1991

Organopalladium approaches to prostaglandins

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Organopalladium approaches to prostaglandins

by

Nam Ho Lee

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:

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For the Major Department

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For the Graduate College

Iowa State University
Ames, Iowa
1991

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CHAPTER IV. PREPARATION OF ALLYLIC ARYL ETHERS VIA π-ALLYLPALLADIUM CHEMISTRY

ABBREVIATIONS

[α]	specific rotation
Ac	acetyl
ADP	adenosine diphosphate
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
Bu	butyl
δ	chemical shift in parts per million downfield shift from tetramethylsilane
dba	dibenzylideneacetone
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
DMF	N,N-dimethylformamide
ED_{50}	dose that is effective in 50 % of test subjects
ee	enantiomeric excess
Et	ethyl
h	hour(s)
HRMS	high resolution mass spectrum
IR	infrared
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
Me	methyl
MOM	methoxymethyl

m/z	mass to charge ratio
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
PDC	pyridinium dichromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl

GENERAL INTRODUCTION

Ever since its discovery in the mid-1960s, the family of compounds known as prostaglandins has been the target of organic synthesis, because of its important biological activity. Recently, organopalladium chemistry has evolved as a powerful technique in organic synthesis. Thus, the development of efficient synthetic routes to prostaglandins utilizing organopalladium chemistry is an attractive subject in organic synthesis.

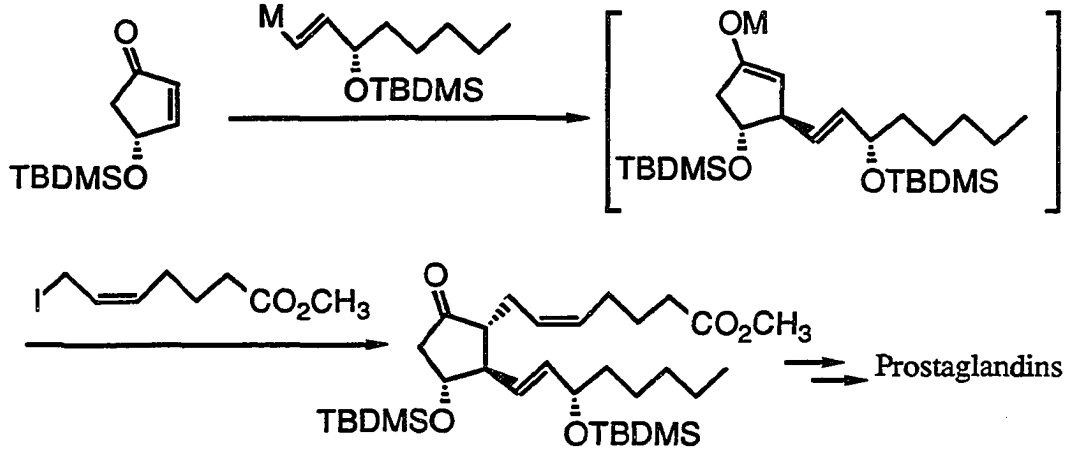
This dissertation is devided into four chapters. The first chapter discusses the synthesis of the prostaglandins $PGF_{2\alpha}$ and 12-epi-$PGF_{2\alpha}$. The second chapter deals with the synthesis of the prostacyclin analogues, benzoprostacyclins, which are known to have potent biological activity. The third chapter deals with the synthesis of 12-epi-carbacyclin. Finally, the last chapter discusses a new Pd(0)-mediated approach to allylic aryl ethers, which was developed during the work on prostaglandin synthesis.

CHAPTER I. ORGANOPALLADIUM APPROACHES TO PROSTAGLANDIN $F_{2\alpha}$ AND 12-EPI-$PGF_{2\alpha}$

INTRODUCTION

Prostaglandins control a wide range of physiological responses in the human body. Several prostaglandins and their modified synthetic analogues are being used as drugs. Many attempts have been made to synthesize prostaglandins with high efficiency. The most attractive strategy to construct prostaglandins seems to be a three-component coupling process[1] utilizing organometallic mediated Michael addition, followed by trapping of the resulting enolate by an allylic iodide (Scheme I).

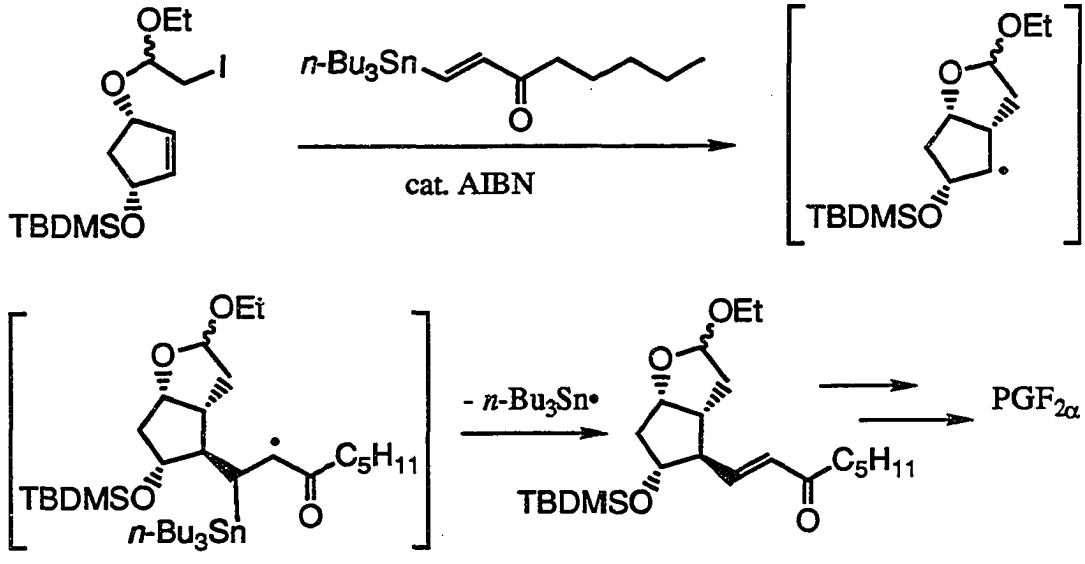
Scheme I.



M = metallic species such as Cu and Zn

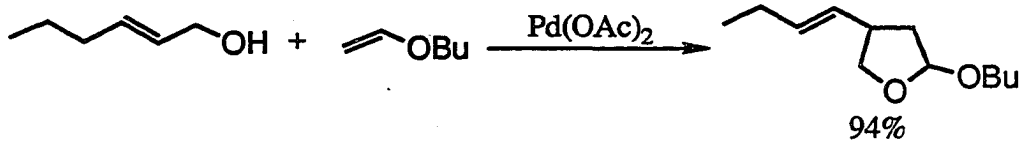
Recently, radical chemistry also has proven useful for construction of the prostaglandin framework. Stork and co-workers[2a] first reported a radical-promoted cyclization-trapping method for the synthesis of $PGF_{2\alpha}$. Later, Keck and Burnett improved this method using an organotin compound as a trapping agent[2b] (Scheme II).

Scheme II.



As a continuing effort to synthesize prostaglandins using organopalladium chemistry, we decided to develop an efficient synthetic route to $PGF_{2\alpha}$ and 12-epi-$PGF_{2\alpha}$ by a palladium-mediated three-component coupling reaction. We invisioned that three different alkenes could be coupled by a palladium-promoted cyclization-coupling procedure. Thus, we decided to explore this exciting possibility.

Fugami and co-workers reported in 1987 that the reaction of acyclic allylic alcohols, vinyl ethers and palladium acetate afforded good yields of 2-alkoxy-4-alkenyltetrahydrofurans (eq 1)[3]. Larock and Stinn later extended this chemistry to the preparation of bicyclic acetals (eq 2)[4].



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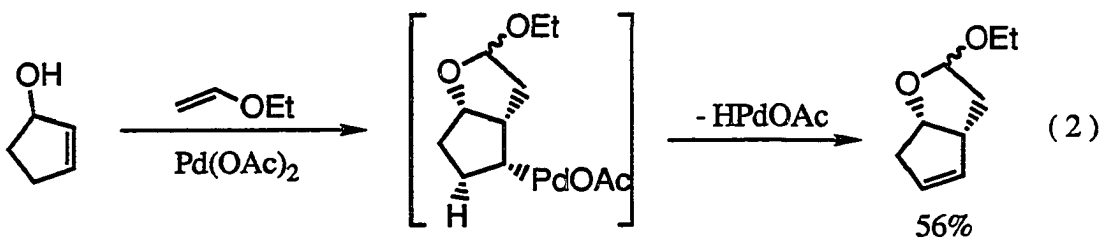
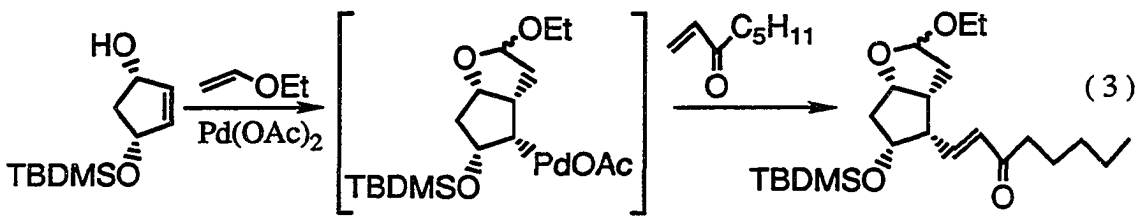


(2)

A close look at the reaction mechanism in equation 2 suggests that the molecular skeleton of prostaglandins can be obtained using this methodology. The reaction of *cis*-4-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol (1), ethyl vinyl ether and palladium acetate should give organopalladium intermediate 2, which might be trapped by 1-octen-3-one to afford compound 3 (eq 3). Therefore, the important intermediate 3 for the synthesis of $PGF_{2\alpha}$

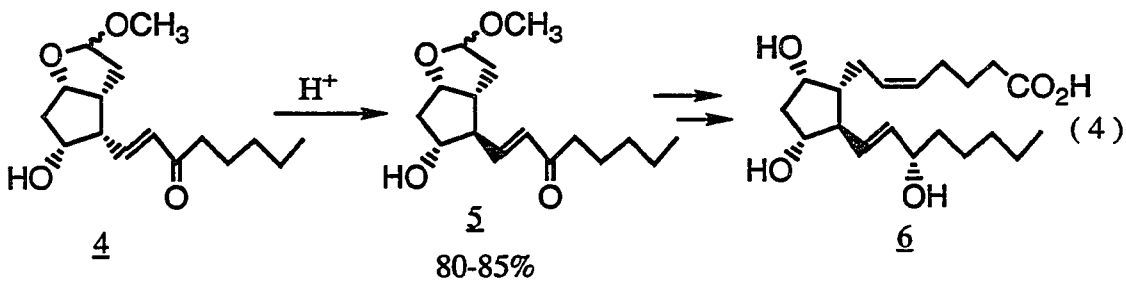


(3)

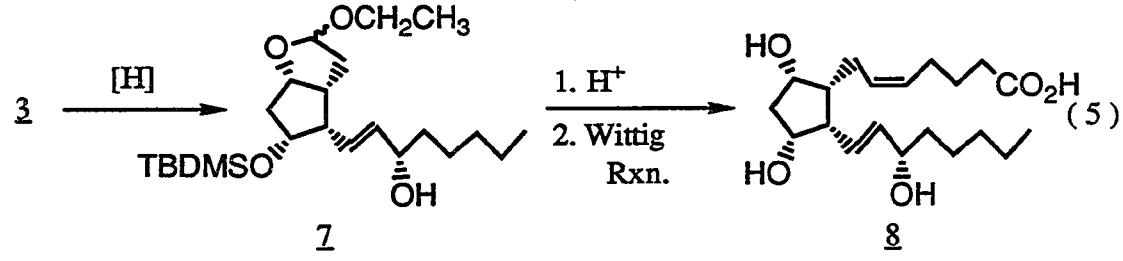
1 2 3

might be prepared by a very efficient three-component coupling process from readily available compound 1.

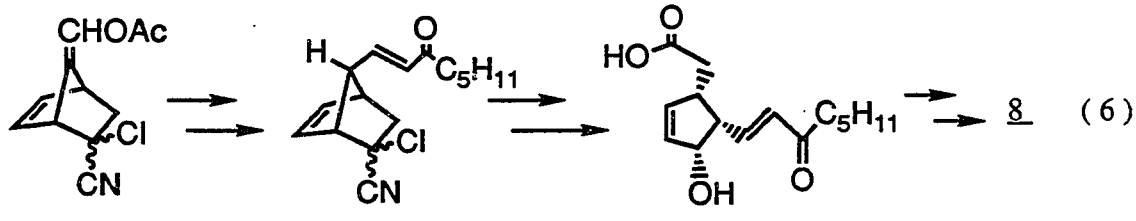
The synthesis of $PGF_{2\alpha}$ requires the natural beta stereochemistry at carbon 12. Fortunately, the required epimerization and the subsequent reactions to $PGF_{2\alpha}$ have already been reported[5] (eq 4). Moreover, the intermediate 3 should be readily converted



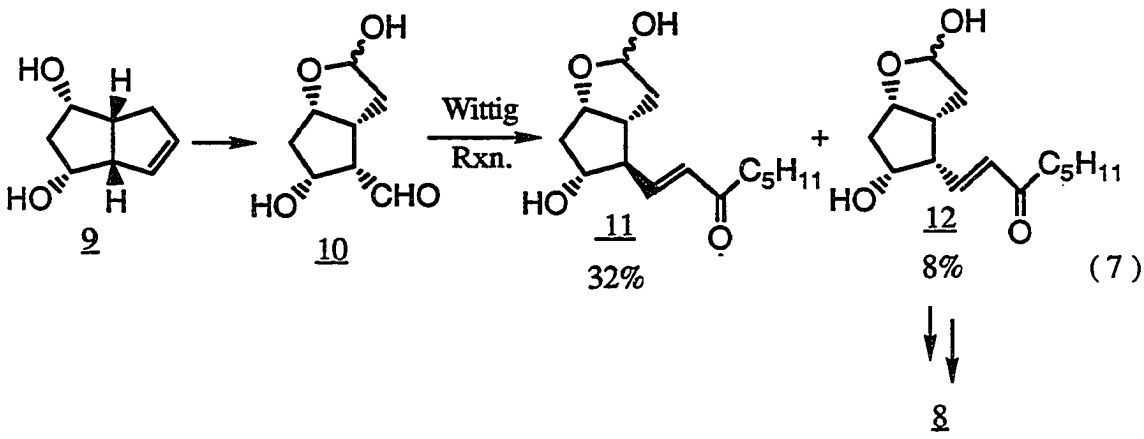
diastereoselectively to the corresponding alcohol 7 and upon subsequent hydrolysis and Wittig reaction to 12-epi-PGF2α (8). The prostaglandin 8 is little known and has not been biologically tested yet.



There are two references to compound 8 in the chemical literature. One is a German patent[6] stating that compound 8 has "prostaglandin-like pharmacological properties". In that patent, compound 8 was prepared via the modified procedure of Corey's PGF2α synthesis (eq 6).

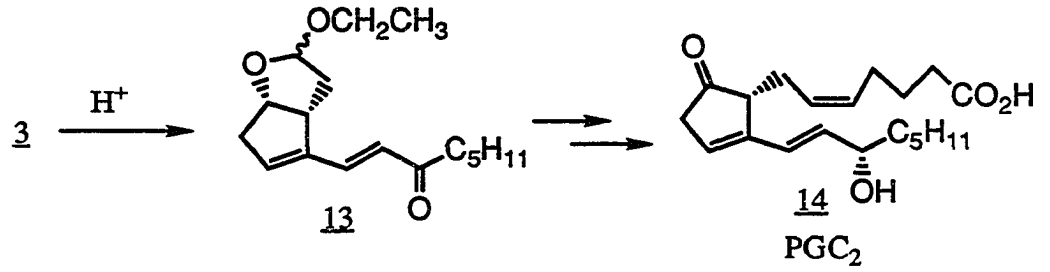


The other report[7] of compound 8 appears in a paper describing the synthesis of natural prostaglandin $F_{2\alpha}$. A Wittig reaction of aldehyde 10 led to a mixture of compounds 11 and 12, where compound 12 was converted into compound 8 (eq 7).



(7)

Compound 3 should also afford a facile route to C prostaglandins[8] by elimination of the silyloxy group (eq 8). A synthesis of PGC_2 was accomplished by Corey and Moinet[9] from the lactol 15 by a double bond migration in the key step (eq 9).



