 25 mL portions of hexanes. The extract was filtered through Celite and concentrated on a rotary evaporator. TLC analysis of the residue did not indicate the presence of any isolable product.

Attempted oxypalladation of 91 with methyl 6-hydroxyhexanoate in THF

Norbornadienepalladium dichloride (0.27 g, 1.0 mmol), 0.20 g (1.4 mmol) of methyl 6-hydroxyhexanoate, and 0.18 g (1.7 mmol) of sodium carbonate were stirred for 48 hours in 10 mL of THF under argon. The suspension was then filtered, affording 0.35 g of a yellow insoluble solid. The product was not soluble enough to obtain an NMR spectrum in either $CDCl_3$ or CD_2Cl_2. On the basis of the infrared spectrum of the crude product it was assumed to consist mainly of 91: IR(KBr) 3040 (HC=CH), 1620 (C=C), 1410, 1310cm^{-1}.

Synthesis of 103

Norbornadienepalladium dichloride (0.27 g, 1.0 mmol) and 0.18 g (1.1 mmol) of silver acetate were stirred for 1 hour in 70 mL of chloroform. The mixture was then filtered through Celite and the solvent removed in vacuo to afford 0.25 g (90%) of 103: ^1H NMR($CDCl_3$) δ 1.13 (3H, t, J=6Hz, CH_3), 1.5-2.2 (2H, m), 2.9 (2H, m), 3.1-3.4 (1H, m), 3.48 (2H, q, J=6Hz, $-OCH_2-$), 4.2 (1H, m, CHPd), 5.8-6.2 (2H, m, vinyl).

Synthesis of 101

Norbornadienepalladium dichloride (269.5 mg, 1.000 mmol), 167.0 mg (1.001 mmol) of silver acetate and 149.2 mg (1.021 mmol) of methyl 6-hydroxyhexanoate were stirred for 1 hour in 10 mL of ethanol-free chloroform. The reaction mixture was then filtered through Celite and

concentrated in vacuo. Di-iso-propylethylamine (0.74 g, 5.7 mmol) was added after which 10 mL of methanol was added. The flask was flushed with nitrogen after which it was cooled to -78°C, flushed with carbon monoxide, and allowed to slowly warm to room temperature. After diluting with ether, the reaction mixture was filtered, washed with water and brine, and dried over magnesium sulfate. Flash chromatography provided 220 mg (76%) of 101: Rf. 30, hexanes: ethyl acetate (4:1); ^{1}H NMR($CDCl_3$) δ 1.1-1.9 (8H, m), 2.28 (2H, t, J=6Hz, $-CH_2CO$), 2.6 (1H, t, J=3Hz), 2.9 (1H, br), 3.05 (1H, br), 3.47 (2H, t, J=6Hz, $-CH_2O-$), 3.70 (7H, s overlapping peaks, OCH_3, -CHO-), 6.05 (2H, m, vinyl); IR(neat) 1740 (C=O), 1630 (C=C)cm^{-1}; ^{13}C NMR($CDCl_3$) 173.83, 137.28, 134.29, 82.78, 69.13, 52.35, 51.18, 47.41, 46.50, 43.70, 33.75, 29.26, 25.56, 24.52; m/z (rel intensity) 264 (.1), 231 (5), 199 (23), 129 (83), 97 (39), 66 (100).

Saponification of 101

Compound 101 (332.3 mg, 1.121 mmol) and 0.28 g (4.99 mmol) of KOH were stirred in 12 mL of 3:1 methanol-water for 12 hours at -5°C. The reaction mixture was then acidified with dilute HCl, diluted with ether, washed with brine, and dried over magnesium sulfate. Chromatography on silica gel afforded 316 mg (77%) of 105: Rf. 28, hexanes: ethyl acetate: acetic acid (30:15:1); ^{1}H NMR($CDCl_3$) δ 1.3-2.0 (8H, m), 2.3 (2H, t, J=6Hz, CH_2CO_2), 2.6-2.75 (1H, m), 2.9 (1H, br s), 3.0-3.2 (1H, m), 3.35-3.7 (3H, m), 3.67 (3H, s, OCH_3), 6.0-6.2 (2H, m, CH=CH), 11.7 (1H, br s, CO_2H).

Synthesis of t-butyl 6-hydroxyhexanoate

6-Hexanolactone (3.65 g, 32.0 mmol) and 3.93 g (35.0 mmol) of potassium t-butoxide were refluxed for 2.5 hours in 100 mL of t-butanol. After diluting with ether and benzene, the reaction mixture was washed with water and brine, dried over magnesium sulfate, and concentrated on a rotary evaporator. Distillation afforded 4.10 g (68%) of t-butyl 6-hydroxyhexanoate: bp 84-86°C (0.4 torr); ^{1}H NMR($CDCl_3$) δ 1.45 (15 H, s overlapping peaks), 2.2 (2H, t, J=7Hz, CH_2CO), 3.03 (1H, s, OH), 3.53 (2H, t, J=6Hz, CH_2OH); IR(neat) 3400 (OH), 1740 (C=O), 1400 [$C(CH_3)_3$], 1375 [$C(CH_3)_3$], 1160 (ester C-O)cm^{-1}; m/z 132.07840 [Calcd for $C_6H_{12}O_3(M^{\cdot+}-C_4H_8)$, 132.07865].

Synthesis of 106 and 112

Norbornadienepalladium dichloride (270 mg, 1.00 mmol), 207 mg (1.10 mmol) of t-butyl 6-hydroxyhexanoate, and 183 mg (1.10 mmol) of silver acetate were stirred for 1 hour in 10 mL of methylene chloride and then filtered through Celite. After removal of the methylene chloride, 0.64 g (5.0 mmol) of di-iso-propylethylamine was added and the mixture was dissolved in 10 mL of methanol under nitrogen. After stirring for 10 minutes the mixture was cooled to -78°C, flushed with carbon monoxide, and allowed to warm to room temperature overnight. The mixture was then diluted with ether, washed with water and saturated ammonium chloride, and dried over magnesium sulfate. Purification by flash chromatography provided 230 mg (68%) of 106: Rf .30, hexanes: ethyl acetate (6:1); ^{1}H NMR($CDCl_3$) δ 1.4 [9H, s, $C(CH_3)$], 1.4-1.9

(8H, m), 2.18 (2H, t, J=6Hz, CH_2CO), 2.6 (1H, t, J=3Hz), 2.9 (1H, br), 3.1 (1H, br), 3.47 (2H, t, J=6Hz, $-CH_2O-$), 3.63 (4H, s overlapping peaks, OCH_3, -CHO-), 6.05 (2H, m, vinyl); IR(neat) 1735 (C=O), 1635 (C=C), 730 (C=C)cm^{-1}; m/z (rel intensity) 282 (1), 217 (31), 185 (22), 151 (42), 115 (65), 66 (100).

Compound 112 was prepared similarly in 52% yield except that di-iso-propylethylamine was excluded. Rf .28, hexanes: ethyl acetate (5:1); ^1H NMR($CDCl_3$) δ 1.1-1.9 (11H, m), 1.4 [9H, s, $C(CH_3)_3$], 1.9-2.3 (3H, m), 2.4 (1H, t, J=1Hz), 3.3 (2H, t, J=6Hz, $-OCH_2-$), 3.63 (3H, s, OCH_3), 3.7 (1H, s, -CHO). IR(neat) 1730 (C=O)cm^{-1}.

Attempted reduction of 106

Compound 106 (212.7 mg, 0.6285 mmol) was dissolved in 8 mL of THF under nitrogen and cooled to -78°C. Sodium bis-(2-methoxyethoxy)-aluminum hydride (0.11 mL, 0.37 mmol) was added via syringe. The reaction mixture was stirred for 1 hour at -78°C and 1 hour at 0°C after which 1 mL of methanol was added. After diluting with ether, the reaction mixture was washed with dilute HCl and brine, and dried over magnesium sulfate. Analysis of the product by NMR showed that only starting material was present.

Synthesis of 107

Compound 106 (1.04 g, 3.07 mmol) and 0.54 g (9.6 mmol) of KOH were heated for 30 minutes at 60°C in 30 mL of a 5:1 mixture of methanol and water. After diluting with ether, the reaction mixture was acidified with dilute HCl, washed with water and brine, and dired over magnesium sulfate. Purification by chromatography afforded 170 mg (16%) of recovered 106, and 0.60 g (71%) of 107: Rf .35, hexanes: ethyl acetate: acetic acid (160:80:1); ^{1}H NMR($CDCl_3$) δ 1.3-1.9 (8H, m), 1.4 [9H, s, $-C(CH_3)_3$], 2.2 (2H, t, J=6Hz, $-CH_2CO$), 2.7 (1H, t, J=3Hz), 2.8 (1H, br), 3.0 (1H, br), 3.45 (2H, $-CH_2O$), 3.6 (1H, br, -CHO-), 5.9-6.2 (2H, m, vinyl), 10.7 (1H, s, CO_2H); IR(neat) 1740 (ester C=O), 1715 (acid C=O), 1635 (C=C)cm^{-1}.

