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Krishnaswamy Narayanan
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Narayanan, Krishnaswamy

ORGANOMERCURY, -RHODIUM AND -PALLADIUM INTERMEDIATES IN ORGANIC SYNTHESIS

Iowa State University PH.D. 1985

Organomercury, -rhodium and -palladium intermediates in organic synthesis

by

Krishnaswamy Narayanan

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signatures have been redacted for privacy.

Iowa State University
Ames, Iowa

1985

TABLE OF CONTENTS

DEDICATION

To
My Mother

ABBREVIATIONS

The following abbreviations have been used in this thesis.

Ac	acetyl
n-Bu	n-butyl
i-Bu	isobutyl
t-Bu	tert-butyl
COD	cyclooctadienyl
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
GC	gas chromatography
g	grams
h	hour(s)
HMPA	hexamethylphosphoramide
MCPBA	m-chloroperoxybenzoic acid
min	minute(s)
Me	methyl
mg	milligram(s)
NBS	N-bromosuccinimide
Ph	Phenyl
i-Pr	isopropyl
pTsA	p-toluenesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
Ts	p-toluenesulfonyl

ABSTRACT

Chapter I describes the synthesis of arylolefins in fair to good yield by the cross-coupling reaction of arylmercurials and vinyl halides catalyzed by 10% $ClRh(PPh_3)_3$. The reaction appears to involve initial oxidative addition of the vinyl halide to the rhodium(I) catalyst to yield a vinyl rhodium(III) species and subsequent arylation by the organomercurial to generate an aryl vinyl rhodium(III) intermediate which reductively eliminates the olefin and regenerates the catalyst.

Chapter II details an improved, stereospecific synthesis of vinylmercurials from alkynes using catecholborane, followed by mercuric acetate plus sodium acetate. A vinylmercurial useful in prostaglandin synthesis is prepared using this procedure.

Chapter III summarizes our efforts towards the total synthesis of brefeldin-A using the reaction of a vinylpalladium species with cyclopentene derivatives as a first key step. Even though the reactions lead to the expected product(s), the yields could not be optimized. An alternative approach using the reaction of a vinylcuprate with cyclopentadiene monoepoxide also leads to the expected key intermediate, but the yield again could not be optimized.

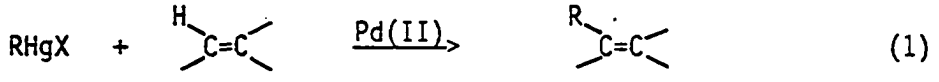
In Chapter IV, new synthetic methodology is developed for the synthesis of an ethano-bridged prostaglandin endoperoxide analogue using the selective ozonolysis of a double bond in the presence of an acetylenic bond as a key step. The second part of Chapter IV details

our unsuccessful efforts to synthesize an etheno-bridged prostaglandin endoperoxide analogue by the reaction of soft carbanions with norbornadiene-palladium dichloride.

CHAPTER I. RHODIUM(I)-CATALYZED ALKENYLATION OF ARYLMERCURIALS

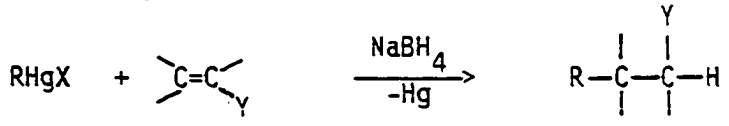
Introduction

Organomercurials are attractive synthetic intermediates due to their ready availability, chemical and thermal stability, and ability to accommodate almost all important organic functional groups. A number of important synthetic applications of these compounds are now known.[1] Until recently, however, there have been few methods available for the direct alkylation of organomercurials. Lately, procedures based on organopalladium intermediates[2] (eq. 1), free radical[3] (eq. 2) and organocopper cross-coupling reactions[4] (eq. 3) have helped to fill this void.



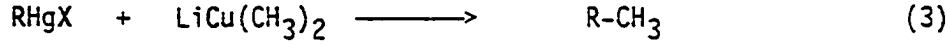
(1)

R=aryl, alkenyl



(2)

R=alkyl Y=electron-withdrawing group



(3)

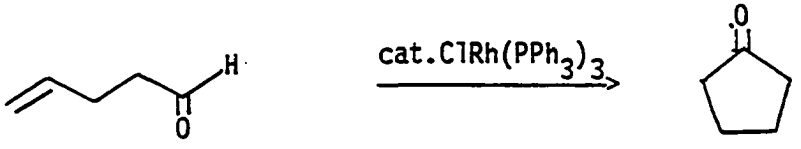
R=aryl, alkenyl, alkyl

Organomercury compounds undergo transmetallation reactions with other metallic elements such as Pd, Al, Ni and Co. These more reactive organometallic compounds can undergo a variety of reactions leading to the formation of new carbon-carbon bonds. The chemistry of Pd(II) and Rh(III) is very similar which suggests that Rh(III)

complexes might also function well in transmetallation reactions with mercurials. Accordingly, rhodium(I)-catalyzed dimerization of vinyl- and aryl-mercurials[5] (eq. 4), hydroacylation of unsaturated aldehydes[6] (eq. 5) and methylation of vinyl- and aryl-mercurials[7] (eq. 6) were successfully investigated in this research group. Although the last cross-coupling reaction could be affected using methyl iodide and

$$2RHgCl \xrightarrow{cat.[ClRh(CO)_2]_2} R\text{-}R \qquad (4)$$

R-aryl, alkenyl



(5)

$$RHgX + CH_3RhI_2(PPh_3)_2 \text{ (stoichiometric)} \longrightarrow R\text{-}CH_3 \qquad (6)$$

catalytic amounts of Wilkinson's catalyst, $ClRh(PPh_3)_3$, the catalytic turnover was very low (eq. 7). The major difficulty appeared to be

$$RHgX + CH_3I \xrightarrow{cat.ClRh(PPh_3)_3} R\text{-}CH_3 \qquad (7)$$

dimerization of the organomercurial by the rhodium catalyst. To overcome this problem, we reasoned that we must employ organomercurials which neither contain a β-hydrogen (in order to avoid β-hydride elimination), nor undergo facile rhodium-catalyzed dimerization. Since arylmercurials are dimerized by Wilkinson's catalyst much less readily than vinylmercurials[5] and contain no β-hydrogens, they appeared to be the organomercurials of choice. It was also evident that the organic halide employed must undergo rapid

oxidative addition to the rhodium(I) catalyst. Since β-bromostyrene is reported to oxidatively add to PdL_n and PtL_n complexes 100 times faster than methyl iodide,[8] vinyl halides appeared most suitable as the organic halides in our cross-coupling reaction.

Results and Discussion

The prototype reaction between phenylmercuric chloride and vinyl bromide mediated by Wilkinson's catalyst, $ClRh(PPh_3)_3$, was briefly investigated previously in this group[7] (eq. 8). The reaction went very well both with stoichiometric and 10 mole percent of the

$$PhHgCl + H_2C{=}CHBr \xrightarrow[\substack{HMPA,\ LiCl\\ 70^oC,\ 6\ h}]{ClRh(PPh_3)_3} PhCH{=}CH_2 \qquad (8)$$

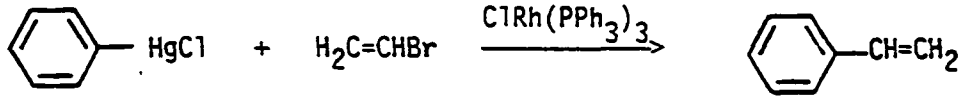
rhodium catalyst. It was thought appropriate, first to optimize the conditions for the formation of styrene. The results of the various experiments are summarized in Table I. Several conclusions can be drawn.

(i) Reaction times greater than 12 h decreased the yield of styrene.

(ii) The sequence of addition of the reagents did not affect the yield of styrene (eqs. 9-11). In all these cases, a small amount (10-15%) of biphenyl was also detected by gas chromatography.

$$PhHgCl + H_2C{=}CHBr \xrightarrow[\substack{HMPA\\ 70^oC,\ 10\ min}]{LiCl} \xrightarrow[6\ h]{10\%ClRh(PPh_3)_3} \underset{87\%}{PhCH{=}CH_2} \qquad (9)$$

Table I. Reaction of Phenylmercuric Chloride with Vinyl Bromide



solvent	% $ClRh(PPh_3)_3$	additional reagent	temp (°C)	time (h)	GC Yield[a] (%)
THF	10	LiCl	reflux	6	0
Benzene	10	LiCl	reflux	6	0
DMSO	10	LiCl	70	6	45
DMF	10	LiCl	70	6	67
HMPA	10	LiCl	70	6	82
	10	LiCl	70	12	81
	10	LiCl	70	24	67
	5	LiCl	70	6	43
	1	LiCl	70	6	23
	10	--	70	6	10

[a] n-Decane was used as an internal standard.

$$PhHgCl + 10\%ClRh(PPh_3)_3 \xrightarrow{LiCl} \xrightarrow[6\ h]{C_6H_5HgCl} \qquad 77\% \quad (10)$$

$$H_2C{=}CHBr + 10\%ClRh(PPh_3)_3 \xrightarrow[6\ h]{LiCl} \xrightarrow[6\ h]{C_6H_5HgCl} \qquad 81\% \quad (11)$$

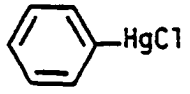
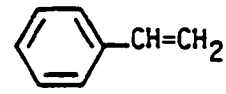
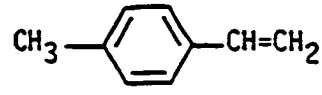
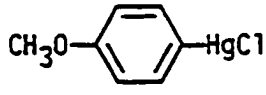
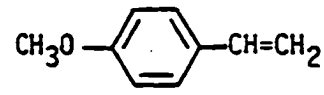
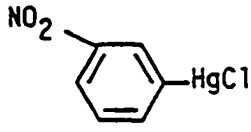
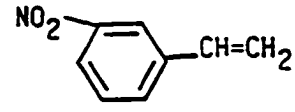
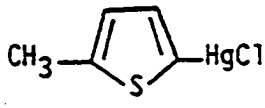
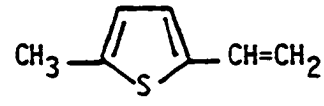
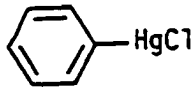
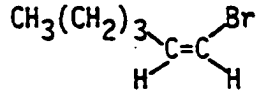
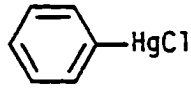
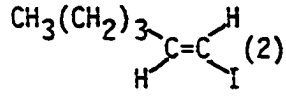
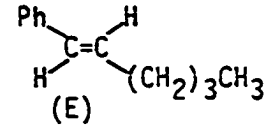
(iii) Hexamethylphosphoramide (HMPA) is the best solvent for the reaction.

(iv) Lithium chloride is necessary for the reaction, since the yield of styrene was only 10% in its absence. However, it is not certain which step of the reaction requires LiCl.

(v) Attempts to significantly reduce the amount of the rhodium catalyst were not fruitful, since the yield drops off considerably with less than 10% of the catalyst.

Hence, the standard conditions chosen for the cross-coupling were 10%$ClRh(PPh_3)_3$ as the catalyst, dry HMPA as the solvent, the addition of excess LiCl, and a reaction temperature of 70°C for 6-12 h. We next examined the cross-coupling of a variety of arylmercurials and vinyl halides using these conditions. The results are summarized in Table II. Diarylmercurials, arylmercuric chlorides bearing electron-donating and -withdrawing groups, and heterocyclic mercurials can all be satisfactorily employed in this reaction (entries 2-5, 12). Not surprisingly, vinyl iodides gave higher yields than vinyl bromides due to their ease of oxidative addition to the Rh(I) catalyst (comparing entry 6 with 7 and 8) and need not be used in excess. While E-1-hexenyl iodide gave the corresponding E-coupling product (entry 7), the corresponding Z-vinyl iodide (entry 8) gave a Z/E mixture with the

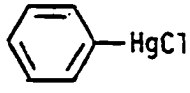
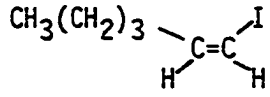
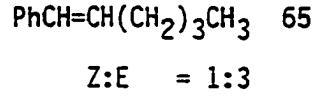
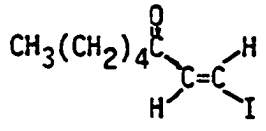
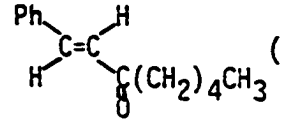
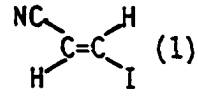
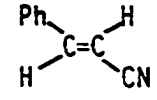
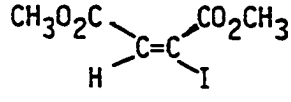
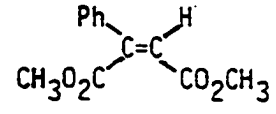
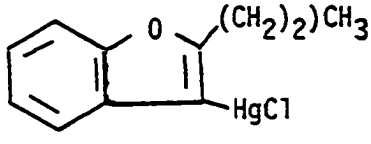
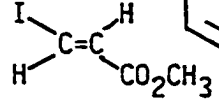
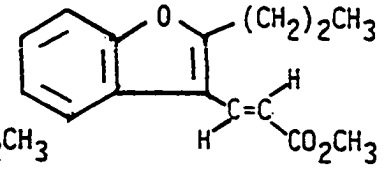
Table II. Alkenylation of Arylmercurials

entry	arylmercurial	vinyl halide	product(s)	% yield[a]
1		$H_2C{=}CHBr$ (10)		82
2				75[b]
3				80
4				64
5				(40)
6		 (2)	$PhCH{=}CH(CH_2)_3CH_3$	trace
7		 (2)	 (E)	72

[a] Yields determined by gas liquid chromatography using an internal standard and appropriate correction factor (isolated yields in parentheses).

[b] Based on utilization of only one aryl group.

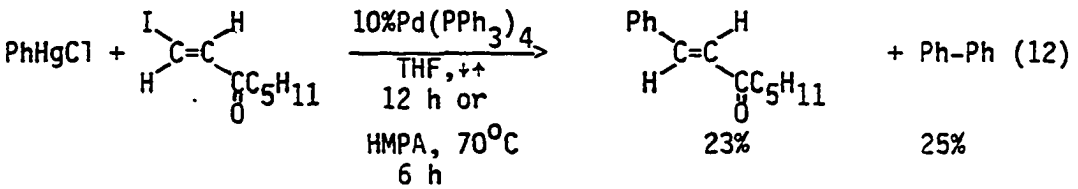
Table II (continued)

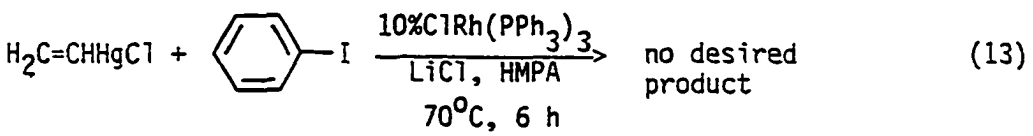
entry	arylmercurial	vinyl halide (equivalents)	product(s)	% yield
8		 (2)	 Z:E = 1:3	65
9		 (1)		(70)
10		 (1)		(31)[c]
11				trace
12				(50)

[c] 1.2 Equivalents of phenylmercuric chloride were employed.

trans product predominating. Better results are obtained when one uses vinyl iodides bearing electron-withdrawing groups as seen in entry 9. The only significant side reaction observed is dimerization of the arylmercurial.

It should be noted here that this cross-coupling reaction gave a low yield of the product when a Pd(0) catalyst, $Pd(PPh_3)_4$, was used (eq. 12) and the reverse coupling reaction of a vinylmercurial with an aryl halide did not give any of the expected product (eq. 13).

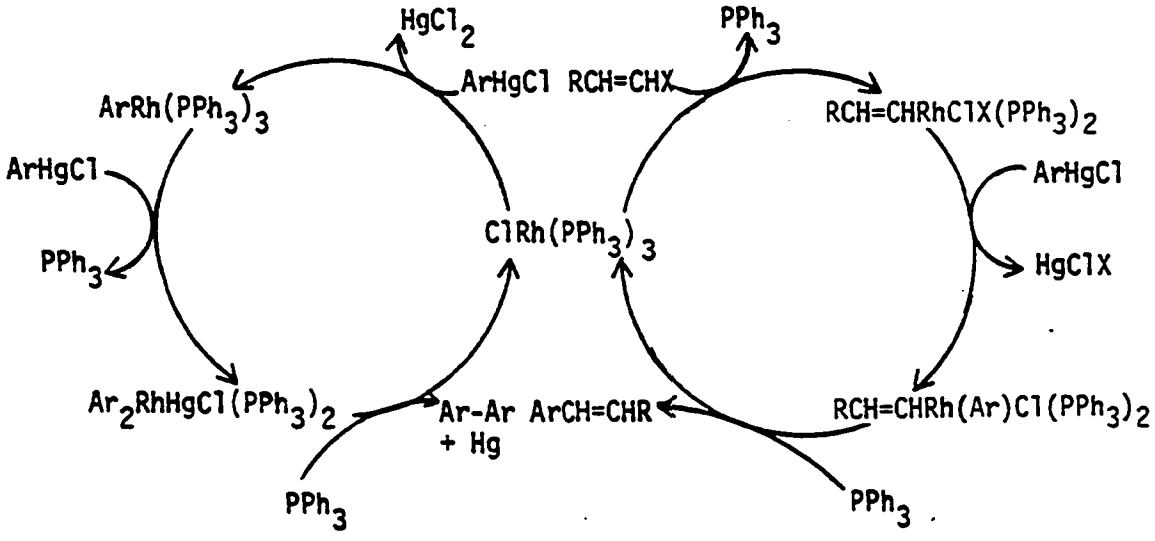




The mechanism shown in Scheme I best accounts for the products observed in these cross-coupling reactions. Oxidative addition of the vinyl halide to the Rh(I) catalyst generates a Rh(III) intermediate which undergoes transmetallation with the arylmercurial. The resulting arylvinylrhodium intermediate undergoes reductive elimination to give the expected product and regenerates the Rh(I) catalyst. The fact that a small amount of dimerization product from the arylmercurial was also detected by gas chromatography shows that the oxidative addition of the vinyl halide is in competition with transmetallation of the arylmercurial. Vinyl halides, such as trans-1-iodo-1-octen-3-one (entry 9) which should undergo facile oxidative

addition to the rhodium(I) catalyst give only a trace of dimerization product, consistent with the competition shown in Scheme 1.

Scheme 1



Conclusion

Arylmercurials and vinyl halides can be cross-coupled to yield arylolefins in fair to good yield using 10%$ClRh(PPh_3)_3$. Since arylmercurials can accommodate most important organic functional groups, which is not the case with Grignard reagents or organocuprates formed from organolithium compounds, this reaction provides an attractive alternative route to aryl olefins. Palladium(0) reagents do not appear to catalyze this reaction effectively. Even the Heck reaction which employs arylmercurials and olefins uses a large excess of olefin in the reaction.

Experimental Section

Reagents

All reagents were used as obtained commercially unless otherwise noted. Tetrahydrofuran (THF) was distilled from calcium hydride. HMPA was distilled from calcium hydride at reduced pressure.

Phenylmercuric chloride (Aldrich) and di-p-tolylmercury (Eastman) were obtained commercially. p-Anisylmercuric chloride,[9] 2-chloromercurio-5-methylthiophene[10] and m-nitrophenylmercuric chloride[11] were prepared using literature procedures. 3-Chloromercurio-2-n-propylbenzofuran was kindly provided by Mr. L.W. Harrison of Iowa State University.[12] Wilkinson's catalyst, $ClRh(PPh_3)_3$, was prepared from $RhCl_3 \cdot 3\ H_2O$ according to the literature procedure.[13]

The following vinyl halides were prepared according to the literature procedures: cis-1-iodo-1-hexene,[14] trans-1-iodo-1-hexene,[15] trans-1-iodo-octen-3-one,[16] trans-3-iodo-acrylonitrile,[17] dimethyl-2-iodomaleate[18] and cis-1-bromo-1-hexene.[19] Vinyl bromide was obtained from Aldrich and used directly.

Equipment

Gas chromatographic analyses were carried out on a Varian model 3700 gas chromatograph with a flame ionization detector. The retention times of authentic samples were used to identify products. In addition, a Finnegan 4023 gas chromatograph-mass spectrometer was employed to verify the identity of the products. All gas chromatographic yields were determined by using hydrocarbon internal

standards and appropriate correction factors. ^1H NMR spectra were obtained on Varian A-60 or EM-360 instruments with tetramethylsilane as an internal standard.

Alkenylation of Arylmercurials

The following procedure for the reaction of phenylmercuric chloride with vinyl bromide is representative. Approximately 0.25 g (6 mmol) of lithium chloride was placed in a 25 ml round-bottom flask equipped with a septum inlet, gas inlet tube and magnetic stirring bar. The lithium chloride was dried using a hot air gun under vacuum and 0.023 g (0.025 mmol) of phenylmercuric chloride were added while backflushing with nitrogen. A condenser was placed on the flask, approximately 1.5 ml (10 equiv) of vinyl bromide was added and the gas inlet tube was reattached to the top of the condenser. n-Decane (0.0355 g, 0.25 mmol) (internal standard) and 2.5 ml of dry, freshly distilled HMPA was added by syringe. After the mixture had stirred the appropriate time at 70°C, 5 ml of water and 2 ml of benzene were added and the benzene layer was analyzed by gas chromatography.

Synthesis of trans-1-Phenyl-1-octen-3-one

Lithium chloride (3.36 g, 80 mmol) was placed in a 250 ml round-bottom flask with a sidearm gas inlet tube and a magnetic stirring bar. The LiCl was dried using a hot air gun under vacuum. Phenylmercuric chloride (2.507 g, 8 mmol) and $ClRh(PPh_3)_3$ (0.747 g, 0.8 mmol) were added while backflushing with nitrogen. The trans-1-iodo-1-octen-3-one (2.016 g, 8 mmol) was then added, followed by 80 ml of HMPA. The reaction mixture was heated at 70°C for 6 h and then

poured into ice. Pentane was added and the suspension formed was filtered off. The residue was washed with pentane. The organic layer was separated and the aqueous layer was extracted twice with pentane. The pentane layer was washed with water, dilute HCl, water and dilute NaOH, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Purification by flash column chromatography using 9:1 hexane:ethyl acetate (R_f 0.38) gave 1.10 g of the product (70% yield): ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $\underline{J}$=6 Hz, CH_3), 1.0-1.75 (m, 6H, CH_2's), 2.48 (br t, 2H, $\underline{J}$=5 Hz, CH_2CO), 6.55 (d, 1H, $\underline{J}$=18 Hz, =CHCO), 7.0-7.6 (m, 6H, C_6H_5CH); IR (nujol) 3100, 3065, 3020, 1695, 1670, 1615, 980, 740, 680 cm^{-1}; mass spectrum m/e 202 (M^+).