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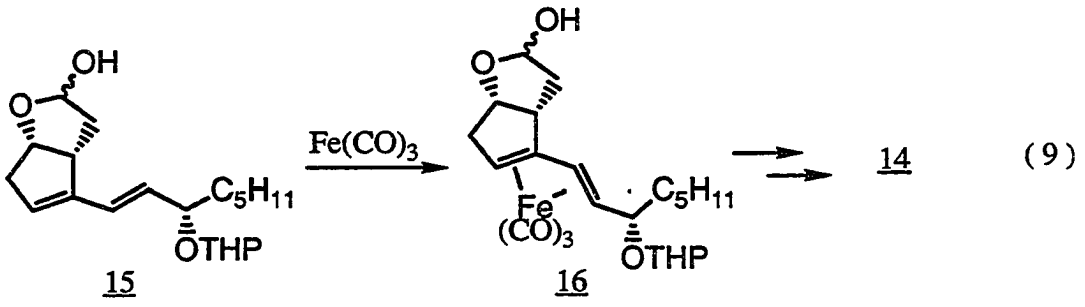
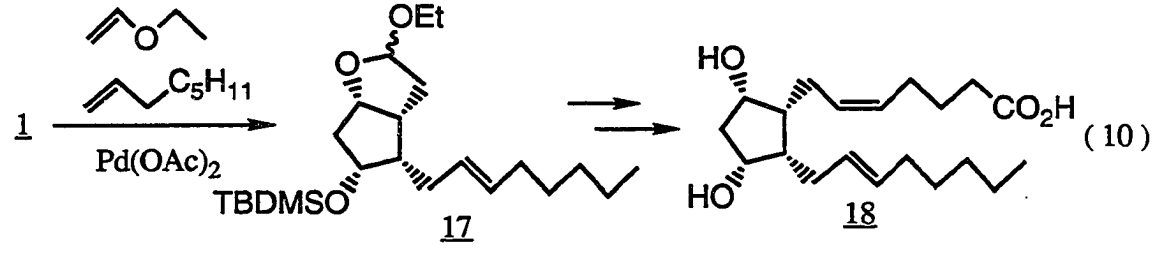
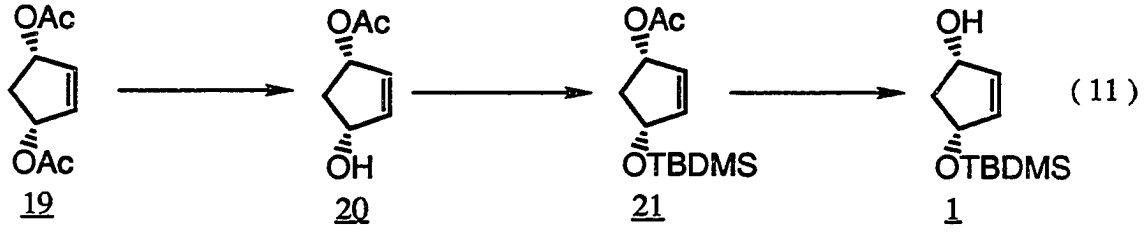


We might also hope to introduce different functionality into the lower side chain by employing different alkenes in place of 1-octen-3-one. One example might be a simple alkene like 1-octene (eq 10).



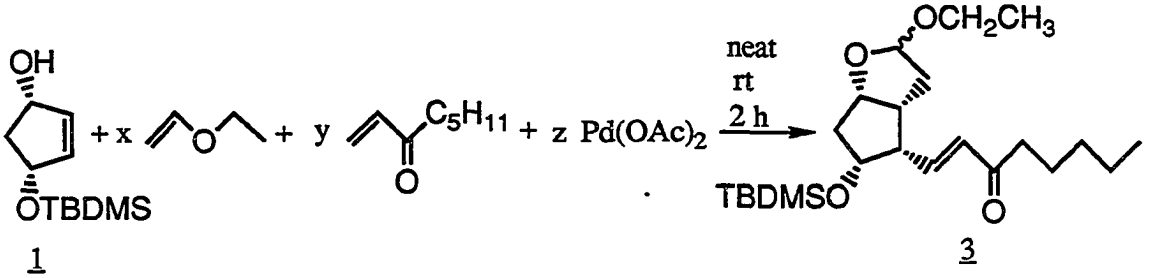
Above all, a very attractive feature of this palladium process is that allylic alcohol 1 is readily available in enantiomerically pure form. It is known[10] that enzymatic hydrolysis of *cis*-1,4-diacetoxy-2-cyclopentene (19) affords enantiomerically pure monoester 20. Subsequent protective group manipulations provide optically pure 1[2a] (eq 11).



RESULTS AND DISCUSSION

An efficient, one-pot procedure for three-component coupling to prepare compound 3 was conducted under various conditions. The results are summarized in Table 1.

Table 1. Reaction conditions for the synthesis of compound 3

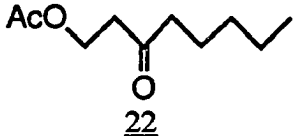


1 3

Entry	x	y	z	Base	Additive	% Isolated Yield
1	3	5	1.2	none	none	27
2		10				40
3			2.5	2.4 Et_3N		< 10
4			2.7	5 NaOAc		44
5		13	1.2	none		44
6		16				55
7		20				57
8	6					57
9	3				0.2 NaI	58[a]
10	4		1.5			72
11				2 NaOAc		72

[a]16% of the starting material 1 was recovered.

The best results are presented in entries 10 and 11. In entries 2 - 4, the effect of a base on the reaction was examined. With triethylamine as the base, less than 10% of the desired product 3 was obtained. This reaction also gave a 41% yield of compound 22, which was probably generated by 1,4-addition of acetate to 1-octen-3-one (entry 3). The addition of



22

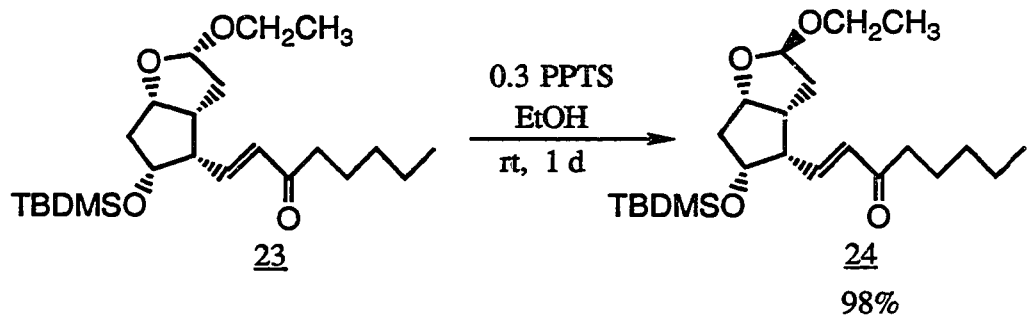
sodium acetate, however, provided slightly better results (entry 4). As seen in Table 1, the product yield is dependent on the amount of 1-octen-3-one employed (entries 1, 2 and 5 - 7); the yield improved from 27% to 57% as the amount of 1-octen-3-one was increased from 5 to 20 equivalents. This observation indicates that the crucial step in the three-component coupling is the Heck-type addition of 1-octen-3-one to the organopalladium intermediate 2. Six equivalents of ethyl vinyl ether was tried, instead of three equivalents, figuring that the acetic acid generated might destroy the vinyl ether initially added (entry 8).

During work on the synthesis of a carbacyclin in Chapter III of this dissertation, it was observed that the addition of sodium iodide to the reaction system increased the yield of the desired product. This observation led me to investigate the reaction using a catalytic amount of sodium iodide (entries 9-11). When 0.2 equivalents of sodium iodide was added to the reaction conditions shown in entry 8, the desired product was obtained in a 58% yield, along with recovery of 16% of the starting material. It was assumed that Pd(II) was being destroyed for some unknown reason. Hence, the reaction was conducted with 1.5 equivalents of $Pd(OAc)_2$. The product 3 was then obtained in a 72% yield (entry 10). When

the reaction was carried out with sodium acetate as a base in entry 11, the same result was obtained.

The reason for the improvement in product yield when using sodium iodide in this reaction is not clear. One might think that the reactive species is an organopalladium iodide, rather than an organopalladium acetate.

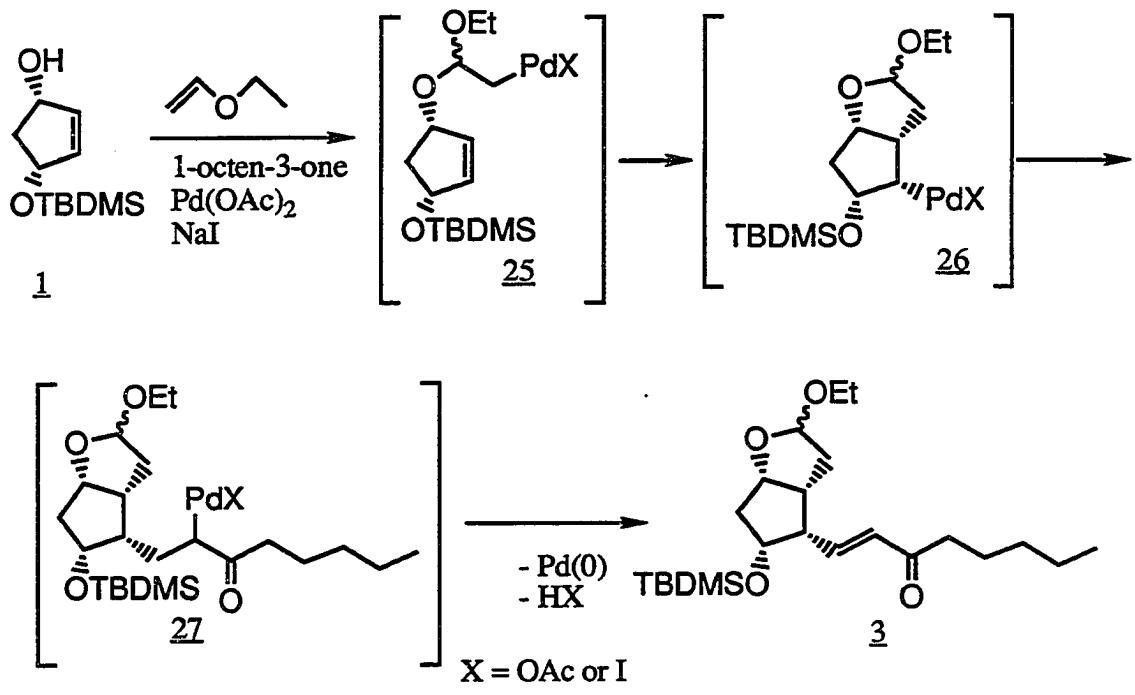
Product 3 was obtained as a mixture of exo and endo diastereomers, whose ratio ranges from 1:1 to 5:1, depending on the experimental conditions. The diastereomers exo 24 and endo 23 are separable by flash chromatography. Moreover, the endo isomer 23 can be cleanly isomerized to the exo isomer 24 with a catalytic amount of pyridinium *p*-toluenesulfonic acid in ethanol (eq 12).



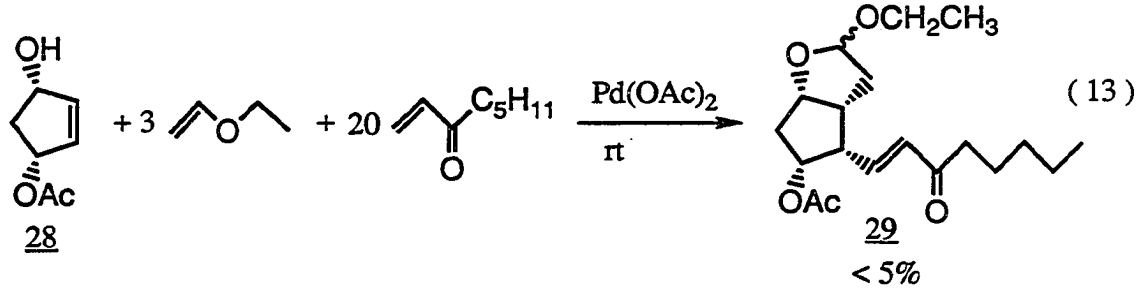
(12)

The reaction mechanism for the formation of the product 3 is proposed in Scheme III. Electrophilic alkoxypalladation of ethyl vinyl ether by compound 1 produces the intermediate 25, which undergoes cyclic carbopalladation, followed by Heck-type insertion of 1-octen-3-one. Accordingly, a remarkably simple one-step process for the synthesis of 3 is accomplished via a series of three alkene couplings.

Scheme III.

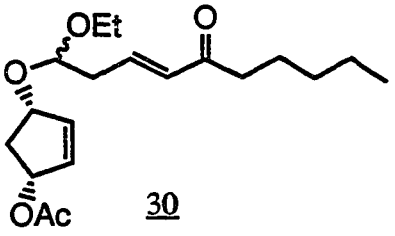


With the knowledge that *cis*-4-acetoxy-2-cyclopenten-1-ol (28) is more readily available in optically pure form[11], we examined the use of racemic 28 as the starting material (eq 13). The reaction gave only a trace amount of the desired product 29. Compound 30 or



(13)

31, as judged solely by ^{1}H NMR spectral analysis, was obtained as a major product in approximately a 10% yield.



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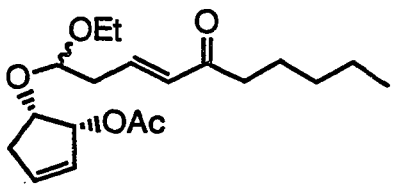
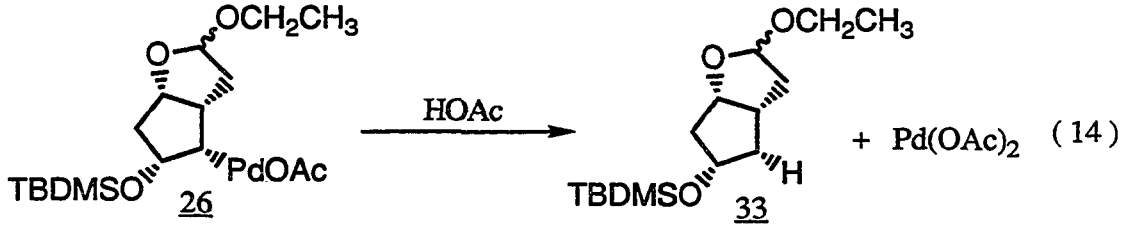


31

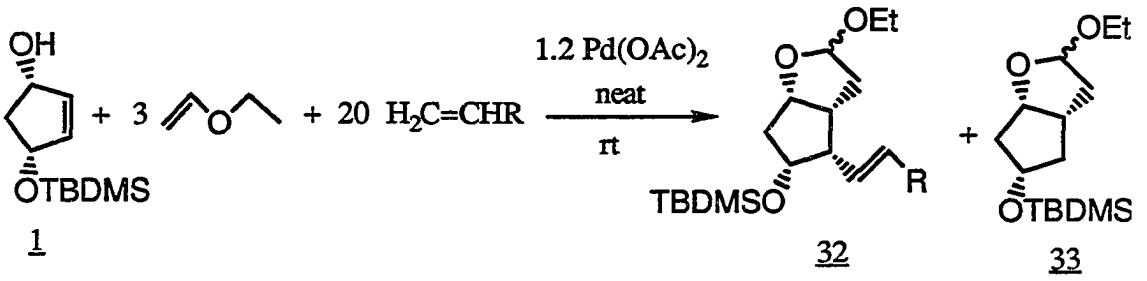
The interesting feature of this approach to prostaglandins lies in the versatility for introducing a variety of ω-side chains. A number of different olefins were examined extensively in this reaction. These results are summarized in Table 2.