Synthesis of 108

Compound 107 (0.36 g, 1.11 mmol), 0.42 g (4.4 mmol) of methyl chloroformate, and 0.65 g (5.0 mmol) of di-iso-propylethylamine were stirred in 18 mL of THF for 1 hour at 0°C. After removal of the THF, the crude product was dissolved in 32 mL of 6:1 THF-H_2O at 0°C, after which 0.25 g (6.6 mmol) of sodium borohydride was added. This was stirred for an additional hour. The reaction mixture was then diluted with ether, acidified with dilute HCl, washed with brine, and dried over magnesium sulfate. Oxidation of the crude alcohol (0.42 g, 1.36 mmol) with 0.44 g (2.04 mmol) of pyridinium chlorochromate using

Corey's (107) procedure was accomplished by stirring in 5 mL of methylene chloride for 2 hours. The mixture was then diluted with 25 mL of ether and decanted into a short Florisil column. The black residue from the flask was washed twice with 10 mL of ether and this was added to the column. Elution of the column with 500 mL of ether afforded 318 mg (76%) of 108: ^{1}H NMR($CDCl_3$) δ 1.0-1.8 (8H, m), 1.43 [9H, s, $-C(CH_3)_3$], 2.17 (2H, t, J=6Hz, $-CH_2CO$), 2.6 (1H, m), 2.9 (1H, br), 3.0 (1H, br), 3.3-3.5 (2H, m, $-CH_2O-$), 3.57 (1H, br s, -CHO-), 5.8-6.2 (2H, m, vinyl), 9.39 (1H, d, J=2Hz, CHO); IR(neat) 2710 (CHO), 1740 (ester C=O), 1715 (aldehyde C=O)cm^{-1}.

Synthesis of 113

Compound 112 (492.5 mg, 1.455 mmol) and 0.41 g (7.3 mmol) of KOH were refluxed for 30 minutes in 20 mL of 5:1 methanol-H_2O. After diluting with ether, the mixture was acidified with dilute HCl, washed with brine, and dried over magnesium sulfate. The crude acid thus obtained was treated with 0.55 g (5.8 mmol) of methyl chloroformate and 0.75 g (5.8 mmol) of di-iso-propylethylamine in 20 mL of THF for 1 hour at 0°C. After removal of the THF, the crude product was dissolved in 28 mL of 6:1 THF-H_2O at 0°C, after which 0.33 g (8.7 mmol) of sodium borohydride was added. This solution was stirred for an additional hour. The reaction mixture was then diluted with ether, acidified with dilute HCl, washed with brine, and dried over magnesium

sulfate. Purification by flash chromatography afforded 266 mg (64%) of 113: Rf .32, hexanes: ethyl acetate (1:1); ^{1}H NMR($CDCl_3$) δ 1.0-2.3 (15H, br m), 1.43 [9H, s, $-C(CH_3)_3$], 3.2-3.7 (4H, m, $-CH_2OH$), $-CH_2O$), 3.73 (1H, s, -CHO-), 4.3 (1H, br, -OH); IR(neat) 3440 (OH), 1735 (C=O)cm^{-1}.

Synthesis of 114

Compound 113 (260 mg, .838 mmol) and 0.27 g (1.25 mmol) of pyridinium chlorochromate were stirred for 2 hours in 5 mL of methylene chloride. The mixture was then diluted with 25 mL of ether and decanted onto a 6 inch Florisil column. The black residue was washed twice with 10 mL of ether and this was added to the column. The product was then eluted with ether, providing 189 mg (73%) of 113: ^{1}H NMR($CDCl_3$) δ 1.1-1.7 (9H, m), 1.45 [9H, s, $-C(CH_3)_3$], 1.9 (1H, br s), 2.0-2.5 (5H, m), 3.35 (2H, t, J=6Hz, $-CH_2O-$), 3.64 (1H, br s, -CHO-), 9.77 (1H, d, J=2Hz, -CHO); IR(neat) 1715 (C=O)cm^{-1}.

Synthesis of 109 and 115

The synthesis of 109 is representative. Sodium hydride (67%) (51.4 mg, 1.43 mmol) was washed several times with hexanes under nitrogen. After drying for approximately 5 minutes under a gentle stream of nitrogen, this was suspended in 15 mL of DME. Dimethyl (2-oxoheptyl)phophonate (0.370 g, 1.67 mmol) in 3 mL of DME was added,

and the reaction was stirred for 1 hour. Compound 108 (275 mg, 0.892 mmol) in 3 mL of DME was then added via syringe. After stirring for 3 hours, 0.5 mL of acetic acid was added after which the solvent was removed with a rotary evaporator. The product was then extracted with 40 mL of hexanes and filtered through Celite. After concentration, chromatography of the residue afforded 265 mg (76%) of 109: Rf .33, hexanes: ethyl acetate (7:1); ^{1}H NMR($CDCl_3$) δ .86 (3H, t, J=5Hz, CH_3), 1.1-1.9 (13H, m), 2.0-3.0 (8H, m), 3.13 (1H, br s), 3.33 (2H, t, J=5Hz, CH_2O), 6.00 (1H, d, J=15.5Hz, =CHCO), 6.03 (2H, m, vinyl), 6.46 (1H, dd, J=8, 15.5 Hz, CH=CCO).

Compound 115: 99% yield; Rf .29, hexanes: ethyl acetate (7:1); δ .87 (3H, t, J=5Hz, CH_3), 1.0-2.6 (17H, m), 1.4 [9H, s, $C(CH_3)_3$], 3.3 (2H, t, J=6Hz, CH_2O), 3.6 (1H, br s, CHO), 6.08 (1H, d, J=16Hz, =CHCO), 6.78 (1H, dd, J=6, 16Hz, CH=CCO).

Synthesis of 110 and 116

The synthesis of 110 is representative. Compound 109 (190 mg, 0.469 mmol) was dissolved in 6 mL of THF and cooled to 0°C. A solution of 0.10 g (0.82 mmol) of 9-BBN in 2 mL of THF was added via syringe. After stirring for 2 hours at 0°C, 0.5 mL of methanol was added to destroy excess hydride. The boronic acid derivative was oxidized by addition of 0.27 mL of 3N aqueous sodium hydroxide followed

by addition of 0.22 mL of 30% hydrogen peroxide. This mixture was then stirred for 1 hour after which it was diluted with ether, washed twice with brine and five times with water to remove 1,5-cyclooctanediol, and dried over magnesium sulfate. Purification by chromatography afforded 193 mg (100%) of 110: Rf .38, hexanes: ethyl acetate (3:1); ^{1}H NMR($CDCl_3$) δ .9 (3H, t, J=6Hz, CH_3), 1.1-2.5 (29H, m), 2.6-2.9 (2H, m), 3.1 (1H, br s), 3.38 (2H, t, J=6Hz, CH_2O), 4.0 [1H, br, CH(OH)], 5.3-5.6 [2H, m, trans-CH=CHC(OH)], 5.9-6.2 (2H, m, cis-CH=CH); IR(neat) 3410 (OH), 1730 (C=O), 1140 (C-O)cm^{-1}.

Compound 116: 100% yield; Rf .31, hexanes: ethyl acetate (3:1); ^{1}H NMR($CDCl_3$) δ .87 (3H, t, J=5Hz, CH_3), 1.0-2.4 (32H, m), 3.32 (2H, t, J=6Hz, $-CH_2O-$), 3.67 (1H, br s, -CHO-), 4.0 (1H, br, -CHO-), 6.4-6.6 (2H, m, trans-CH=CH); IR(neat) 3410 (OH), 1730 (C=O)cm^{-1}.

Synthesis of 111 and 117

The synthesis of 117 is representative. Compound 116 (158 mg, 0.3886 mmol) and 0.22 g (3.9 mmol) of KOH were refluxed for 2.5 hours in 10 mL of 4:1 methanol-H_2O. After cooling, the reaction mixture was diluted with ether, acidified with dilute HCl, washed with brine, and dried over magnesium sulfate. Flash chromatography afforded 105 mg (77%) of 117: Rf .26, hexanes: ethyl acetate: acetic acid (30:15:1); ^{1}H NMR($CDCl_3$) δ .87 (3H, t, J=5Hz, $-CH_3$), 1.1-2.5 (23H, m), 3.33 (2H, t, J=6Hz, $-CH_2O-$), 3.67 (1H, br s, -CHO-), 4.1 (1H, br,

-CHOH-), 5.5 (2H, m, -CH=CH-), 8.3 (2H, br s, OH, CO_2H); IR(neat) 3400 br(OH), 1720 (C=O), 1160 (C-O)cm^{-1}; ^{13}C NMR($CDCl_3$) 177.96, 133.51, 131.23, 131.10, 82.07, 73.08, 68.67, 46.17, 37.07, 33.95, 31.67, 30.89, 29.52, 25.69, 25.03, 24.45, 22.50, 20.68, 17.04, 13.92, 13.79, 12.62; m/z 3332.23676 (calcd for $C_{21}H_{32}O$, (M^{+}-H_2O), 332.23515).

Compound 111: 82% yield; Rf .29, hexanes: ethyl acetate: acetic acid (30:15:1); ^{1}H NMR($CDCl_3$) δ .85 (3H, t, J-5Hz, $-CH_3$), 1.0-2.0 (15H, m), 2.1-2.4 (4H, m), 2.5-2.9 (2H, m), 3.0 (1H, br s, -CHO-), 3.38 (2H, t, J-6Hz, $-CH_2O-$), 3.8-4.1 [1H, br, CH(OH)], 5.2-5.5 (2H, m, trans-CH=CH-), 5.9-6.2 (2H, m, cis-CH=CH-); IR(neat) 3420 br(OH), 1715 (C=O), 1090 (C-O)cm^{-1}; ^{13}C NMR($CDCl_3$) 178.96, 137.86, 134.94, 134.03, 132.86, 86.23, 73.09, 69.00, 50.59, 47.67, 47.47, 46.95, 46.43, 46.24, 37.07, 33.95, 31.60, 29.46, 25.69, 25.04, 24.45, 22.57, 13.98; m/z 332.23574 (calcd for $C_{21}H_{32}O_3$, (M^{+}-H_2O), 332.23515).