Other compounds prepared using this basic procedure are:

Cinnamonitrile: (31% yield) ^1H NMR ($CDCl_3$) δ 5.70 (d, 1H, $\underline{J}$=18 Hz, =CHCN), 7.0-7.45 (m, 6H, C_6H_5CH); IR (neat) 3070, 3030, 2210, 1620, 965, 745, 680 cm^{-1}; mass spectrum m/e 129 (M^+).

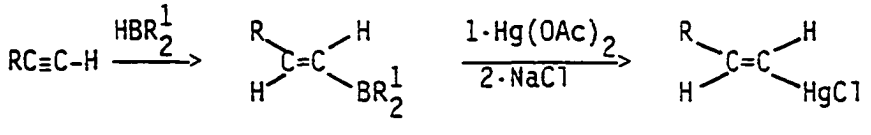
2-Methyl-5-vinylthiophene: (40% yield) ^1H NMR ($CDCl_3$) δ 2.66 (s, 3H, CH_3), 4.73-5.36 (m, 3H, vinyl), 6.40-6.86 (m, 2H, thiophene); IR (neat) 3100, 3080, 2970, 2920, 2880, 1620, 1450 cm^{-1}; mass spectrum m/e 124 (M^+).

Methyl <u>trans</u>-3-(2-<u>n</u>-propyl-3-benzofuryl)acrylate: (50% yield) ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, $\underline{J}$=6 Hz, CH_3), 1.67 (m, 2H, $C\underline{H}_2CH_3$), 2.78 (t, 2H, $\underline{J}$=7 Hz, CH_2), 3.69 (s, 3H, OCH_3), 6.45 (d, 1H, $\underline{J}$=18 Hz, vinyl), 7.1-7.84 (m, 6H, aryl and vinyl); IR (neat) 3020, 2970, 2880, 1720, 1635, 1580, 1455, 1435, 1300, 1270, 1170, 965, 850, 750 cm^{-1}; mass spectrum m/e 244.10974 (calcd for $C_{15}H_{16}O_3$, 244.10995).

CHAPTER II. AN IMPROVED STEREOSPECIFIC SYNTHESIS OF VINYLMERCURIALS VIA HYDROBORATION-MERCURATION OF ALKYNES

Introduction

In recent years vinylmercurials have proven to be valuable intermediates in the synthesis of symmetrical[5,20] and unsymmetrical[21] 1,3 dienes; 1,4 dienes;[22] α,β-unsaturated ketones,[23] carboxylic acids and esters;[24] enol esters;[25] butenolides[26] and π-allylpalladium compounds.[27,28] Some years ago Larock and Brown reported a convenient approach to vinylmercurials via hydroboration of alkynes with either dicyclohexylborane[29] or catecholborane[30] and subsequent transmetallation by mercuric acetate (eq. 14). In that work, alkynes of low molecular weight, usually containing eight or less carbons, were employed and the overall hydroboration-mercuration procedure was observed to be highly stereospecific. In the intervening years, carbonylation of these organomercurials (eq. 15) has established that the mercuration step is not stereospecific for alkynes of higher



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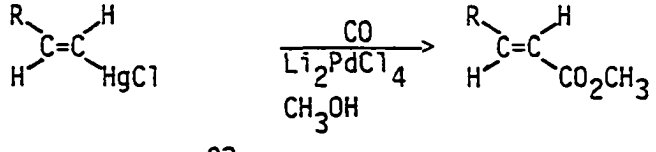


(15)

molecular weight.[23] The low stereospecificity of this reaction has proven to be a serious problem in our group's recent efforts to utilize vinylmercurials in the synthesis of natural products,

particularly prostaglandins. To overcome these difficulties we decided to reexamine this approach to vinylmercurials.

Results and Discussion

Our initial work focused on the mercuration of vinylboranes derived from 1-decyne, since it is with that alkyne that the lack of stereospecificity was originally observed. It was first established by NMR and IR spectral analysis that the vinylboranes derived from dicyclohexylborane and catecholborane were the expected pure trans isomers. A variety of mercuration conditions were then examined. The results are summarized in Table III. Yields of vinylmercurials varied from 60-90%. Stereochemical analysis was most easily carried out by carbonylation of the vinylmercurials, followed by NMR and/or gas chromatographic analysis of the resulting methyl esters. The esters were obtained in 70-80% isolated yields.

Best results were obtained using the catecholborane-derived mercurial (entries 1-10). The corresponding boronic acid (entries 11-13) is more difficult to prepare and no more stereospecific in its reactions. The dicyclohexylborane products (entries 14-16) lacked stereospecificity. The best reagents for mercuration of the trans-1-decenylcatecholborane were either $Hg(OAc)_2$ plus NaOAc (entry 7) or $HgCl_2$ (entries 9, 10). Unfortunately, in attempting to extend the latter procedure to the siloxy-substituted vinylborane of entry 17, we

Table III. Mercuration and Subsequent Carbonylation of Vinylboranes

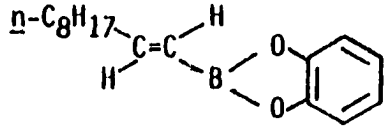
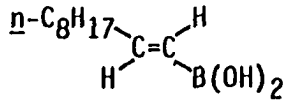
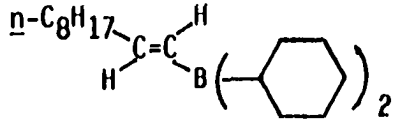
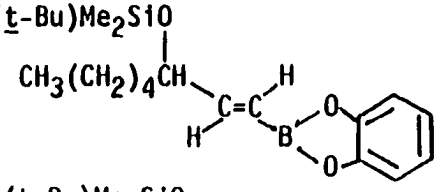
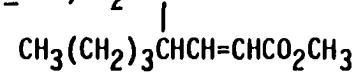
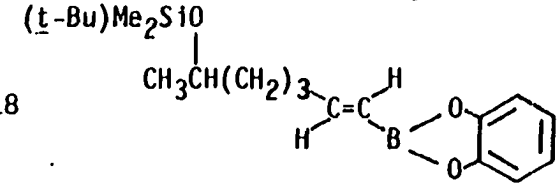
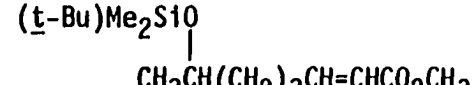
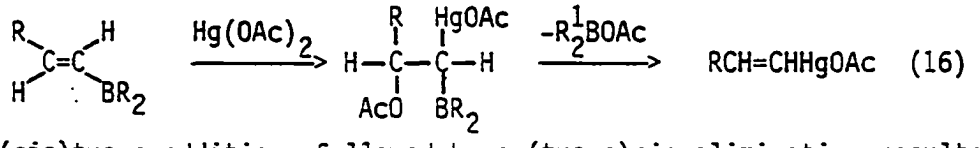
entry	vinylborane	reaction conditions	additional reagents	mercuric salt	methyl ester	trans:cis ratio
1		CH_3CN 0→25°C	---	$Hg(O_2CCH_3)_2$	n-$C_8H_{17}CH{=}CHCO_2CH_3$	50:50
2		HMPA 0→25°C	---			77:23
3		CH_2Cl_2 -78→25°C	---			50:50
4		25°C	---			75:25
5			---	$Hg(O_2CCF_3)_2$		84:16
6		THF -78→25°C	---	$Hg(O_2CCH_3)_2$		43:57
7			NaO_2CCH_3			98:2
8			---	$Hg[O_2C(CH_2)_2CH_3]_2$		52:48
9			---	$HgCl_2$		99:1
10			$NaOCH_3$			99:1

Table III (continued)

entry	vinylborane	reaction conditions	additional reagents	mercuric salt	methyl ester	trans:cis ratio
11		-78→0°C	---	$Hg(O_2CCH_3)_2$		98:2
12		-78→25°C	---	$HgCl_2$		90:10
13		-78→0°C	2 NaOH (-40→0°C)			97:3
14		0°C		$Hg(O_2CCH_3)_2$		67:33
15		-78→25°C				90:10
16			NaO_2CCH_3			86:14
17		-78→0°C	NaO_2CCH_3			98:2
18						95:5

observed unreacted organoborane and an absence of vinyl peaks corresponding to the vinylmercurial in the NMR spectrum. However, the $Hg(OAc)_2$/NaOAc procedure worked nicely on this vinylborane as well as that of entry 18. The vinylmercurial of entry 17 has proven very valuable in the synthesis of prostaglandins and has recently been prepared in optically active form from (S)-1-octyn-3-ol by other members of the Larock group. Application of the last vinylmercurial in this study to the total synthesis of Brefeldin-A will be discussed in the following chapter.

Mechanistically, we believe that these reactions proceed by an addition-elimination sequence (eq. 16).[31]



(16)

A (cis)trans addition, followed by a (trans)cis elimination results in overall retention. The stereospecificity is apparently lost during one or both of the two steps. Addition of sodium acetate promotes a more stereospecific reaction, perhaps by base-promoted trans elimination of the boron and acetate groups.[31]

Conclusion

The use of catecholborane, followed by mercuric acetate plus sodium acetate, provides an improved, stereospecific method for the conversion of alkynes to vinyl-mercurials.

Experimental Section

Equipment

Gas chromatographic analyses were carried out on a Varian model 3700 gas chromatograph with a flame ionization detector. In addition, a Finnegan 4023 gas chromatograph-mass spectrometer was employed to identify the products. Exact masses were measured on a MS-902 Mass Spectrometer. ^{1}H NMR spectra were obtained on a Varian EM-360 using tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Reagents

All reagents were used as obtained commercially unless otherwise noted. All solvents were distilled prior to use. 3-t-Butyldimethylsiloxy-1-octyne was prepared from commercially available 1-octyn-3-ol (Aldrich). 6-t-Butyldimethylsiloxy-1-heptyne was synthesized according to the published procedure starting from 3-methylcyclohexen-1-one (Aldrich).[32]

The vinylcatecholboranes were prepared from the corresponding acetylenes using the standard hydroboration procedure.[33] The trans-1-decenylboronic acid was prepared by hydrolysis of the corresponding catecholborane.[33]

E-3-t-Butyldimethylsiloxy-1-octenylcatecholborane: ^{1}H NMR ($DCCl_3$) δ 0.09 (6H, s, $SiMe_2$), 0.93 (9H, s, t-Bu), 0.7-1.8 (11H, m, C_5H_{11}), 4.26 (1H, m, -CHO-), 6.91 (1H, dd, J=18 and 2 Hz, vinyl), 6.76-7.30 (5H, m, vinyl and aryl); mass spectrum, m/e 360.23053 (calcd for $C_{20}H_{33}O_3BSi$, 360.22921).

E-6-t-Butyldimethylsiloxy-1-heptenylcatecholborane: ^{1}H NMR ($DCCl_3$) δ 0.06 (6H, s, $SiMe_2$), 0.8 (9H, s, t-Bu), 1.05 (3H, d, J=6 Hz, CH_3), 1.3-1.6 (4H, m, CH_2's), 2.0-2.3 (2H, m, $=CCH_2-$), 3.66-4.0 (1H, m, -CHO-), 5.7 (1H, dt, J=1.5 and 16 Hz, -BCH=), 6.7-7.25 (6H, m, -BC=CH- and aryl); mass spectrum, m/e 345.20657 (calcd for M^+-H, $C_{19}H_{30}BO_3Si$, 345.20573).

Representative procedure for the stereospecific synthesis of vinylmercurials

trans-1-Decenylcatecholborane (3 mmol) was dissolved in 3 ml of THF and cooled to -78°C. One equivalent of sodium acetate was added and the mixture was stirred for 10-15 min. Mercuric acetate (0.954 g, 3 mmol) was added and the reaction mixture warmed up to 0°C. The solution was poured into ice cold water containing 3 mmol of sodium chloride and the THF layer was removed on a rotary evaporator. The trans-1-decenylmercuric chloride was collected on a filter funnel, washed with water and dried to yield 1.0 g (89%) of white solid.[24]

In the case of the two siloxy mercurials which turned out to be oils at room temperature, after the evaporation of THF, the resulting oil was extracted with pentane and dried over $MgSO_4$. Evaporation of the solvent gave the colorless oil. Purification was effected by column chromatography using 1:1 hexane/ethyl acetate.

E-3-t-Butyldimethylsiloxy-1-chloromercurio-1-octene: 72% yield; ^{1}H NMR (C_6D_6) δ 0.06 (6H, bs, $SiMe_2$), 0.8-1.8 (20H, m, alkyl), 3.96 (1H, m, -CHO-), 5.37 (2H, m, vinyl); ^{13}C NMR ($DCCl_3$) δ 152.30, 132.14, 74.65, 37.91, 31.73, 25.88, 24.65, 22.50, 18.14, 13.98, -4.29, -4.81;

IR ($HCCl_3$) 3000, 2942, 2920, 2845, 1600 (w), 1460, 1350, 1248 cm^{-1}. Anal. calcd for $C_{14}H_{29}ClHgOSi$: C, 35.21; H, 6.12; Hg, 42.01. Found: C, 35.37; H, 6.26; Hg, 41.72. E-6-t-Butyldimethylsiloxy-1-chloromercurio-1-heptene: 80-85% yield; ^1H NMR ($DCCl_3$) δ 0.06 (6H, s, $SiMe_2$), 0.8 (9H, s, t-Bu), 1.05 (3H, d, J=6 Hz, CH_3), 1.3-1.6 (4H, m, CH_2's), 2.0-2.3 (2H, m, $C=CCH_2$), 3.66-4.0 (1H, m, -CHO-), 5.66 (2H, m, vinyl); ^{13}C NMR ($DCCl_3$) δ 150.57, 133.24, 68.23, 36.27, 30.36, 26.73, 25.92, 23.80, 18.06, -4.30, -4.63; IR ($HCCl_3$) 3010, 2960, 2920, 2860, 1600 (w), 1460, 1370, 1245, 1200 cm^{-1}. Anal. calcd for $C_{13}H_{27}ClHgOSi$: C, 33.76; H, 5.84; Hg, 43.29. Found: C, 34.32; H, 6.01; Hg, 41.08.

General Carbonylation Procedure

Palladium chloride (1 mmol) and lithium chloride (2 mmol) were stirred with 10 ml of methanol and cooled to -78°C. 2 M of magnesium oxide or diisopropylethylamine and 1 mmol of the vinylmercurial were added at -78°C. The flask was flushed with carbon monoxide and a balloon of carbon monoxide was attached. The reaction mixture was allowed to warm to room temperature overnight and filtered through Celite. The Celite was washed with ether. The combined ether layers were washed with water and saturated NH_4Cl, dried over $MgSO_4$ and evaporated.

Methyl E-2-undecenoate: ^1H NMR ($DCCl_3$) δ 0.7-1.0 (3H, m, CH_3), 1.1-1.67 (10H, m, CH_2's), 2.0-2.3 (2H, m, $C=CCH_2$), 3.70 (3H, s, CO_2CH_3), 5.75 (1H, dt, J=17 and 1.5 Hz, =CHCO-), 6.97 (1H, dt, J=17 and 6 Hz, $=CHCH_2$).

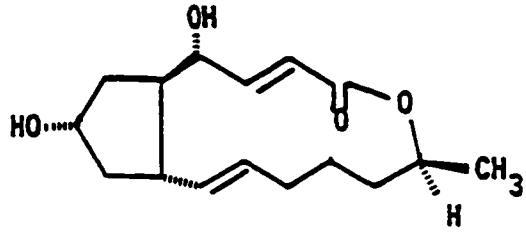
Methyl E-4-t-butyldimethylsiloxy-2-nonenoate: ^1H NMR ($DCCl_3$) δ 0.06 (6H, s, $SiMe_2$), 0.8 (9H, s, t-Bu), 2.0-2.57 (8H, m, CH_2's), 3.66 (3H, s, CO_2CH_3), 4.0-4.33 (1H, m, -CHO-), 5.81 (1H, dd, J=16 and 1.5 Hz, =CHCO-), 6.83 (1H, dd, J=16 and 4 Hz, =CHCH-); mass spectrum, m/e 300, 285, 269, 242, 229, 211.

Methyl E-7-t-butyldimethylsiloxy-2-octenoate: ^1H NMR ($DCCl_3$) δ 0.06 (6H, s, $SiMe_2$), 0.8 (9H, s, t-Bu), 1.05 (3H, d, J=6Hz, CH_3), 1.3-1.6 (4H, m, CH_2's), 2.0-2.3 (2H, m, $C=CCH_2$), 3.66-4.0 (4H, s and m, CO_2CH_3 and -CHO-), 5.78 (1H, dt, J=18 and 1.5 Hz, =CHCO-), 6.66-7.18 (1H, dt, J=18 and 6 Hz, $=CHCH_2$); mass spectrum, m/e 255 (M^+-31), 229 (M^+-57), 197, 159, 95, 89, 81, 75.

CHAPTER III. SYNTHETIC STUDIES ON BREFELDIN-A

Introduction

Brefeldin-A(1) was first isolated in 1958 from Penicillium decumbens by Singleton, Bohonos, and Ullstrup.[34] The metabolite has subsequently been found in cultures of Penicillium cyaneum,[35] Penicillium brefeldianum,[36] and Asochyta imperfecta,[37] as well



1 (+) Brefeldin-A

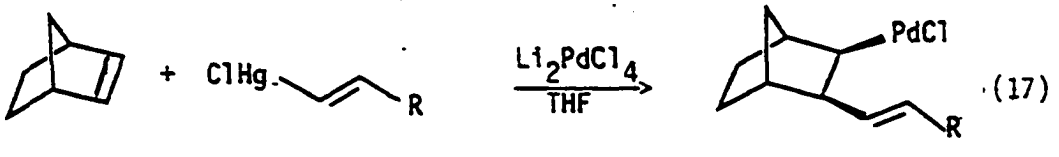
as in those of a wide variety of other organisms.[38-42] The identity of the metabolites,[37,43] however, has not in all cases been immediately apparent, thus producing for this compound the names cyocnein[35] and ascotoxin,[37] in addition to decumbin[34] and brefeldin-A.[36] Work[43] on the elucidation of the structure and stereochemistry, carried out over 14 years, was finally concluded through a definitive x-ray crystallographic study by Weber, Hauser and Sigg[44] in 1971, indicating formula 1 for (+)-brefeldin-A.

Extensive biological testing, largely effected by Betina and collaborators, has established a wide range of biological activity for this compound, including antiviral,[45] antifungal[46], antimitotic[47] and antitumor[36,48] effects. Although it has been found that brefeldin-A

is derived completely from acetate, several aspects of its biosynthesis remain obscure in spite of considerable investigation.[49]

Synthetic studies on natural brefeldin-A by Corey and co-workers[50] led to the discovery of certain selective reactions, which subsequently not only facilitated this group's first total synthesis of racemic brefeldin-A,[51] but also aided much of the synthetic effort that has followed in this area.[52-61] This rather considerable effort in a number of laboratories has to date produced several additional syntheses of racemic brefeldin-A,[53-57,59,62] as well as a lengthy one[56] of (+)-brefeldin-A, the naturally occurring form of this substance.

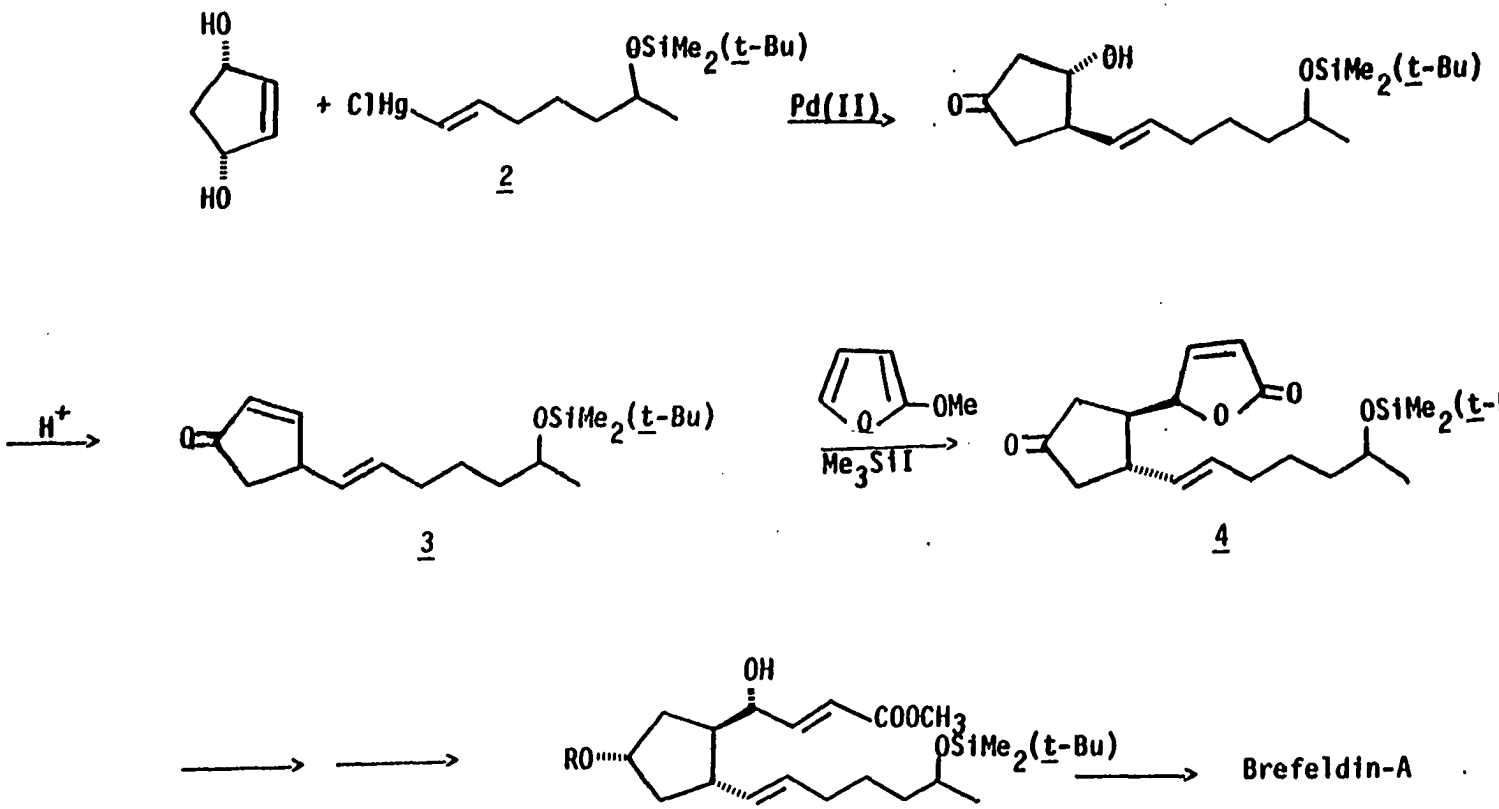
Our own interest in this natural product stemmed from our prostaglandin synthesis program. We have shown that vinylmercurials undergo transmetallation by palladium(II) compounds and the resulting vinylpalladium intermediates add to a variety of olefins in a stereospecific manner[63] (eq. 17). It appeared that this chemistry



(17)

might prove applicable to the efficient synthesis of brefeldin-A. Besides, most of the syntheses of brefeldin-A suffer from the fact that the α sidechain of brefeldin-A (C_1-C_4) is not introduced in a direct fashion, which reduces the efficiency and elegance of the overall synthesis. Our initial strategy towards this end is shown in Scheme 2.