The following comments are noteworthy. First, the reaction was governed by the electronic and steric environment present in the olefin. Electron-deficient olefins, such as α,β-unsaturated ketones, gave better yields than simple olefins. Steric effects can be compared in entries 12 to 17. While the sterically unhindered olefin 1-octene gave the product in fair yield, only low yields were obtained using sterically hindered acetyl- and silyl-protected 1-octen-3-ol derivatives (entries 13, 14 and 16). Secondly, the product yield is usually improved with addition of a catalytic amount of sodium iodide. A big increase in the product yield was observed in the reaction of 1-heptene and 1-octene when adding sodium iodide (entries 15-17). Thirdly, when the reactivity of the olefin towards organopalladium addition is low, the reaction sometimes gave compound 33. Compound 33 can be produced possibly via the protonolysis of the intermediate 26 (eq 14). Efforts to reduce the amount

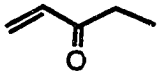
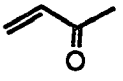
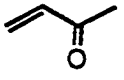
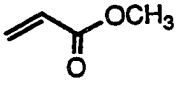
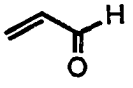


26 33 (14)

Table 2. The synthesis of compound 32 using different olefins

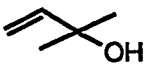
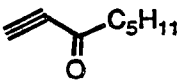
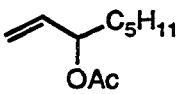
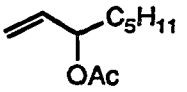
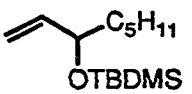
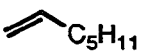
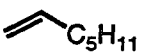
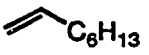


1 32 33

Entry	H_2C=CHR	Time (h)	Additive	% Isolated Yield 32	33	1
1		2	-	65	-	-
2		2	-	35	-	26
3[a]		5	0.2 NaI	39	-	40
4		1	-	26	-	-
5		1	-	17	5	-
6		0.5	-	13	7	-
7		2	-	10	-	-

[a]The reaction was conducted with 2 NaOAc and 1.5 $Pd(OAc)_2$

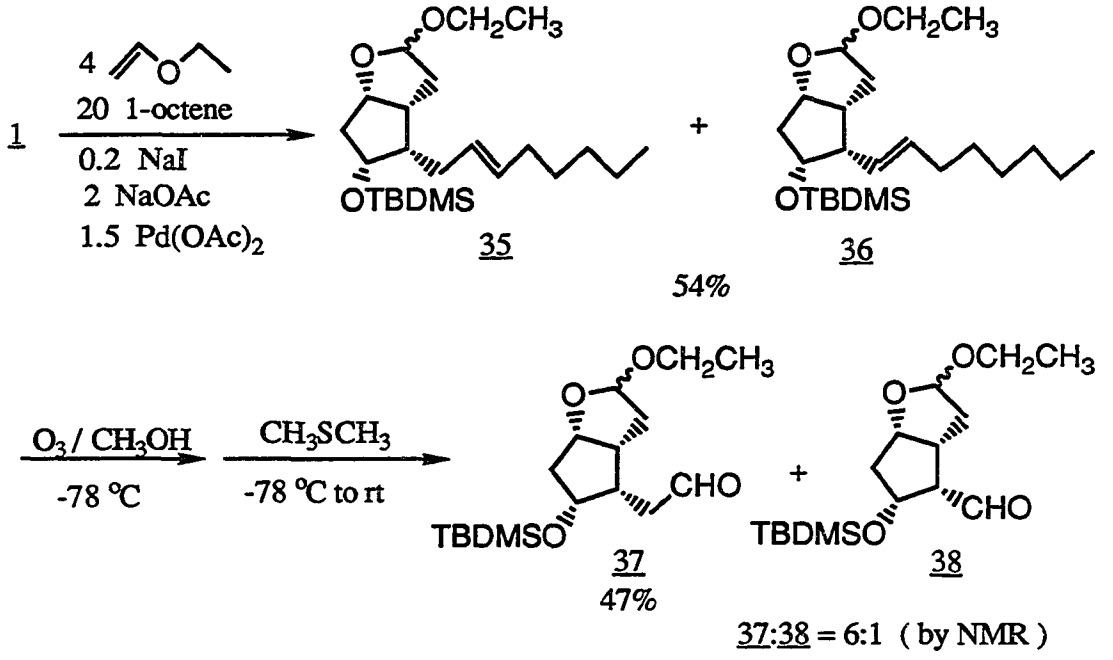
Table 2. Continued

Entry	H_2C=CHR	Time (h)	Additive	% Isolated Yield 32	33	1
8		4	-	10	-	30
9[a]		4	0.2 NaI	15	-	20
10		5 min	-	0	-	-
11	H_2C=CH_2	2	-	0	-	-
12		2	-	4	-	-
13[a]		2	0.2 NaI	15	-	-
14[a]		2	0.2 NaI	<5	-	-
15		2	-	13	4	4
16[a]		2	0.2 NaI	58	-	-
17[a]		2	0.2 NaI	54	-	-

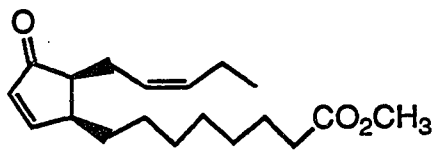
of compound 33 by adding a base, such as sodium acetate, were not successful.

In terms of the synthesis of a prostaglandin analogue, we needed to further explore the reaction of 1-octene (entry 17). The product was obtained as an inseparable mixture of exo and endo cyclic acetals, which was isomerized to the clean exo compound using PPTS in ethanol. From ^{1}H NMR spectral analysis, however, it was not clear whether the product was compound 35 or 36. Therefore, ozonolysis was conducted to identify the product. The result is illustrated in Scheme IV. Ozonolysis of the product afforded two products, 35 and 36, present in a ratio of 6 to 1. The product ratio was calculated by integration of the formyl hydrogens by proton NMR spectroscopy. Furthermore, aldehydes 37 and 38 are separable by flash chromatography.

Scheme IV.

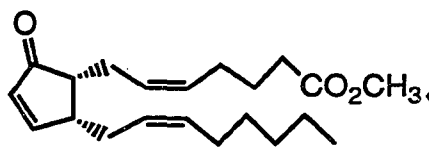


This simple three-component coupling process would appear to be quite useful for the synthesis of other natural products. Possible target molecules include the compounds 39[12], 40[13] and 41[14].



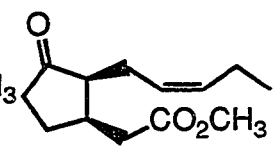
39

12-oxophytodienoic acid



40

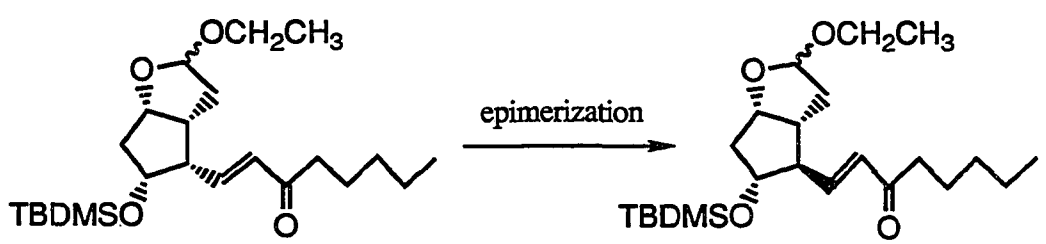
(-) preclavulone A



41

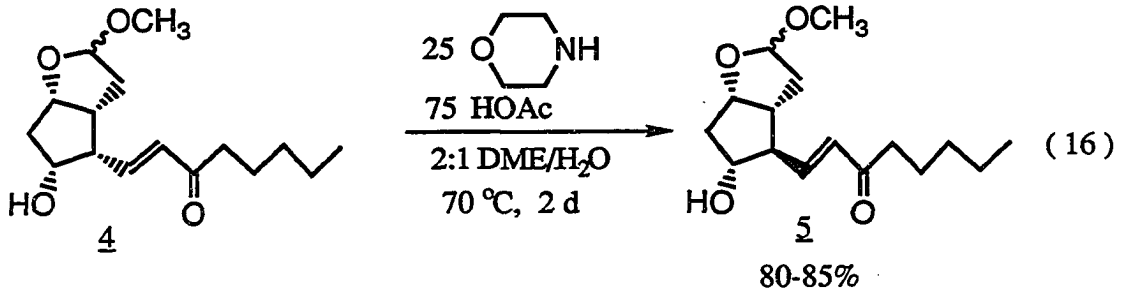
(+)-Z-methylepijasmonate

With the important intermediate 3 at hand, we tried to epimerize the lower side chain in compound 3 to the corresponding natural β-configuration present in compound 42 (eq 15). In 1984, Corey and co-workers[5] reported a successful epimerization of compound 4 to

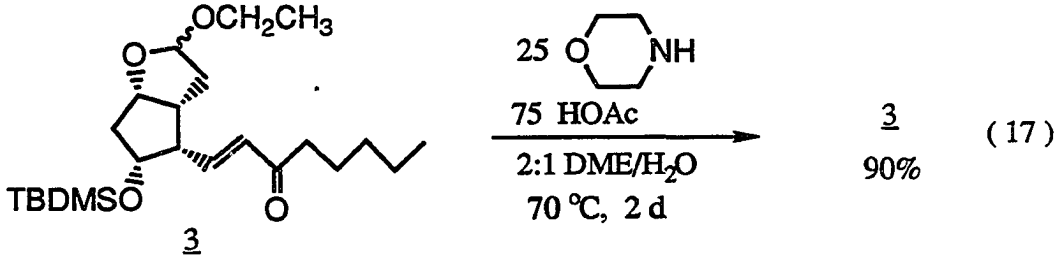


3 42 (15)

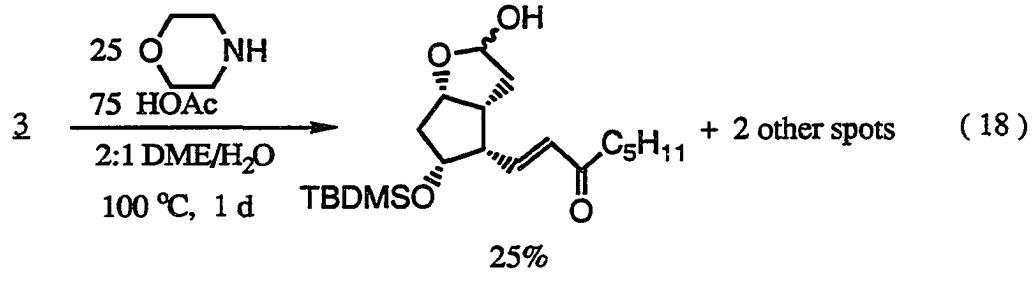
compound 5 in high yield (eq 16). Since the structures of compounds 3 and 4 are very similiar, we decided to apply Corey's reaction conditions to the epimerization of compound 3. Attempts to epimerize compound 3 to compound 42, however, were unsuccessful (eqs 17 and 18). When the reaction was conducted at 70 °C, only starting material was recovered after 2 days of stirring. With a higher temperature, up to 100 °C, the lactol was obtained



(16)



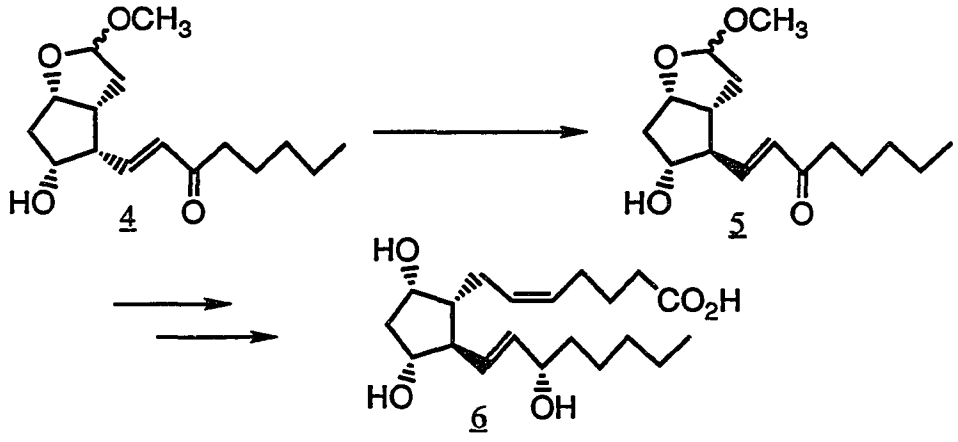
(17)



(18)

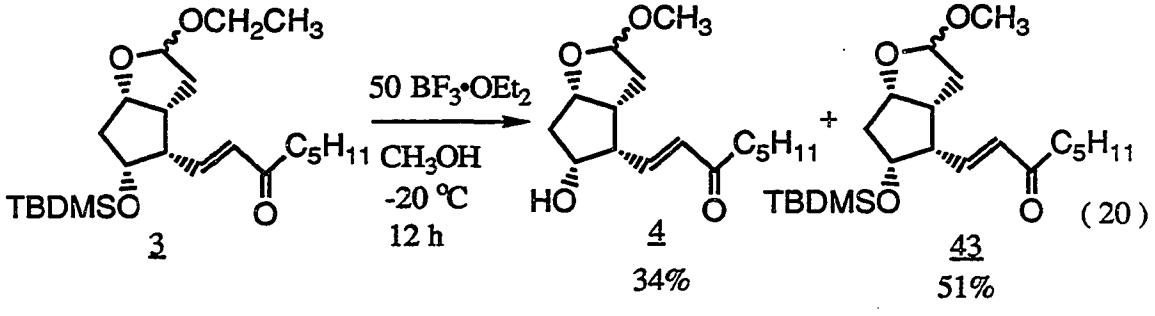
in a 25% yield, along with two unidentified products, which are not the desired products as determined by ^{1}H NMR spectral analysis (eq 18).

The synthesis of compound 4 from compound 3 was desirable to accomplish the formal total synthesis of PGF2α (eq 19)[5]. Various reagents, including aqueous HF[15], BF_3•OEt_2[16], *n*-Bu4NF[17], acetic acid[17], NaH/HMPA[18], NBS[19] and PPTS[20] were examined to deprotect the silyl group in compound 3. The most promising reagents to obtain enone 4 in one step seemed to be BF_3•OEt_2[16] or aqueous HCl in methanol. With BF_3•OEt_2, we need to keep the reaction temperature at about -20 °C, but the reaction is very



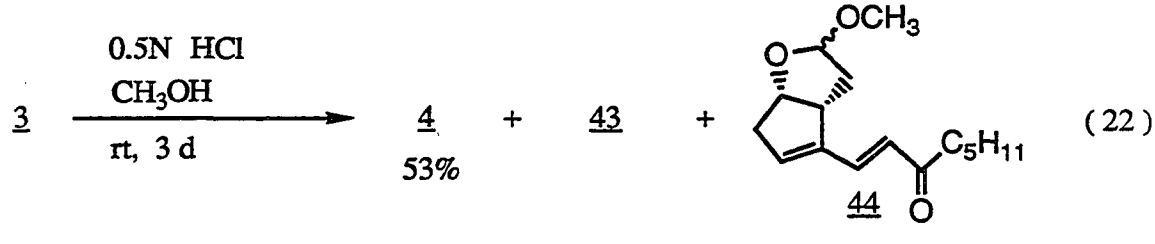
(19)

slow at this temperature (eqs 20 and 21). The best reagent actually turned out to be 0.5N aqueous HCl in methanol at room temperature (eq 22). With a catalytic amount of 0.5N



(20)

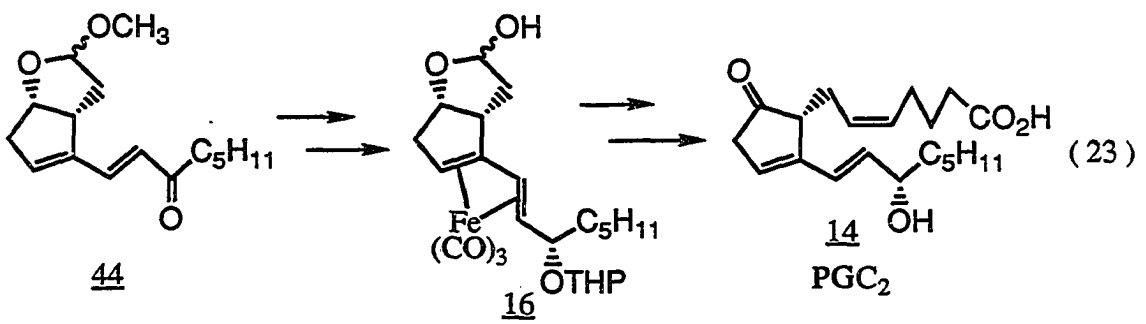
(21)



(22)

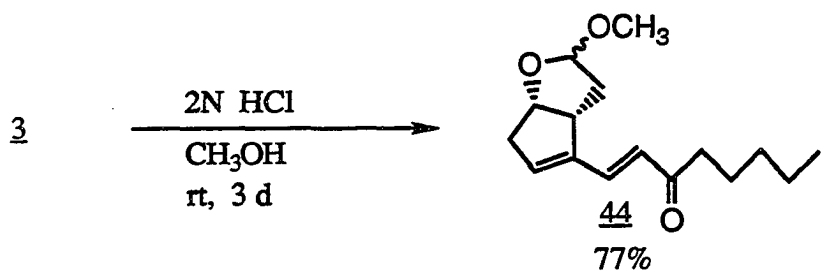
aqueous HCl in methanol, enone 4 was obtained in a 53% yield, along with only a small amount of compounds 43 and 44 (eq 22).