CHAPTER IV. ORGANOCOPPER-ORGANOMERCURY CROSS-COUPLING REACTIONS

Introduction

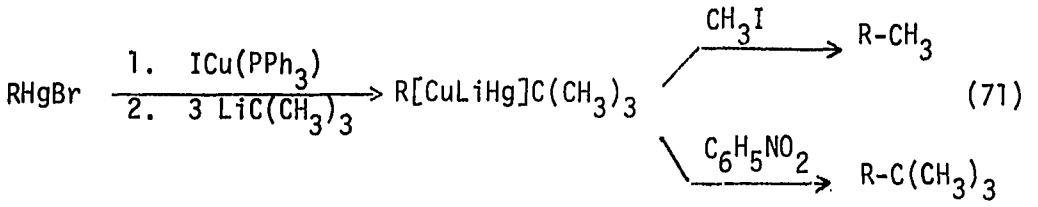
In the preceding chapter, a method for the synthesis of 7-oxa bicyclic prostaglandin analogues via alkoxymercuration of norbornene was investigated. In order to develop a method for the introduction of the trans-allylic alcohol side chain, the alkylation of organomercurials was considered. Unfortunately, the direct alkylation of organomercurials is not easily effected.

In general, organomercurials are inert towards alkyl halides. Only under forcing conditions (109-112) or in the presence of aluminum bromide (113) can low to modest yields of cross-coupled products be obtained. The cross-coupling of organorhodium(III) compounds with alkenyl-, alkynyl-, and arylmercurials using only catalytic amounts of rhodium has been reported (eq. 70) (114). However,

$$CH_3I \xrightarrow{ClRh(PPh_3)_3} CH_3RhI_2(PPh_3)_2 \xrightarrow{RHgCl} R\text{-}CH_3 \quad (70)$$

the catalyst turnover is generally quite low. Bergbreiter and Whitesides have reported that the reaction of primary and secondary alkylmercurials, iodo(tri-n-butylphosphine)copper(I), and t-butyllithium gives an intermediate of unknown composition that may either be alkylated with methyl iodide or oxidatively coupled with nitrobenzene (eq. 71)

(115). It was concluded that the intermediate is a ternary ate complex containing all three metals and not a simple organocuprate



(71)

reagent, since conjugate addition to mesityl oxide could not be effected. Unfortunately, arylmercurials could not be cross-coupled with alkyl halides and alkenylmercurials were not examined. With the recent report that organomercurials undergo a number of radical anion chain reactions (116) and given the propensity of organocopper reagents to undergo similar reactions (117), we decided to reinvestigate the reactions of organomercurials and organocopper reagents as a potentially useful new way to alkylate organomercurials.

Results and Discussion

Alkylation of arylmercurials

While arylmercurials could not be alkylated by alkyl halides using Whitesides' procedure (115), we have obtained our best yields of cross-coupled products using these organomercurials. Initially, the reaction of phenylmercuric chloride, 118, and methylcopper reagents

was chosen as a model system on which to study the effect on the yield of toluene of each of the following reaction variables: oxidizing agents, solvent, temperature, transition-metal salts, methylcopper stoichiometry, methyl iodide addition, ligands, and the use of heterocuprate reagents. These results are summarized in Table 6.

The oxidation of organocopper-organic halide cross-coupling reactions prior to hydrolysis has been shown to significantly increase the yield of cross-coupled product (118, 119). The effect of different oxidizing agents was therefore examined on the reaction of 118 and lithium dimethylcuprate, 119, (5 equiv) (eq. 72). Compound 118 was added to 119 at -78°C and maintained at that temperature for 1 hour, before warming to 0°C (1 hour) and either flushing with pure oxygen or adding excess nitrobenzene. Both

$$\underset{\underline{118}}{C_6H_5HgCl} + \underset{\underline{119}}{LiCu(CH_3)_2} \longrightarrow C_6H_5\text{-}CH_3 \qquad (72)$$

oxidation procedures gave essentially the same result, a 45% yield of toluene and small amounts of biphenyl (<5%). All subsequent work was carried out by using oxygen due to its convenience.

Table 6. Methylation of phenylmercuric chloride[a]

entry	methylcopper reagent	added reagents	reaction procedure[b]	quenching agent	% yield of toluene[c]
1	$LiCuMe_2$	...	A	O_2	45
2		...	B		48
3		$PdCl_2$[d]			57
4		$NiCl_2$[d]			60
5		$FeCl_2$[d]			59
6	CuMe	...			6
7	Li_2CuMe_3	...	A		60
8		...	B		66
9	$LiCuMe_2$	...		MeI	34
10		...	A		55

[a]Reactions were carried out by adding 0.5 mmol of 118 to 2.5 mmol of methylcopper reagent dissolved in 10 mL of diethyl ether unless otherwise noted, followed by quenching with methyl iodide and/or oxygen and finally aqueous ammonium chloride.

[b]Procedure A: reaction maintained at -78°C for 1 hour, warmed to 0°C for 1 hour, and then quenched. Procedure B: -78°C for 1 hour before quenching.

[c]Yields were determined by gas chromatography using an internal standard.

[d]0.025-0.05 mmol.

Table 6 continued

entry	methylcopper reagent	added reagents	reaction procedure[b]	quenching agent	% yield of toluene[c]
11		...		MeI, O_2	76
12	Li_2CuMe_3	...		MeI, O_2	92
13		...			65[e]
14	$LiCuMe_2 \cdot SMe_2$	SMe_2	A	O_2	52
15		SMe_2	B		51
16		SMe_2	A	MeI, O_2	81
17	$Li_2CuMe_3 \cdot SMe_2$	SMe_2			92
18	$LiCuMe_2 \cdot PBu_3$	...	B	O_2	68
19	$LiCuMe_2 \cdot HMPA$	...			53
20	LiCu(CN)Me	...			31
21	LiCu(SPh)Me[f]	...			11
22	LiCu(C≡CCMe$_2$OMe)Me[f]	...			18
23	LiCu(O-t-Bu)Me[f]	...	A	MeI, O_2	28

[e] 1.0 mmol of Li_2CuMe_3.

[f] Reaction run in THF solvent.

Both diethyl ether and tetrahydrofuran (THF) have been examined as possible solvents for these reactions. The reaction of 118 and 119 (5 equiv) was carried out at -78°C for 1 hour in ether and THF and quenched with oxygen and aqueous ammonium chloride. Yields of 48% and 43%, respectively, were obtained. Since little difference was observed, all subsequent methylcopper reactions with 118 were run in ether, except the heterocuprate reactions where literature procedures employing THF were utilized. However, it was observed in later work that n-butyl- and vinylcopper reactions generally gave higher yields in THF.

The temperature range at which these reactions can be run is limited by the stability of the organocopper reagent employed. Methylcopper reagents appear stable even at room temperature, while vinylcopper species are unstable above 0°C. n-Butylcopper reactions were best run at -78°C. With 119, essentially identical results were obtained from reactions run at either -78°C for 1 hour and then quenched (48% yield) or at -78°C for 1 hour followed by warming to 0°C for 1 hour prior to quenching (45%) (entries 1 and 2, Table 6).

In a further effort to increase the yield of cross-coupled product, the effect of several transition-metal salts was investigated. It has been shown that iron(II) chloride and nickel(II) bromide catalyze

the coupling of 119 with iodobenzene (119). We therefore added 5-10% of iron(II) chloride, nickel(II) chloride, and palladium(II) chloride to the reaction of 118 and 119. While the yield of toluene after oxidation increased from 48% in the absence of salts to 57-60% in their presence (entries 3-5), the salts produced no substantial increase in yield without oxidation.

Ashby has reported that by using appropriate ratios of methyllithium and copper(I) iodide, organocuprates of the composition $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ may be prepared (120). The reactivity of these reagents has been studied, and $Li_2Cu(CH_3)_3$ has been found to be superior to 119 in coupling reactions with organic halides (121, 122). We have also examined the effect of a variety of different methylcopper reagents on the yield of cross-coupled product from 118 (entries 6-8). Methylcopper proved totally ineffective (6%), but $Li_2Cu(CH_3)_3$, 120, gave increased yields (60-68%) and appears to be the reagent of choice for this system.

Corey and Posner (123) and Whitesides et al. (119) have reported that in the coupling reactions between an alkyl halide RX and an organocuprate reagent R'_2CuLi, addition of R'X often substantially increases the yield of cross-coupled product. It has been postulated that this is due to metal halogen exchange. We have observed the same effect in the methylation of 118 (entries 9-12). Reacting 118 and 120 (5 equiv) for 1 hour at -78°C, warming to 0°C for 1 hour, adding excess

methyl iodide and stirring for 30 minutes, flushing with oxygen, and finally quenching with aqueous ammonium chloride solution, we were able to obtain a 92% yield of toluene. Decreasing the amount of 119 from 5 to 2 equiv resulted in only a 65% yield. The addition of the corresponding alkyl iodide has not always improved the yield, however. In some instances to be discussed later, addition of alkyl halides lowered the yield of cross-coupling product.

While an excellent yield of cross-coupled product can be obtained by using a large excess of the methylcopper reagent, we have examined several methods by which we hoped to be able to employ smaller amounts of methyllithium. Ligands often have a profound effect on organocopper reactions. House has recommended the use of organocopper reagents generated in the presence of excess dimethyl sulfide (124). We have examined the effect of this ligand on the methylation of 118 (entries 14-17). Dimethyl sulfide does appear to slightly increase the yield of toluene in some cases. However, in later studies to be described, it has also proven detrimental. No clear conclusions can be drawn at this time as to the advantages or disadvantages of this ligand. Trialkylphosphines have also been employed as ligands in organocopper reactions (119). While the dimethylcuprate reagent derived from iodo(tri-n-butylphophine)copper(I) and 2 equiv of methyllithium gave an improved yield of toluene (68%) (entry 18), this procedure is not very attractive due to the difficulties presented by the phosphine upon workup. Hexamethylphosphoramide (HMPA) proved less effective (53%) (entry 19).