Scheme 2


HO
HO
+ ClHg
OSiMe2(t-Bu)
2
Pd(II)
OH
O
OSiMe2(t-Bu)
H+
O
OSiMe2(t-Bu)
3
OMe
O
Me3SiI
O
O
O
OSiMe2(t-Bu)
4
OH
COOCH3
RO
OSiMe2(t-Bu)
Brefeldin-A

We envisioned two key steps in the total synthesis of brefeldin-A. The reaction of vinylmercurial 2 with cyclopent-2-en-1,4-diol or its anion, in the presence of palladium(II) salts should lead to the key intermediate 3. Dehydration and subsequent condensation of cyclopentenone 3 with 2-methoxyfuran in the presence of trimethylsilyl iodide would yield another key intermediate 4.[64] The lactone 4 on standard organic transformations should lead to brefeldin-A. This chapter discusses our efforts to effect the overall strategy and synthesize brefeldin-A.

Results and Discussion

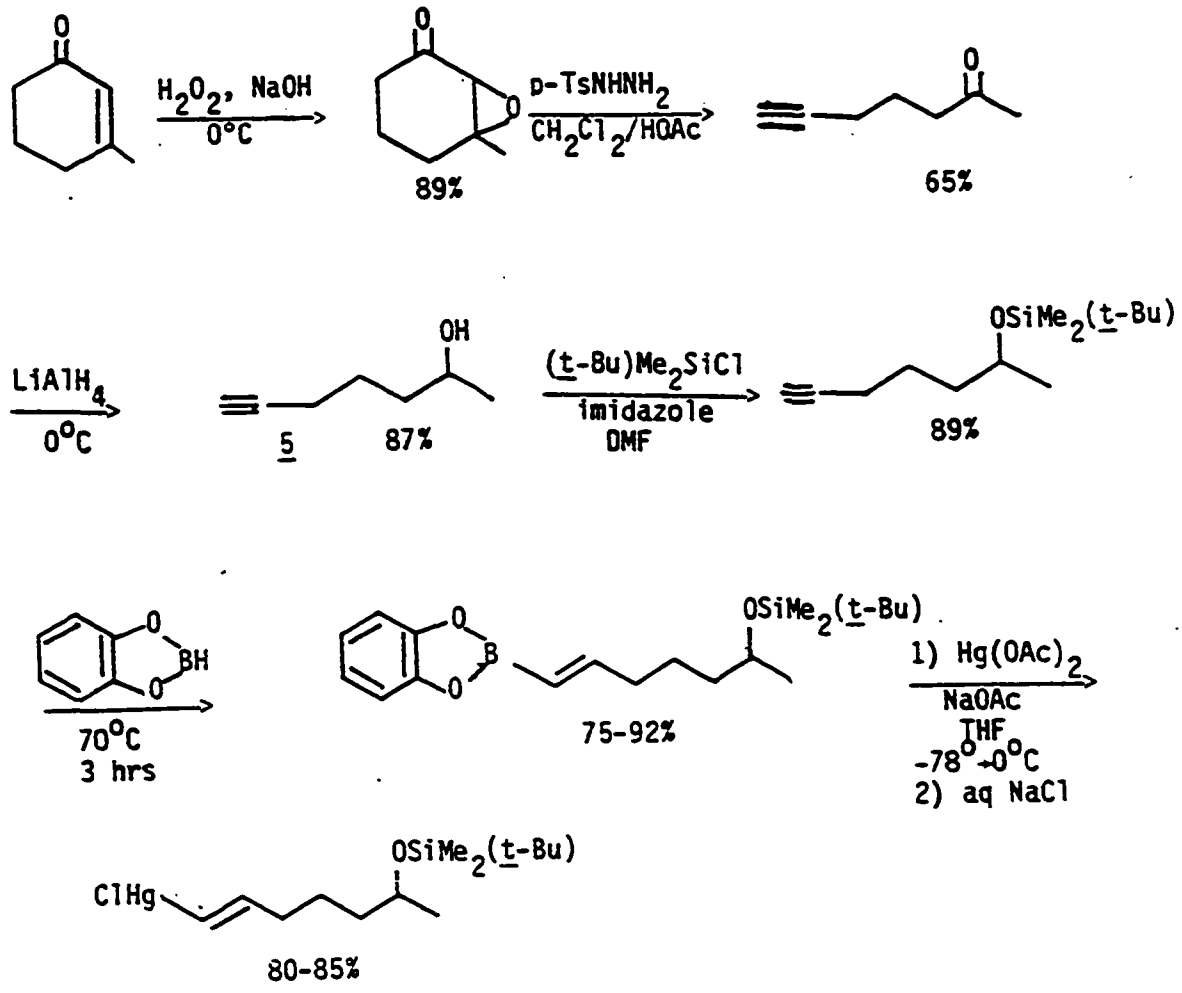
Our initial efforts were directed towards the synthesis of the required vinylmercurial 2. The synthesis is shown in Scheme 3. The acetylenic alcohol 5 was prepared using a published procedure.[62] Later in this work, we developed a more convenient procedure to synthesize 5. Thus, commercially available 4-heptyn-2-ol was isomerized to 5 using lithium-1,3-diaminopropane (eq. 18).[65] The silyl-protected acetylenic alcohol 5 was hydroborated and mercurated using the modified procedure described in the previous chapter.

$$CH_3CH_2C{\equiv}CCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \xrightarrow[KO\underline{t}\text{-}Bu]{\text{Li-APA}} HC{\equiv}CCH_2CH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \qquad (18)$$

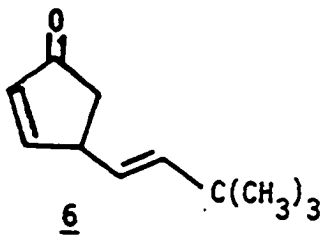
60-64%

Next, optimum conditions for the reaction of cyclopent-2-en-1,4-diol with the vinylmercurial were explored. For this trans-3,3-dimethyl-but-1-enylmercuric chloride was chosen as the model system.

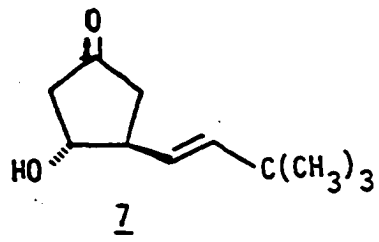
Scheme 3


H2O2, NaOH
0°C
89%
p-TsNHNH2
CH2Cl2/HOAc
65%
LiAlH4
0°C
5
87%
(t-Bu)Me2SiCl
imidazole
DMF
OSiMe2(t-Bu)
89%
70°C
3 hrs
75-92%
1) Hg(OAc)2
NaOAc
THF
-78°→0°C
2) aq NaCl
ClHg
80-85%

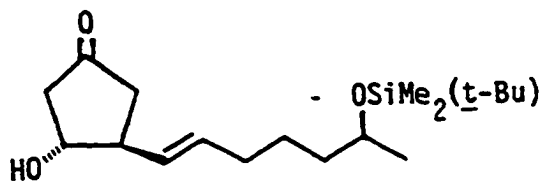
The results are shown in Table IV. Using the dianion of the diol formed by treating the diol with 2 equivalents of n-BuLi in THF, the reaction was conducted under various conditions (entries 1-4). Under the first two sets of reaction conditions, compound 6 was the major product albeit in low yield. Conditions 3 and 4 did not yield any of



6



7



8

the expected product. Then, the reaction was tried using the diol itself, this time under different conditions. The hydroxy ketone 7 was obtained in 25% and 50% yields respectively (entries 5 and 6). Keeping these reactions in mind, we then applied these reaction conditions to the real system, namely, the vinylmercurial 2. The results are also shown in Table IV. The best yield obtained of the expected product 8 was only 16%. Unfortunately, the best reaction conditions in Table IV, for the model system (entry 6), when applied to the real system, resulted only in the reductive elimination product, enol acetate 9 (eq. 19).

TABLE IV. Reaction of Cyclopent-2-en-1,4-diol with Vinylmercurials

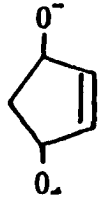
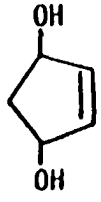
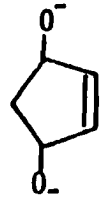
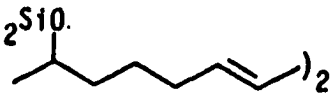
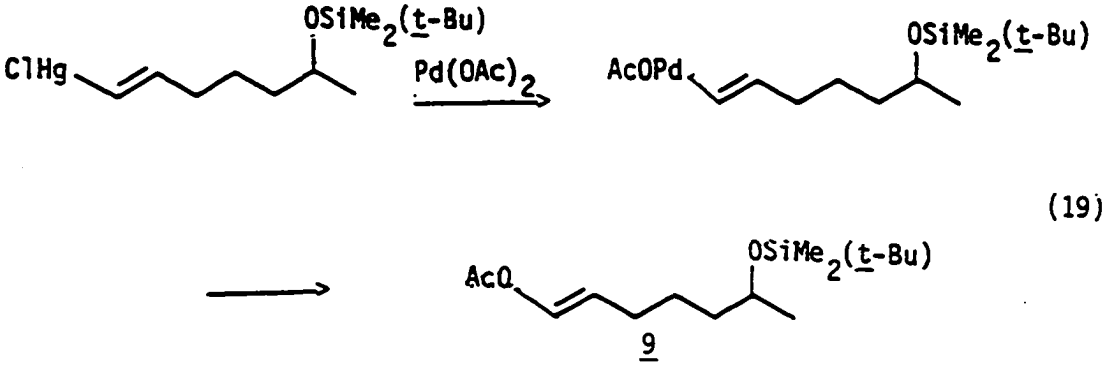
entry	substrate	vinylmercurials	source of palladium	solvent	temp. (°C)	products (% yield)
1			Li_2PdCl_4, $2K_2CO_3$	THF	-78°→RT	<u>6</u> + <u>7</u> (20%) (10%)
2			Li_2PdCl_4	THF	-78°→RT	(25%) (3-4%)
3			$PdCl_2$	THF	-78°→RT	no product
4			$(CH_3CN)_2PdCl_2$	THF	-40°→RT	mess
5			$(CH_3CN)_2PdCl_2$	CH_3CN	-40°→RT	<u>7</u> (25%)
6			$Pd(OAc)_2$	CH_3CN	-40°→RT	<u>7</u> (50%)

Table IV (continued)

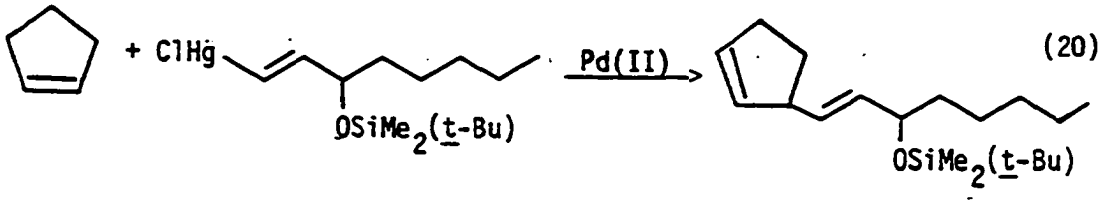
entry	substrate	vinylmercurials	source of palladium	solvent	temp. (°C)	products (% yield)
7		2	Li_2PdCl_4	THF	-78°→RT	8 (16%)  (40%)
8		2	$Pd(OAc)_2$	CH_3CN	-40°→RT	9 (~50%)
9		2	Li_2PdCl_4, $3Et_3N$	THF	-78°→RT	8 (16%)
10		2	$(CH_3CN)_2PdCl_2$, Et_3N	CH_3CN	-20°→RT 1 day	8 (10.5%)
11		2	Li_2PdCl_4, $2K_2CO_3$	THF	-20°, 4h →RT	8 (13%)



(19)

9

We next looked for an olefinic substrate which would give an improved yield on reacting with the mercurial 2 and at the same time lead to the key intermediate 3. Since cyclopentene was shown to react with vinylmercurial 10 in the presence of dilithium tetrachloropalladate in good yield (eq. 20),[66] cyclopent-3-en-1-ol

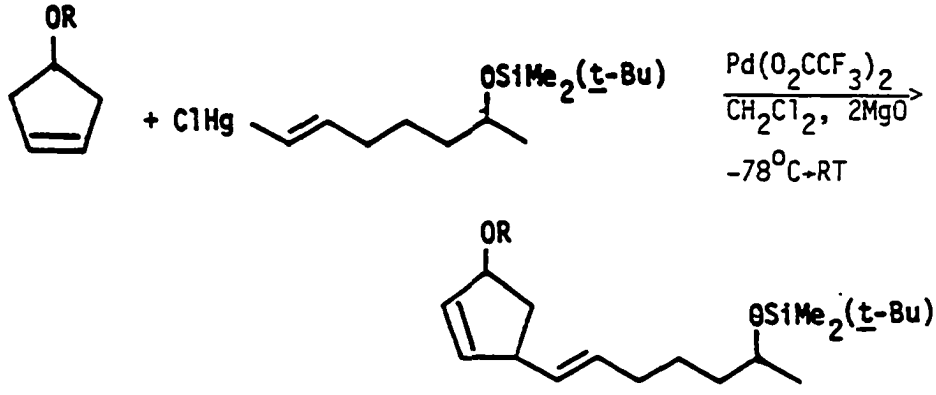


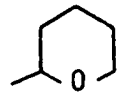
(20)

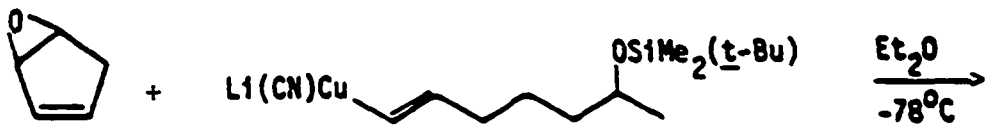
appeared to be the right choice. Accordingly, various protected cyclopent-3-en-1-ol compounds were prepared and reacted with vinylmercurial 2. The results are shown in Table V. Compounds 11 and 12 gave the expected products, but in low yield (20-22%). Compounds 13 and 14 did not give any of the expected product. Since the yield was low for the first key step, we decided to change our strategy.

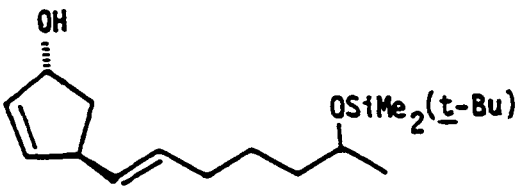
This time the key step involved the reaction of a vinylcuprate with cyclopentadiene monoepoxide (eq. 21), a reaction developed by Joseph Marino in his prostaglandin work.[67] The reaction was shown

TABLE V. Reaction of cyclopent-3-en-1-ol derivatives with vinylmercurial 2



entry	R	product (% yield)
1	 11	(22)
2	$-OCH_2OCH_2CH_2OCH_3$ 12	(20)
3	$-OCOCH_3$ 13	no product
4	$-CH_2SCH_3$ 14	no product



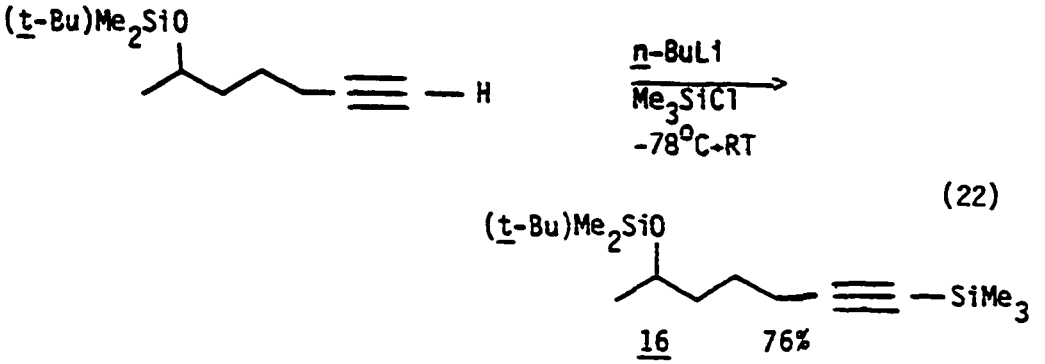


(21)

15

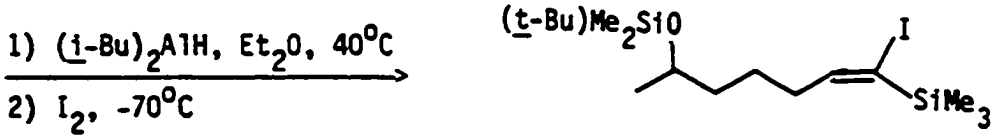
by Marino to result in predominant formation of the 1,4 addition product over the 1,2 addition product.

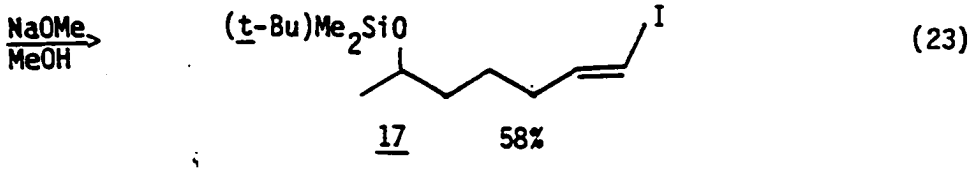
Accordingly, the required starting materials were prepared as shown in equations 22, 23 and 24.



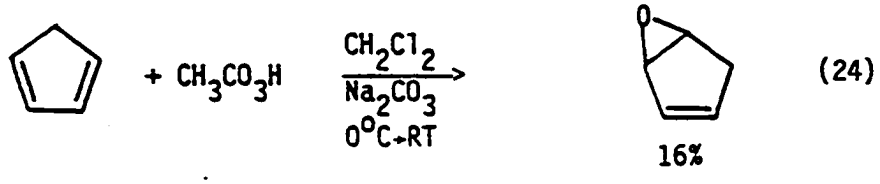
(22)

16 76%





17 58% (23)



(24)

The synthesis of compound 16 was necessitated by the fact that terminal acetylenes with ether functionality elsewhere in the carbon chain do not undergo standard hydroalumination, whereas alkynylsilanes undergo hydroalumination with ease.[68] The reaction in equation 21 was first attempted using the published procedure[67] [Table VI, entry (1)]. The desired allylic alcohol 15 was obtained in 20% yield, along with 7% of the 1,2 addition product. A significant amount of what appeared to be the dimerization product from the vinylcuprate was also obtained. Apparently, the vinylcuprate did not react completely under the reaction conditions and simply dimerized upon warming up. Hence,

TABLE VI. Reaction of cyclopentadiene monoepoxide with vinyl cuprate

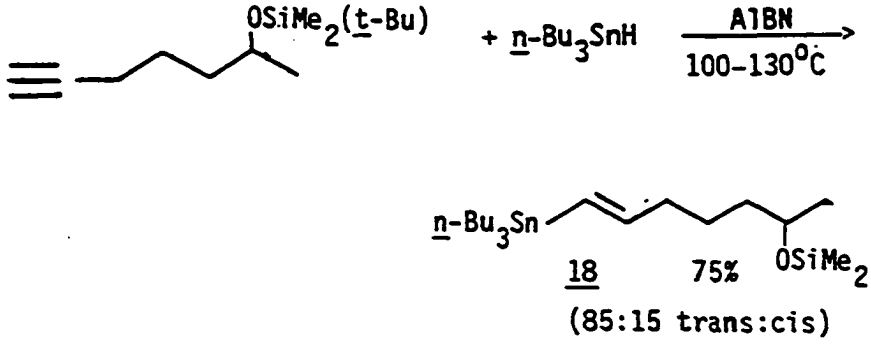
entry	vinyl substrate	step 1	step 2	step 3	product (% yield)	
1	17	2 t-BuLi, ether, -78°C, 2h	Added to CuCN, ether, -40°C, 1h	epoxide (1 equiv) -78°C, 6h→RT	15 + 1,2 addition product (20)	(7)
2				epoxide (1 equiv) -78°C, 8h	(17-20)	(7-10)
3				-78°C, 10h	(17-20)	(7-10)
4				-78°C, 7h →RT, overnight	(10)	
5		2.1 t-BuLi, ether, -78°C, 3h	2.1 CuCN, ether, -40°C, 2h	epoxide (2 equivs) -40°C, 2h →RT, 5h	(12)	(12)

Table VI (continued)

entry	vinyl substrate	step 1	step 2	step 3	product (% yield)
6	18	0.85 equiv n-BuLi, -78°→-0°C	Added to n-$C_3H_7C{\equiv}CCu$ + HMPT, -100°C, 1h	epoxide, -100°C, 2h; (1 equiv) -60°C, 4h	no product
7			CuCN, THF -50°C, 1.5h	epoxide, -70°C, 6h	no product
8			CuCN, ether, -50°C, 1.5h	epoxide, -70°C, 6h	no product

the reaction was run for longer reaction times (entries 2-4). But this made no difference in the yield. After a telephone conversation with Dr. Marino, the reaction was tried under slightly different conditions (entry 5). Unfortunately, the total yield of the reaction products was only 25% and the ratio of 1,4 addition to 1,2 addition product seemed to be 1:1, judging from ^{1}H NMR and thin layer chromatography.

At this point, we decided to change the nature of the cuprate as well as the method of formation. Hence, the vinylstannane 18 was prepared from the corresponding acetylene as shown in equation 25. The cuprate was formed by reacting the vinylstannane with n-BuLi,



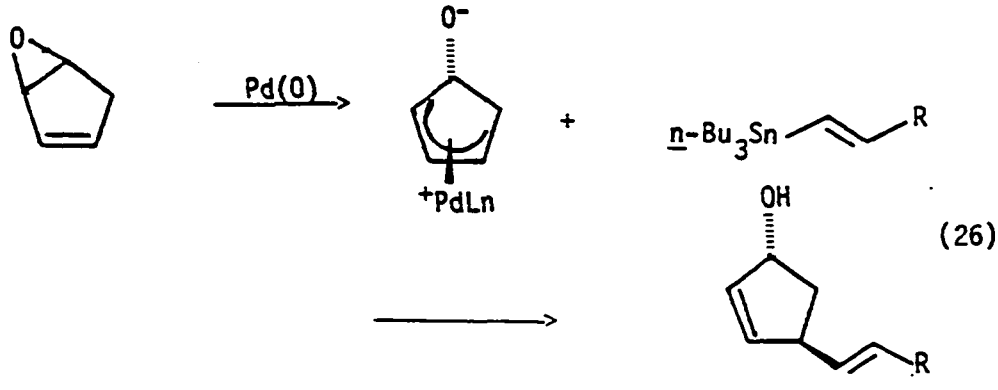
(25)

18 75% (85:15 trans:cis)

followed by treatment with 1-pentynyl copper in hexamethylphosphoramide, and then reacted with cyclopentadiene monoepoxide [entry 6 in Table VI]. The reaction did not result in any of the desired product. The reaction was also attempted using CuCN in tetrahydrofuran and ether solvents (entries 7, 8), but without success.