Interestingly, compound 44 might provide a convenient route to Corey's intermediate 16 used previously in the synthesis of PGC_2[9] (eq 23). The compound 44 was obtained



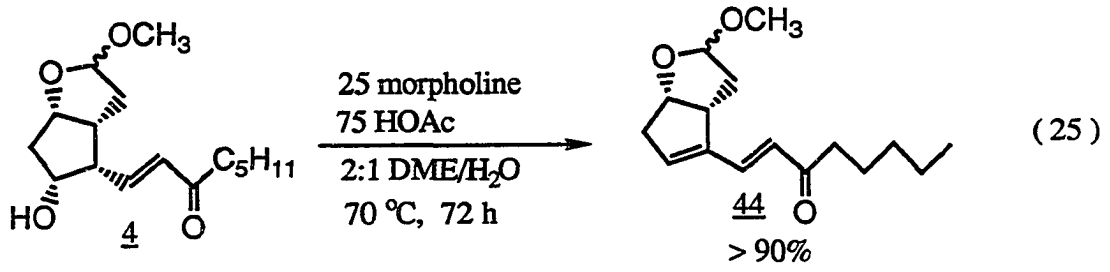
(23)

cleanly and in good yield using 2N aqueous HCl in methanol solvent (eq 24).

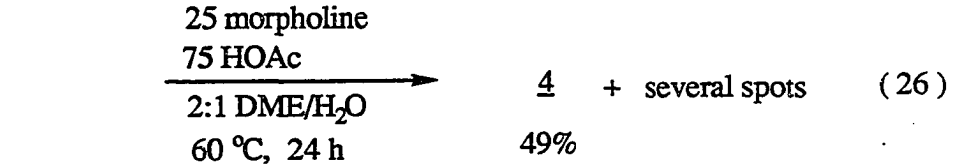


(24)

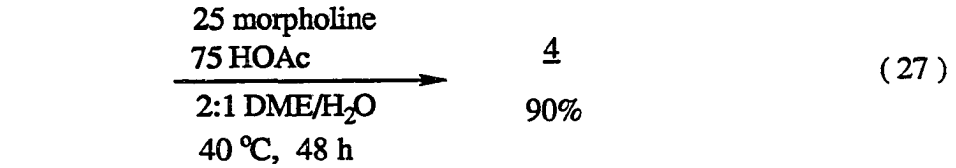
Enone 4 was also subjected to epimerization following the reported Corey reaction conditions[5]. Surprisingly, all attempts to epimerize compound 4 failed (eqs 25 - 27). When the reaction was carried out using the literature procedure[5], only the eliminated product 44 was obtained (eq 25). Upon variation of the reaction temperature, no evidence was found to support the presence of the epimerized product (eqs 26 and 27).



(25)

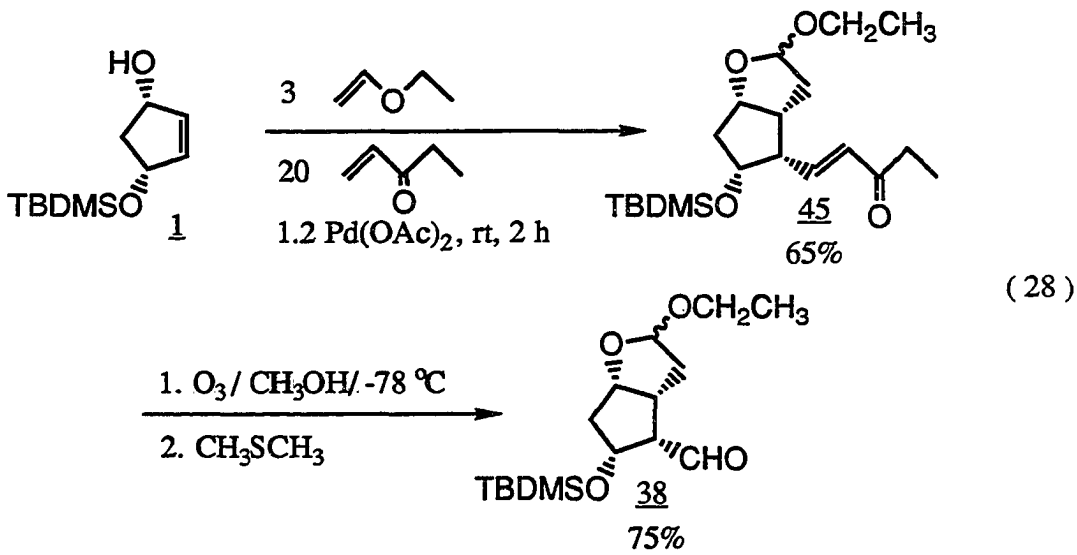


(26)



(27)

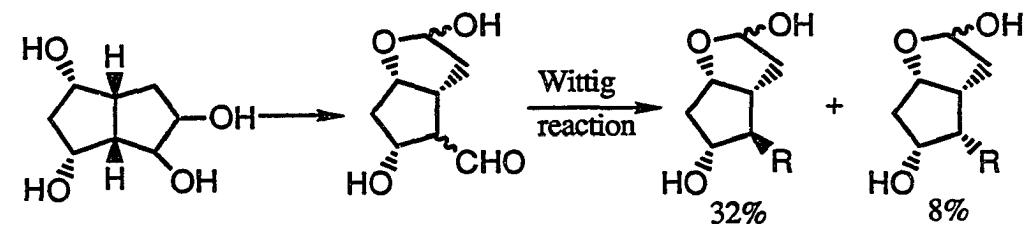
Since the epimerization of compounds 3 and 4 proved to be troublesome, we decided to introduce a formyl group as the lower side chain by ozonolysis of compound 45 and to examine its epimerization. When ozone was bubbled through the substance 45 in methanol at



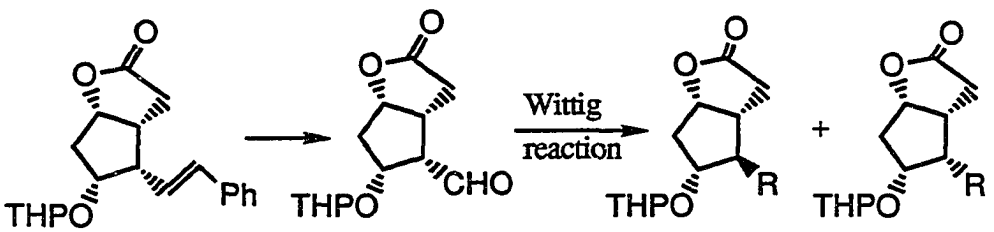
(28)

-78 °C, followed by reductive decomposition of the ozonide by dimethyl sulfide, the product 38 was obtained in 75% yield (eq 28). Unlike literature reports[7,22,23] of the instability of similar aldehydes (no spectral data could apparently be obtained), compound 38 was quite stable.

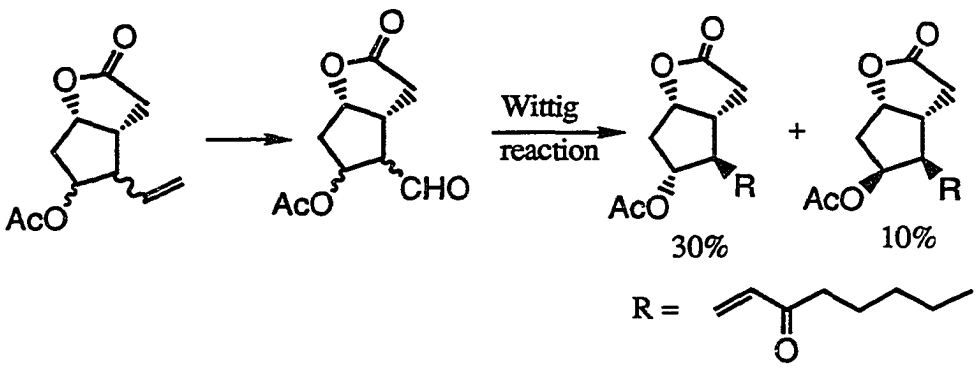
There are reports of the epimerization of the α-isomer of similar aldehydes to the more stable β-configuration during a Wittig reaction (eqs 29[7], 30[22] and 31[23]). With the



(29)

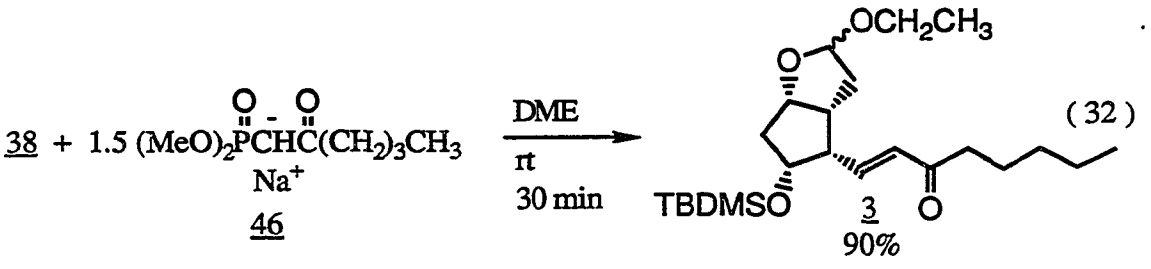


(30)



(31)

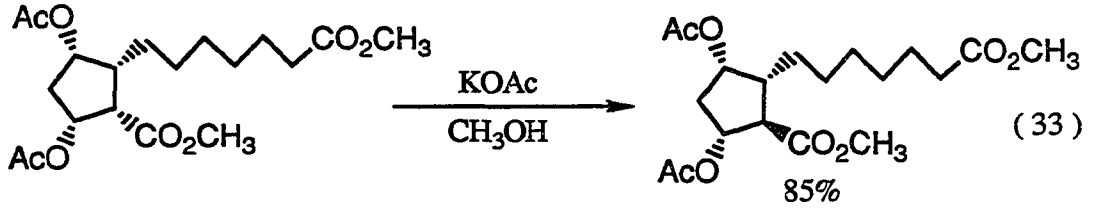
information above, compound 38 was subjected to the Wittig reaction using 1.5 equivalents of the ylide 46 (eq 32). To our surprise, enone 3 was obtained as the sole product. No



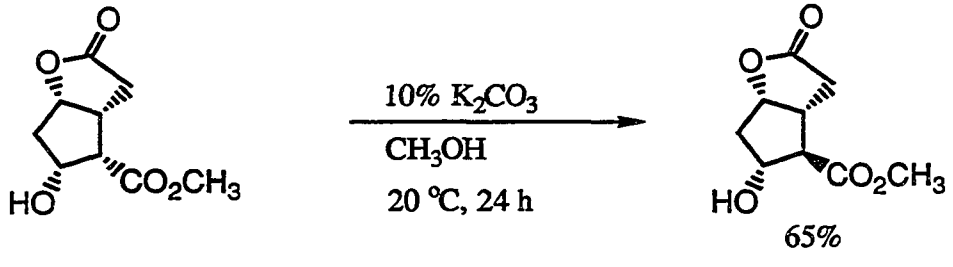
(32)

epimerized or eliminated product was observed. The relative stability of compound 38, contrary to literature reports,[7,22,23] might be the explanation for this result.

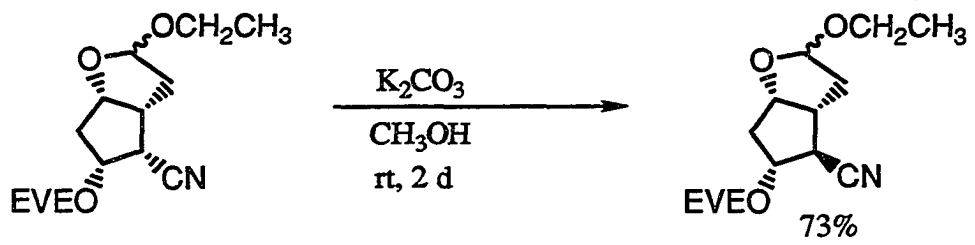
As an alternative path to the natural prostaglandin configuration, we decided to examine the epimerization of compound 38. Functional groups such as esters and nitriles have been reported to undergo analogous epimerization (eqs 33[22], 34[22] and 35[24]).



(33)



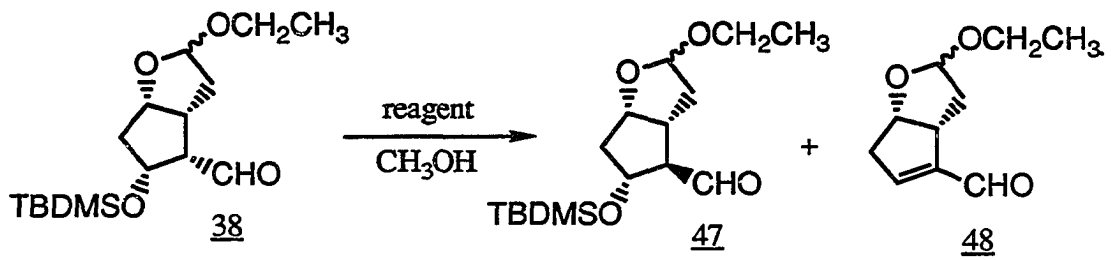
(34)



(35)

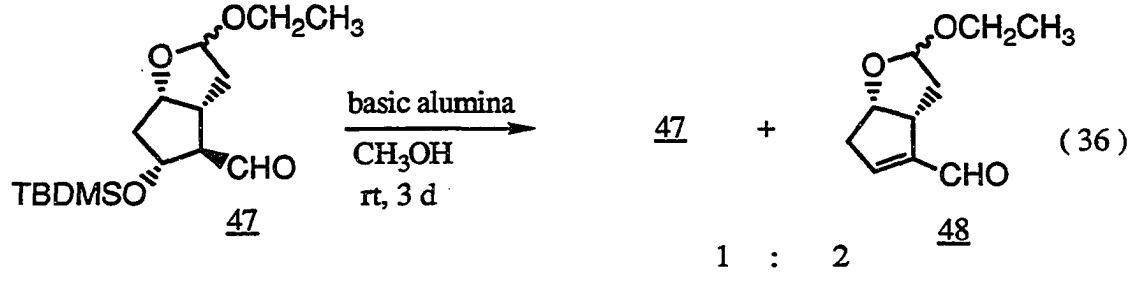
A number of reagents were examined for the epimerization of aldehyde 38. The results are summarized in Table 3.

Table 3. Attempted epimerization of compound 38



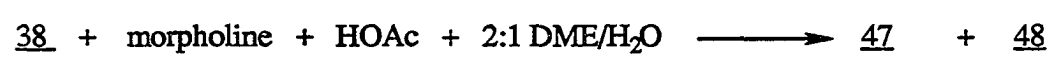
Entry	Reagent	Temperature	Time	Product Ratio 38 : 47 : 48		
1	1.5 K_2CO_3	rt	10 min	30	24	46
2	1.5 Na_2CO_3		10 min	25	20	55
3	6.0 Et_3N	44 °C	24 h	100	0	0
4	1.5 KOAc	rt	5 h	91	0	9
5	1.5 HOAc		24 h	100	0	0
6	basic alumina	14-19 °C	2 d	50	40	10
7	acidic alumina	rt	1 d	67	13	20
8	silica gel		2 d	40	48	12

The product ratio of compounds 38, 47 and 48 was determined by ^1H NMR spectral analysis, because these products show characteristic aldehyde peaks. In addition, they are clearly separable by flash chromatography; the R_f values of 38, 47 and 48 are 0.40, 0.53 and 0.26 respectively using 4:1 hexane/ethyl acetate. Among the reagents tested in Table 3, basic alumina and silica gel turned out to be better than general bases or acetic acid. Generation of the elimination product 48, however, proved troublesome. The most discouraging observation was that the desired β-epimer 47 also eliminated to give enal 48 (eq 36).



Corey's epimerization conditions[5] were also examined. The results are presented in Table 4. The results was quite comparable to those using silica gel or basic alumina. The major problem was still that the epimerized product 47 was apparently slowly converted to enal 48 (compare entries 1 and 2). The reaction was dependent on the amount of morpholine and acetic acid employed (entries 2, 5, 6 and 7). Also, the reaction temperature was important (entries 2 - 4). It was found that morpholine was a better base than piperidine (entry 8).