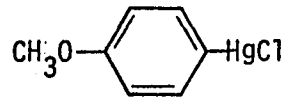
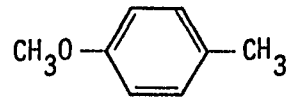
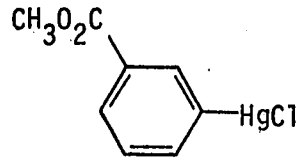
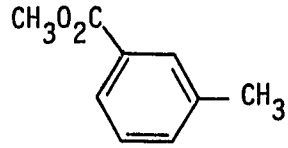
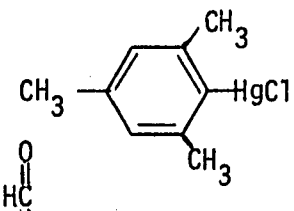
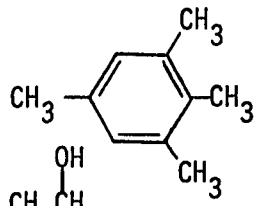
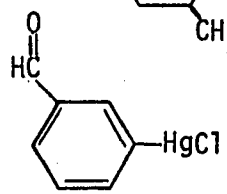
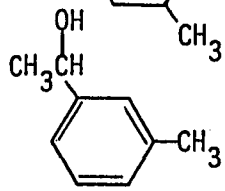
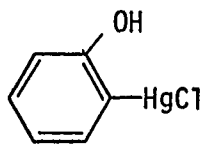
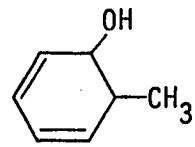
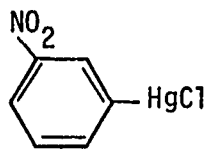
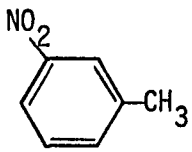
On occasions heterocuprate reagents have been employed to make more effective use of the organic groups attached to copper. Unfortunately, none of the mixed organocopper reagents investigated by us, lithium methylcyanocuprate (31%), lithium methyl(thiophenoxy)-cuprate (11%), lithium methyl(3-methyl-3-methoxy-1-butynyl)cuprate (18%), or lithium methyl-t-butoxycuprate (28%) gave yields as high at 119 (entries 20-23).

With use of the optimum conditions for 118 as determined above, the scope of the methylation of arylmercurials was examined on a variety of other arylmercuric chlorides (eq. 73). The results are

$$ArHgCl + 5\ Li_2CuMe_3 \xrightarrow{xsMeI} \xrightarrow{O_2} \xrightarrow{NH_4Cl} Ar\text{-}CH_3 \qquad (73)$$

summarized in Table 7. Arylmercurials bearing electron- donating and -withdrawing groups gave good yields (entries 1 and 2), as did sterically demanding mesitylmercuric chloride (entry 3). The aldehyde group present in m-chloromercuribenzaldehyde proved too reactive, however, and only the product of methyl addition to the aldehyde could be obtained, even when the temperature was maintained at -78°C throughout. o-Chloromercuriphenol gave only a very low yield of o-cresol, and (m-nitrophenyl)mercuric chloride, not surprisingly, failed to give any cross-coupling product. As noted earlier, nitroaromatics readily oxidize organocopper reagents. To our disappointment,

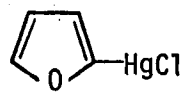
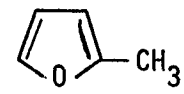
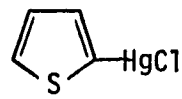
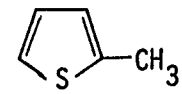
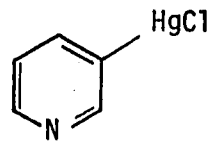
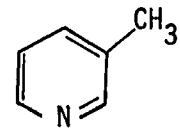
Table 7. Methylation of arylmercurials[a]

entry	arylmercurial	product	% yield[b]
1			65
2			82
3			75
4			86
5			7
6			0

[a]For reaction conditions see entry 12, Table 6.

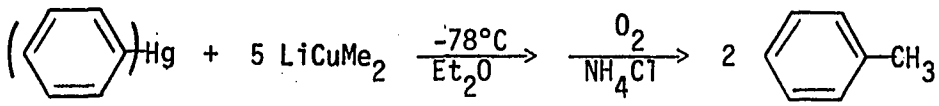
[b]Yields were determined by gas chromatography using an internal standard.

Table 7 continued

entry	arylmercurial	product	% yield[b]
7			30
8			19
9			0

2-chloromercurifuran and 2-chloromercurithiophene gave only low yields. It is not obvious why this should be so. Finally, no 3-methylpyridine was observed from the reaction of 120 and 3-chloromercuripyridine. It is not clear if this is simply due to methylation of the anticipated product by methyl iodide or a failure of the organomercurial to react.

It is worth noting that diphenylmercury also reacts with 119 to give toluene in modest yield (based on both phenyl groups) (eq. 74).



(74)

40%

Presumably under our optimal conditions, much higher yields could be obtained if so desired.

The scope of the reaction with 118 has also been examined by using several other organocuprate reagents (Table 8). Organocopper reagents derived from n-butyllithium give greatly reduced yields of cross-coupled product no matter what stoichiometry, solvent, or reaction procedure was used. As a solvent, THF appears to give better results than ether (compare entries 1 and 2, and 4 and 6). Maintaining the reaction at -78°C (procedure B) also seems to promote better cross-coupling (entries 4 and 5). The stoichiometry of the organocopper reagent or its complexation with dimethyl sulfide seemed to have little effect (entries 2, 6, and 8). Quite surprising was the observation that quenching with n-butyl iodide sharply reduced the yield of n-butylbenzene, contrary to what was observed in the cross-coupling of 118 and methylcopper compounds. sec-Butylcopper reagents gave still lower yields of cross-coupled product. Again, the reagent itself does not seem terribly important. Best results are obtained in THF at low temperatures. Using vinylcopper reagents, one can obtain significantly better yields than with either of the butylcopper reagents. Contrary to previous results, ether gives better yields than THF and warming the reaction up to 0°C (procedure A) is also generally beneficial. Unfortunately, from these reactions no clear picture emerges as to exactly what procedure is preferable. Each system must be examined individually.

Table 8. Alkylation of phenylmercuric chloride[a]

entry	organocuprate reagent	solvent	reaction procedure[b]	product	% yield[c]
1	$LiCu(\underline{n}\text{-}C_4H_9)_2$	Et_2O	B	$\underline{n}\text{-}C_4H_9C_6H_5$	18
2		THF			42
3					21[d]
4	$LiCu(\underline{n}\text{-}C_4H_9)_2 \cdot SMe_2$	Et_2O			30
5			A		19
6		THF	B		37
7					11[d]
8	$Li_2(Cu\underline{n}\text{-}C_4H_9)_3$				40
9					15[d]
10	$Li_2Cu(\underline{n}\text{-}C_4H_9)_3 \cdot SMe_2$				13[d]

[a]Reactions were carried out by adding 0.5 mmol of 118 to 2.5 mmol of organocopper reagent dissolved in 10 mL of solvent. All reactions were quenched with oxygen and finally aqueous ammonium chloride.

[b]Procedure A: reaction maintained at -78°C for 1 hour, warmed to 0°C for 1 hour, and then quenched. Procedure B: -78°C for 1 hour before quenching.

[c]Yields were determined by gas chromatography using an internal standard.

[d]Reaction was quenched with excess n-butyl iodide prior to oxygen.

Table 8 continued

entry	organocuprate reagent	solvent	reaction procedure[b]	product	% yield[c]
11			A		18
12	$LiCu(\underline{s}\text{-}C_4H_9)_2$		B	$\underline{s}\text{-}C_4H_9C_6H_5$	35
13	$LiCu(\underline{s}\text{-}C_4H_9)_2 \cdot SMe_2$				25
14	$Li_2Cu(\underline{s}\text{-}C_4H_9)_3$				30
15	$Li_2Cu(\underline{s}\text{-}C_4H_9)_3 \cdot SMe_2$		A		24
16		Et_2O			12
17	$Li_2Cu(\underline{s}\text{-}C_4H_9)_3 \cdot PBu_3$	THF			25
18	$LiCu(CH{=}CH_2)_2$		B	$H_2C{=}CHC_6H_5$	5
19		Et_2O			28
20	$LiCu(CH{=}CH_2)_2 \cdot SMe_2$				52
21	$Li_2Cu(CH{=}CH_2)_3$	THF			14
22			A		54
23	$Li_2Cu(CH{=}CH_2)_3 \cdot SMe_2$				59
24			B		10
25		Et_2O			51
26			A		56

Alkylation of alkenylmercurials

Alkenylmercurials can also be alkylated by using these cross-coupling reactions (Table 9). Yields of 44-66% have been obtained. In the reaction of trans-1-hexenylmercuric chloride and methylcopper, quenching with methyl iodide lowered the yield of methyl olefin, quite the opposite from what is observed with arylmercurials. Especially noteworthy is the fact that n-butyl and vinyl groups can be introduced in reasonable yield. Unfortunately, (E)-3-acetoxy-4-chloromercuri-3-hexene did not give any of the desired methylation product (entry 15). Substantial amounts of 3-hexyne were observed upon gas chromatographic analysis of the reaction products.