Using the cuprate formed from trans-1-iodo-1-hexene as a model system, we also attempted some reactions in order to improve the yield of the reaction with cyclopentadiene monoepoxide. The results are shown in Table VII. In entries 1 and 2, the cuprate was reacted with cyclopent-2-en-1-one and 4-bromocyclopent-2-en-1-one, respectively, under the conditions shown. The reaction resulted only in a significant amount of dimer from the cuprate and none of the desired product. In entry 3, the cuprate was reacted with cyclopentadiene monoepoxide in the presence of boron trifluoride-etherate complex in the hope that the $BF_3 \cdot Et_2O$ would presumably enhance the rate of the reaction. Although the reaction did give the expected 1,4 addition product, it also resulted in significant amounts of 1,2 addition product and the dimer from the cuprate.

We also tried some reactions using palladium(0) chemistry which unfortunately did not lead to any of the desired product as can be seen from Table VIII. The reactions were attempted in the hope that the substrates cyclopentadiene monoepoxide[69] and 4-bromocyclopent-2-en-1-one[70] would form a π-allylpalladium intermediate which would then



(26)

TABLE VII. Attempted reaction of 1-hexenylcuprate with various cyclopentene derivatives

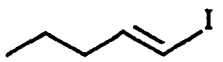
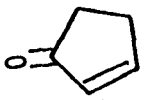
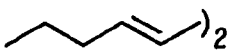
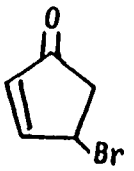
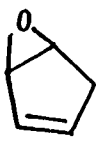
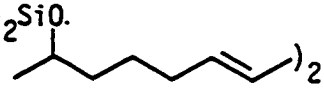
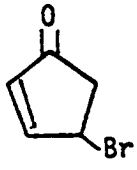
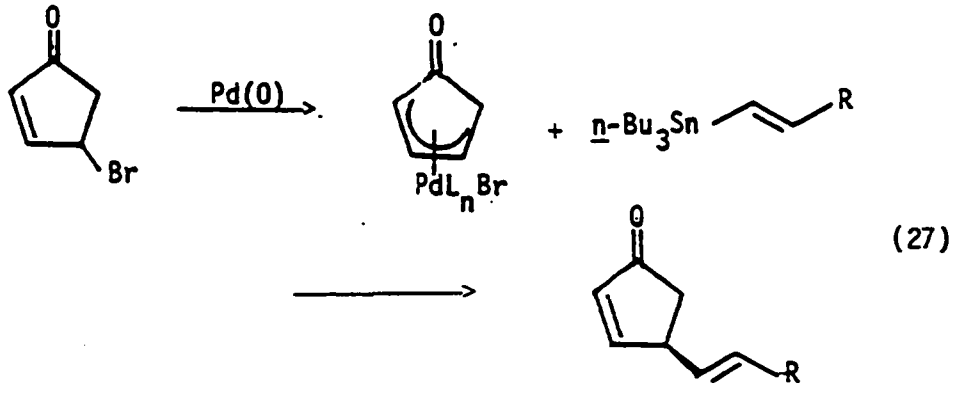
entry	substrate	step 1	step 2	step 3	product(s)
1		2.1 t-BuLi, ether, -78°C, 3h	Added to ether, -40°C, 2h	 -78°C, 2h, →RT, overnight	 60-65%
2				 -78°C, 2h; -40°C, 3h; RT overnight	same result
3			Added $BF_3 \cdot Et_2O$ (1 equiv)	 (2 equiv), -78°C, 2h; -40°C, 4h; RT, overnight	1,4 adduct + 1,2 adduct (40% total yield)

TABLE VIII. Attempted reaction of compound 18 with cyclopentene derivatives

entry	substrate	reaction conditions	product
1		5% $Pd(PPh_3)_4$, THF, -40°→0°C→RT (overnight)	mainly 
2		5% $Pd(PPh_3)_4$, CH_2Cl_2 0°→RT (1 day)	same result
3		5% $Pd(DBA)_2$, 10% PPh_3, THF, 50°C, 1 day	same result



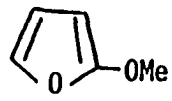
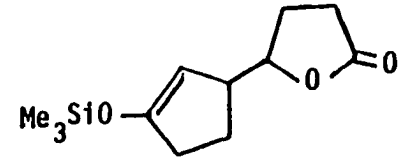
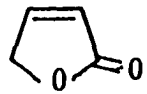
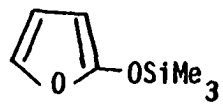
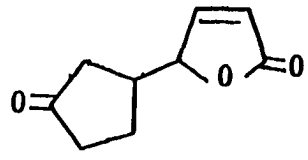
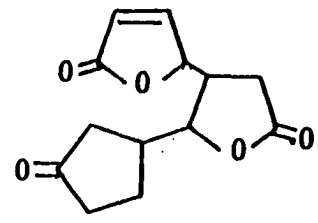
(27)

Meanwhile, we also studied a model system for the second key step of the synthesis shown in Scheme 2 (page 25), to get the intermediate 4. Cyclpent-2-en-1-one was chosen as the model system and was reacted with various four carbon synthons under different conditions as shown in Table IX. We first tried the reaction of 2-methoxyfuran with cyclopentenone in the presence of trimethylsilyl iodide.[64] The reaction gave the expected product in only 30-34% yield. The reaction that was successful was the reaction between cyclopentenone and 2-trimethylsiloxyfuran in the presence of tin tetrachloride.[71] This reaction gave the desired product 19 along with what seemed to be a product resulting from further addition of 2-trimethylsiloxyfuran to 19, in a ratio of 85:15 in 95% total yield. Hence, this reaction looks promising and can be applied to the real system once the first key step to get the intermediate 3 is worked out.

Conclusion

A study was made towards the total synthesis of brefeldin-A using the reaction of vinylpalladium species with cyclopentene derivatives.

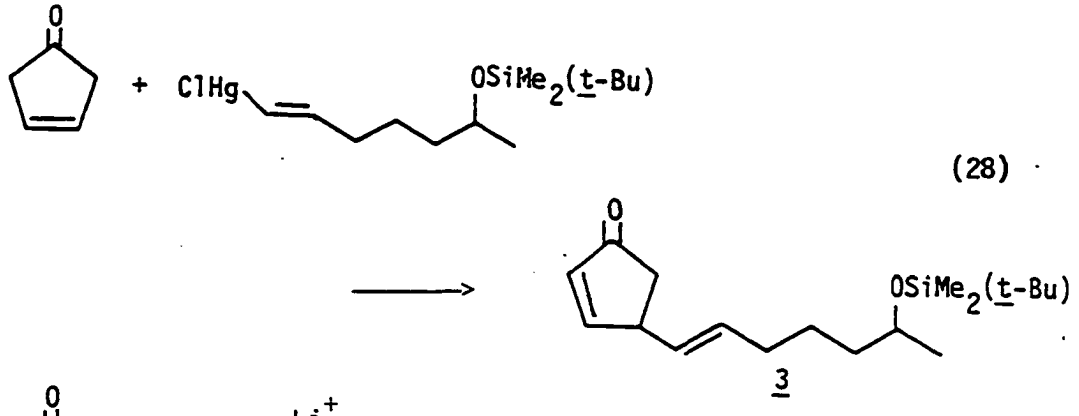
TABLE IX. Reaction of cyclopent-2-en-1-one with various four carbon equivalents

entry	four carbon equivalent	reagents	reaction conditions	result
1		Me_3SiI, 2-methyl-2-butene	CH_2Cl_2, -78°C 3 h	 30-34%
2		0.1 equiv, KOH	-50°C→RT	no product
3		LDA	-78°C→0°C	no product
4		$SnCl_4$	-78°C, 2 h	 85  15 (95% yield)

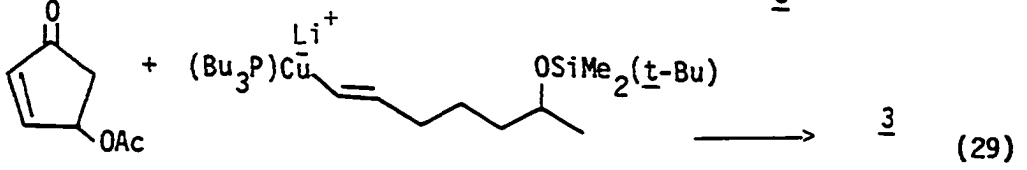
as a first key step. Even though the reactions led to the expected product(s), the yields could not be optimized. An alternative approach using the reaction of a vinylcuprate with cyclopentadiene monoepoxide also led to the expected key intermediate, but the yield again could not be optimized.

Future Work

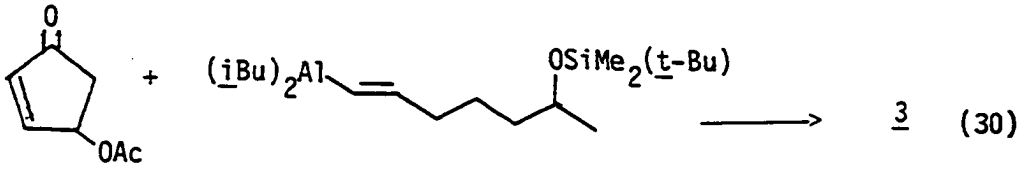
The reactions which are worth at least a try in the future for the first key step in the synthesis of brefeldin-A are the following:



(28)



(29)

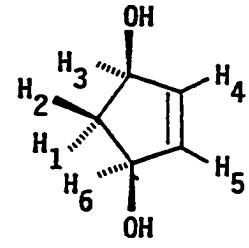


(30)

Experimental Section

All chemicals were used as obtained unless otherwise noted. All solvents were distilled before use. Tetrahydrofuran and ether were distilled from lithium aluminum hydride immediately before use. 3-Methylcyclohex-2-en-1-one was obtained from Aldrich. ^{1}H NMR spectra were recorded on a Varian EM-360 and Nicolet 300 MHz. ^{13}C NMR spectra were also recorded on a Nicolet 300 MHz instrument. A Finnigan 4023 gas chromatograph-mass spectrometer was employed to identify the products. Exact masses were measured on a MS-902 Mass Spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Synthesis of cis-cyclopent-2-en-1,4-diol[72]



Methanol (600 ml) was cooled to -10°C while bubbling oxygen through the solvent. Freshly distilled cyclopentadiene (20 ml, 16 g), rose-bengal (200 mg) and thiourea (14.6 g) were added. The reaction flask was irradiated with light from an Hanoaka lamp, while continuously bubbling oxygen through the solution. The solution was maintained at -10°C the entire time. The irradiation was stopped after 5 h and the reaction mixture was allowed to warm up to room temperature overnight. The reaction mixture was filtered and methanol was removed by roto-evaporator. Water (70 ml) was added and the aqueous solution was washed with benzene to remove soluble organic

side products. The water layer was removed by use of a roto-evaporator (40°C). The residue was left under vacuum to remove the rest of the water. The residue was distilled under reduced pressure (bp 120°C/15 mm Hg) to give 8.26 g of the title compound (34%): ^1H NMR ($CDCl_3$) δ 1.64 (dt, 1H, J=14 and 2 Hz, H_1), 2.66 (dt, 1H, J=14 and 6 Hz, H_2), 4.1-4.90 (m, 4H, H_3, H_6 and -OH), 6.0 (s, 2H, H_4 and H_5); IR (nujol) 3280 cm^{-1} (C=C stretch not seen due to symmetry).

Synthesis of E-6-(tert-butyldimethylsiloxy)-1-(chloromercurio)-1-heptene 2

Synthesis of 2,3-Epoxy-3-methylcyclohexanone This compound was prepared according to the published procedure.[73] To a solution of 3-methylcyclohex-2-en-1-one (14.0 g, 0.127 mol) in methanol (127 ml) at 10°C was added over 10 min 38.74 ml of 30% hydrogen peroxide followed by dropwise addition of 0.7 ml of 5N sodium hydroxide. After being stirred for 3 h at 10°C, the reaction mixture was poured into cold brine. The crude product was extracted with methylene chloride and dried over magnesium sulfate. Distillation (80°C/11 mm Hg) provided 14.23 g (89%) of the title compound; IR (neat) 1705, 1255, 810, 770 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.45 (s, 3H, CH_3), 1.6-2.6 (m, 6H, CH_2's) 3.05 (s, 1H, -HCO).

Synthesis of hept-6-yn-2-one This compound was prepared according to the published procedure.[73] 2,3-Epoxy-3-methyl-cyclohexanone (0.111 mol, 14.0 g) in methylene chloride (220 ml) and acetic acid (110 ml) was cooled to -30°C. p-Tosylhydrazide (0.117 mol) in the same amount of methylene chloride and acetic acid was also

cooled to -30°C. The former solution was added to the latter and the mixture was stirred at -15°C for 2 h and then left in the cold room (3-4°C) overnight. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was evaporated to remove methylene chloride and ether (300 ml) was added. Solid sodium bicarbonate was added until effervescence ceased. The ether layer was separated, dried over $MgSO_4$ and evaporated by the use of a roto-evaporator. Purification by column chromatography (11% ether in pentane) provided 8.29 g (67%) of the acetylenic ketone: IR 3290, 2120, 1720 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.8 (t, $\underline{J}$=2.5 Hz, 1H, HC≡C), 2.1 (s, 3H, $COCH_3$), 1.2-2.3 (m, 4H, CH_2's), 2.5 (t, $\underline{J}$=6.15 Hz, 2H, CH_2CO).

<u>6-Heptyn-2-ol</u> This compound was prepared according to the published procedure.[74] A solution of 6-heptyn-2-one (8.5 g, 77.44 mmol) in 20 ml of ether was added over 5 min, to a stirred suspension of 1.51 g (39.6 mmol) of lithium aluminum hydride. After stirring for 20 min excess hydride was destroyed by the sequential and dropwise addition of 1.5 ml H_2O, 1.5 ml 15% NaOH and 3 ml H_2O). The reaction mixture was filtered and washed with ether. The ether layer was dried over $MgSO_4$ and evaporated to yield 7.62 g (87%) of the title compound: IR 3340, 3300, 2120 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.1 (d, $\underline{J}$=6 Hz, 3H, CH_3), 1.3-1.7 (m, 4H, CH_2's), 1.75 (t, $\underline{J}$=2.5 Hz, 1H, HC≡C), 2-2.3 (m, 3H, -OH and CH_2C≡C), 3.45-3.9 (m, 1H, $\underline{H}COH$).

<u>6-(tert-Butyldimethylsilyloxy)-1-heptyne</u> This compound was prepared according to the published procedure.[75] A solution of 7.43 g (66.34 mmol) of 6-heptyn-2-ol and 4.56 g of imidazole in 30 ml of DMF

was treated under nitrogen with stirring with 9.95 g of tert-butyldimethylchlorosilane (66.34 mmol). After being stirred for 2.5 h at 35°C, the reaction mixture was poured into water and the crude product was extracted with pentane and purified by column chromatography (1.5% ether in pentane) to yield 13.35 g (89%) of the title compound: IR 3370, 2120, 1260, 840, 780 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.0 (S, 6H, $SiMe_2$), 0.8 (s, 9H, t-Bu), 1.05 (d, J=6 Hz, 3H, CH_3), 1.3-1.6 (m, 4H, CH_2's), 1.7 (t, J=2.5 Hz, 1H, HC≡C), 1.9-2.2 (m, 2H, $CH_2C{\equiv}C$), 3.5-3.9 (m, 1H, CHOSi).

Synthesis of (E)-6-(tert-butyldimethylsiloxy)-1-heptenyl catecholborane This compound was prepared according to the published general procedure.[76] Catecholborane (2.07 g, 17.25 mmol) was added to the above acetylene (3.16 g, 14 mmol) under nitrogen and heated at 70°C for 3 h. Distillation (bp 150-155°C/0.25 mm Hg) provided the trans-6-(tert-butyldimethylsiloxy)-1-heptenyl-dioxoborole in 92% yield: ^1H NMR ($DCCl_3$) δ 0.0 (s, 6H, $SiMe_2$), 0.8 (s, 9H, t-Bu), 1.05 (d, J=6 Hz, 3H, CH_3), 1.3-1.6 (m, 4H, CH_2's), 2-2.3 (m, 2H, $C{=}CCH_2$), 3.66-4.0 (m, 1H, CHOSi), 5.7 (td, J=1.5 Hz and 16 Hz, 1H, BCH=C), 6.7-7.25 (m, 5H, BC=CH and aromatic); mass spectrum, m/e 345.20657 (calcd for $C_{19}H_{30}BO_3Si$ (M^+-H) 345.20573).

Synthesis of vinylmercurial 2 The vinylborane prepared above (2 mmol, 0.692 g) was dissolved in THF (2 ml) and cooled to -78°C. One equivalent of sodium acetate was added and the reaction mixture was stirred for 15 min at -78°C. Mercuric acetate was added and the reaction mixture was allowed to warm up to 0°C after stirring for 10

min at -78°C. The reaction mixture was poured into water containing one equivalent of sodium chloride. After the THF layer was evaporated, the water layer was extracted with pentane and dried over anhydrous magnesium sulfate. Purification by column chromatography (2:1 hexane: EtOAc) gave 0.750 g of an oil (82%): ^{1}H NMR ($DCCl_3$) δ 0.06 (6H, s, $SiMe_2$), 0.8 (9H, s, t-Bu), 1.05 (3H, d, J=6 Hz, CH_3), 1.3-1.6 (4H, m, CH_2's), 2.0-2.3 (2H, m, $C=CCH_2$), 3.66-4.0 (1H, m, -CHO), 5.66 (2H, m, vinyl); ^{13}C NMR ($DCCl_3$) δ 150.57, 133.24, 68.23, 36.27, 30.36, 26.73, 23.80, 18.06, -4.30, -4.63; IR ($HCCl_3$) 3010, 2960, 2920, 2860, 1600(w), 1460, 1370, 1245, 1200 cm^{-1}. Anal. calcd for $C_{13}H_{27}ClHgOSi$: C, 33.76; H, 5.84; Hg, 43.29. Found: C, 34.32; H, 6.01; Hg, 41.08.

Isomerization of 4-heptyn-2-ol

The title compound was prepared according to a published general procedure.[65] Under a slight positive pressure of nitrogen, 1,3-diaminopropane (24 ml, previously distilled from BaO and stored over 4°A molecular sieves) was added to lithium (47.14 mmol washed free of mineral oil with hexane). The mixture was heated and stirred at 70°C for approximately 2 h until the blue color had discharged and a milky white suspension of the lithium salt was obtained. The mixture was cooled to room temperature and potassium t-butoxide (3.12 g, 30 mmol) was added all at once affording a pale yellow solution. After stirring for 15 min, 4-heptyn-2-ol (0.812 g, 7.25 mmol) was added in one portion and stirring was continued for 30 min. The mixture was poured into ice water and extracted with chloroform. The combined

organic layer was washed successively with water, dil. HCl and saturated NaCl solution and then dried over Na_2SO_4. Evaporation of the solvent and distillation provided 0.520 g of 6-heptyn-2-ol (64%). The physical data were identical with literature data for 6-heptyn-2-ol.[74]

Synthesis of compounds 6 and 7

Cyclopent-2-en-1,4-diol (1 mmol, 0.100 g) was dissolved in 10 ml of THF and cooled to -78°C. n-Butyllithium in hexane (2 mmol, 0.9 ml, 2.2 M) was added and the solution was warmed up to -25°C. The solution was cooled back to -78°C and dilithium tetrachloropalladate (1 mmol) in 10 ml of THF was added through a canula, followed by 1 mmol of E-3,3-dimethylbut-1-enylmercuric chloride and 2 mmol of K_2CO_3. The reaction mixture was warmed up to room temperature and stirred overnight. A few drops of methanol were added and the reaction mixture was filtered through Celite and washed with ether. The ether solution was washed with water and saturated ammonium chloride, dried over $MgSO_4$ and concentrated. Purification by column chromatography gave a 25% yield of 6 and 4% of 7.

Compound 6: ^1H NMR ($DCCl_3$) δ 0.95 (9H, s, t-Bu), 2.22 (1H, d, J=2 Hz, ring CH), 2.49 (1H, d, J=6 Hz, ring CH), 3.52 (1H, m, doubly allylic H), 5.30 (1H, dd, J=16 Hz and 7.2 Hz, C=CH), 5.63 (1H, dd, J=16 Hz and 1.2 Hz, HC=C), 6.17 (1H, dd, J=6 Hz and 2 Hz, ring HC=C), 7.52 (1H, dd, J=6 Hz and 3 Hz, ring C=CH); IR (film) 1710 cm^{-1}; mass spectrum, m/e 164, 162, 149, 147, 121, 108, 95, 83, 70, 57.

Compound 7: ^{1}H NMR ($DCCl_3$) δ 1.01 (9H, s, t-Bu), 2.16 (1H, dd, J=7 Hz and 2 Hz, ring CH), 2.26 (1H, dd, J=7 Hz and 2 Hz, ring CH), 2.52 (1H, s, OH), 2.58 (1H, t, J=2.52 Hz, ring CH), 2.72 (1H, quintet, J=7.5 Hz, ring CH), 4.16 (1H, q, J=6.6 Hz and 1.2 Hz, HCOH), 5.30 (1H, dd, J=16 Hz and 7 Hz, C=CH), 5.62 (1H, dd, J=16 Hz and 1.2 Hz, HC=C), IR (film) 3430, 1740, 900 cm^{-1}; mass spectrum, m/e 182, 164, 110, 95.

Synthesis of compound 8 using vinylmercurial 2

The above procedure was employed (13% yield); ^{1}H NMR ($DCCl_3$) δ 0.0 (6H, s, $SiMe_2$), 0.9 (9H, s, t-Bu), 1.05 (3H, d, J=6 Hz, CH_3), 1.3-1.6 (m, 4H, CH_2's), 2.0-2.63 (m, 6H, ring CH_2's, CH_2C=C), 3.5-4.16 (m, 2H, CHOSi and CHOH), 5.12-5.67 (m, 2H, vinyl); IR (neat) 3420, 2960, 2920, 2860, 1740 cm^{-1}; mass spectrum, m/e 269.15712 (calcd for $C_{18}H_{34}O_3Si$ (M^+-57) 269.15730).