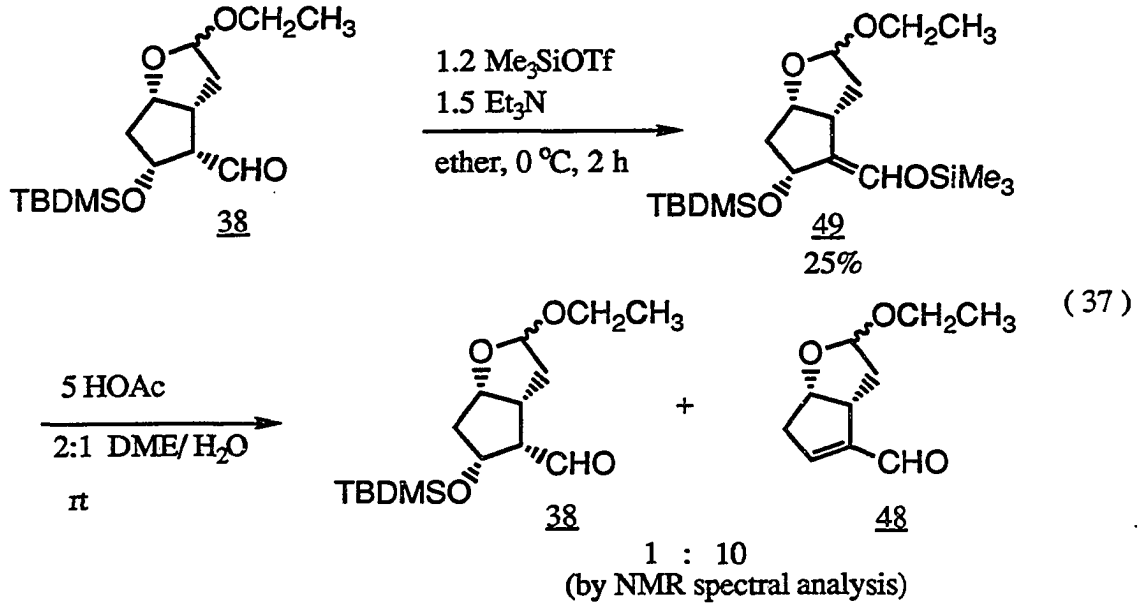
Table 4. Attempted epimerization of compound 38 using Corey's procedure[5].



	Equivalents				Product Ratio		
Entry	morpholine	HOAc	Temperature	Time	38	47	48
1	25	75	rt	1 d	1.0	51	48
2				5 h	34	48	18
3			14 °C	15 h	48	24	28
4			44 °C	3 h	21	54	25
5		25	rt	7 h	32	39	29
6	5	75		5 h	100	0	0
7	15			7 h	56	0	44
8	25[a]			12 h	36	0	64

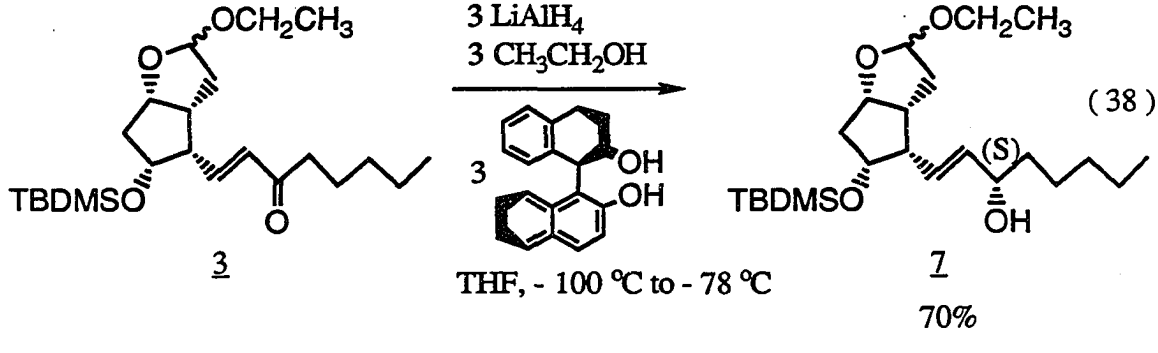
[a]25 equivalents of piperidine was used instead of morpholine.

As an alternative procedure for the epimerization of 38, the silyl enol ether 49 was prepared and subjected to hydrolysis (eq 37). Surprisingly, none of the desire product 47 was observed. The hydrolysis of 49 led to aldehydes 38 and 48, thereby showing that electrophilic addition of the proton occurred exclusively on the exo face.



(37)

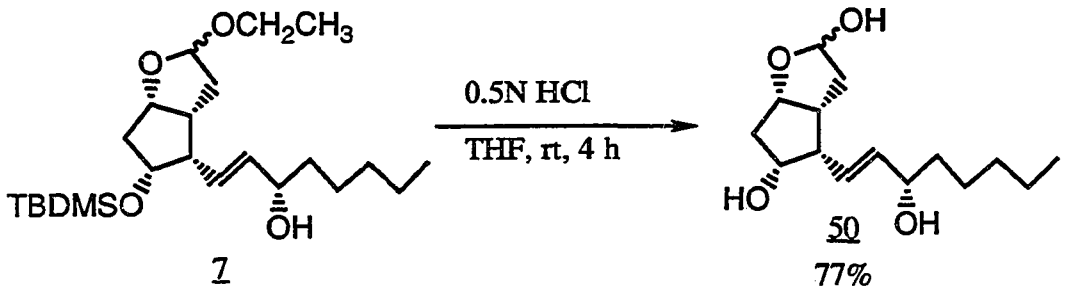
Although all attempts at the clean epimerization of compounds 3, 4 and 38 turned out to be unsuccessful, compound 3 should be readily converted to 12-epi-PGF2α (7). The diastereoselective reduction of the C15 carbonyl group was achieved using Noyori's (S)-BINAH-H[25] (eq 38). The reaction was very clean. No spots other than alcohol 7 were



(38)

observed by TLC analysis. Since the reagent, (S)-BINAL-H, has been known to reduce a variety of unsaturated compounds in a predictable manner[25], it is quite reasonable to assign the stereochemistry at C15 to the (S)-configuration.

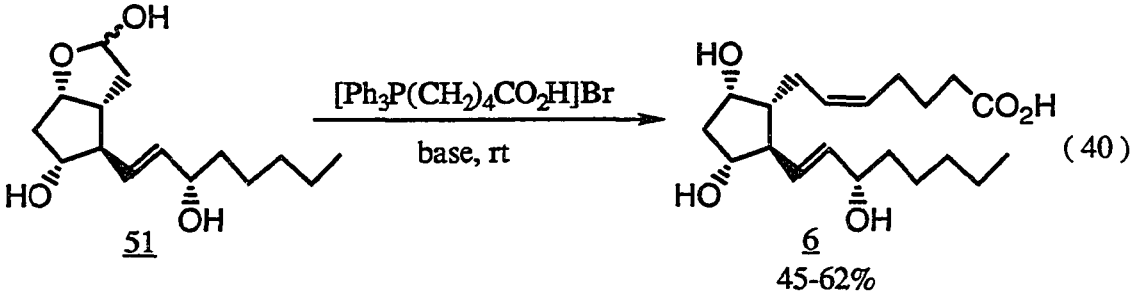
Deprotection of the silyl group and hydrogenolysis of the cyclic acetal in compound 7 were effected in one step by aqueous HCl to give compound 50 in 77% yield (eq 39).



7 50 77%

(39)

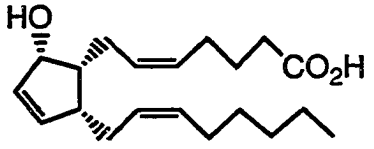
A subsequent Wittig reaction on compound 50 should give 12-epi-PGF2α (7). A literature survey[26,27] revealed that PGF2α was obtained from lactol 51 by treatment of the appropriate phosphonium salt with methylsulfinyl carbanion in DMSO[26] or potassium *t*-butoxide in THF[27] (eq 40). Subjection of lactol 50 to these literature procedures[26,27],



51 6 45-62%

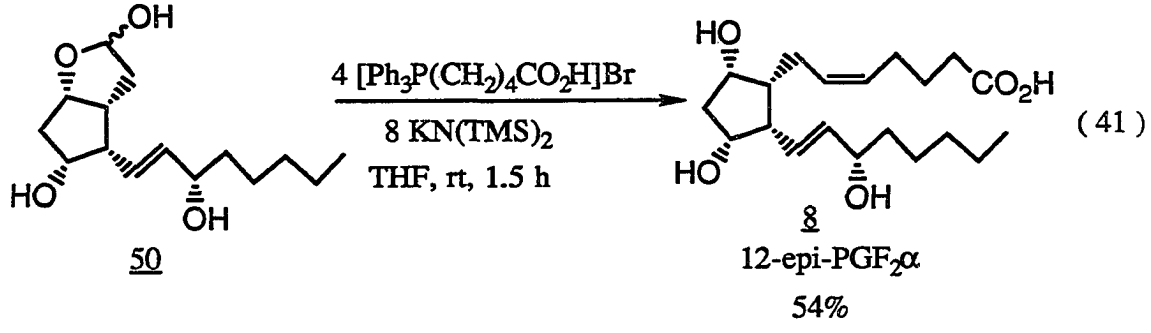
(40)

however, provided no new spot upon TLC analysis, giving the starting material back in 70 % yield. It was assumed that the sterically congested configuration around the cyclopentane ring in compound 50 might be causing difficulties in the Wittig reaction. Hence, another base was tried. Potassium hexamethyldisilazide was considered for use as a base, because it has been used[13] in the synthesis of compound 52 which has side chains with a *cis* configuration.



52

We were quite pleased to see that potassium hexamethyldisilazide was the right choice. The target molecule 8 was obtained as a single product in 54% yield (eq 41). Compound 8 was

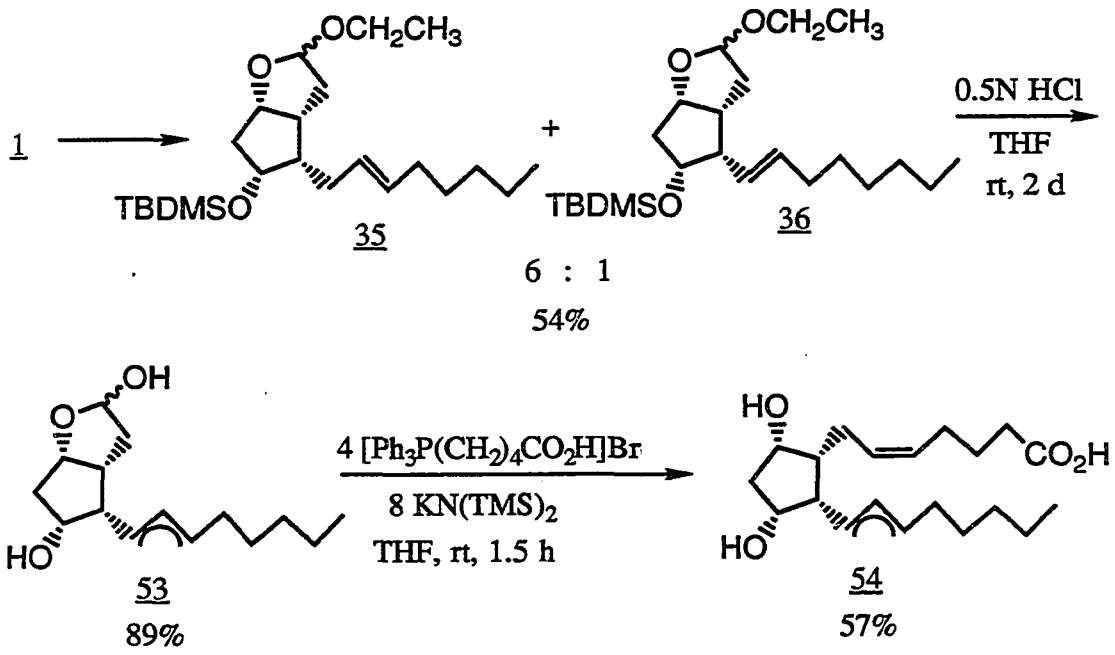


50 8 12-epi-$PGF_2\alpha$ 54% (41)

characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy, plus high resolution mass spectrometry. Also, satisfactory result was obtained in elemental analysis.

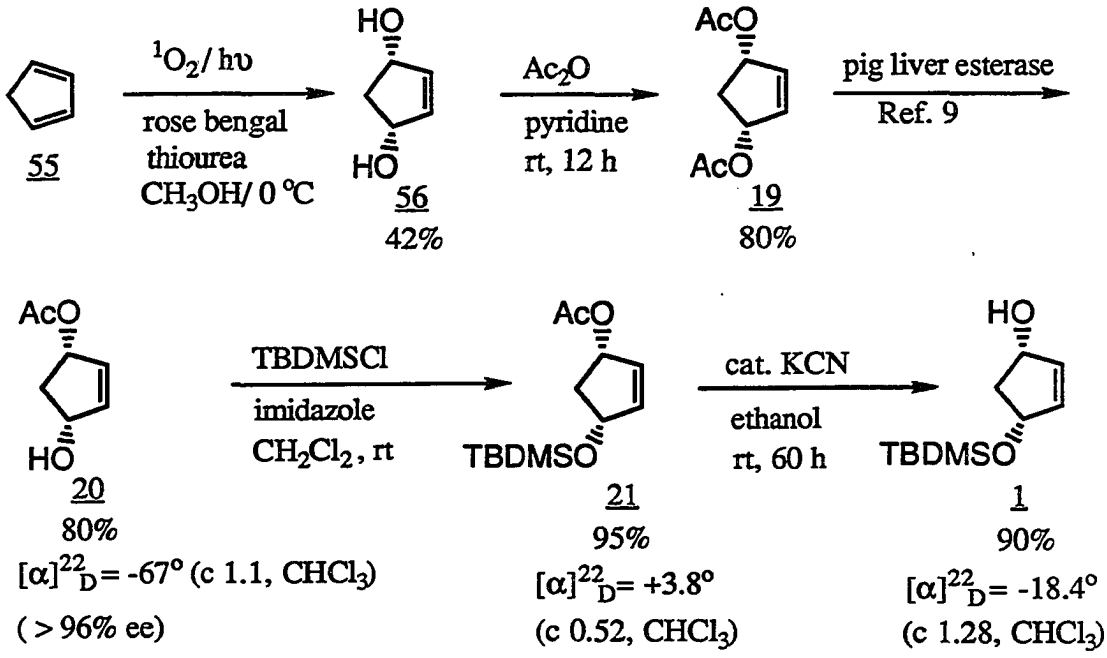
A concise, three-step synthesis of another $PGF_2\alpha$ analogue from alcohol 1 was also accomplished as shown in Scheme V. Since compounds 35 and 36 are present as an inseparable mixture in a 6:1 ratio, the product 54 should consist of a similar mixture. Due to the predominance of one isomer, the ^1H and ^{13}C NMR spectra were clean enough to identify the major product. Unfortunately, however, the two regioisomer olefins could not be separated by flash chromatography.

Scheme V.



The asymmetric synthesis of a chiral compound which has interesting pharmacological properties is of great importance. Enantiomerically pure starting material 1 was thus prepared following the sequence depicted in Scheme VI. *cis*-2-Cyclopenten-1,4-diol (56) was prepared via dye-sensitized photooxygenation in which metastable singlet

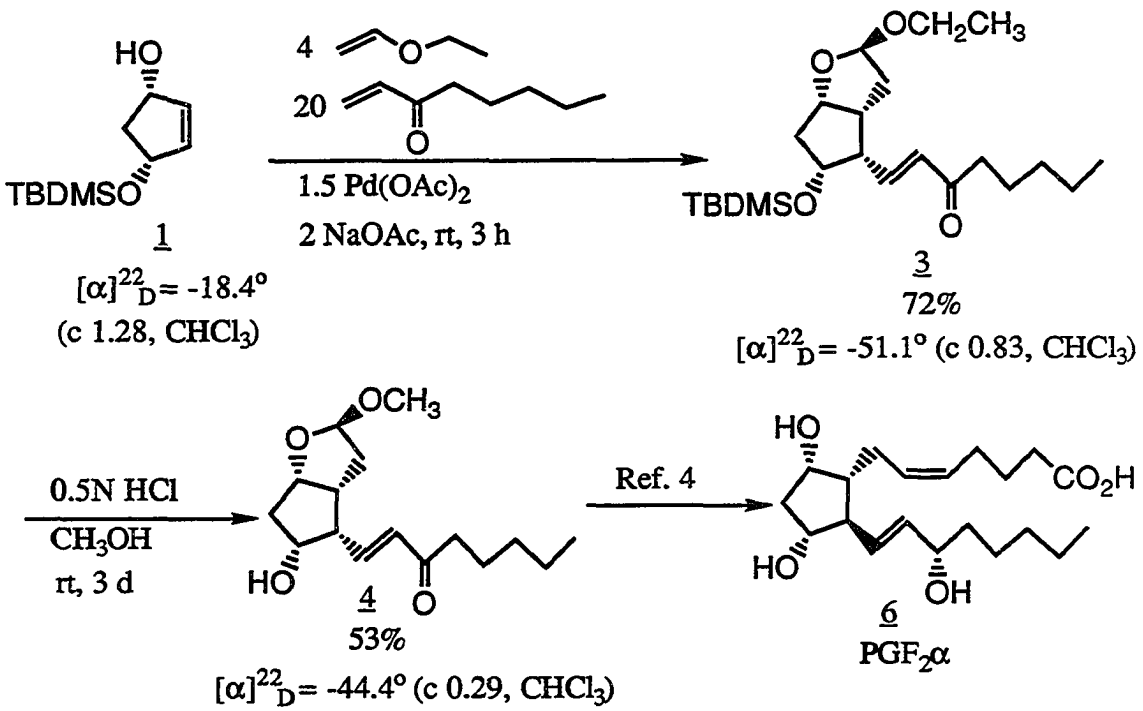
Scheme VI.