In the methylation of trans-3,3-dimethyl-1-butenylmercuric chloride, substantial amounts of the corresponding symmetrical diene were also observed (eq. 75). The stereospecificity of the cross-coupling

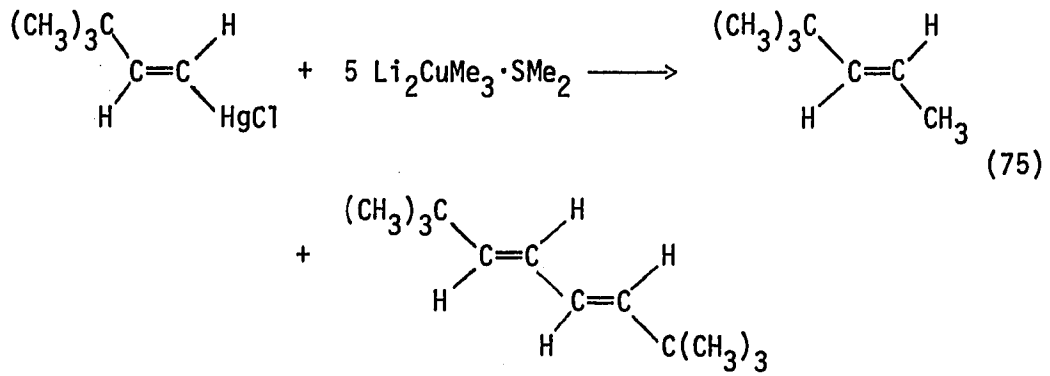
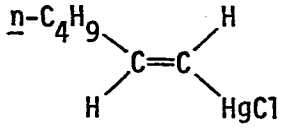
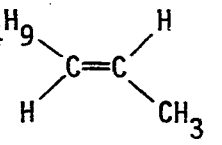


Table 9. Alkylation of alkenylmercurials[a]

entry	alkenylmercurial	organocopper reagent	sol-vent	reaction procedure[b]	product	% yield[c]
1		$LiCuMe_2 \cdot SMe_2$	Et_2O	A		57, 20[d]
2		Li_2CuMe_3				34
3			THF			41
4		$Li_2CuMe_3 \cdot SMe_2$	Et_2O			56, 26[d]
5				B		44, 35[d]
6			THF	A		36[e]

[a]Reactions were carried out by adding 0.5 mmol of organomercurial to 2.5 mmol of organocopper reagent dissolved in 10 mL of solvent, followed by quenching with oxygen and finally aqueous ammonium chloride.

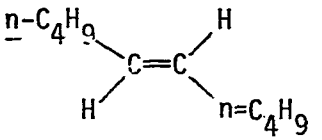
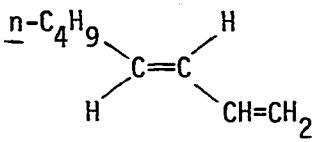
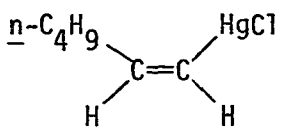
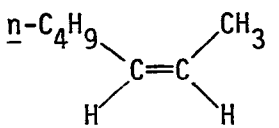
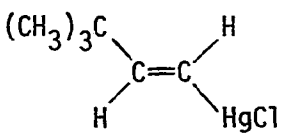
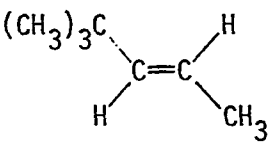
[b]Procedure A: reaction maintained at -78°C for 1 hour, warmed to 0°C for 1 hour, and then quenched. Procedure B: -78°C for 1 hour before quenching.

[c]Yields were determined by gas chromatography using an internal standard.

[d]Reaction quenched with excess methyl iodide prior to oxygen.

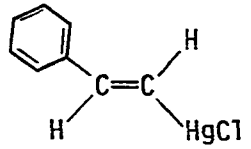
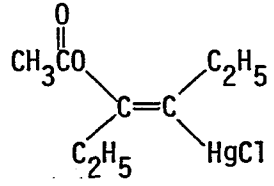
[e]26% yield of trans,trans-5,7-dodecadiene also present.

Table 9 continued

entry	alkenylmercurial	organocopper reagent	solvent	reaction procedure[b]	product	% yield[c]
7		$LiCu(\underline{n}\text{-}C_4H_9)_2 \cdot SMe_2$		B		44
8		$Li_2Cu(CH{=}CH_2)_3 \cdot SMe_2$	Et_2O	A		66
9		$LiCuMe_2 \cdot SMe_2$				62
10						32[f]

[f] 55% yield of trans,trans-2,2,7,7-tetramethyloctadiene also present.

Table 9 continued

entry	alkenylmercurial	organocopper reagent	sol-vent	reaction procedure[b]	product	% yield[c]
11				B		45
12		$Li_2CuMe_3 \cdot SMe_2$		A		27[g]
13		$LiCuMe_2$		B		51
14		$LiCuMe_2 \cdot SMe_2$		A		59
15		$Li_2CuMe_3 \cdot SMe_2$				0

[g]62% yield of trans,trans-2,2,7,7-tetramethyloctadiene also present.

reaction has been examined on both cis- and trans-1-hexenylmercuric chloride (entries 1 and 9). Each alkenylmercurial was observed to give 99% retention of configuration upon methylation, as determined by comparison of gas chromatographic retention times of authentic samples of cis- and trans-2-heptene.

Alkylation of alkylmercurials

Unlike the earlier work on the rhodium-promoted alkylation of organomercurials, using organocopper reactions allows the alkylation of alkylmercurials. Some examples are included in Table 10. Primary alkylmercurials react to give fair yields of alkylated product, while secondary alkylmercurials give significantly lower yields. The ability to alkylate organomercurials prepared via oxymercuration of alkenes provides a novel method for the overall hydroxyalkyation of olefins (eq. 76). Unfortunately, β-hydroxymercurials derived from

$$\underline{n}\text{-}C_4H_9CH{=}CH_2 \longrightarrow \underline{n}\text{-}C_4H_9\overset{OH}{\overset{|}{C}}HCH_2HgCl \longrightarrow \underline{n}\text{-}C_4H_9\overset{OH}{\overset{|}{C}}HCH_2CH_3 \qquad (76)$$

internal olefins give only low yields upon organocopper cross-coupling. When the reaction is carried out at -78°C, retention of the stereochemistry of the organomercurial is retained (eq. 77). No methylation product was formed from the reaction of trans-2-methoxycyclohexylmercuric chloride. Whitesides obtained similar results using his approach (115).

Table 10. Alkylation of alkylmercurials[a]

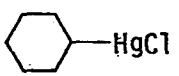
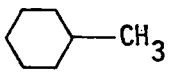
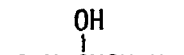
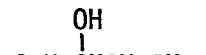
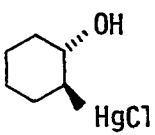
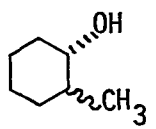
entry	alkylmercurial	organocopper reagent	reaction procedure[b]	alkyl iodide quench	product	% yield[c]
1	n-C_4H_9HgCl	$Li_2Cu(CH{=}CH_2)_3$	A	—	n-$C_4H_9CH{=}CH_2$	17
2			B	—		5
3		$Li_2Cu(CH{=}CH_2)_3 \cdot SMe_2$	A	—		28
4			B	—		7
5	n-$C_6H_{13}HgCl$	Li_2CuMe_3	A	+	n-C_7H_{16}	62
6		$LiCu(n\text{-}C_4H_9)_2$		—	n-$C_{10}H_{22}$	5
7		$Li_2Cu(n\text{-}C_4H_9)_3$	B	—		49
8				+		57

[a]Reactions were carried out by adding 0.5 mmol of organomercurial to 2.5 mmol of organocopper reagent dissolved in 10 mL of ether. Some reactions were quenched with an alkyl iodide corresponding to the organocopper reagent and then with oxygen and aqueous ammonium chloride.

[b]Procedure A: reaction maintained at -78°C for 1 hour, warmed to 0°C for 1 hour, and then quenched. Procedure B: -78°C for 1 hour before quenching.

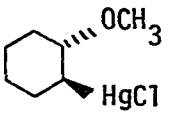
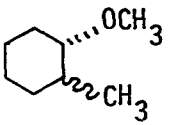
[c]Yields were determined by gas chromatography using an internal standard.

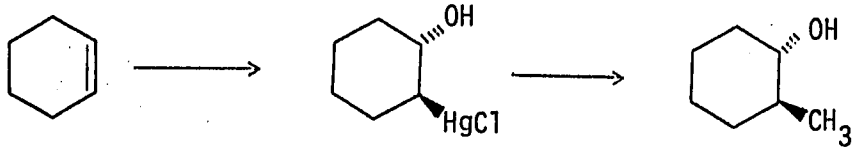
Table 10 continued

entry	alkylmercurial	organocopper reagent	reaction procedure[b]	alkyl iodide quench	product	% yield[c]
9		Li_2CuMe_3	A	+		39
10		$Li_2CuMe_3 \cdot SMe_2$		+		36
11		Li_2CuMe_3	B	+		51, 10[d]
12		$Li_2CuMe_3 \cdot SMe_2$	A	—		4
13				+		4
14			B	+		33
15		Li_2CuMe_3		+		4
16		$Li_2CuMe_3 \cdot SMe_2$		+	95:5 trans/cis	27
17			A	—		8

[d]THF used as the solvent.

Table 10 continued

entry	alkylmercurial	organocopper reagent	reaction procedure[b]	alkyl iodide quench	product	% yield[c]
18				+	43:57 trans/cis	31
19		Li_2CuMe_3	B	+		0
20		$Li_2CuMe_3 \cdot SMe_2$	A	+		0



(77)

95:5 trans:cis

In light of the failure of the methylation of organomercurials containing β- acetoay or -alkoxy groups, this reaction does not appear to be applicable to the synthesis of 7-oxa bicyclic prostaglandin analogues via oxymercuration.