Synthesis of cyclopent-3-en-1-ol[77]

To a solution of freshly distilled cyclopentadiene (45 g, .68 mol) in ether was added 200 ml of a 1M solution of BH_3•THF (0.2 mol). The reaction mixture was stirred at 0°C for 2 h. The solvent and excess cyclopentadiene were removed under vacuum. The residue was redissolved in ether. Sodium hydroxide (66 ml, 3M NaOH) and hydrogen peroxide (66 ml, 30%) were added dropwise at 0°C. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were dried over anhydrous $MgSO_4$. The ether was distilled at atmospheric pressure and the residue was distilled at 30 mm (bp 60-62°C) to give the title compound in 25% yield: ^{1}H NMR

($DCCl_3$) δ 2.21-2.63 (m, 4H, CH_2's), 3.00-3.33 (m, 1H, OH), 4.14-4.64 (m, 1H, C<u>H</u>OH), 5.66 (s, 2H, ring olefinic protons).

<u>Synthesis of O-tetrahydropyranylcyclopent-3-en-1-ol</u>

Cyclopent-3-en-1-ol (2.0 g, 24 mmol) was stirred at room temperature overnight with dihydropyran (8.13 g, 95 mmol) and p-toluenesulfonic acid (10 mg). Potassium carbonate was added and the reaction mixture was filtered and evaporated. The residue was distilled from potassium carbonate at reduced pressure to afford a 95% yield of the title compound. ^1H NMR ($DCCl_3$) δ 1.33-1.79 (m, 6H, CH_2's in THP ring), 2.33-2.67 (m, 4H, CH_2's in cyclopentene ring), 3.3-4.0 (m, 2H, OCH_2), 4.33-4.67 (m, 2H, OC<u>H</u>O and C<u>H</u>OTHP), 5.67 (s, 2H, ring olefinic protons); IR 3060, 2940, 2860, 1610(w) cm^{-1}; mass spectrum, m/e 168.1152 (calcd for $C_{10}H_{16}O_2$ 168.11503).

<u>Synthesis of O-acetylcyclopent-3-en-1-ol</u>

Cyclopent-3-en-1-ol (0.420 g, 5 mmol) was dissolved in 3 ml of pyridine and 3 ml of acetic anhydride and stirred at room temperature for 18 h. The reaction mixture was poured into cold water and extracted twice with ether. The ether layer was washed with dil. NaOH, dil. H_2SO_4, water and brine successively and then dried over $MgSO_4$ and evaporated. Purification by column chromatography gave 0.570 g (90%) of the title compound: ^1H NMR ($DCCl_3$) δ 2.0 (s, 3H, O_2CCH_3), 2.33-2.67 (m, 4H, CH_2's), 5.12-5.48 (m, 1H, C<u>H</u>OAc), 5.67 (s, 2H, ring olefinic protons).

Synthesis of O-methoxyethoxymethyl cyclopent-3-en-1-ol

This compound was prepared using a general published procedure.[78] Cyclopent-3-en-1-ol (5 mmol, 0.420 g) was dissolved in methylene chloride. Methoxyethoxymethyl chloride (0.93 g, 7.5 mmol) and diisopropylethylamine (1.3 ml, 7.5 mmol) were added and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with methylene chloride. It was dried over anhydrous $MgSO_4$ and evaporated. Purification by column chromatography gave 0.77 g (90%) of the title compound: ^1H NMR ($DCCl_3$) δ 2.33-2.67 (m, 4H, ring CH_2's), 3.33 (s, 3H, OCH_3), 3.39-3.82 (m, 4H, OCH_2CH_2O), 4.33-4.60 (m, 1H, -CHO-), 4.70 (s, 2H, OCH_2O), 5.67 (s, 2H, ring olefinic protons); IR 3060, 1610 cm^{-1}.

Synthesis of O-methylthiomethyl cyclopent-3-en-1-ol

This compound was prepared using the published general procedure.[79] Cyclopent-3-en-1-ol (0.420 g, 5 mmol) and chloromethyl methyl sulfide (0.5 ml, 6 mmol) in dry benzene (2.5 ml) was added to a stirred mixture of silver nitrate (0.94 g, 5.5 mmol), triethylamine (0.84 ml, 6 mmol) and dry benzene (2.5 ml), and the mixture was then heated at 60°C. After 12 h, the reaction mixture was filtered through a dry Celite column. The filtrate was washed successively with 3% aqueous phosphoric acid, saturated $NaHCO_3$ and water, dried, concentrated and purified by column chromatography to give 0.360 g (50%) of the title compound: ^1H NMR ($DCCl_3$) δ 2.06 (s, 3H, SMe),

4.33-4.67 (s and m, 3H, OCH_2S and CHO), 5.67 (s, 2H, ring olefinic protons).

Synthesis of O-tetrahydropyranyl-4-[E-6-tert-butyldimethylsiloxy-1-heptenyl]cyclopent-2-en-1-ol

Palladium trifluoroacetate (0.664 g, 2 mmol) was stirred in 15 ml of dry methylene chloride for 10 min. The suspension was cooled to -78°C. O-Tetrahydropyranyl cyclopent-3-en-1-ol (0.504 g, 3 mmol) and vinylmercurial 2 (0.924 g, 2 mmol) were added as a solution in methylene chloride, followed by two equivalents of MgO. The reaction mixture was allowed to warm up to room temperature and stirred for 20 h. The reaction mixture was filtered through Celite and washed with ether. The organic layer was washed with saturated NH_4Cl and water, dried over $MgSO_4$ and evaporated. Purification by column chromatography provided 0.170 g of the title compound (22% yield); ^1H NMR ($DCCl_3$) δ 0.0 (s, 6H, $SiMe_2$), 0.77 (s, 9H, t-Bu), 1.0 (d, 3H, J=6 Hz, CH_3CH), 1.15-1.67 (m, 12H), 1.67-2.0 (m, 2H, $CH_2C=C$), 3.33-4.0 (m, 4H, $-OCH_2$, SiOCH and doubly allylic H), 4.39-4.77 (m, 2H, -CHOTHP and OCHO), 5.09-5.42 (m, 2H, sidechain vinyl), 5.66-5.79 (m, 2H, ring olefinic protons); mass spectrum, m/e 309.22536 (calcd. for $C_{18}H_{33}O_2Si$ (M^+-85) 309.22499).

Synthesis of O-methoxyethoxymethyl-4-[E-6-tert-butyldimethylsiloxy-1-heptenyl]-cyclopent-2-en-1-ol

The same procedure as above was employed (20% yield): ^1H NMR ($DCCl_3$) δ 0.0 (s, 6H, $SiMe_2$), 0.77 (s, 9H, t-Bu), 1.0 (d, 3H, J=6 Hz, CH_3CH), 1.15-1.35 (m, 4H, CH_2's on vinyl side chain), 1.67-2.0 (m, 2H,

$CH_2C{=}C$), 3.33 (s, 3H, OCH_3) 3.39-3.76 (m, 4H, OCH_2CH_2O), 4.42-4.76 (m and s, OCH_2O and CHOMEM), 5.12-5.39 (m, 2H, sidechain vinyl), 5.67-5.79 (m, 2H, ring olefinic protons); mass spectrum, m/e 309 (M^+-89), 292, 235, 160, 133, 118.

Preparation of cyclopentadiene monoepoxide[80]

To an ice-cold, mechanically stirred mixture of 45 g (0.68 mole) of freshly cracked cyclopentadiene and 290 g of powdered, anhydrous sodium carbonate in 750 ml of methylene chloride was added dropwise 144 g (0.67 mole) of 35% peracetic acid which had been pre-treated with a small amount of sodium acetate. The mixture was stirred at room temperature for 2 h. The solid salts were removed by filtration and washed well with additional solvent. The solvent was removed by distillation and the residue was distilled under reduced pressure along with some methylene chloride. This was redistilled under reduced pressure to give 9.0 g (16%) of 3,4-epoxy-cyclopentene: bp 39-41°C (46 mm); ^1H NMR ($DCCl_3$) δ 2.4 (m, 2H, CH_2), 3.7 (m, 2H, CH-CH), 6.0 (m, 2H, ring olefinic protons); IR 3075, 2925, 1680, 910 830, 810 cm^{-1}; mass spectrum, m/e 82 (M^+), 54, 39.

Synthesis of 1-trimethylsilyl-6-t-butyldimethylsiloxyhept-1-yne

This compound was prepared according to the published general procedure.[68] A solution of the acetylene, 6-t-butyldimethyl-siloxyhept-1-yne (10.62 g, 47 mmol) in 15 ml of ether was treated consecutively at -70°C with a solution of n-butyllithium (2.35 M in hexane, 20.61 ml) and trimethylchlorosilane (5.4 g, 47 mmol, 6.31 ml). The reaction mixture was allowed to warm up to room temperature

where it was stirred for 2 hour and then quenched in ice water. The layers were separated, and the aqueous layer was extracted with n-pentane. The combined pentane extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Distillation of the residue gave 10.64 g (76%) of the product: ^1H NMR ($CDCl_3$ without TMS) δ 0.0 (s, 9H, $SiMe_3$), 0.09 (s, 6H, $SiMe_2$), 0.82 (s, 9H, t-Bu), 1.1 (d, 3H, J=6 Hz, CH_3), 1.33-1.67 (m, 4H, CH_2's), 2.0-2.33 (m, 2H, $CH_2C{\equiv}C$), 3.66-4.0 (m, 1H, CHOSi); IR (neat) 2185, 1251, 843 cm^{-1}.

Synthesis of trans-1-iodo-6-t-butyldimethylsiloxyhept-1-ene

This compound was prepared according to the published general procedure.[68] Into a dry three necked flask equipped with a condenser and nitrogen inlet was placed 10.64 g of the above alkynylsilane (35.7 mmol). Diisobutylaluminum hydride (1M in ether, 72 ml) was added at 0°C for 15 min. Then the mixture was heated at 40°C for 5 h. The reaction mixture was cooled to -78°C, and was treated with a solution of iodine (16.5 g, 65 mmol) in ether at such a rate as to maintain the temperature below -75°C. The resulting brown reaction mixture was stirred for 1 hour at -70°C and then allowed to warm to 0°C. After stirring for an additional 15 min at 0°C, the yellow reaction mixture was slowly poured into a stirred mixture of 10% hydrochloric acid and ice. The mixture was then extracted with pentane. The combined organic extracts were washed successively with aqueous 1N sodium hydroxide, 1M sodium thiosulfate and brine, dried and concentrated. The residue was diluted with methanol and added to a solution of sodium methoxide (100 mmol, 4 equiv) in methanol. The resultant

ammonium chloride solution and the resulting inorganic salts were removed by filtration through Celite. The organic phase was separated, washed with brine and dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo gave a light brown oil which was purified by flash column chromatography (1:1 hexane: ether): yield 20%; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.0 (s, 6H, $SiMe_2$), 0.82-0.84, (s, 9H, t-Bu), 1.03-1.08 (d, 3H, J=6 Hz, CH_3), 1.26-1.40 (m, 4H, CH_2's on vinyl side chain), 1.78-1.99 (m, 4H, ring CH_2 and $CH_2C=C$), 3.37-3.49 (m, 1H, double allylic), 3.67-3.81 (m, 1H, CHOSi), 4.79-4.87 (m, 1H, H α to OH), 5.12-5.24 (m, 1H), 5.31-5.44 (m, 1H) 5.78-5.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 139.1, 132.98, 129.93, 114.5, 68.47, 47.08, 41.29, 39.08, 32.32, 25.88, 25.42, 24.97, 23.73, 23.47, 18.07, -4.42, -4.68; IR (neat) 3350, 2960, 2920, 2860, 1640, 1620(w), 1250, 830 cm^{-1}; mass spectrum, m/e 292.22263 (calcd for $C_{18}H_{32}OSi$ (M^+-18) 292.22225).

Synthesis of 4-(E-6-t-butyldimethylsiloxy-1-heptenyl]cyclopent-2-en-1-one

Collins reagent (CrO_3. 2Py) [0.670 g, 2.6 mmol] was dissolved in 25 ml of CH_2Cl_2 and cooled to 0°C. The allylic alcohol prepared above (0.080 g, 0.26 mmol) was added and the solution warmed to room temperature and stirred for 2 h. The solution was decanted and evaporated. The residue was taken up in ether, washed with sodium bicarbonate and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification by flash column chromatography provided 40 mg of the unsaturated ketone (50%): ^{1}NMR ($CDCl_3$) δ 0.0 (s, 6H, $SiMe_2$), 0.9 (s, 9H, t-Bu), 1.1 (d, 3H, J=6 Hz, $CHCH_3$), 1.20-1.67 (m,

4H, CH_2's), 2.0-2.67 (m, 4H, ring CH_2 and $CH_2C{=}C$), 3.33-4.0 (m, 2H, double allylic H and -CHOSi), 5.15-5.48 (m, 2H, vinyl), 6.12 (dd, 1H, J=6 Hz, 1 Hz), 7.45 (dd, J=6 Hz, 1 Hz); mass spectrum, m/e 307.21020 (calcd for $C_{18}H_{31}O_2Si(M^+-H)$ 307.20934). ^{13}C NMR ($CDCl_3$) δ 209.46, 166.93, 133.64, 132.46, 129.80, 68.4, 44.15, 41.6, 39.7, 39.3, 25.9, 23.8, 18.1, 15.28, -4.29, -4.61.

Synthesis of 6-(tert-butyldimethylsilyloxy)-1-(tri-n-butylstannyl)-1-heptene 18

The title compound was prepared according to the published procedure.[62] 6-t-Butyldimethylsiloxy-1-heptyne (6.60 g, 29 mmol) was heated at 95°C with tributyltin hydride (8.85 g, 30.5 mmol) and 40 mg of azobisisobutyronitrile (AIBN) for 2 h. An additional 50 mg of tributyltin hydride and 10 mg of AIBN were then added, and the mixture was heated for 3 h at 100°C, after which another 15 mg of tributyltin hydride and 10 mg of AIBN were added, followed by heating at 130°C for 2 h. Direct distillation afforded 11.0 g (75%) of the product; bp 130-140°C (0.02 torr); IR 1600, 1260, 840, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6H, $SiMe_2$), 0.85 (s, 9H, t-Bu), 1.1 (d, J=7 Hz, 3H), 0.7-2.2 (m, 33H), 3.7-3.9 (m, 1H, CHOSi), 5.85-6.0 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 149.6 and 149.1 (C-2), 127.2 and 127.8 (C-1).

Reaction of the vinylcuprate derived from compound 18 with cyclopentadiene monoepoxide

A general literature procedure was used.[62] Vinylstannane 18 (5.12 g, 10 mmol) was added to n-butyllithium (8.5 mmol, 4.4 ml of 1.95 M in hexane) in 11 ml of tetrahydrofuran at -78°C (dry ice-

isopropanol). The solution was allowed to warm to 0°C and was stirred for 50 min at this temperature. After being cooled to -100°C (pentane-liquid N_2), this solution was added to a solution of 1.30 g (10 mmol) of pentynyl copper and 3.66 ml (20 mmol) of tris(dimethylamino)phosphine in 14 ml of THF, also at -100°C. After being stirred for 1.5 h at -100°C, the resultant cuprate was treated at -100°C with 1.0 g (12 mmol) of cyclopentadiene monoepoxide. The resultant mixture was stirred for 2 h at -100°C and 4 h at -60°C, and then a saturated aqueous ammonium chloride solution was added, and the mixture was poured into ether-aqueous ammonium chloride containing a few drops of ammonium hydroxide. After this mixture was stirred for 1 hour, the ether layer was separated and the aqueous layer was extracted with ether. The ether layer was dried over $MgSO_4$ and concentrated. TLC analysis showed only a faster running product and none of the desired compound.

The above reaction was repeated using cuprous cyanide in tetrahydrofuran and ether as solvents.

Reaction of cyclopent-2-en-1-one with 2-methoxyfuran

A general published procedure was employed.[64] Cyclopent-2-en-1-one (0.440 g, 5 mmol) was dissolved in 15 ml of CH_2Cl_2 and cooled to -78°C under nitrogen. Trimethylsilyl iodide (1.10 g, 1.1 equiv) was added and the solution stirred at -78°C for 1 hour. 2-Methoxyfuran (0.490 g, 5 mmol) and 2-methyl-2-butene (1 ml) were added sequentially and the reaction mixture stirred at -78°C for 3 h. $(Me_3Si)_2NH$ was added at -78°C and the solution warmed up to room temperature. Hexane

was added and the reaction mixture was filtered through Celite and concentrated. Purification by column chromatography (1:1 hexane: EtOAc) provided 0.400 g of the product, 34% yield: ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H, t-Bu), 2.0-2.33 (m, 4H, ring CH_2's) 2.67-3.0 (m, 1H, ring CH), 4.33-4.39 (br s, 1H, HC=COTMS), 4.67-4.96 (m, 1H, -CHO-), 5.96-6.06 (dd, J=6 Hz and J=2 Hz, 1H), 7.24-7.36 (dd, J=6 Hz and J=1 Hz); mass spectrum, m/e 238, 155, 73.

Preparation of γ-Butenolide

The compound was prepared using the literature procedure.[81] In a 250 ml three necked flask fitted with a reflux condenser and a dropping funnel was placed a solution of 41.5 g of α-bromo γ-butyrolactone and 100 ml of dry ether. Triethylamine (35 ml) was added dropwise while the solution was heated to reflux, with stirring. The stirring under reflux was continued for 24 h. The brown precipitate was removed by filtration. The solvent was evaporated and distillation of the residue provided 6.0 g (50%) of the lactone: bp 107-109°C (24 mm Hg); ^{1}H NMR ($DCCl_3$) δ 4.97 (t, 2H), 6.15 (dt, 1H), 7.85 (dt, 1H).

Synthesis of 2-trimethylsiloxyfuran

The compound was prepared using literature procedure.[71] Diethyl trimethylsilylamine (2.90 g, 20 mmol) was dissolved in 4 ml of ether and cooled to 0°C. Under a nitrogen atmosphere, a solution of γ-butenolide (1.70 g, 20 mmol) was added dropwise and the solution was then warmed to room temperature and stirred for 24 h. Ether was distilled off first and the product was distilled under reduced

pressure: 1.40 g (45%); bp 28-29°C (9-10 mm Hg); ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H), 4.97 (m, 1H), 6.0 (m, 1H), 6.65 (m, 1H).

Reaction of cyclopent-2-en-1-one with 2-trimethylsiloxyfuran

A general published procedure was employed.[71] To a cooled (-78°C) solution of 3 mmol of 2-trimethylsiloxyfuran and cyclopent-2-en-1-one (3 mmol) in dry CH_2Cl_2 (5 ml) under an argon atmosphere and magnetic stirring was rapidly added tin tetrachloride (3 mmol) and the reaction mixture stirred for 2 h. Hydrolytic work up with 0.1 N HCl, followed by evaporation of the organic layer, afforded the crude product in 95% yield, which by GC-MS analysis showed a 85:15 ratio of the product 19 and the product resulting from the addition of 2-trimethylsiloxyfuran to 19. Mass spectrum, m/e 166 (M^+) 138, 124, 110, 83, 55.

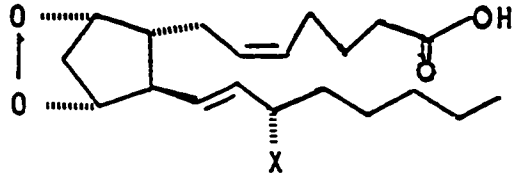
CHAPTER IV. ORGANOPALLADIUM APPROACHES TO PROSTAGLANDIN ENDOPEROXIDE ANALOGUES

General Introduction

The prostaglandins are a class of C-20 unsaturated hydroxy acids. Their wide range of biological activity includes involvement in such physiological processes as smooth muscle contraction, blood platelet aggregation, chemotaxis and inflammation. It is thought that they may have pharmacological use in the treatment of thrombosis, asthma, ulcers, hypertension and inflammation.[82,83] They are also potentially useful in the termination of pregnancy, induction of labor and contraception.[84]

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.[85-87]

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.[88] However, it was not until 1973 that Samuelsson

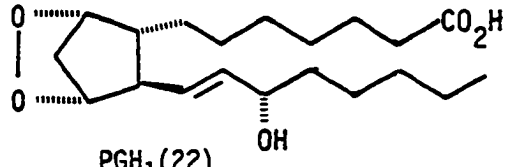


20 x =OH

21 x = OOH

actually isolated the endoperoxide PGH_2 (20).[89] Later studies showed that PGH_2 and PGG_2 (21) were intermediates in the biosynthesis of $PGF_{2\alpha}$, PGE_2 and the thromboxanes, as shown in Scheme 4.[90,91] 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 min.[90]

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 endoperoxide analogue [of PGH_1 (22), at that time a proposed biosynthetic intermediate] was synthesized in 1971, it was not until 1975 that substantial progress

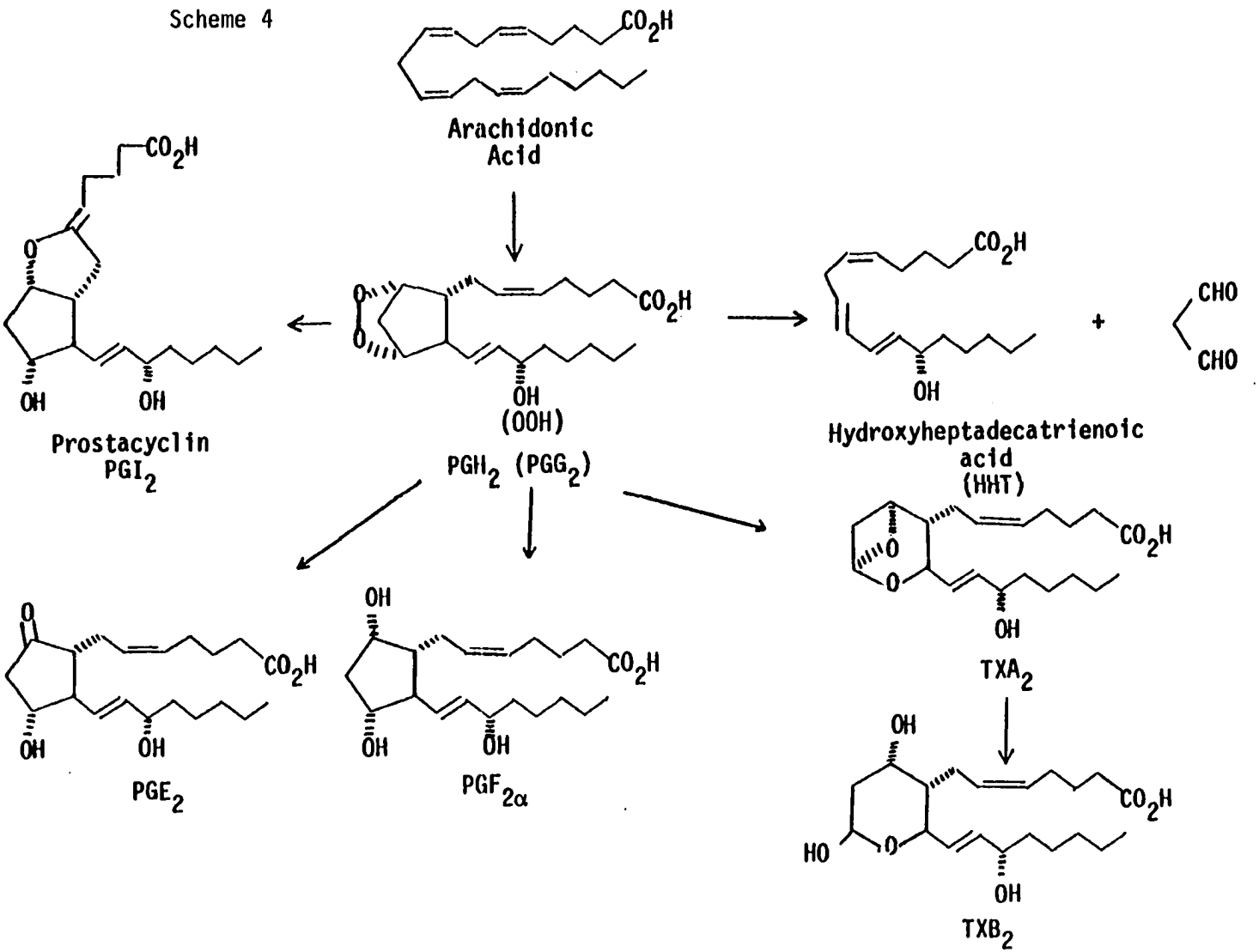


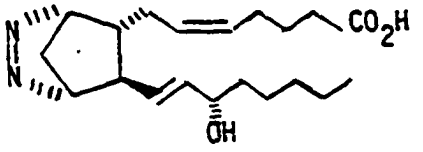
PGH_1(22)

towards this goal was reported. Since then there have been over thirty analogues synthesized. The structures of some of these analogues are shown below, and the pertinent references are given in the parentheses.