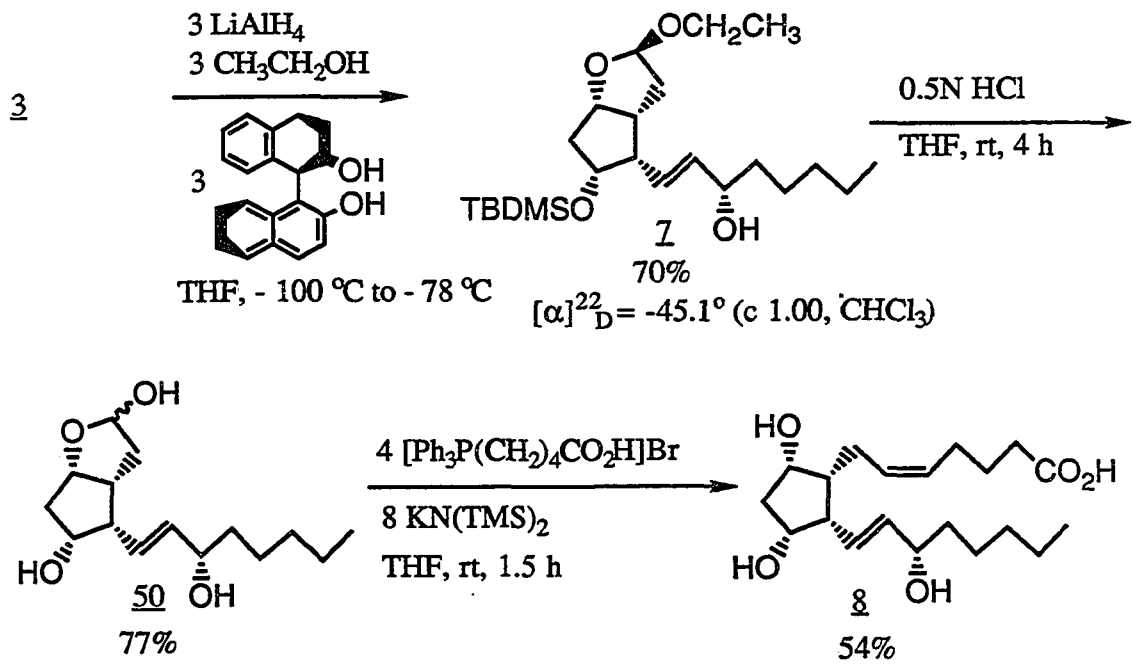
oxygen is involved[28]. The acetylation of diol 56 provided *cis*-1,4-diacetoxy-2-cyclopentene (19). Enzymatic hydrolysis[10] of prochiral diester 19 afforded the optically active monohydrolyzed product 20 ($[\alpha]^{20}_D$ = - 37.4°, c 0.82, CHCl3) in 32% yield and the starting material 19 was recovered in 66% yield. Launen and Schneider[10a] reported that compound 20 was obtained in 86% yield with $[\alpha]^{22}_D$ = - 49.7°. My poor result can be attributed to the failure to accurately control the pH of the reaction solution. Successive recrystallization with 2:1 diethyl ether/skelly B provided crystalline compound 20, $[\alpha]^{20}_D$ = - 58.6° (83% ee). Further effort to increase the ee was not successful. Later, optically pure 20 ($[\alpha]^{22}_D$ = - 67°; c 1.1, CHCl3, >96% ee) was generously provided by Professor Sih at the University of Wisconsin. Protection of the alcohol in compound 20, followed by acetyl hydrolysis,[29] was effected to give optically pure compound 1.

The asymmetric synthesis of $PGF_2\alpha$ and 12-epi-$PGF_2\alpha$ are presented in Schemes VII and VIII respectively. Since the separation of exocyclic acetal 3 from the endocyclic isomer is possible, all subsequent reactions were carried out using only the exo isomer. Thus, optical rotations were also measured on only exo isomers.

Scheme VII.



Scheme VIII.



The biological activity of optically pure 12-epi-PGF2α (8) was tested by the Bristol-Myers Squibb Institute. To our disappointment, compound 8 has relatively little biological activity against blood platelet aggregation; I_{50} > 1000 μM against ADP-induced aggregation, and I_{50} = 178.858 μM against arachidonic acid induced aggregation. The observed biological activity in compound 8 indicates that the natural configuration of the lower side chain at C-12 is of great importance in the biological activity of PGF2α.

CONCLUSION

The formal synthesis of PGF2α (6) was accomplished from optically active *cis*-4-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol (1). A palladium(II)-assisted three-component coupling approach to compound 3 was employed as the key step.

The PGF2α analogue 12-epi-PGF2α (8) was also synthesized from compound 1 in 4 steps with an overall yield of 21%. Compound 3 was used as a key intermediate. Examination of the biological activity revealed that compound 8 has relatively little activity; I_{50} >1000 μM against ADP-induced platelet aggregation, and I_{50} = 178.858 μM against arachidonic acid-induced aggregation.

A concise, three-step synthesis of the PGF2α analogue 54 from the readily available compound 1 was also accomplished.

The one-pot coupling of three different alkenes provides an efficient synthetic route to the prostaglandin framework, which can lead to a variety of prostaglandins including PGF2α and PGC2. Further exploration in this area is warranted.

EXPERIMENTAL SECTION

Equipment

NMR spectra were recorded on a Nicolet NT-300 spectrometer (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz), and chemical shifts are reported in ppm relative to TMS (δ 0.00) as an internal standard. IR spectra were obtained on an IBM IR 98. High-resolution mass spectra were recorded on a Kratos MS-50 spectrometer.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. Tetrahydrofuran was distilled over sodium benzophenone ketal and used immediately. Methanol was distilled over sodium methoxide and stored over 4Å molecular sieves. Methylene chloride was distilled over phosphorous pentoxide and stored over 4Å molecular sieves. Ethanol was distilled azeotropically by adding a small amount of benzene and stored over 4Å molecular sieves.

Preparation of racemic *cis*-4-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol (1)[30]

To a solution of 2.3 g of *cis*-2-cyclopenten-1,4-diol (56) (23.0 mmol) and 3.9 g of imidazole (34.5 mmol) in 10 ml of DMF was added dropwise at room temperature over 2 h 3.46 g of *t*-butyldimethylsilyl chloride (23.0 mmol) in 20 ml DMF. After overnight stirring at room temperature, the reaction was quenched with 10 ml of water. The solution was washed with brine (25 ml x 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography gave 1.63 g of compound 1 (33% yield) as a colorless liquid: R_f = 0.38 (2:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.95 (d, J= 5.7 Hz, 1H, C=CH), 5.90 (d, J = 5.4 Hz, 1H, C=CH), 4.66 (m, 1H, CHO), 4.59 (m, 1H, CHOSi), 2.69 (dt, J = 13.5 and 7.2 Hz, 1H, H_5), 1.66 (m, 1H, OH), 1.51 (dt, J = 13.8 and 4.2 Hz, 1H, H_5), 0.90 (s, 9H, Si^tBu), 0.89 (s, 6H, $SiMe_2$); IR (neat) 3393 (OH), 2957,

2930 cm^{-1}; HRMS m/z 213.13098 [calculated for $C_{11}H_{21}O_2Si$ $(M-H)^+$, m/z 213.13108]; Ammonia CI Mass, m/z 230.0 for $M^+ + NH_4$.

Preparation of optically pure 1[29]

A solution of compound 21 (1.5 g, 5.9 mmol, $[\alpha]^{20}_D$ = +3.8°, c 0.52, $CHCl_3$) and KCN (0.3 g) in 95% ethanol (30 ml) was stirred at room temperature for 4 d. After removal of the solvent, the residue was dissolved in ether. The solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. Purification by flash chromatography gave compound 1 (1.1 g, 90% yield, $[\alpha]^{22}_D$ = +18.4°, c 1.28, $CHCl_3$).

Preparation of 1-octen-3-one

To a solution of 1-octen-3-ol (Aldrich, 20 g, 0.16 mmol) in 50 ml of acetone at 0 °C was added 70 ml of standard Jones' reagent dropwise. After the reaction was completed as indicated by TLC analysis, it was quenched with isopropyl alcohol and water (20 ml). The solution was extracted with ether (80 ml x 2), washed with saturated aqueous NaCl (80 ml x 2) and dried over anhydrous $MgSO_4$. Concentration and vacuum distillation (68 °C/ 0.5 mm Hg) gave the product (8.0 g, 40% yield) as a light yellow liquid: ^1H NMR ($CDCl_3$) δ 6.33 (dd, J = 17.7 and 10.5 Hz, 1H, C=CHCO), 6.19 (d, J = 17.7 Hz, 1H, HC=CHCO), 5.78 (d, J = 9.0 Hz, 1H, HC=CHCO), 2.55 (t, J = 7.2 Hz, 2H, CH_2CO), 1.60 (m, 2H, CH_2), 1.29 (m, 4H, CH_2CH_2), 0.87 (t, J = 6.6 Hz, 3H, CH_3)

Preparation of optically pure 3

In a vial were placed compound 1 (195 mg, 0.91 mmol, $[\alpha]^{22}_D$ = +18.4°, c 1.28, $CHCl_3$), ethyl vinyl ether (262 mg, 3.6 mmol), 1-octen-3-one (2.3 g, 18.2 mmol), sodium acetate (149 mg, 1.8 mmol) and sodium iodide (27 mg, 0.18 mmol). The reaction mixture was stirred for 3 min at room temperature. To this was added palladium acetate (306 mg, 1.4 mmol). After stirring for 3 h at room temperature, the reaction mixture was filtered through a small silica gel pad using 1:1 hexane/ EtOAc. The solution was concentrated under reduced

pressure, and the residue was purified by flash chromatography with 6:1 to 2:1 hexane/EtOAc to give compound 3 (269 mg, 72% yield) as a diastereomeric mixture. Exo isomer: $[\alpha]^{22}_D$ = -51.1° (c 0.83, $CHCl_3$); R_f = 0.41 (4:1 hexane/EtOAc); ^1H NMR($CDCl_3$) δ 6.93 (dd, J = 16.2 and 8.7 Hz, 1H, HC=CHCO), 6.08 (dd, J = 16.2 and 0.9 Hz, 1H, HC=CHCO), 5.10 (d, J = 4.5 Hz, 1H, ROCHOR'), 4.61 (dd, J = 7.2 and 6.9 Hz, 1H, CHOR), 4.19 (dd, J = 3.9 and 4.2 Hz, 1H, CHOSi), 3.64 (ddq, J = 6.9 and 7.2 and 9.6 Hz, 1H, OCH_2CH_3), 3.37 (ddq, J = 6.9 and 7.2 and 9.6 Hz, 1H OCH_2CH_3), 2.99 (dt, J = 16.5 and 8.4 Hz, 1H), 2.58 (dd, J = 4.2 and 8.7 Hz, 1H), 2.51 (dt, J = 7.5 and 2.4 Hz, 2H), 2.33 (ddd, J = 12.8 and 8.5 and 4.2 Hz, 1H), 1.98 (d, J = 15.0 Hz, 1H), 1.90 (dd, J = 6.9 and 4.5 Hz, 1H), 1.83 (dd, J = 12.3 and 9.3 Hz, 1H), 1.58(m, 2H), 1.28 (m, 4H), 1.14 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 0.86 (t, J = 6.1 Hz, 3H, CH_3), 0.83 (s, 9H, *t*-BuSi), 0.01 (s, 3H, SiMe), -0.02 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$) δ 200.60, 145.33, 132.04, 105.12, 83.26, 77.68, 62.14, 50.19, 45.80, 42.21, 39.51, 33.78, 31.53, 25.69, 24.18, 22.47, 17.96, 15.28, 14.43, - 4.46, - 5.44; IR (neat) 2959, 2930, 1676 (C=O), 1474, 1371, 1254, 1107 cm^{-1}; HRMS calculated for $C_{23}H_{41}O_4Si$ 409.27742, found 409.27796. Endo isomer: R_f = 0.32 (4:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.07 (dd, J =16.2 and 9.6 Hz, 1H, HC=CHCO), 5.96 (d, J = 16.2 Hz, 1H, HC=CHCO), 5.07 (t, J = 8.1 Hz, 1H, OCHRO), 4.53 (m, 1H, CHOR), 4.19 (m, 1H, CHOSi), 3.79 (m, 1H, OCH_2), 3.45 (m, 1H, OCH_2), 2.72-2.29 (m, 8H), 1.59 (m, 2H), 1.29 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 6.6 Hz, 3H, CH_3), 0.85 (s, 9H, *t*-BuSi), 0.02 (s, 3H, SiMe), -0.02 (s, 3H, SiMe).

Preparation of compound 3 from compound 38

Dimethoxy-2-oxoheptylphosphonate (Aldrich, 66 mg, 0.30 mmol) in dry DME (5 ml) at 0 °C, was treated in portions with NaH (50% dispersion in oil, 14 mg, 0.30 mmol) with stirring. The mixture was allowed to warm to room temperature, and stirring was continued

for 1 h. The gel formed was transferred with swirling to a solution of aldehyde 38 (63 mg, 0.20 mmol) in dry DME (2 ml), and the resultant mixture was passed through silica gel to obtain 97 mg of crude product. The crude product was very clean by ^1H NMR spectral analysis and identified to be compound 3 (ca. 90% yield).

Preparation of optically pure 4

To a solution of compound 3 (47 mg, 0.11 mmol, $[\alpha]^{22}_D = -51.1^o$, c 0.83, $CHCl_3$) in 3.4 ml of methanol was added 0.11 ml of 0.5N aqueous HCl at room temperature. After being stirred for 3 d at room temperature, the mixture was neutralized by aqueous NaOH, then poured into 60 ml of $CHCl_3$. The overall solution was washed with saturated aqueous NaCl. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed with 1:1 hexane/EtOAc to give 17 mg (53% yield) of compound 4: $R_f = 0.23$ (1:1 hexane/EtOAc); $[\alpha]^{22}_D = -44.4^o$ (c = 0.29, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.01 (dd, J = 16.2 and 8.1 Hz, 1H, HC=CHCO), 6.21 (dd, J = 16.2 and 0.9 Hz, 1H, HC=CHCO), 5.04 (d, J = 4.8 Hz, 1H, OCHRO), 4.07 (t, J = 6.3 Hz, 1H, CHOR), 4.22 (m, 1H, -CHOH), 3.29 (s, 3H, OCH_3), 3.01 (ddt, J = 17.1 and 2.1 and 8.7 Hz, 1H), 2.61 (m, 1H), 2.57 (t, J = 7.5 Hz, 2H, $O=CCH_2$), 2.18 (dd, J = 7.5 and 3.0 Hz, 1H), 2.04 (d, J = 7.2 Hz, 1H), 1.95 (dd, J = 13.2 and 9.6 Hz, 1H), 1.60 (m, 4H), 1.30 (m, 4H, CH_2CH_2), 0.87 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 200.69, 143.74, 132.68, 105.89, 83.89, 72.22, 54.38, 50.17, 44.45, 40.92, 40.07, 36.11, 31.53, 24.04, 22.52, 13.97; IR (neat) 3450 (OH), 2940, 2920, 1660 (C=O), 1090, 1040 cm^{-1}; HRMS m/z 281.17466 [calculated for $C_{16}H_{25}O_4$ $(M-H)^+$, m/z 281.17529], m/z 264.17160 [calculated for $C_{16}H_{24}O_3$ $(M-H_2O)^+$, m/z 264.17253]; Ammonia CI Mass, m/z 300.2 for $M^+ + NH_4$. The ^1H NMR spectra for these compounds are identical to those found in supplementary material in the literature[5].