Mechanism

The mechanism of these cross-coupling reactions seems best represented by Scheme XII, the important feature of which is the formation of a mixed diorganocopper intermediate LiCuRR' which can either oxidatively or thermally cross-couple to give the observed products. The following observations are consistent with this

Scheme XII

$$RHgCl + LiCuR'_2 \longrightarrow RHgR' + CuR' + LiCl$$

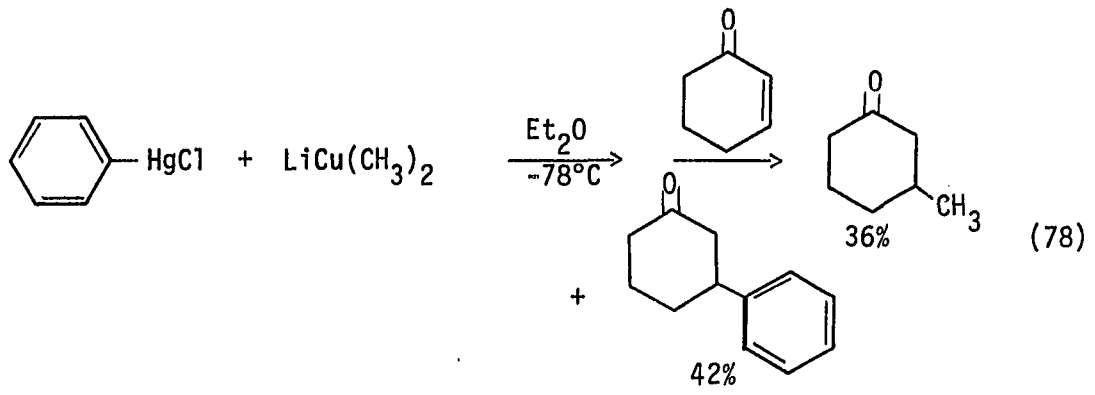
$$RHgR' + CuR' + LiCl \longrightarrow LiCuRR' + R'HgCl$$

$$RHgR' + LiCuR'_2 \longrightarrow LiCuRR' + HgR'_2$$

$$LiCuRR' \xrightarrow{O_2} R\text{-}R'$$

$$LiCuRR' + R'I \longrightarrow R\text{-}R'$$

mechanism. Upon adding phenylmercuric chloride to a clear colorless solution of $LiCuMe_2$ in ether, one observes the immediate formation of a heavy yellow precipitate presumed to be insoluble methylcopper. Within 15-30 minutes, the precipitate disappears, presumably due to lithium methylphenylcopper formation. Addition of phenylmercuric chloride to a suspension of methylcopper followed by oxidation gives only small amounts of toluene. However, treatment of methylcopper with either diphenylmercury or methylphenylmercury (prepared in situ from phenylmercuric chloride and methyllithium) followed by oxidation afforded toluene in good yield. These observations support initial formation of a diorganomercury intermediate which eventually transfers its original organic group to copper to form a mixed diorganocopper species which would be expected to cross-couple as indicated. The high stereospecificity (>99%) of the alkenylmercurial methylation reations (Table 9, entries 1 and 9) seems to rule out any sort of radical anion chain mechanism for this cross-coupling. It should also be pointed out that our intermediates behave significantly different from the ternary complexes of lithium, copper, and mercury described by Bergbreiter and Whitesides (115). Their intermediate fails to undergo conjugate addition to mesityl oxide while ours adds readily to cyclohexenone (eq. 78). They also report that arylmercurials do not cross-couple with alkyl halides under their conditions, while



(78)

we observe a significant increase in the yield of alkylbenzene upon addition of the corresponding alkyl iodide to our arylmercurial reactions. While the exact nature of either species is unknown, all observations in our work are consistent with the formation of "simple" organocopper species and their subsequent thermal or oxidative cross-coupling.

Conclusion

A general method for carbon-carbon bond formation between organomercurials and organocopper reagents has been discovered. Optimal conditions for the cross-coupling of a variety of aryl-, alkenyl-, and alkylmercurials with primary and secondary alkyl- and alkenylcuprate reagents have been examined. Lithium diorganocuprates and dilithium triorganocuprates give the best results with yields tending to decrease in the order methyl > vinyl > primary alkyl > secondary alkyl. With organomercurials, yields tend to decrease as follows:

aryl > vinyl > primary alkyl > secondary alkyl. However, substantial deviations from this ordering have been observed as one varies reaction conditions. These reactions appear to proceed via mercury-copper transmetalation to generate a mixed diorganocopper species which then thermally or oxidatively eliminates the cross-coupled product. Consistent with this picture is the fact that an organic group originally attached to mercury can be readily added in a conjugate fashion to α,β-unsaturated ketones, a reaction typical of an organocopper species.

Experimental

Equipment

Infrared spectra were recorded on a Beckman IR-4250 infrared spectrometer. NMR spectra were recorded on a Varian HA-100 or Hitachi Perkin-Elmer R-20B NMR spectrometer. Mass spectra were recorded 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 chromotograph was used for all gas chromatographic analyses. Most analyses were performed by using a 6 Ft x 1/8 in 5% SE-30 column, while isomer distributions were determined by using a 30 m SE-30 capillary column from J. W. Scientific. All GLC yields were determined by addition of a hydrocarbon internal standard and use of appropriate correction factors determined from authentic samples.

Reagents

All chemicals were used directly as obtained commercially unless otherwise indicated. THF and diethyl ether were distilled from calcium hydride under nitrogen. Copper(I) iodide was obtained from Alfa and purified by a literature procedure (87). Methyllithium, sec-butyllithium, n-butyllithium, and tert-butyllithium were obtained from Alfa, while vinyllithium was purchased from Org-Met. Methyllithium was titrated by the method of Watson and Eastham (86), while other alkyllithium reagents were titrated with 2,5-dimethoxybenzyl alcohol (85). Dimethyl sulfide was obtained from Aldrich and methyl iodide from Eastman.

Phenylmercuric chloride and diphenylmercury were obtained from Aldrich. p-Anisylmercuric chloride (125), m-carbomethoxyphenylmercuric chloride (39), m-nitrophenylmercuric chloride (39), 2-chloromercurithiophene (59), 2-chloromercurifuran (112), 3-chloromercuripyridine (126), o-hydroxyphenylmercuric chloride (127), 3-chloromercuribenzaldehyde (39), and mesitylmercuric chloride (39) were all prepared according to literature procedures.

The majority of the alkenylmercurials were prepared by published hydroboration-mercuration procedures (89, 128). (E)-3-Acetoxy-4-chloromercuri-3-hexene was prepared according to a literature procedure (129).

(Z)-1-Hexenylmercuric chloride was prepared from the corresponding organolithium compound which was obtained as follows. To 20 mmol of dicyclohexylborane (128) in 20 mL of THF was added at 0°C 16 mmol of 1-iodo-1-hexyne. The solution was stirred at 0°C for 1.5 hours, and

5 mL of glacial acetic acid was added. The reaction was then stirred at room temperature for 5 hours, diluted with ether, washed with water and dilute HCl, and dried over sodium sulfate. Removal of the solvent in vacuo and distillation afforded 2.05 g (61%) of (Z)-1-iodo-1-hexene: bp 87-88°C (45 torr); ^{1}H NMR($CDCl_3$) δ 1.02 (3H, t, J=6Hz, CH_3), 1.2-2.0 (4H, m, CH_2CH_2), 2.0-2.5 (2H, m, $=CCH_2$), 6.1-6.45 (2H, m, CH=CH); IR(max)(thin film) 3060, 2950, 2920, 2845, 1605 (C=C), 1270cm^{-1}; m/z 209.9898 (calcd for $C_6H_{11}I$, 209.9905). (Z)-1-Iodo-1-hexene (6.0 mmol) was converted to the corresponding alkenyllithium compound upon treatment with 2 equiv of tert-butyllithium according to the procedure of Corey and Beames (73). The solution of the organolithium compound was decanted away from precipitated lithium iodide via canula into a -78°C solution of mercuric chloride (6.26 mmol) in THF. The lithium iodide was washed once with -78°C pentane, and this solution was also added to the THF solution which was then allowed to warm to room temperature and filtered through Celite. The solvent was removed in vacuo and the residue taken up in methylene chloride which was then washed with water and brine and dried over sodium sulfate. Removal of the solvent and distillation (bp 110°C (0.05 torr), Kugelrohr) afforded 1.5 g (78%) of (Z)-1-hexenylmercuric chloride: ^{1}H NMR($CDCl_3$) δ 0.8-1.1 (3H, m, CH_3), 1.15-2.0 (4H, m, CH_2CH_2), 2.05-2.45 (2H, m, $=CCH_2$), 5.95 (1H, d, J=9Hz, CHHgCl), 6.4-6.8 (1H, m, =CH). Anal. Calcd for $C_6H_{11}HgCl$: C, 22.58; 4, 3.47. Found: C, 22.41; H, 3.53.

n-Hexylmercuric chloride and n-butylmercuric chloride were prepared from the corresponding alkenes by hydroboration-mercuration (130). 1-Chloromercuri-2-hexanol (131), trans-2-chloromercuricyclohexanol (131), and trans-2-methoxycyclohexylmercuric chloride (132) were prepared by solvomercuration of 1-hexene and cyclohexene, respectively, and subsequent treatment with aqueous sodium chloride.

Preparation of authentic samples of reaction products

Toluene, iodobenzene, styrene, n-butylbenzene, sec-butylbenzene, p-methylanisole, 2-methylfuran, 1,2,3,5-tetramethylbenzene, m-tolualdehyde, 1-(3-methylphenyl)ethanol, o-cresol, β-picoline, 2-methylthiophene, 1-phenyl-1-propene, cis- and trans-2-heptene, 4,4-dimethyl-2-pentene, 1,3-octadiene, trans-5-decene, 1-hexene, 3-heptanol, and cis- and trans-2-methylcyclohexanol were all obtained from commercial sources. Methyl 3-methylbenzoate was synthesized via the Grignard reagent of m-bromotoluene and carbon dioxide and subsequent acid-catalyzed esterification in refluxing methanol. trans-2-Methylcyclohexanol was synthesized via hydroboration-oxidation of 1-methylcyclohexene (133). Identity of reaction products was confirmed in each case by comparison of GLC retention times with those of authentic samples and by gas chromatography-mass spectral analysis.

Preparation of organocopper reagents

Lithium dimethylcuprate was prepared by the following procedure. Copper(I) iodide (480 mg, 2.5 mmol) was placed in a round bottom flask with a gas inlet tube and septum inlet. Diethyl ether (7.0 mL)

was added and the suspension cooled to 0°C. To this suspension was added 3.15 mL (5.0 mmol) of methyllithium in ether. The clear solution was stirred for 15 minutes at 0°C. The dimethylsulfide complex was prepared similarly except that copper(I) iodide was first dissolved in 1 mL of dimethyl sulfide before addition of ether. Dilithium trimethylcuprate was prepared similarly except that 3 equiv of methyllithium was employed.