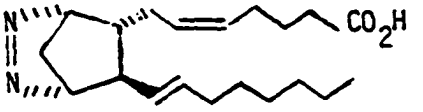
As can be seen from the structures, a wide variety of skeletons has been employed. Among the most common groups substituted for the 9,11-endoperoxide linkage are various heteroatoms, an ethylene bridge and an ethano bridge. A variety of stereochemistries of the

Scheme 4

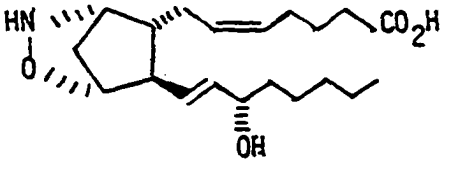

Arachidonic Acid
Prostacyclin PGI2
PGH2 (PGG2)
(OOH)
Hydroxyheptadecatrienoic acid (HHT)
PGE2
PGF2α
TXA2
TXB2



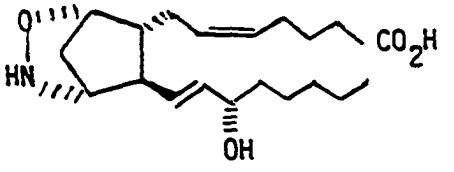
23 (92)



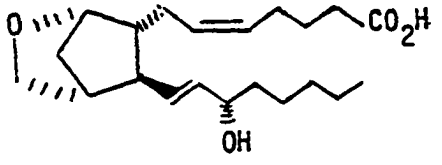
24 (93)



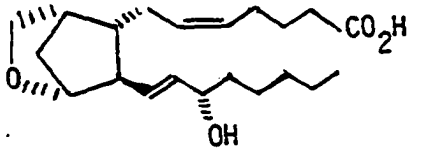
25 (94)



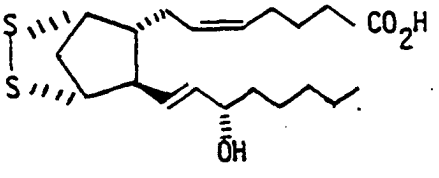
26 (94)



27 (95-97)



28 (95, 98)



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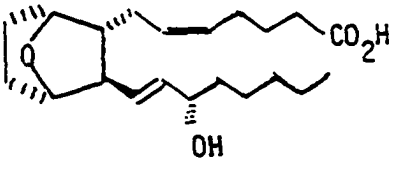

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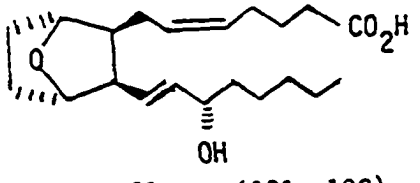
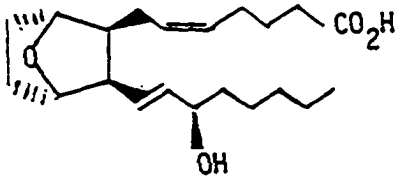
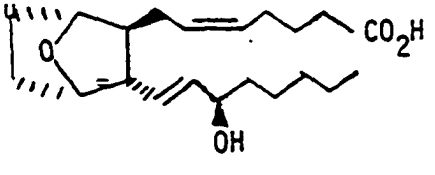


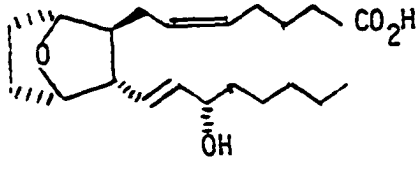
31 (101, 102)



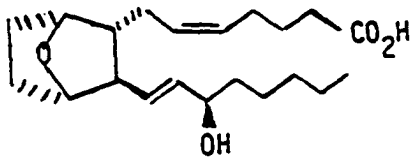
32 (101)



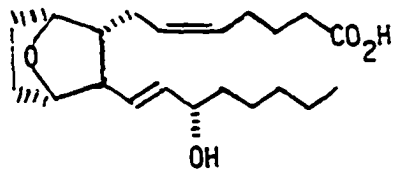
33 (102)



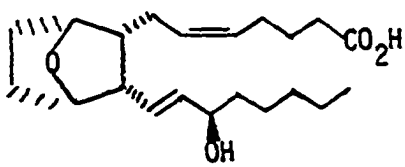
34 (102)



35 (102)



36 (102)



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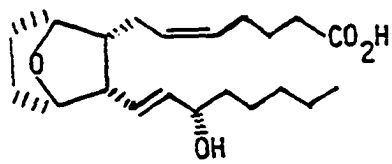

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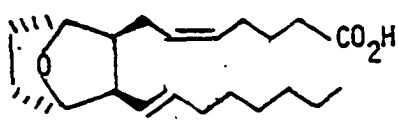
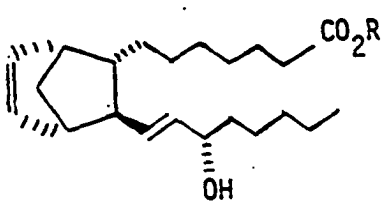
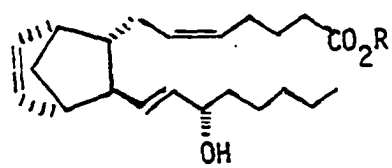


39 (103)

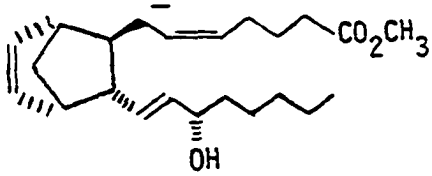
40 (103)



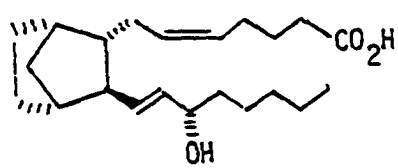
41 a : R=CH_3 (104-106)
b : R=H



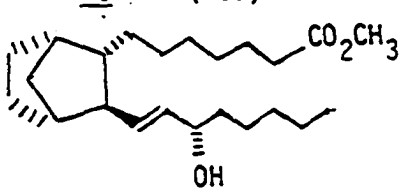
42 a : R=H (107-109)
b : R=CH_3



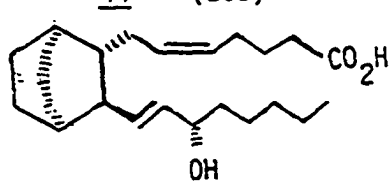
43 (109)



44 (108)



45 (105)



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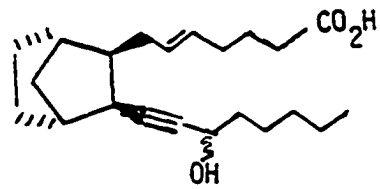
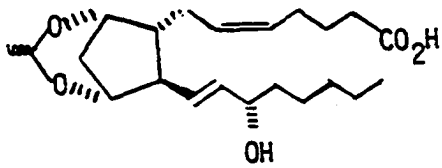
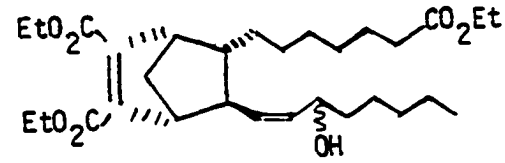


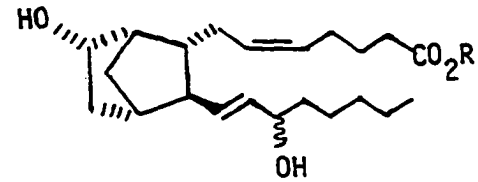
47 (111)



49 (113)



48 (112)



50 a : R=H
b : R=CH_3 (114)

substituents on the bicyclo[2.2.1]heptane ring have also been produced. Most of these isomers possess substantial activity.

While a discussion of the synthesis of each of these compounds is beyond the scope of this thesis, several general comments about the synthetic routes employed can be made. The syntheses of these analogues can be divided into two different basic approaches. Compounds 23-28 and 49 were synthesized by modifying natural prostaglandins. Generally PGA_2 or $PGF_{2\alpha}$, hardly readily available compounds, were used as starting materials. 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 dienophile gives substantial amounts (sometimes up to 40% as in the synthesis 41b) 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 these general approaches to the analogues studied to date.

The prostaglandin endoperoxide analogues synthesized so far exhibit a variety of biological 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.

The objective of this research was to apply the reactions of organopalladium intermediates towards the synthesis of bicyclic

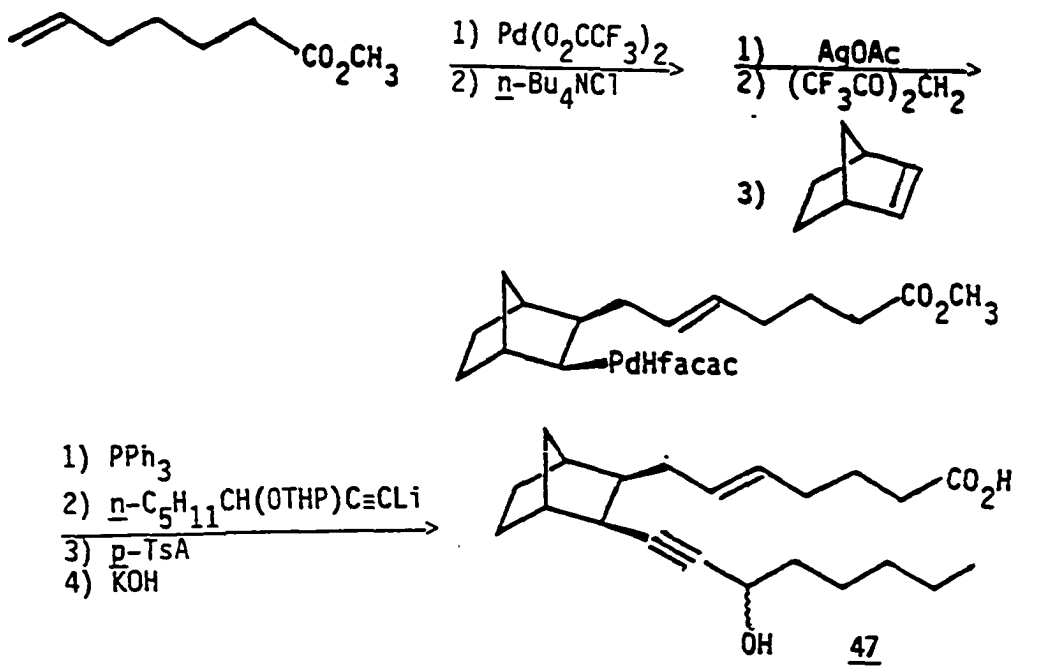
prostaglandin analogues. The first part of this chapter describes the synthesis of an ethano-bridged prostaglandin endoperoxide analogue using the reaction of a π-allylpalladium compound with a strained olefin, namely norbornene and the possible extension of this procedure to other analogues. The second part of this chapter details our efforts to synthesize an etheno-bridged prostaglandin endoperoxide analogue using the reaction of an appropriate soft carbanion with norbornadiene-palladium dichloride complex.

Synthesis of an Ethano-Bridged Prostaglandin Endoperoxide Analogue

Introduction

An initial approach to bicyclic prostaglandin analogues using the addition of π-allylpalladium compounds to bicyclic olefins was reported by Larock and co-workers[111] (Scheme 5). Using this approach, a number of analogues have been synthesized. Several of them,

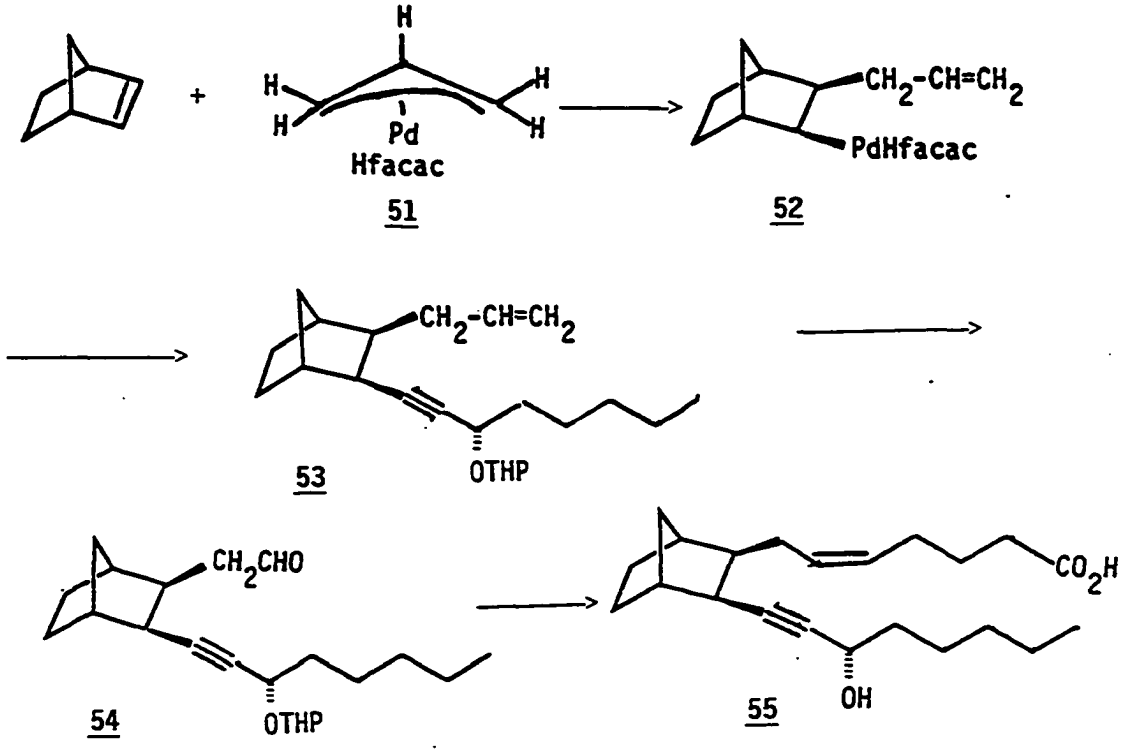
Scheme 5



in particular compound 47, 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 there are no cis-σ-allylpalladium compounds known in acyclic cases, we looked for an indirect way to introduce this cis double bond. The approach of introducing an acetaldehyde unit onto the bicyclic skeleton was particularly appealing since subsequent Wittig reaction of the aldehyde should afford the carboxylic acid side chain with cis C-5 carbon-carbon double bond. Scheme 6 depicts the strategy in this direction. Readily available π-allylpalladium

Scheme 6

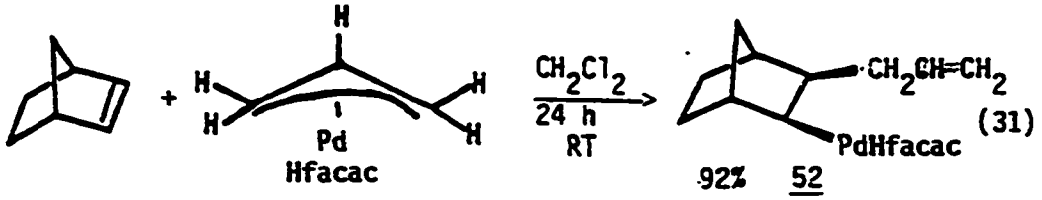


compound 51 appeared to be the compound of choice for the addition to norbornene, since it has the acetaldehyde unit as a masked functional group. Since the addition of 51 to norbornene to give the adduct 52·

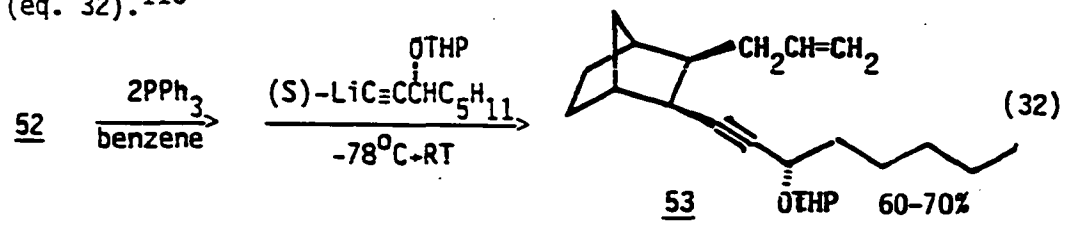
and subsequent displacement of palladium with a lithium acetylide unit have already been established,[111] if one could selectively transform the allyl group in 53 to the acetaldehyde moiety, subsequent Wittig reaction should afford the target molecule 55.

Results and Discussion

First, compound 52 was prepared by the reaction of norbornene with compound 51, using the standard literature procedure (eq. 31).[111,115] Then compound 53 was prepared by the reaction of

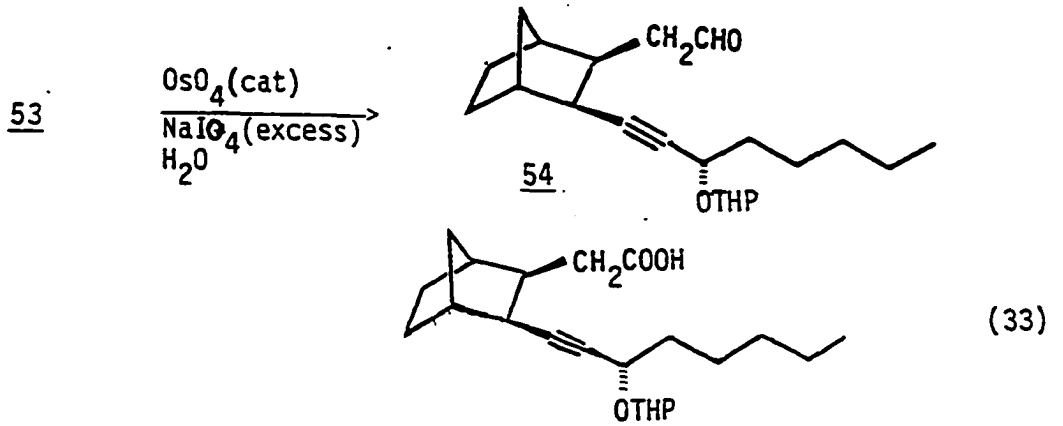


compound 52 with the optically active lithium acetylide of S(-) 3-tetrahydropyranyloxy-1-octyne (56) using the established procedure (eq. 32).[115]



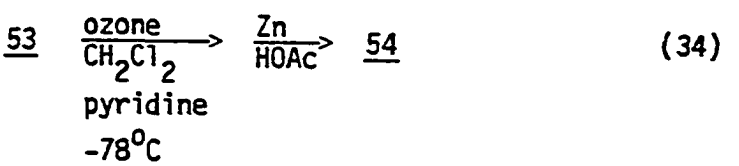
Next, we looked for a selective method to oxidize the double bond of compound 53 to generate aldehyde 54. First we tried the oxidation using catalytic osmium tetroxide in the presence of excess sodium metaperiodate[116] (eq. 33). Unfortunately, under various reaction conditions, viz, different catalytic amounts of OsO_4 (1-4%), varying reaction times (1.5 h-overnight) and different amounts of sodium

periodate (100 to 200%), we were only able to obtain a mixture of the desired compound 54 and significant amounts of the corresponding acid. Hence, we searched for a different oxidation method. Since



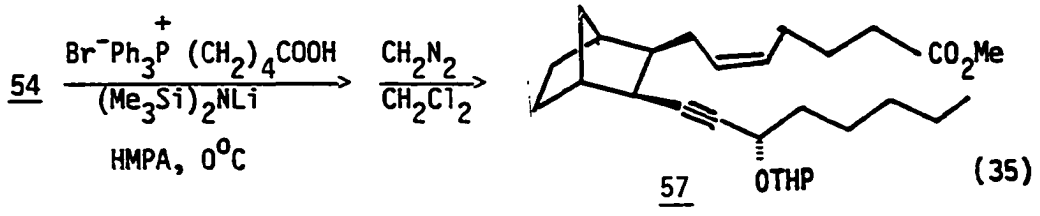
(33)

acetylenes were known to be slow to undergo ozonolysis[117] and selective ozonolysis of the olefinic bond in the presence of an acetylenic bond has been accomplished,[118] we decided to try this method. Accordingly, ozonolysis of compound 53 was attempted in the presence of pyridine, since pyridine was shown to moderate the reactivity of ozone[119] (eq. 34). The reaction gave the desired product 54 in 50% yield.



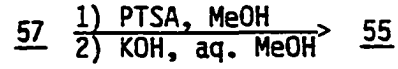
(34)

Next, we attempted the Wittig reaction on compound 54 under the conditions shown in eq. 35.[120] Compound 57 was isolated in 38% yield.



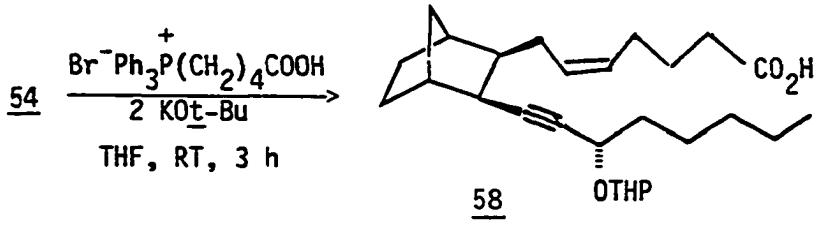
(35)

Deprotection of the tetrahydropyranyl group (85% yield) and hydrolysis of the ester (75% yield) gave the final compound 55 (eq. 36).