Preparation of optically active 7[25]

To a solution of $LiAlH_4$ (Aldrich, 0.539M in THF, 4.0 ml, 2.2 mmol) was added ethanol (2M in THF, 1.1 ml, 2.2 mmol) dropwise over 10 min at room temperature. Subsequently, a THF solution of (S)-binaphthol (Aldrich, $[\alpha] = -34^{o}$, 607 mg in 4.3 ml THF, 2.2 mmol) was added dropwise, and the resulting mixture was stirred for 30 min at room temperature. To this was added the enone 3 [330 mg in 2.6 ml of THF, 0.80 mmol, $[\alpha]^{22}_{D} = -51.1^{o}$ (c 0.83, $CHCl_3$)] dropwise over 3 min at -100 °C (liq. N_2 and methanol bath). The reaction mixture was stirred for 2 h at -100 °C, and then for another 2 h at -78 °C. Methanol (1 ml) was added at -78 °C to destroy the excess reducing agent and the mixture was allowed to warm to room tempoerature. After the addition of water (25 ml) and diethyl ether (30 ml), stirring was continued for 10 min. The reaction solution was neutralized with 2N aqueous HCl, and extracted with ether (3 x 30 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography with 3:1 hexane/EtOAc to give compound 7 (232 mg, 70% yield) as an oil: $[\alpha]^{22}_{D} = -45.1^{o}$ (c 1.00, $CHCl_3$); $R_f = 0.40$ (3:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.80 (dd, J = 15.9 and 8.4 Hz, 1H, HC=C), 5.53 (dd, J = 15.9 and 7.2 Hz, 1H, C=CH), 5.11 (d, J = 4.8 Hz, 1H, OCHROEt), 4.65 (t, J = 7.2 Hz, 1H, CHOR), 4.12 (m, 1H), 4.06 (m, 1H), 3.68 (dq, J = 7.2 and 9.6 Hz, 1H, $OC\underline{H}_2CH_3$), 3.38 (dq, J =7.2 and 9.6 Hz, 1H, $OC\underline{H}_2CH_3$), 2.94 (m, 1H), 2.45 (dt, J = 4.2 and 8.1 Hz, 1H), 2.35 (ddd, J = 12.6 and 8.1 and 4.8 Hz, 1H), 1.95 (d, J = 15.0 Hz, 1H), 1.84 (m, 1H), 1.80 (dd, J = 12.3 and 9.3 Hz, 1H), 1.50 (m, 2H), 1.38 (d, J = 1.2, 1H), 1.29 (m, 6H, CH_2's), 1.17 (t, J = 7.2 Hz, 3H, CH_3), 0.89 (m, 3H), 0.87 (s, 9H, *t*-BuSi), 0.03 (s, 3H, SiMe), 0.01 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$) δ 135.13, 129.74, 105.27, 83.23, 77.62, 73.44, 62.14, 50.00, 45.77, 42.18, 37.29, 35.85, 31.84, 25.83, 25.22, 22.67, 18.10, 15.37,

14.01, -4.97; IR (neat) 3472 (OH), 2957, 2928, 1472, 1464, 1371, 1254 cm^{-1}; HRMS m/z 411.29318 [calculated for $C_{23}H_{43}O_4Si$ $(M-H)^+$, m/z 411.29306]

Preparation of optically active 12-epi-PGF2α (8)

To a solution of (4-carboxybutyl)triphenylphosphonium bromide (Aldrich, dried for 12 h at 100 °C under reduced pressure, 706 mg, 1.6 mmol) in 6.5 ml of freshly distilled THF was added KHMDS (Aldrich, 0.5 M in THF, 6.6 ml, 3.3 mmol) at room temperature under N_2 gas. At this point the reaction mixture turned a deep red color. The reaction was stirred for 15 min at room temperature. To this was slowly added the lactol 50 (110 mg, 0.41 mmol) in 1.5 ml of THF. The reaction mixture turned a deep brown color. After being stirred for 1.5 h at room temperature, the reaction mixture was quenched by the addition of water (25 ml). The reaction mixture was washed with ethyl acetate (25 ml) to remove any organic soluble material. The aqueous layer was acidified by adding 2N aqueous HCl. The solution was extracted with CH_2Cl_2 (20 ml x 2). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography with EtOAc/ MeOH/ HOAc (90 ml/ 15 ml/ 0.1 ml) to give 12-epi-PGF2α (8, 77 mg, 54% yield) as a white solid: R_f = 0.29 (EtOAc/ MeOH/ HOAc (90 ml/ 15 ml/ 0.1 ml); ^1H NMR ($CDCl_3$) δ 5.90-5.70 (br s, 3H, OH's), 5.80 (dd, J = 15.0 and 10.5 Hz, 1H, HC=C), 5.49 (dd, J = 15.0 and 6.9 Hz, 1H, C=CH), 5.38 (m, 2H, HC=CH), 4.19 (m, 2H), 4.10 (m, 1H), 2.72 (m, 1H), 2.32 (t, J = 6.6 Hz, 2H), 2.27 (m, 1H), 2.13 (m, 4H), 1.86 (m, 2H), 1.66 (m, 3H), 1.50 (m, 2H), 1.28 (m, 6H, CH_2's), 0.87 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.06, 187.07, 129.81, 129.29, 129.01, 75.41, 73.51, 72.89, 50.00, 47.15, 42.56, 36.83, 33.18, 31.85, 26.52, 25.30, 24.58, 24.29, 22.72, 14.14; IR (neat) 3387 (OH), 2926, 2856, 1707 (CO_2H), 1439, 1410 cm^{-1}; HRMS m/z 336.22945 [calculated for $C_{20}H_{32}O_4$ $(M-H_2O)^+$, m/z 336.23006]; Ammonia

CI Mass m/z 372.4 (M^++ NH_4). Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.77; H, 9.67. Found C, 67.57; H, 9.52.

Preparation of *cis*-3,5-diacetoxy-1-cyclopentene (19)

To a solution of the diol 56 (1.17 g, 11.7 mmol) in pyridine (2.81 ml, 35.1 mmol) was added 2.59 ml (23.4 mmol) of acetic anhydride dropwise over 30 min at room temperature. After being stirred at room temperature for 15 h, the reaction mixture was poured into 50 ml of water. The overall mixture was extracted with ether (2 x 50 ml). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography with 2:1 hexane/EtOAc yielded compound 19 (1.72 g, 80% yield): ^1H NMR ($CDCl_3$) δ 6.06 (s, 2H, HC=CH), 5.52 (dd, J = 7.5 and 3.9 Hz, 2H, HCOAc), 2.87 (dt, J = 15.0 and 7.5 Hz, 1H), 2.04 (s, 6H, O=CCH_3), 1.71 (dt, J = 15.0 and 3.9 Hz, 1H).

Preparation of optically active *cis*-4-acetoxy-2-cyclopenten-1-ol[9a] (20)

Diacetate 19 (1.71 g, 9.3 mmol) suspended in a 0.1 M phosphate buffer (18 ml, pH = 7.0, T = 32 °C) was treated with 1.3 mg (130 unit) of porcine liver esterase (Sigma) with stirring. By continuous addition of a 0.1N aqueous NaOH solution, the pH was kept constant during the hydrolysis. After being stirred for 2 days, the mixture was extracted with ether. Concentration and flash chromatography afforded compound 20 (0.43 g, 32% yield) as a colorless liquid: $[\alpha]^{22}_D$ = -37.4° (c 0.87, $CHCl_3$, 53% ee); ^1H NMR ($CDCl_3$) δ 6.09 (ddd, J = 5.4 and 1.8 and 1.2 Hz, 1H, HC=C), 5.96 (ddd, J = 4.5 and 1.8 and 0.9 Hz, 1H, C=CH), 5.47 (m, 1H), 4.696 (m, 1H), 2.78 (dt, J = 14.7 and 7.5 Hz, 1H), 2.03 (s, 3H, O=CCH_3), 1.81 (m, 1H), 1.63 (dt, J = 14.4 and 3.9 Hz, 1H); IR (neat) 3412 (OH), 1736 (CO) cm^{-1}.

Preparation of optically active *cis*-3-acetoxy-5-*t*-butyldimethylsilyloxy-1-cyclopentene (21)

To a solution of compound 20 (371 mg, 2.6 mmol, $[\alpha]^{22}_{D}$ = -67.0°, c 1.1, $CHCl_3$, >96% ee) in CH_2Cl_2 (15 ml) were added imidazole (620 mg, 9.1 mmol) and *t*-butyldimethylsilyl chloride (590 mg, 3.9 mmol) at room temperature. Stirring was continued for 20 h, then the reaction was quenched with 20 ml of water. The overall mixture was extracted with hexane (2 x 50 ml). The resulting organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography gave compound 20 (637 mg, 95% yield) as a liquid: ^{1}H NMR ($CDCl_3$) δ 5.94 (dt, J = 5.1 and 1.8 Hz, 1H, HC=C), 5.85 (dt, J = 5.1 and 1.5 Hz, 1H, C=CH), 5.43 (m, 1H), 4.69 (m, 1H), 2.77 (dt, J = 13.8 and 7.2 Hz, 1H), 2.01 (s, 3H, O=CCH_3), 1.58 (dt, J = 13.8 and 5.1 Hz, 1H), 1.87 (s, 9H, *t*-BuSi), 0.09 (s, 6H, $SiMe_2$).

Epimerization of the endocyclic acetal 23 to the exocyclic acetal 24

To a solution of acetal 23 (130 mg, 0.32 mmol) in 3.0 ml of absolute ethanol was added pyridinium *p*-toluenesulfonate (21 mg, 0.08 mmol). The reaction mixture was stirred for 2 d at room temperature, then concentrated in vacuo and flash chromatographed to give acetal 24 (127 mg, 96% yield).

Compound 33

^{1}H NMR ($CDCl_3$) δ 5.15 (d, J = 5.1 Hz, 1H, ROCHR'R"), 4.68 (q, J = 7.2 Hz, 1H), 4.01 (m, 1H), 3.78 (dq, J = 9.6 and 7.2 Hz, 1H, OCH_2), 3.40 (dq, J = 9.6 and 7.2 Hz, 1H, OCH_2), 2.46 (m, 1H), 2.30 (m, 1H), 2.05 (m, 2H), 1.85 (m, 2H), 1.72 (m, 1H), 1.20 (t, J = 6.9 Hz, 3H, CH_3), 0.87 (s, 9H, *t*-BuSi), 0.04 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 105.89, 82.83, 73.38, 62.54, 43.63, 41.28, 38.90, 38.64, 25.94, 18.18, 15.21, -4.57.

Preparation of compound 35

In a vial were placed alcohol 1 (86 mg, 0.4 mmol), ethyl vinyl ether (116 mg, 1.6 mmol), 1-octene (896 mg, 8.0 mmol), sodium acetate (66 mg, 0.8 mmol) and sodium iodide (14 mg, 0.093 mmol). The reaction mixture was stirred for 2 min at room temperature, then palladium acetate (135 mg, 0.6 mmol) was added. Stirring was continued for 6 h at room temperature. The reaction mixture was passed through a silica gel pad using 3:1 hexane/ EtOAc as eluent. Concentration and flash chromatography yielded compound 35 (85 mg) in 54% yield. Later compound 35 was found to be present as a mixture with compound 36 in a 6:1 ratio. Exo isomer: R_f = 0.38 (10:1 hexane/ EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.43 (m, 2H, HC=CH), 5.09 (d, J = 4.8 Hz, 1H, ROCHR'OR"), 4.63 (t, J = 7.2 Hz, 1H, HCOR), 4.06 (t, J = 3.9 Hz, 1H, HCOSi), 3.67 (dq, J = 9.6 and 7.2 Hz, 1H, OCH_2), 3.39 (dq, J = 9.6 and 7.2 Hz, 1H, OCH_2), 2.90 (m, 1H), 2.31 (ddd, J = 12.6 and 9.3 and 4.8 Hz, 1H), 2.16 (m, 1H), 1.93 (m, 4H), 1.77 (m, 3H), 1.27 (m, 6H), 1.17 (t, J = 7.2 Hz, 3H, CH_3), 0.86 (s, 9H, *t*-BuSi), 0.86 (m, 3H, CH_3), 0.03 (s, 3H, SiMe), 0.00 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$) δ 131.36, 128.81, 105.27, 83.31, 75.94, 62.01, 47.85, 43.90, 42.16, 33.10, 32.66, 31.48, 29.78, 29.31, 25.81, 22.60, 18.02, 13.38, 14.12, -4.46, -5.12; IR (neat) 2950, 1455, 1380, 1250, 1110 cm^{-1}; HRMS m/z calculated for $C_{23}H_{44}O_3Si$ 396.30598, found 396.30499.

Ozonolysis of compound 35 to compound 37

Ozone was passed into a solution of compound 35 (50 mg, 0.13 mmol) in 3 ml of methanol at -78 °C until a green color persisted. After the reaction was flushed with N_2 at -78 °C, 0.5 ml of dimethyl sulfide was added to the reaction. Stirring was continued for 30 min at -78 °C, then for 1 h at 0 °C, and finally for an additional 20 min at room temperature. The reaction mixture was poured into 60 ml of ether. The overall solution was washed with H_2O (10 ml) and brine (10 ml). After the organic phase was dried and concentrated, the

crude product was purified by flash chromatography to give compound 37 (20 mg, 47 % yield): R_f = 0.44 (4:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 9.82 (t, J = 1.2 Hz, 1H, CHO), 5.10 (d, J = 4.8 Hz, 1H, ROCHOEt), 4.65 (t, J = 7.2 Hz, 1H, CHOR), 4.19 (t, J = 3.9 Hz, 1H, CHOSi), 3.69 (dq, J = 9.6 and 6.9 Hz, 1H, OCH_2), 3.39 (dq, J = 9.6 and 6.9 Hz, 1H, OCH_2), 3.00 (m, 1H), 2.75 (ddd, J = 18.0 and 6.3 and 1.2 Hz, 1H, CH_2C=O), 2.57 (ddd, J = 13.8 and 9.3 and 4.8 Hz, 1H, CH_2CHOEt), 2.35-2.16 (m, 2H), 1.94 (d, J = 15.0 Hz, 1H), 1.80 (m, 2H), 1.17 (t, J = 6.9 Hz, 3H, CH_3), 0.86 (s, 9H, *t*-BuSi), 0.04 (s, 3H, SiMe), 0.03 (s, 3H, SiMe).

Preparation of compound 38

Ozone was passed through a solution of the compound 45 (85 mg, 0.23 mmol) in 5 ml of methanol at -78 °C until the blue color of ozone persisted. The solution was purged with N_2, then 3 ml of dimethyl sulfide was added. After the solution had been warmed to ice bath temperature, it was stirred at that temperature for 1 h, then at room temperature for 1 h. The reaction mixture was diluted with 60 ml of ether, and then washed with water (2 x 25 ml). The aqueous layer was extracted with ether (20 ml). The combined organic layer was dried with anhydrous $MgSO_4$, then concentrated under reduced pressure. Crude product (66 mg, 90% yield) was obtained, which turned out to be pure by ^{1}H NMR spectral analysis. Subsequent purification by flash chromatography with 1:1 hexane/ EtOAc gave 55 mg (75% yield) of the product 38: R_f= 0.66 (1:1 hexane/ EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.83 (d, J = 1.5 Hz, 1H, CHO), 5.11 (d, J = 4.8 Hz, 1H, ROCHR'OEt), 4.67 (m, 2H), 3.65 (dq, J = 9.6 and 6.9 Hz, 1H, OCH_2), 3.39 (dq, J = 9.6 and 6.9 Hz, 1H, OCH_2), 3.11 (m, 1H), 2.59 (ddd, J = 8.1 and 4.2 and 1.5 Hz, 1H), 2.32 (m, 2H), 2.14 (dd, J = 12.6 and 9.3 Hz, 1H), 1.97 (d, J = 14.7 Hz, 3H, CH_3), 1.91 (ddd, J = 15.0 and 6.9 and 4.8 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H, CH_3), 0.81 (s, 9H, *t*-BuSi), 0.05 (s, 3H, SiMe), 0.01 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$) δ 202.57, 105.23, 82.92, 75.73, 62.20, 59.47, 42.20, 41.89, 36.64,

25.59, 17.86, 15.25, -4.63, -5.33; IR (neat) 2920, 2850, 1720 (C=O), 1470, 1250, 1100 cm^{-1}; HRMS m/z 313.18403 [calculated for $C_{16}H_{29}O_4Si$ $(M-H)^+$, 313.18352]; Ammonia CI Mass m/z 332.4 (M^++ NH_4).