Lithium divinylcuprate was prepared as follows. Copper(I) iodide (480 mg, 2.5 mmol) was placed in a round-bottom flask as described above and dissolved in 1.0 mL of dimethyl sulfide. Diethyl ether (8.0 mL) was added, and the solution was cooled to -78°C whereupon 2.15 mL (5.0 mmol) of vinyllithium in THF was added. The dark red solution was then stirred for 30 minutes at -78°C. Dilithium trivinylcuprate was prepared by an analogous procedure.

Lithium di-n-butylcuprate-dimethyl sulfide was prepared by the following procedure. Copper(I) iodide (480 mg, 2.5 mmol) was placed in a round bottom flask as described above and dissolved in 1.0 mL of dimethyl sulfide and 8.0 mL of THF. This solution was then cooled to -78°C, and 2.12 mL (5.0 mmol) of n-butyl lithium in hexane was added. The resulting dark red solution was then stirred for 30 min at -78°C

before use. Dilithium tri-n-butylcuprate-dimethyl sulfide, lithium di-sec-butylcuprate, and dilithium tri-sec-butylcuprate were all prepared analogously.

Lithium methylcyanocuprate (134), lithium dimethylcuprate-tri-n-butylphosphine (119), lithium dimethylcuprate-HMPA (135), lithium methyl(thiophenoxy)cuprate (136), lithium methyl-tert-butoxycuprate (136), and lithium methyl(3-methyl-3-methoxy-1-butynyl)cuprate (74) were all prepared according to literature procedures.

Methylation of arylmercurials

Procedure A is representative of those used in the methylation of 118 (Table 6). To a 10 mL solution of methylcopper reagent (2.5 mmol) in THF or diethyl ether was added 160 mg of solid phenylmercuric chloride (0.50 mmol) while back-flushing with nitrogen. The solution was stirred for 1 hour at -78°C followed by 1 hour at 0°C. The reaction was then quenched by adding 0.75 mL of methyl iodide by syringe and stirring 15-30 minutes at that temperature and/or flushing with pure oxygen after which saturated aqueous ammonium chloride and an appropriate hydrocarbon internal standard were added and the organic layer was analyzed by gas chromatography. In procedure B, the reaction mixture was never warmed to 0°C. In procedure B with only methyl iodide as a quenching agent (entry 9), the reaction mixture was allowed to warm to room temperature before hydrolysis. Otherwise, all

quenching and hydrolysis reactions were carried out at either -78°C or 0°C depending on the procedure employed. In certain reactions, 0.025-0.05 mmol of transition-metal reagents (5-10%) were added immediately after 118 or 1 mL of dimethyl sulfide was added prior to 118.

In the methylation of other arylmercurials summarized in Table 7, dilithium trimethylcuprate (5 equiv) was employed and the reaction was carried out for 1 hour at -78°C and then 1 hour at 0°C, followed by methyl iodide and oxygen quenching and hydrolysis as described above.

The following preparation of p-methylanisole is illustrative of the procedure used to isolate the methylation products. To a solution of 10.5 mmol of dilithium trimethylcuprate in 40 mL of diethyl ether at -78°C was added 1.03 g of p-anisylmercuric chloride (3.0 mmol). The reaction mixture was stirred for 1 hour at -78°C and then warmed to 0°C for 1 hour. Methyl iodide (5 g) was then slowly added by syringe, and the mixture was stirred for 10 minutes before flushing with oxygen. After hydrolysis with saturated aqueous ammonium chloride, the mixture was diluted with ether, washed with saturated aqueous ammonium chloride until the washes were colorless, and then dried over anhydrous sodium sulfate. The solvent was removed on a rotary evaporator, and the residue (330 mg) was chromatographed on 40 g of silica gel by using 19:1 hexane/ethyl acetate affording 230 mg of p-methylanisole (63% yield). All spectra were identical with those of an authentic sample.

Alkylation of 118

The following procedure is representative of that used to study the alkylation of 118 (Table 8). To a solution of 2.5 mmol of organocopper reagent in 10 mL of THF or ether was added 0.50 mmol of 118 while back-flushing with nitrogen. The reaction mixture was maintained at -78°C for 1 hour and then flushed with oxygen or warmed to 0°C for 1 hour and then oxidized. After hydrolysis and addition of an appropriate hydrocarbon internal standard, the reaction was analyzed by GLC analysis.

Alkylation of alkenylmercurials

The following procedure for the reaction of di- and triorganocuprates with alkenylmercurials is representative of that used to obtain the results reported in Table 9. To a -78°C solution of organocopper reagent (2.5 mmol) in THF or ether was added 0.5 mmol of alkenylmercurial. The reaction was stirred at -78°C for 1 hour, in some cases warmed to 0°C for 1 hour, and then quenched as described earlier by either methyl iodide and/or oxygen. After hydrolysis by saturated aqueous ammonium chloride, an appropriate hydrocarbon internal standard was added and the solution was analyzed by GLC analysis.

The stereochemical outcome of these reaction was ascertained by using the following procedure. cis- or trans-1-Hexenylmercuric chloride (0.96 g, 3.0 mmol) was added to a -78°C solution containing

9.0 mmol of lithium dimethylcuprate-dimethyl sulfide in 20 mL of diethyl ether. The reaction was stirred at -78°C for 1 hour, warmed to 0°C for 1 hour, and then flushed with oxygen. The mixture was then hydrolyzed with saturated aqueous ammonium chloride and diluted with 50 mL of ether. The ether layer was washed with ammonium chloride solution until the washes were colorless, dried over sodium sulfate, and carefully concentrated by fractional distillation to a volume of about 10 mL which was analyzed on a 30-m SE-30 capillary gas chromatography column. The trans-alkenylmercurial afforded 98.9% trans-2-heptene and 1.1% cis-2-heptene, while the cis-alkenylmercurial gave 99.0% cis-2-heptene and 1.0% trans-2-heptene. The exact stereochemical purity of the starting alkenylmercurials is unknown.

Alkylation of alkylmercurials

The results summarized in Table 10 were obtained by using procedures essentially identical with those described above. The following preparation of 3-heptanol is representative of the isolation procedure used in helping to characterize the products of alkylation. To a solution of 12 mmol of dilithium trimethylcuprate in 50 mL of ether at -78°C was added 1.35 g of 1-chloromercuri-2-hexanol (4.0 mmol).

The solution was stirred for 1 hour at -78°C, warmed to 0°C for 1 hour, and quenched with 5.0 g methyl iodide for 10 minutes. After oxidation, the mixture was hydrolyzed with saturated ammonium chloride, diluted with ether, washed with ammonium chloride until the washes were colorless, and dried over sodium sulfate. The ether was removed on a rotary evaporator, and the residue (300 mg) was chromatographed on 50 g of silica gel by using 4:1 hexane/ethyl acetate (R_f=0.33) to afford 150 mg 3-heptanol (35% yield). All spectra were identical with those of an authentic sample.

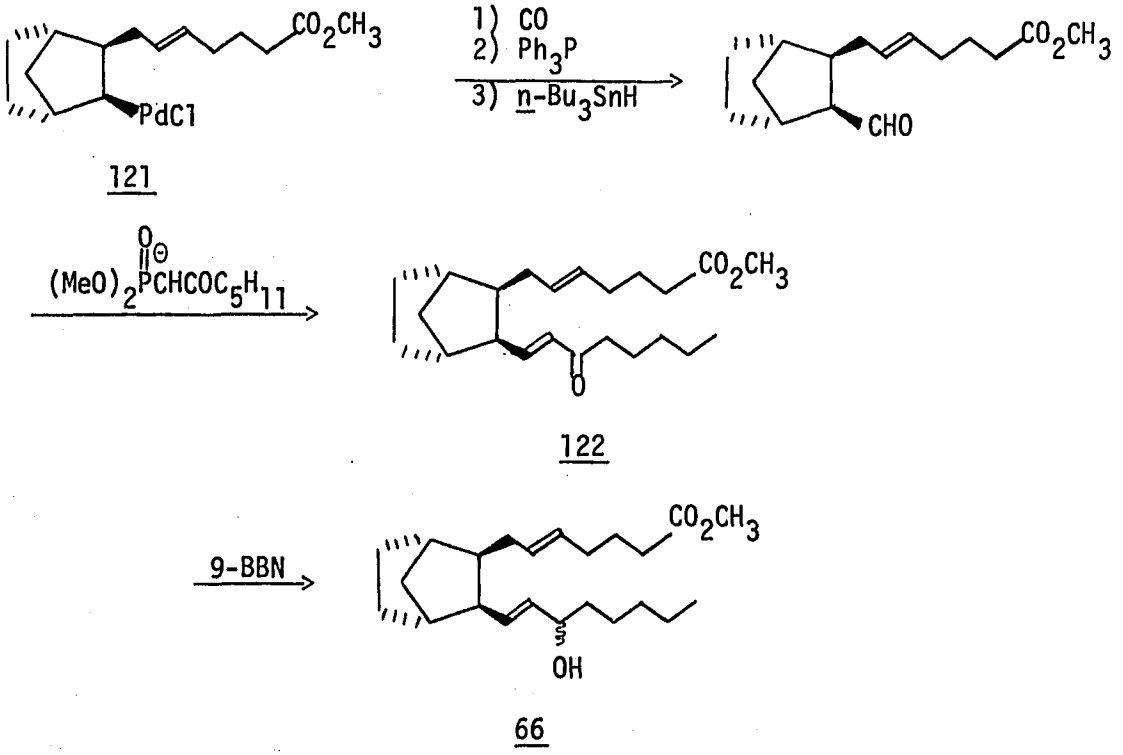
The stereochemistry of substitution was determined as follows. To a solution of 2.5 mmol of dilithium trimethylcuprate-dimethyl sulfide in 10 mL of ether was added 165 mg of solid (trans-2-hydroxycyclohexyl)mercuric chloride (0.49 mmol) while back-flushing with nitrogen. After the solution was stirred for 1 hour at -78°C, an excess of methyl iodide was slowly added and the solution stirred 15 minutes before flushing with oxygen. After hydrolysis with saturated aqueous ammonium chloride, analysis by glass capillary gas chromatography indicated trans- and cis-2-methylcyclohexanol in a ratio of 95:5.