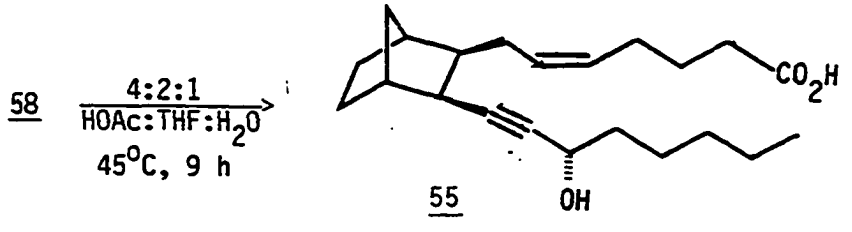
(36)

In order to improve the yield of the Wittig reaction, the reaction was done under different conditions[121] as shown in eq. 37. Compound 58 was isolated in 55% yield. Compound 58 on treatment with a 4:2:1



(37)

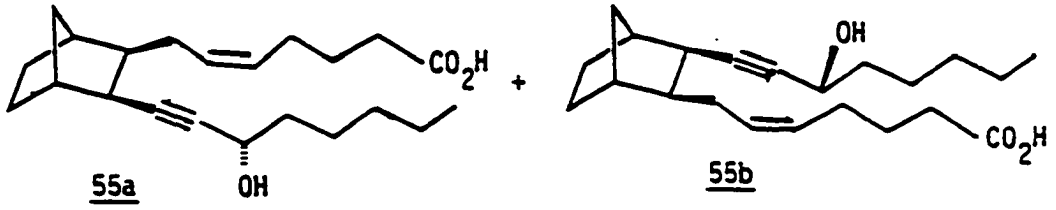
acetic acid:THF:water mixture[122] at 45°C gave compound 55 in 90% yield (eq. 38).



(38)

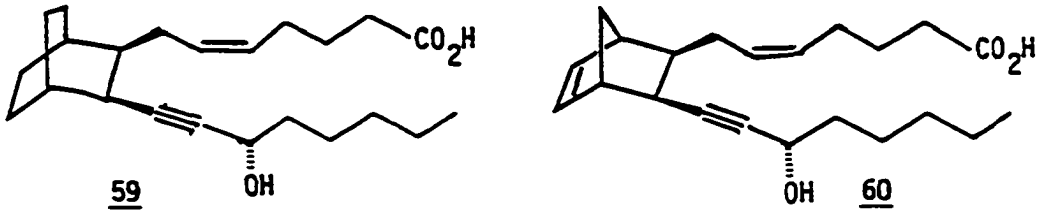
It should be noted here that compound 55 is inherently a pair of diastereomers, but they could not be separated by TLC analysis. ^{13}C

NMR analysis indicated only two extra peaks in the aliphatic region. Compound 55 is undergoing biological testing and the results are awaited.



55a 55b

It was desirable to extend this methodology to synthesize the analogues 59 and 60. Accordingly, the corresponding organopalladium



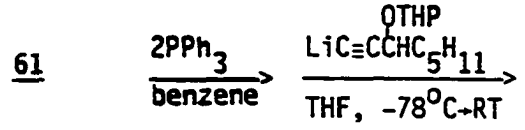
59 60

compounds were prepared using the standard procedure[115] (eqs. 39 and 40). Compounds 61 and 62 were reacted with the racemic lithium

61 (39)

62 (40)

acetylide derived from O-tetrahydropyranyl-(±)-1-octyn-3-ol, under the same conditions as used for compound 52 (eqs. 41 and 42). While compound 62 gave the expected product 65, the yield was only 33%.



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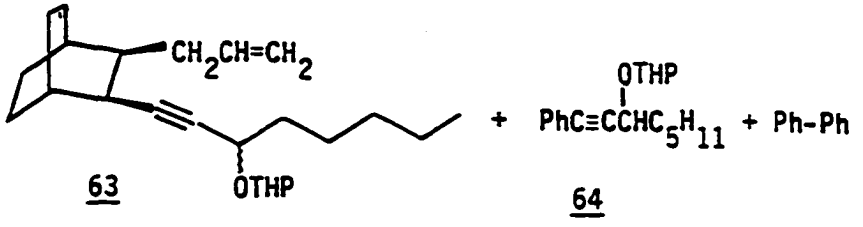
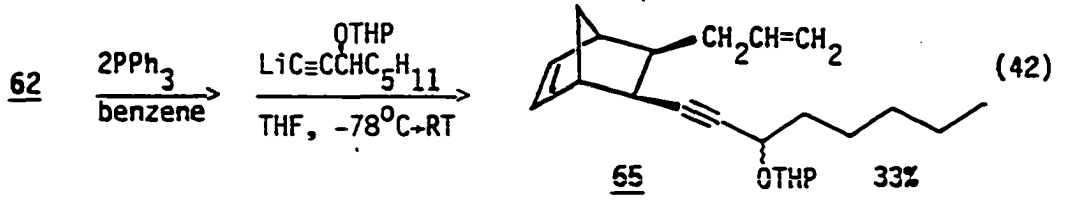
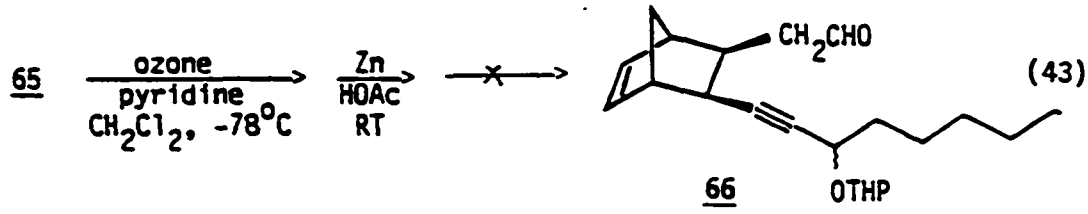




(42)

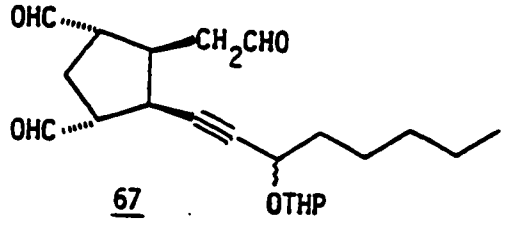
Compound 61 gave the expected product 63 along with product 64 which was the major product as shown by GC-MS analysis (63:64≅1:2). It is plausible that the unusual product 64 is formed by the reaction of a phenylpalladium intermediate with the lithium acetylide.

The ozonolysis reaction was then attempted on compound 65 to see if selective ozonolysis could be accomplished (eq. 43). After the work-up, ^{1}H NMR and IR analysis of the product showed that both the



(43)

olefinic bonds had reacted. The mass spectrum of the product showed two peaks with molecular ions (M^+) of 418, which is 42 mass units more than the anticipated side product 67. Both the proton NMR and IR analysis showed the presence of an aldehyde and ^{13}C NMR showed the



presence of at least two different aldehyde carbons. But it is not certain at this point what exactly is the structure of the product.

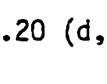
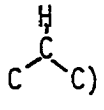
Conclusion

New methodology was developed for the synthesis of an ethano-bridged prostaglandin endoperoxide analogue, using the selective ozonolysis of a double bond in the presence of an acetylenic bond as a key step. Unfortunately, this approach could not be extended to the synthesis of the other desired analogues 59 and 60.

Experimental Section

All chemicals were used as obtained commercially unless otherwise noted. Triphenylphosphine was recrystallized from ethanol. Tetrahydrofuran was distilled from lithium aluminum hydride. π-Allylpalladium chloride was prepared according to the literature procedure.[123] S-(-)-1-Octyn-3-ol was kindly provided by Dr. Fumihiko Kondo. 3-Tetrahydropyranyloxy-S-(-)-1-octyne was prepared from the alcohol using standard literature procedure.[124]

The synthesis of compound 52

π-Allylpalladium chloride dimer (0.910 g, 2.5 mmol) and purified silver acetate (0.880 g, 5.25 mmol) were added to chloroform (200 ml). The mixture was stirred at room temperature for 70 min and then filtered to remove the silver chloride precipitate. Hexafluoroacetylacetone (1.10 ml, 7.5 mmol) was added to the filtrate, stirred for 40 min, and the resultant solution was filtered through Celite and evaporated to dryness on a rotary evaporator. The yellow solid was freed of acetic acid by placing it under a high vacuum for 1-2 h. The yield of compound 51 was 94%: ^{1}H NMR ($CDCl_3$) δ 3.13 (d, 2H, J=12 Hz, ), 4.20 (d, 2H, J=7 Hz, ), 5.70 (overlapping tt, 1H, J=12, 7 Hz, ), 6.09 (s, 1H, Hfacac).

Norbornene (0.480 g, 5.06 mmol) and compound 51 (1.63 g, 4.6 mmol) were dissolved in methylene chloride (21 ml). The solution was

stirred at room temperature for 24 h and then chromatographed on a florisil column using methylene chloride as the eluant. Compound 52 was obtained as yellow solid after removal of methylene chloride in 92% yield: ^{1}H NMR ($CDCl_3$) δ 1.0-2.60 (m, 11H), 3.28 (dd, 1H, J=7 Hz and 2 Hz, PdCH), 4.28 (dd, 1H, J=14 Hz and 1 Hz, cis C-C=C-H), 4.39 (dd, 1H, J=8 Hz and 1 Hz, trans-C-C=C-H), 5.79 (m, 1H, C-CH=C), 5.97 (s, 1H, Hfacac).

The synthesis of compound 53[115]

Compound 52 (1.80 g, 4 mmol) was weighed into an oven-dried round bottom flask fitted with a septum and gas inlet tube. The system was flushed with nitrogen and 30 ml of freshly distilled benzene was added through a syringe, followed by triphenylphosphine (2.10 g, 8 mmol). The mixture was stirred for 5 min and the benzene was evaporated on a rotary evaporator followed by a high vacuum pump. Tetrahydrofuran (34 ml) was added by syringe and the reaction mixture was then cooled to -78°C. The lithium acetylide solution, the preparation of which is outlined below, was added using a stainless steel transfer needle. The acetylide solution was prepared as follows. 3-Tetrahydropyranyloxy-S-(-)-1-octyne (0.880 g, 4.20 mmol) and tetrahydrofuran (25 ml) were added to an oven-dried round bottom flask fitted with a septum and gas inlet tube. The system was flushed with nitrogen and cooled to -78°C. n-Butyllithium (4.70 mmol) was added with stirring, to the solution of acetylene. The reaction was stirred at -78°C for 10 min, warmed to -25°C for 20 min, and then cooled again to -78°C prior to addition to the palladium compound. After addition, the

combined reaction mixture was stirred at -78°C for 1 hour, warmed to -25°C for 3 h, and then warmed to room temperature. The reaction mixture was stirred at room temperature for 36 h. Methanol (1 ml) was added to quench the reaction and the solvent was removed on a rotary evaporator. The resultant gummy, black residue was extracted with hexane (3 x 50 ml) and the combined extracts were filtered. After removal of the solvent, the extraction process was repeated twice more and the resultant orange oil was chromatographed using benzene:ethyl acetate (19:1) as the eluant. Compound 53 was obtained in 60% yield: ^{1}H NMR ($CDCl_3$) δ 0.80-2.40 (m, 28H), 2.48 (bd, 1H, J=8 Hz, HCC≡C), 3.29-4.78 (m, 4H, CH_2O, C≡CCHO- and -OCHO-), 4.92 (d, 1H, J=9 Hz, trans-C-C=C-H), 4.96 (d, 1H, J=17 Hz, cis C-C=C-H), 5.58-6.00 (m, 1H, C-CH=C); IR (neat) 3060, 2950, 2870, 2220, 1640, 1465, 1070, 980, 910, 865, 670 cm^{-1}.

The synthesis of compound 54

The general published procedure was employed.[119] A solution of compound 53 (0.791 g, 2.3 mmol) in dry methylene chloride (23 ml) and freshly distilled pyridine (0.22 ml) was cooled to -78°C. Ozone was bubbled through the solution at approximately 1 mmol/min. After approximately 1.6 equivalents of ozone were added, the reaction was stopped and the solution was added immediately to zinc dust (1.18 g) in a round bottom flask. Glacial acetic acid (2.36 ml) was also added and the flask was warmed to room temperature by means of a water bath. After the reaction mixture was stirred for 2 h, it was filtered, diluted with hexane (25 ml) and washed three times with

water. Crushed ice was added and washing was continued with 10 ml portions of 5% sodium hydroxide and then with water. Each washing was extracted with 1:1 methylene chloride/hexane. The combined extracts were dried over sodium sulfate and concentrated. Purification by column chromatography using hexane:ethyl acetate (4:1) gave compound 54 (0.398 g) in 50% yield: ^{1}H NMR ($DCCl_3$) (300 MHz) δ 0.82-2.41 (m, 28H), 2.56-2.66 (d, 1H, J=8 Hz, CH-C≡C-), 3.45-4.05 (m, 2H, CH_2O), 4.20-4.41 (m, 1H, C≡CCHO-), 4.69.-4.94 (m, 1H, -OCHO-), 9.74-9.84 (broad s, 1H, aldehyde); IR (neat) 2940, 2860, 2710, 2220, 1715, 1440, 1430, 1100, 1060, 1010, 970, 900, 710 cm^{-1}; ^{13}C NMR ($DCCl_3$) δ 14.05, 19.54, 22.63, 25.07, 25.29, 28.17, 29.70, 30.70, 31.61, 34.16, 36.14, 38.66, 39.64, 39.75, 41.60, 44.51, 44.66, 47.61, 62.34, 65.32, 82.67, 83.69, 86.93, 95.47, 98.00, 201.91; mass spectrum, m/e 290.1879 [calcd for $C_{19}H_{26}O_3(M^+-C_4H_8)$, 290.1882].

Synthesis of compound 57

A solution of n-butyllithium (3.55 ml, 7.82 mmol, 2.20 M) in hexane was added to bis(trimethylsilyl)amine (0.908 g, 7.82 mmol) in 9 ml of dry ether at 0°C under nitrogen. The solvents were evaporated under a current of dry nitrogen and the resulting lithium bis(trimethylsilyl)amide was dissolved in 9 ml of dry HMPA. The solution was transferred into a solution of (4-carboxybutyl) triphenylphosphonium bromide (1.73 g, 3.908 mmol dried at 110°C, 0.02 torr, 6 h) in 4.3 ml of HMPA. The dark red solution of the corresponding ylide was stirred under nitrogen for 1 hour, then slowly transferred (25 min) into a cooled (0°C) solution containing the

aldehyde 54 (0.338 g, 0.977 mmol) in 4.3 ml of HMPA using a double tip needle under nitrogen pressure. After stirring at room temperature for 20 min, the solution was diluted with ether (100 ml) and ice water and was acidified to pH-2 with a 0.2 M solution of sodium bisulfate. The organic phase was dried and concentrated to give an oil which was dissolved in 10 ml of dichloromethane and 5 ml of methanol and treated with an excess of diazomethane in ether. Unreacted reagent was destroyed by silica gel and the solution was filtered and concentrated. Purification by column chromatography using hexane:ethyl acetate (2:1) gave 165 mg of compound 57 (38% yield): ^1H NMR ($CDCl_3$) (300 MHz) δ 0.8-2.60 (m, 35H), 3.45-4.00 (m, 2H, $-CH_2O-$), 3.65 (s, 3H, OCH_3), 4.40 (m, 1H, C≡CCHO-), 4.90 (m, 1H, -OCHO-), 5.15-5.45 (m, 2H, CH=CH); IR (neat) 2940, 2860, 1735, 1440, 1430, 1010, 890, 860, 800, 720 cm^{-1}; mass spectrum, m/e 444.32397 (calcd for $C_{28}H_{44}O_4$ 444.32380).

Removal of the THP group from compound 57

Compound 57 (160 mg, 0.360 mmol) and 5 mg of p-TsOH (cat. amount) in 10 ml of methanol were heated under reflux for 30 min. The reaction mixture was then cooled and the solvent was removed under vacuum. The residue was taken up in hexane and the hexane layer was washed with water and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residue was chromatographed using 1:1 hexane:ether; 110 mg of the alcohol was obtained: ^1H NMR ($CDCl_3$) (300 MHz) δ 0.8-2.60 (m, 29H), 3.65 (s, 3H, OCH_3), 4.2-4.3 (m, 1H, C≡C-CHO), 5.2-5.45 (m, 2H, HC=CH); ^{13}C NMR ($CDCl_3$) δ 13.94, 22.61,

24.95, 24.99, 26.88, 28.50, 29.99, 30.70, 31.61, 33.53, 33.87, 38.41, 39.01, 40.41, 44.88, 45.80, 51.41, 62.85, 83.89, 86.67, 128.79, 130.89, 174.02; IR ($CDCl_3$) 3440, 2940, 2860, 1720, 1440, 1425, 890, 720 cm^{-1}.

Hydrolysis of the ester group

The above hydroxy ester (110 mg, 0.306 mmol) was heated in 5 ml of methanol and 2 ml of 2N KOH for 30 min. After cooling to room temperature, methanol was removed under vacuum. The residue was taken up in ether and the organic layer was washed with 2N H_2SO_4, followed by water, and dried over sodium sulfate. After concentration, the residue was chromatographed using 1:1 hexane-ethyl acetate as the eluant. Compound 55 was obtained (79 mg; 75% yield): ^1H NMR ($CDCl_3$) (300 MHz) δ 0.8-2.60 (m, 29H), 4.40 (C≡CCHO-), 5.25-5.60 (m, 2H, CH=CH), 6.2-6.8 (b, 2H, OH and COOH); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.64, 24.37, 24.98, 26.35, 28.49, 29.92, 30.59, 31.55, 32.58, 33.78, 38.12, 38.20, 38.98, 39.99 44.73, 44.79, 45.53, 63.03, 83.08, 86.97, 128.57, 131.40, 177.64; IR (neat) 3600-2400 (acid, OH), 2940, 2860, 2220, 1710, 900, 720 cm^{-1}; mass spectrum, m/e 346.25093 (calcd for $C_{22}H_{34}O_3$ 346.25080). Anal calcd for $C_{22}H_{34}O_3$; C, 76.24; H, 9.90. Found: C, 76.47; H, 10.07. Compound 55 is inherently a pair of diastereomers, but they could not be separated by TLC and ^{13}C NMR shows only two extra peaks in the aliphatic regions.

Synthesis of compound 58

The general published procedure was employed.[121] Potassium t-butoxide (0.550 g, 4.93 mmol) was slowly added with stirring to a dry

THF solution (9 ml) of (4-carboxybutyl)triphenylphosphonium bromide (1.06 g, 2.46 mmol) under an atmosphere of nitrogen at room temperature. The deep red solution was then stirred for 15 min. To this was slowly added aldehyde 54 (0.210 g, 0.6069 mmol) in dry THF (6 ml). The solution turned chocolate brown and was stirred for 3 h. Water (50 ml) and 2N H_2SO_4 (30 ml) were then added. Extraction with diethyl ether gave an organic fraction which was again washed with 2N H_2SO_4 (2 x 20 ml) and water (3 x 20 ml) and dried. Purification by column chromatography using 1:1 hexane:ethyl acetate gave 160 mg (55%) of the title compound.

Removal of THP group from compound 58

Compound 58 was dissolved in 2.13 ml of acetic acid, 1.06 ml of THF and 0.53 ml of water (4:2:1) and heated at 45°C for 9 h.[122] The solvents were evaporated. The residue was taken up in ether and washed with water, dried over magnesium sulfate and concentrated. Column chromatography using 1:1 hexane:ethyl acetate plus a few drops of acetic acid gave 115 mg of compound 55 (90%).

Synthesis of compounds 61 and 62

The same procedure as that used for compound 52 was employed,[115] except that the reaction times for compounds 61 and 62 were 48 h and 12 h respectively. In the case of compound 62, 4 equivalents of norbornadiene were employed.

Compound 61 (75% yield): ^1H NMR ($CDCl_3$) δ 1.33-2.60 (m, 13H), 3.66-4.00 (m, 1H, ring proton adjacent to PdHfacac), 4.40-4.80 (m, 2H, $C=CH_2$), 5.66-6.0 (m, 1H, CH=C), 6.09 (s, 1H, Hfacac).

Compound 62 (50-55% yield): ^{1}H NMR ($CDCl_3$) δ 1.33-2.94 (m, 8H), 3.11-3.22 (br s, 1H), 4.18-4.53 (m, 2H, C=CH_2), 5.90-6.30 (m, 4H, CH=C, CH=CH and Hfacac).

Synthesis of compound 65

The same procedure as used for compound 53 was employed (33% yield): ^{1}H NMR ($CDCl_3$) δ 0.78-3.00 (m, 25H), 3.45-4.18 (m, 2H, -CH_2O-), 4.18-4.63 (m, 1H, C≡CCHO-), 4.63-5.24 (m, 3H, C=CH_2 and -OCHO-), 5.72-6.30 (m, 3H, HC=CH and CH=C); IR (neat) 3070, 2940, 2880, 1640, 1470, 1460, 1440, 1200, 1120, 1080, 1030, 980, 910, 815, 730, 710 cm^{-1}.

Attempted synthesis of compound 63

The same procedure as used for compound 53 was employed. GC-MS analysis of the purified reaction mixture showed compound 64 and compound 63 in the ratio of ~ 2:1.

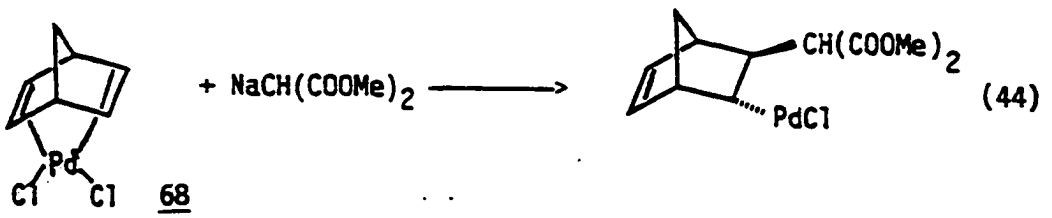
Attempted ozonolysis of compound 65

The same procedure as used for the synthesis of compound 54 was employed. But the reaction did not result in any of the desired product 66. The ^{1}H NMR, ^{13}C NMR and IR analyses showed the absence of olefinic bonds and the presence of an aldehyde. The GC-MS analysis showed two peaks with m/e of 418, which is 42 mass units more than the anticipated product 67. Hence, it is not certain at this point what exactly is the structure of this product.

Soft Carbanion Approach to an Etheno-Bridged Prostaglandin Endoperoxide Analogue

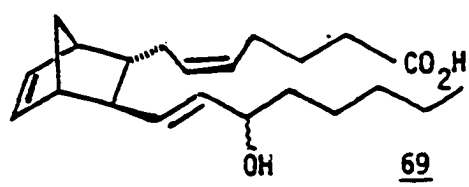
Introduction

Vedejs and co-workers reported[125] the addition of a malonate anion to norbornadiene-palladium dichloride (68) to give a trans addition compound [eq. 44]. Although not easily isolated, this



68 (44)

compound appeared to be sufficiently stable to utilize in subsequent reactions. It was envisioned that analogous use of an allylic sulfoxide anion should provide a unique approach to an etheno-bridged prostaglandin endoperoxide analogue, namely compound 69. The strategy is depicted in Scheme 7. The reaction of the anion from



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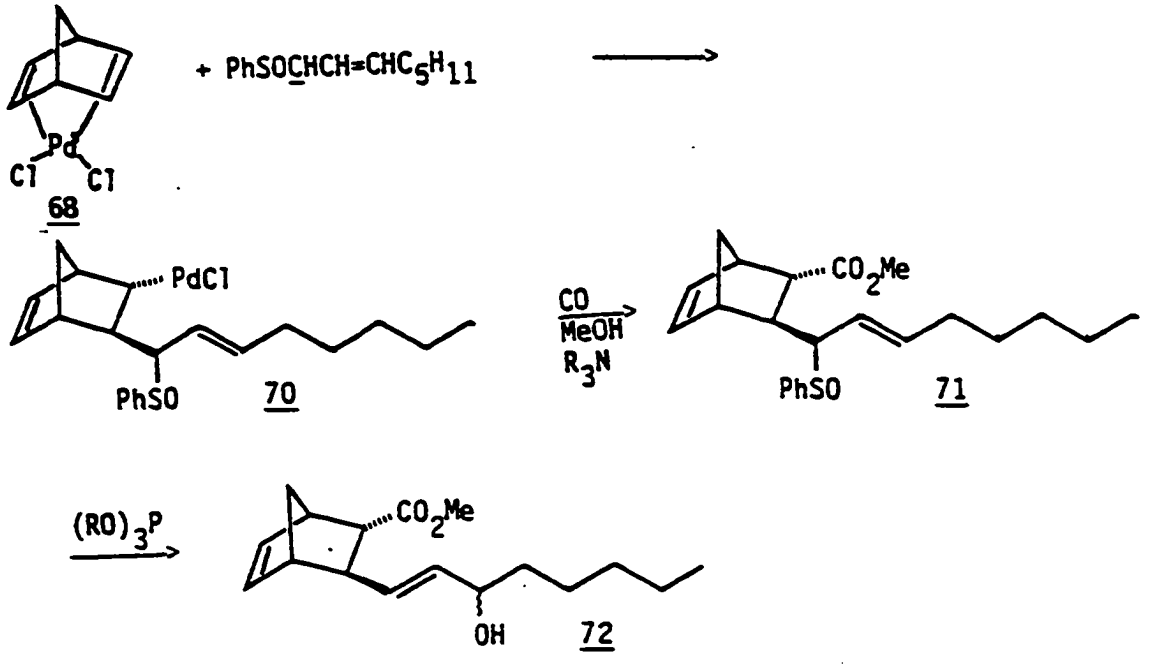
1-phenylsulfinyl-2-octene with norbornadiene-palladium dichloride should give the σ-palladium intermediate 70 which on carbonylation should provide the ester 71. Allylic sulfoxide rearrangement should give the allylic alcohol 72 which on standard transformations should lead to compound 69.

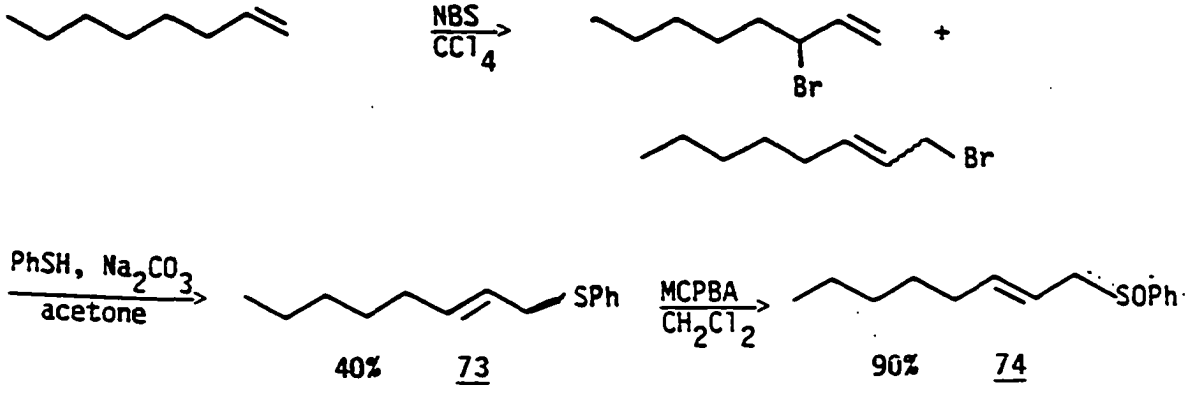
Scheme 7



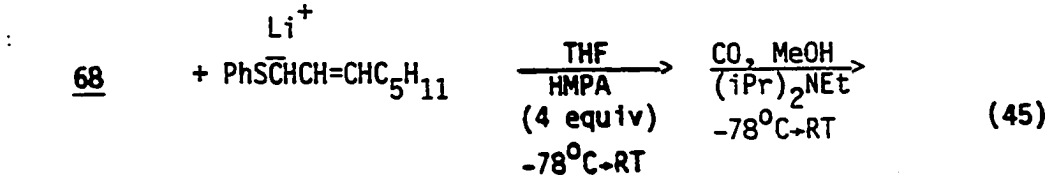
Results and Discussion

First the required allylic sulfoxide 74 was prepared according to the published procedure[126] (Scheme 8). Then, the following reaction

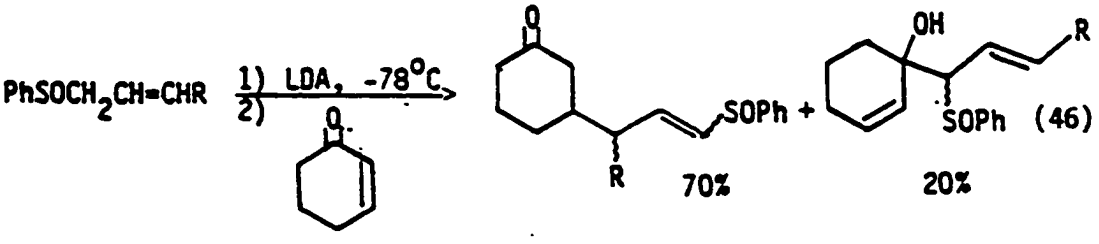
Scheme 8



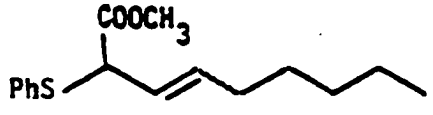
sequence was attempted (eq. 45). The anion was prepared from compound 73 for the reason that the anion from compound 74, when reacted with



cyclic enones was found to give a mixture of regioisomers whereas the former anion gave only one regioisomer (eq. 46).[126] Gas chromatographic analysis of the reaction mixture after carbonylation



showed some of the starting allylic sulfide and three other peaks. Two of the peaks had a highest fragment ion of m/e 276 and the third minor peak had a highest fragment ion m/e 260. The peaks with m/e 276 could be assigned structure 75 or its isomer 76 and the peak with m/e 260 could be the desired product 77. In order to get the desired



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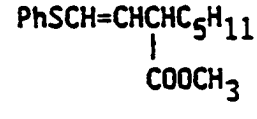

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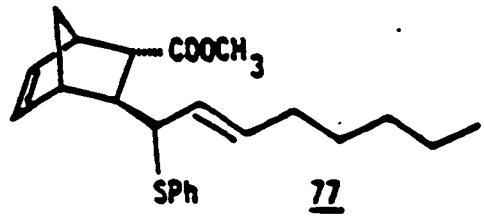
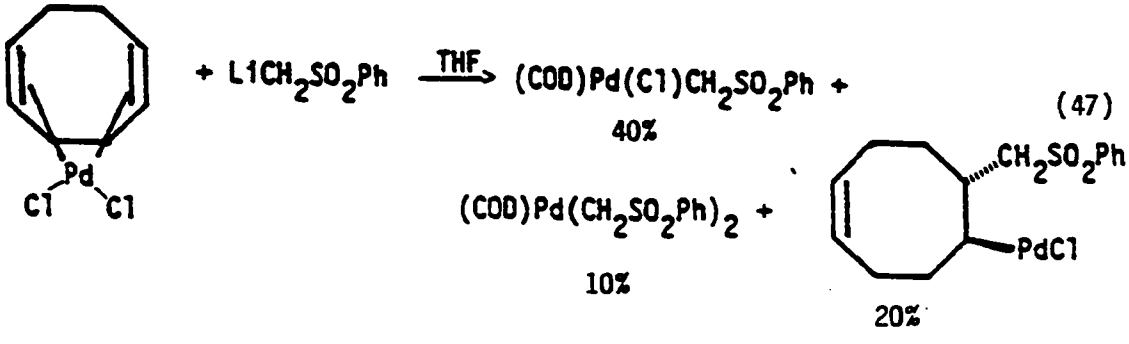


77

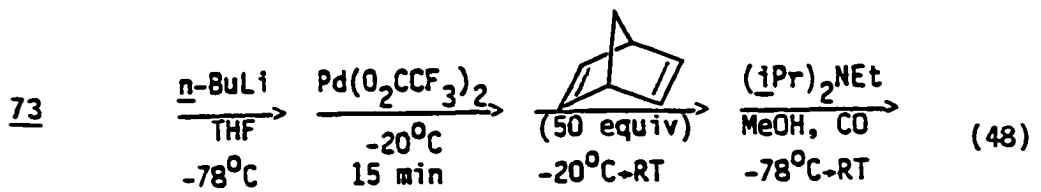
product in higher yield, different reaction conditions were tried both with compound 73 and compound 74. The reaction of the anion from compound 73 with norbornadiene-palladium dichloride was done under the following conditions: (1) THF, -78°C to room temperature for 3 h; (2) THF, -25°C for 3 h. The reactions with the anion from compound 74 were done under the following conditions: (1) THF, -78°C to room temperature for 3 h; (2) CH_3CN, -20°C to room temperature for 3 h. Unfortunately, none of the reactions, after carbonylation, resulted in any desired product. Only the starting allylic sulfide or sulfoxide and presumably their isomers were isolated in low yields.

At this time, it came to our knowledge[127] that when lithium phenylsulfonylmethane is reacted with 1,5-cyclooctadiene-palladium dichloride, one gets a mixture of complexes as shown in eq. 47.



(47)

Hence, it appeared to us that the anions from compounds 73 and 74 might be mainly attacking palladium instead of carbon. We then tried the following reaction sequence (eq. 48). The aim in running this

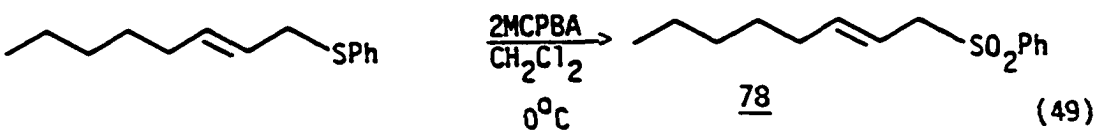


(48)

73 + PhSCH(COOMe)CH=CHC5H11

reaction was to form a π-allylpalladium complex from the allylic sulfide in situ, which in turn would react with norbornadiene to give the σ-palladium complex which might undergo further carbonylation. But GC-MS analysis of the reaction mixture showed the starting allylic sulfide and a compound with m/e 276, which could presumably be the carbonylation product 75 or an allylic isomer resulting from the small amount of π-allylpalladium complex formed from the allylic sulfide.

Next 1-phenylsulfonyl-2-octene (78) was prepared[126] in order to be tried in the reaction and to ascertain its mode of reaction



78 (49)

(eq. 49). The following reaction was then attempted (eq. 50). Analysis of the reaction mixture by GC-MS showed apart from the sulfone 78, a peak corresponding to m/e 168 with a long retention

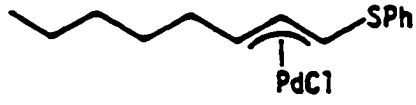
time. This could be assigned the structure 79 (310(M^+)-$PhSO_2H$) or its allylic isomer. Again, the anion from the allylic sulfone is

$$\underline{68} + C_5H_{11}CH{=}CH\underline{C}HSO_2Ph \xrightarrow[\substack{HMPA\\(1\ equiv)\\0^oC\text{-}RT}]{THF} \xrightarrow[\substack{CO,\ MeOH\\-78^oC\text{-}RT}]{(^iPr)_2NEt} \underline{78} + MeOOCCH(PhSO_2)CH{=}CHC_5H_{11} \quad (50)$$

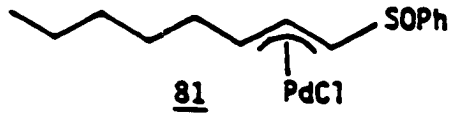
$$\underline{79}$$

presumably attacking the palladium first, and some of this imtermediate is then undergoing carbonylation to give the product 79.

Since we have shown previously [115] that π-allylpalladium compounds add with ease to bicyclic olefins, we decided to prepare the π-allylpalladium complexes 80 and 81 from compounds 73 and 74 respectively. Accordingly, compound 73 was reacted under the following conditions: (1) $Pd(O_2CCF_3)_2$, acetone, room temperature, 30 min, n-Bu_4NCl; (2) $(PhCN)_2PdCl_2$, benzene, room temperature; (3) Na_2PdCl_4, refluxing ethanol; (4) NaOAc, NaCl, $CuCl_2$, $PdCl_2$ in acetic anhydride-acetic acid mixture at 95°C for 2 h. Compound 74 was reacted under the following conditions: (1) $Pd(O_2CCF_3)_2$, acetone, room temperature, n-Bu_4NCl; (2) n-BuLi, THF, -78°C, then $PdCl_2$ at -78°C; (3) Li_2PdCl_4, NaOAc in refluxing THF. Unfortunately, none of the reaction conditions described above led to either of the desired π-allylpalladium complexes 80 or 81.



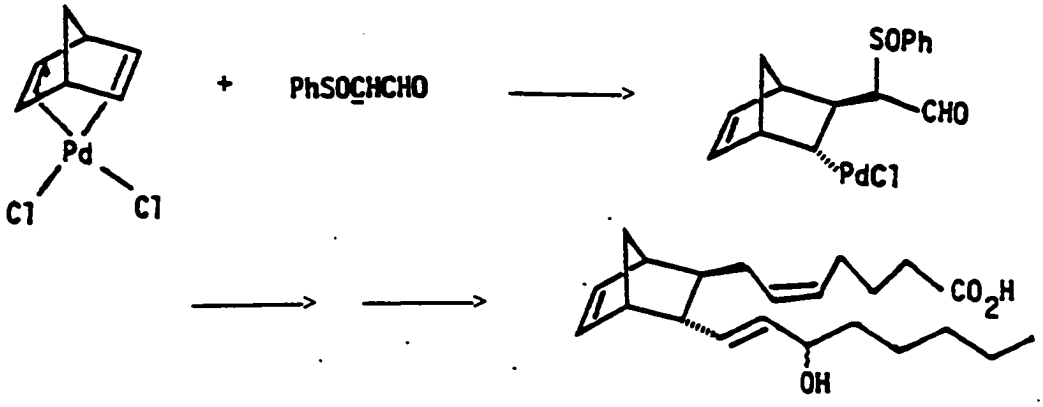
80



81

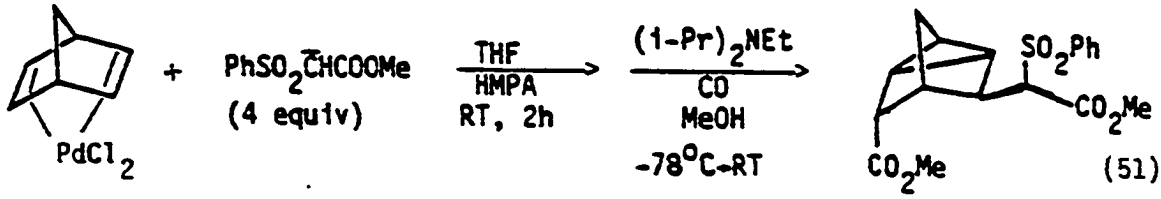
We also envisioned another approach to a PGH_2 endoperoxide analogue 82 as shown in Scheme 9.

Scheme 9



82

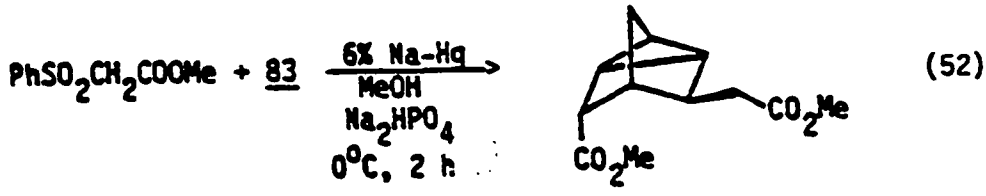
As a model reaction, the following reaction was studied (eq. 51). The ^1H NMR spectrum of the crude reaction mixture showed no olefinic



(51)

83

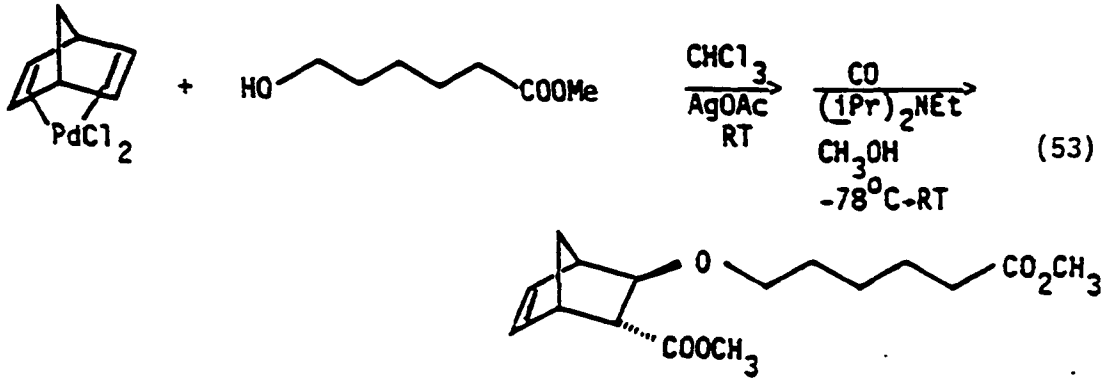
protons and the IR spectrum showed a C-H bending frequency of 810 cm^{-1} which is characteristic of the nortricyclic system. There was some difficulty in separating the product 82 from the excess methyl phenylsulfonylacetate since they had the same R_f values. Treatment of the mixture with a stoichiometric amount of 6% Na-Hg removed the phenylsulfonyl group and the product 83 was isolated in 75% yield (eq. 52). The stereochemistry of the carbomethoxymethyl group was assigned



(52)

84

exo, in analogy to the reaction of malonate anion with norbornadiene-palladium dichloride which was shown to be an exo attack.[125] We had to drop this approach, since the reaction led to a nortricyclic product rather than the desired norbornenyl product. It is interesting to note here that the reaction of an alcohol with norbornadiene-palladium dichloride followed by carbonylation led to a norbornenyl product[128] (eq. 53).



(53)

Conclusion

There are two facts which have been learned from the reaction of soft anions with norbornadiene-palladium dichloride: (1) Lithium anions can attack at palladium instead of at carbon; (2) when the carbanion is fairly stabilized as in the case of sodium methyl phenylsulfonylacetate, the anion does attack at carbon, but unfortunately the σ-palladium intermediate formed rearranges upon carbonylation to a nortricyclic intermediate. It seems that the nature of the anion and solvents may have a profound influence in these reactions.

Experimental Section

Norbornadiene-palladium dichloride was prepared according to the literature procedure.[129] 1-Phenylthio-2-octene, 1-phenylsulfinyl-2-octene and 1-phenylsulfonyl-2-octene were all prepared using the literature procedure.[126]

Reaction of the anion from 1-phenylsulfinyl-2-octene with norbornadiene-palladium dichloride

The following procedure is representative. 1-Phenylsulfinyl-2-octene (0.142 g, 0.6 mmol) was dissolved in 4 ml of THF and cooled to -78°C under a nitrogen atmosphere. n-Butyllithium (0.35 ml, 0.637 mmol, 1.82 M in hexane) was added and the solution was warmed to -40°C for 30 min. Meanwhile, norbornadiene-palladium dichloride (0.135 g, 0.5 mmol) was stirred in 0.5 ml of THF at -78°C. The anion solution prepared above was cooled to -78°C and HMPA (0.26 ml) was added. The

solution was then added to the palladium complex in one portion. The reaction mixture was allowed to warm up to room temperature for 3 h. Diisopropylethylamine (0.5 ml) and 5 ml of methanol were added and the solution was cooled to -78°C. A balloon of carbon monoxide was placed on the flask and the solution was allowed to warm up to room temperature overnight. The solution was filtered and washed with ether. The ether solution was washed with water and saturated ammonium chloride and dried over $MgSO_4$. The solution was concentrated and analyzed by GC-MS.

Reaction of methyl phenylsulfonylacetate anion with norbornadiene-palladium dichloride

Sodium hydride (0.072 g, 2 mmol) was washed with hexane and blown dry under nitrogen. THF (2 ml) was added, followed by methyl phenylsulfonylacetate (0.428 g, 2 mmol). The solution was stirred for 15 min at room temperature. Meanwhile, norbornadiene-palladium dichloride (0.5 mmol) was stirred in 3.5 ml of THF at room temperature. The solution of the anion prepared above was added through a canula in one portion. The reaction mixture was stirred at room temperature for 3 h after which diisopropylethylamine (0.5 ml) and methanol (5 ml) were added and the solution was cooled to -78°C. A balloon of carbon monoxide was placed on the flask and the solution was warmed to room temperature overnight. The reaction mixture was filtered through Celite, washed with ether and the solution was concentrated. The residue was dissolved in ether, washed with water and saturated ammonium chloride solution and dried over $MgSO_4$. The

solvent was removed on a rotary evaporator. There was a problem in isolating the product because both the product and methyl(phenylsulfonyl)acetate had similar R_f values. Hence the following reduction procedure[130] was carried out on the mixture.

To the crude reaction mixture and anhydrous disodium hydrogen phosphate (1.5 g) in 30 ml of dry methanol cooled to 0°C, was added freshly prepared pulverized 6% sodium amalgam (4.5 g). The reaction mixture was stirred for 2 h and poured into water and extracted with ether. The ether layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography yielded the product 83 in 75% yield: ^1H NMR ($CDCl_3$) δ 1.1-1.60 (m, 6H), 2.0-2.42 (m, 4H, CHCO, CH_2CO and ring CH), 3.67 (s, 6H, methyl groups on ester); IR (neat) 2960, 1745, 810 cm^{-1}; mass spectrum, m/e 224 (M^+).

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