CHAPTER V. CONCLUSIONS

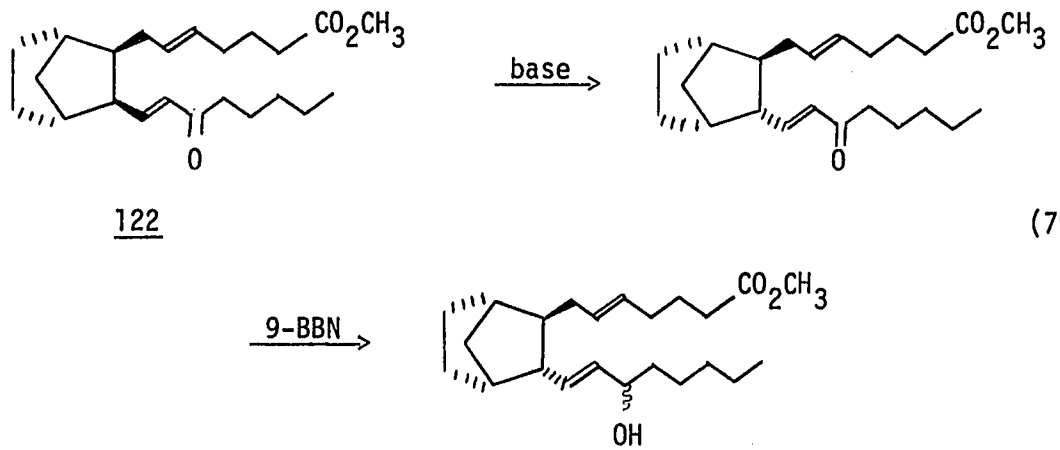
In this work several approaches to a number of bicyclic prostaglandin analogues have been developed. Thiophene-containing bicyclic prostaglandin analogues have been synthesized by the addition of thienylpalladium compounds, generated from thienylmercuric chlorides and palladium salts, to bicyclic olefins to form intermediate σ-bonded palladium compounds. These were elaborated to the desired bicyclic prostaglandin analogues by reactions with substituted lithium acetylides and vinylcuprates. A three step method for introducing the trans-allylic alcohol side chain involving carbonylation and tri-n-butyltin hydride reduction, Wittig olefination, and enone reduction with 9-BBN has also been developed. The reaction of a substituted vinyl cuprate has also been used to synthesize the trans-allylic alcohol analogue of 28, a potent inhibitor of arachidonic acid-induced blood platelet aggregation. Lastly, silver assisted alkoxypalladation of norbornadiene-palladium dichloride with t-butyl-6-hydroxyhexanoate, followed by carbonylation in methanol afforded an intermediate ester that could be elaborated to a 7-oxa bicyclic prostaglandin analogue in three steps. While biological results are not available for the 7-oxa bicyclic prostaglandin analogues, the thiophene-containing compounds that have been examined have exhibited only moderate activity.

A number of possibilities exist for the extension of this work. The three step sequence developed for the introduction of the trans-allylic alcohol prostaglandin side chain may be applied in the synthesis of compound 66 from compound 121 (Scheme XIII). This should result in a much higher yield of 66. Compound 122 also provides the

Scheme XIII



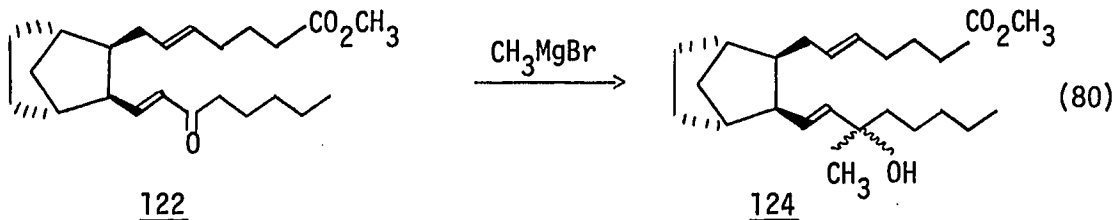
opportunity to prepare several other potentially active analogues. Base catalyzed epimerization of the δ-carbon of the enone (C-12) should provide the exo-endo analogue, 123, after reduction (eq. 79). This would provide a comparison of the effects on activity of different side chain geometries. Compound 122 should also provide the corresponding



122 (79)

123

15-methyl analogue upon treatment with methylmagnesium bromide (eq. 80). Compound 124 might be particularly active because it should be inert

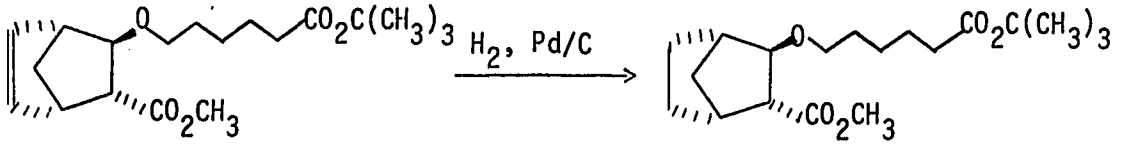


122 124 (80)

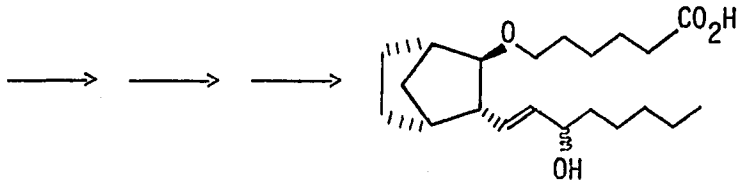
towards oxidation of the C-15 alcohol by prostaglandin C-15-dehydrogenase, which is a primary pathway for metabolic deactivation.

Several possibilities also exist for extension of the synthesis of 7-oxa bicyclic prostaglandin analogues. Hydrogenation of diester 106, followed by introduction of the trans-allylic alcohol side chain would provide the dihydro compound 125, which might provide useful comparisons to compound 111 (Scheme XIV).

Scheme XIV

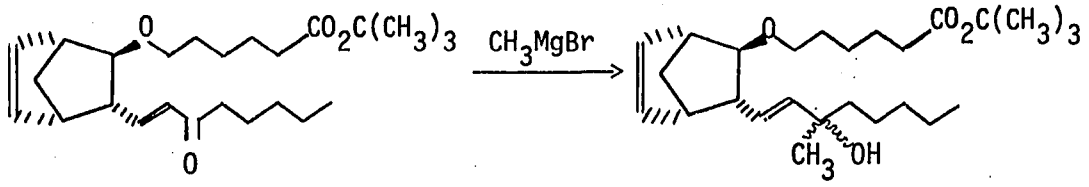


106

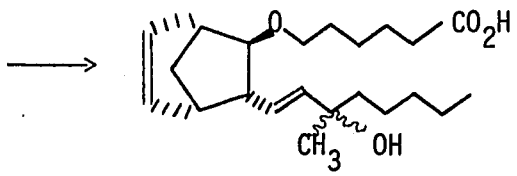


125

As with compound 122, addition of methylmagnesium bromide to compound 109 would provide the 15-methyl analogue, 126, which may show interesting activity (eq. 81).



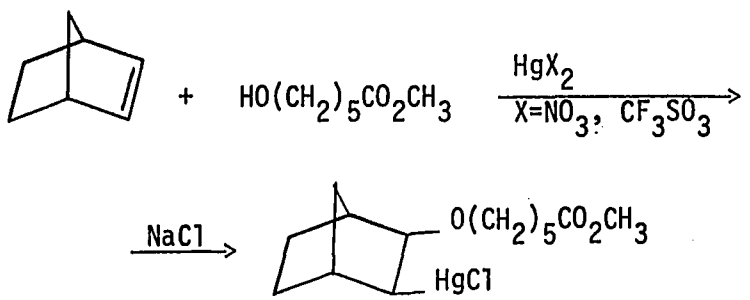
109



126

(81)

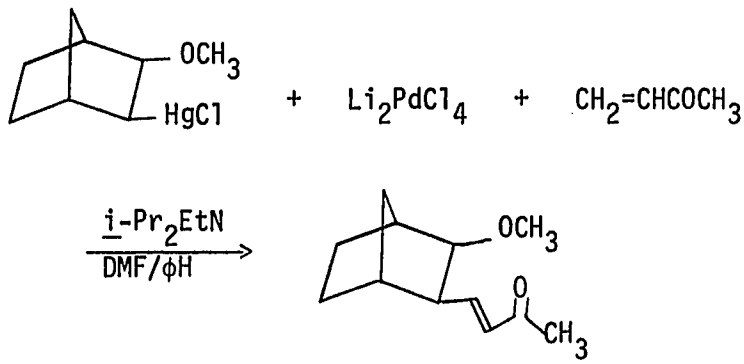
Lastly, further work on the oxymercuration of norbornene with methyl 6-hydroxyhexanoate should be pursued. The use of more reactive mercury salts such as mercuric nitrate or mercuric triflate in particular may prove useful (eq. 82). Once the mercurial, 127, has been obtained,



127

(82)

introduction of the trans-allylic alcohol chain should be straightforward. Studies on a model system have shown that this can be accomplished in approximately 50% yield using a Heck reaction (eq. 83).



(83)

The yield for this reaction was not optimized and further work could result in a higher yield.

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