Compound 43

R_f = 0.70 (1:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.95 (dd, J = 15.9 and 8.4 Hz, 1H, HC=CHCO), 6.09 (d, J = 15.9 Hz, HC=CHCO), 4.98 (d, J = 4.8 Hz, 1H, CHOCH3), 4.66 (t, J = 7.2 Hz, 1H, CHOR), 4.19 (m, 1H, CHOSi), 3.27 (s, 3H, OCH_3), 2.96 (m, 1H), 2.59-2.46 (m, 4H), 2.35 (ddd, J = 12.8 and 8.5 and 4.2 Hz, 1H), 2.04-1.76 (m, 3H), 1.56 (m, 2H), 1.27 (m, 4H), 0.85 (m, 12 H, CH_3 and *t*-BuSi), 0.02 (s, 3H, SiMe), -0.02 (s, 3H, SiMe).

Preparation of compound 44

To a solution of compound 3 (41 mg, 0.10 mmol) in 3.0 ml of methanol was added 0.1 ml of 2N HCl at room temperature. After the reaction was stirred for 3 d at room temperature, it was neutralized with aqueous NaOH, and then poured into 60 ml of ether. The overall solution was washed with H_2O (10 ml) and brine (10 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by passing through a silica gel pad. The product 44 (22 mg) was obtained in 77% yield as a mixture of diastereomers with R_f = 0.59 and 0.53 (1:1 hexane/ EtOAc). Diastereomer of R_f = 0.59: ^1H NMR ($CDCl_3$) δ 7.27 (d, J = 15.9 Hz, 1H, HC=C), 6.04 (m, 1H, HC=C), 6.01 (d, J = 15.9 Hz, C=CH), 5.04 (d, J = 4.8 Hz, 1H, CHOCH3), 4.82 (t, J = 6.3 Hz, 1H, CHOR), 3.49 (m, 1H), 3.34 (s, 3H, OCH_3), 2.79 (m, 1H), 2.61 (d, J = 20.1 Hz, 1H), 2.57 (t, J = 7.5 Hz, 2H), 2.29 (dd, J = 13.2 and 9.3 Hz, 1H), 1.75 (dt, J = 13.2 and 6.0 Hz, 1H), 1.60 (m, 2H), 1.28 (m, 4H, CH_2CH_2), 0.88 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 200.97, 143.41, 137.97, 137.20, 127.14, 105.81, 81.25, 54.40, 47.06, 40.65, 39.64,

38.09, 31.57, 24.19, 22.53, 13.99; IR (neat) 2920, 1660 (C=O), 1610, 1360, 1200, 1045 cm^{-1}; HRMS calculated for $C_{16}H_{24}O_3$ 264.17255, found 264.17249.

Preparation of compound 45

To a solution of compound 1 (107 mg, 0.5 mmol) in ethyl vinyl ether (108 mg, 1.5 mmol) and ethyl vinyl ketone (840 mg, 10.0 mmol) was added $Pd(OAc)_2$ (134 mg, 0.6 mmol). The resulting mixture was stirred at room temperature for 2 h, and diluted with hexane (10 ml). The mixture was filtered through silica gel and concentrated under reduced pressure. The residue was purified by flash chromatography using 4:1 hexane /EtOAc. Compound 45 (119 mg, 65% yield) was obtained as a mixture of diastereomers with R_f = 0.38 and 0.30 (4:1 hexane/EtOAc). Exo diastereomer (R_f = 0.38): ^1H NMR ($CDCl_3$) δ 6.95 (dd, J = 16.2 and 8.4 Hz, 1H, HC=C), 6.11 (d, J = 16.2 Hz, 1H, C=CHC=O), 5.12 (d, J = 4.8 Hz, 1H, ROCHR'OEt), 4.68 (t, J = 6.9 Hz, 1H, CHOR), 4.20 (m, 1H, CHOSi), 3.66 (dq, J = 9.9 and 7.2 Hz, 1H, OCH_2), 3.40 (dq, J = 9.9 and 7.2 Hz, 1H, OCH_2), 3.00 (m, 1H), 2.56 (m, 3H), 2.34 (ddd, J = 12.3 and 9.0 and 5.1 Hz, 1H), 1.99 (d, J = 14.7 Hz, 1H), 1.91 (dd, J = 6.9 and 4.5 Hz, 1H), 1.85 (dd, J = 12.6 and 9.6 Hz, 1H), 1.15 (t, J = 6.9 Hz, 3H, CH_3), 1.09 (t, J = 7.5 Hz, 3H, CH_3), 0.86 (s, 9H, *t*-BuSi), 0.03 (s, 3H, $SiCH_3$), -0.01 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 200.80, 145.16, 131.74, 105.15, 83.23, 77.72, 62.13, 50.24, 45.72, 42.23, 35.80, 32.71, 25.71, 17.20, 15.30, 8.39, -4.81, -5.18; IR (neat) 2955, 1674 (C=O), 1256 cm^{-1}.

Compound 47

^1H NMR ($CDCl_3$) δ 9.70 (d, J = 1.8 Hz, 1H, CHO), 5.22 (d, J = 4.5 Hz, 1H), 4.51 (dt, J = 3.6 and 7.2 Hz, 1H), 4.41 (q, J = 6.6 Hz, 1H), 3.69 (dq, J = 9.6 and 7.2 Hz, 1H), 3.42 (dq, J = 9.6 and 7.2 Hz, 1H), 2.94 (m, 1H), 2.69 (dt, J = 1.8 and 6.9 Hz, 1H), 2.20 (dd, J = 13.5 and 6.6 Hz, 1H), 2.13 (d, J = 13.2 Hz, 1H), 2.00 (dt, J = 12.9 and 5.3

Hz, 1H), 1.84 (ddd, J = 13.8 and 6.3 and 7.2 Hz, 1H), 1.18 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H, *t*-BuSi), 0.05 (s, 3H, SiMe), 0.04 (s, 3H, SiMe).

Compound 48

^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1H, CHO), 6.73 (m, 1H), 5.11 (d, J = 4.8 Hz, 1H), 4.80 (t, J = 6.3 Hz, 1H), 3.72 (dq, J = 9.6 and 7.2 Hz, 1H), 3.52 (m, 1H), 3.44 (dq, J = 9.6 and 7.2 Hz, 1H), 2.50 (dd, J = 21.0 and 6.0 Hz, 1H), 2.72 (d, J = 20.4 Hz, 1H), 2.31 (dd, J = 13.5 and 9.6 Hz, 1H), 1.89 (dt, J = 13.5 and 5.1 Hz, 1H), 1.20 (t, J = 7.2 Hz, 3H).

Preparation of compound 49 from aldehyde 38

To a solution of TMSOTf (Aldrich, 22.8 mg, 0.10 mmol) and triethylamine (13 mg, 0.13 mmol) in ether (5 ml) was added aldehyde 38 (27 mg, 0.085 mmol, dissolved in 4 ml of ether) dropwise at 0 °C under a N_2 atmosphere. After stirring for 2 h at 0 °C, the reaction mixture was taken up with 50 ml of ether. The mixture was washed with 25 ml of cold saturated NaCl. After drying and concentration, the mixture was purified by flash column chromatography using 6:1 hexane/EtOAc to give compound 49: 11 mg, 25% yield; R_f = 0.67 (6:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.23 (s, 1H), 5.20 (d, J = 4.8 Hz, 1H), 4.62 (m, 1H), 4.49 (m, 1H), 3.72 (dq, J = 9.9 and 7.2 Hz, 1H, OCH_2), 3.45 (m, 2H), 2.27 (m, 1H), 1.93 (m, 3H), 1.20 (t, J = 6.9 Hz, 3H), 0.87 (s, 9H, *t*-BuSi), 0.17 (s, 9H, $SiMe_3$), 0.05 (s, 3H, SiMe), 0.04 (s, 3H, SiMe).

Preparation of optically active 50

To a solution of compound 7 (220 mg, 0.53 mmol, $[\alpha]^{22}_D$ = -45.1°, c 1.00, $CHCl_3$) in 5.3 ml of THF was added 5.3 ml of 0.5N aqueous HCl at room temperature. After the reaction was stirred for 4 hr at room temperature, it was neutralized with 0.9 ml of 3N NaOH. The organic phase was extracted with CH_2Cl_2 (2 x 25 ml and then 10 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography

with 10:1 EtOAc/ MeOH gave compound 50 (111 mg, 77% yield) as an inseparable 10:8 mixture of exo and endo diastereomers: $R_f = 0.17$ (EtOAc); ^1H NMR ($CDCl_3$) δ 5.91 (dd, J = 15.0 and 8.1 Hz, 1H, HC=C), 5.82 (dd, J = 15.0 and 8.1 Hz, 0.8H, HC=C), 5.65-5.55 (m, 2.8 H), 4.50 (m, 1H), 4.84 (t, J = 6.3 Hz, 0.8H), 4.74 (t, J = 6.9 Hz, 1H), 4.21-4.07 (m, 4H), 2.88 (m, 3H), 1.69 (m, 1.2 H), 2.56 (m, 1H), 2.29-1.89 (m, 9H), 1.54 (m, 4H), 1.30 (m, 10H), 0.89 (t, J = 6.6, 6H, CH_3) (since this compound was obtained as an inseparable mixture of diastereomers in about a 10:8 ratio, the assignment and integration of proton peaks was difficult); IR (neat) 3356 (OH), 2930, 2858, 1456, 1340 cm^{-1}; HRMS m/z 252.17222 [calculated for $C_{15}H_{24}O_3$ $(M-H)^+$, m/z 252.17254]

Preparation of compound 53

To a solution containing a 6:1 mixture of compounds 35 and 36 (69 mg, 0.17 mmol) in 5.1 ml of THF was added 5.1 ml of 0.5N aqueous HCl. After the reaction was stirred for 2 d at room temperature, it was neutralized with 3N aqueous NaOH. The mixture was then extracted with ethyl acetate (25 ml x 2). The organic phase was washed with brine (15 ml), dried, and concentrated. The crude product was flash chromatographed using 1:2 hexane/ EtOAc to give compound 53 (46 mg, 84% yield) as a diastereomeric mixture: $R_f = 0.27$ (1:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.59-5.31 (m, 3H, HC=CH and ROCHOH), 4.82 (t, J = 6.6 Hz, 0.5 H), 4.72 (t, J = 6.6 Hz, 0.5 H), 4.09 (m, 1H), 3.51 (br s, 1H), 2.95-2.78 (m, 1H), 2.25-1.82 (m, 8H), 1.22 (m, 5H), 0.87 (t, J = 6.9 Hz, 3H, CH_3) [since this compound was obtained as an inseparable mixture of diastereomers, the assignment and integration of proton peaks was difficult. However, disappearance of protons corresponding to the *t*-butyldimethylsilyl (1.00-0.00 ppm) group and acetal methylene (OCH_2, 4.00-3.00 ppm) in compounds 35 and 36 was cleanly observed]; IR (neat) 3605 (OH), 3346 (OH), 2955, 1717, 1464, 1377 cm^{-1}; HRMS calculated for $C_{15}H_{26}O_3$, 254.18820, found 254.18804.

Preparation of racemic 54

To a solution of (4-carboxybutyl)triphenylphosphonium bromide (dried for 15 h under vacuum pressure at 100 °C, 559 mg, 1.29 mmol) in 5.5 ml of THF was added KHMDS (0.5 M in toluene, 5.2 ml, 2.6 mmol) at 0 °C. After the reaction mixture was allowed to warm to room temperature, it was stirred for 10 min at room temperature. To this was added compound 53 (82 mg, 0.32 mmol) in 1.5 ml of THF. The reaction mixture was stirred for 20 h at room temperature, then quenched by adding 25 ml of H_2O. After the resulting mixture was washed with 25 ml of ethyl acetate to remove organic soluble material, the aqueous layer was acidified by 2N aqueous HCl, and then extracted with CH_2Cl_2 (25 ml x 2, then 10 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using EtOAc/ MeOH/ AcOH (90 ml/5 ml/0.5 ml) to give compound 54 as a mixture of olefin isomers (62 mg, 57% yield): R_f = 0.33 (18:1 EtOAc/MeOH); ^1H NMR ($CDCl_3$) δ 5.50 (m, 4H, HC=CH, HC=CH), 4.28 (m, 1H, CHOH), 4.22 (m, 1H, CHOH), 2.36 (m, 3H), 2.15 (m, 7H), 1.97 (m, 4H), 1.80 (dt, J = 14.4 and 4.5 Hz, 1H), 1.71 (t, J = 7.5 Hz, 2H), 1.28 (m, 8H), 0.88 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.92, 131.68, 130.58, 129.77, 129.18, 75.55, 75.47, 45.80, 45.28, 41.56, 33.45, 32.63, 31.43, 29.38, 29.26, 26.68, 24.58, 23.99, 22.57, 14.12 (small peaks corresponding to minor isomer was not showed up cleary); IR (neat) 3400 (OH), 2928, 2856, 1711, 1439, 1379 cm^{-1}; HRMS calculated for $C_{20}H_{34}O_4$, 338.24572, found 338.24578.

Preparation of compound 56[28]

To a solution of rose bengal (0.3 g) and thiourea (7.8 g) in 850 ml of methanol precooled to 0 °C was added freshly distilled cyclopentadiene (12 ml, 10 g). The reaction flask was irradiated with light from a Hanovia lamp, while continuously bubbling oxygen through the solution at 0 °C. The irradiation and oxygen bubbling were stopped after 2.5 h

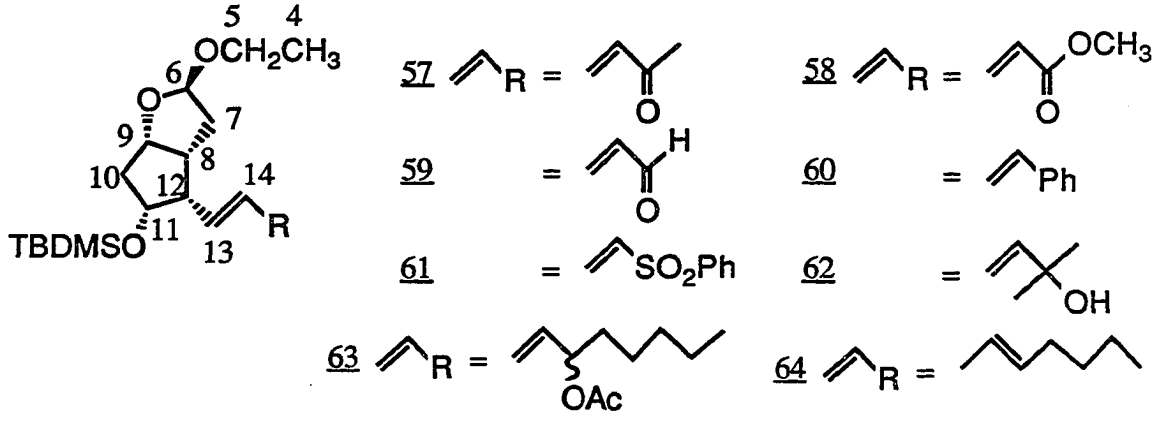
and the reaction mixture was allowed to warm to room temperature and to stand overnight. After the methanol was removed by rotary evaporator, water (200 ml) was added. The insoluble residue was filtered and the aqueous solution was washed with benzene (150 ml x 2) to remove soluble organic side products. The water layer was removed by use of a rotary evaporator. The residue was distilled under reduced pressure (bp 105 °C / 0.7 mm Hg) to give 6.35 g of the product 56 (42% yield); ^{1}H NMR ($CDCl_3$) δ 6.00 (s, 2H, HC=CH), 4.9-4.1 (m, 4H, CHOH), 2.66 (dt, J = 14.0 and 6.0 Hz, 1H, CH), 1.64 (dt, J = 14.0 and 2.1 . Hz, 1H, CH).

Typical procedure for the reactions summarized in Table 1

See preparation of compound 3.

Typical procedure for the reaction summarized in Table 2

See preparation of compound 45.



Compound 57

^{1}H NMR ($CDCl_3$) δ 6.95 (dd, J = 16.2 and 8.4 Hz, 1H, H_{13}), 6.10 (d, J = 16.2 Hz, 1H, H_{14}), 5.14 (d, J = 4.8 Hz, 1H, H_6), 4.69 (t, J = 4.5 Hz, H_9), 4.23 (m, 1H, H_{11}), 3.68 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 3.41 (dq, J = 9.6 and 7.2, 1H, H_5), 3.03 (dt, J =

16.3 and 8.4 Hz, 1H, H_{10}), 2.61 (dt, J = 4.2 and 8.4, 1H, H_{12}), 2.36 (ddd, J = 12.3 and 8.4 and 4.8 Hz, 1H, H_7), 2.26 (s, 3H, $COCH_3$), 1.51 (d, J = 15.0 Hz, H_{10}), 1.94 (dd, J = 6.6 and 4.5 Hz, 1H, H_8), 1.88 (dd, J = 12.0 and 9.0 Hz, 1H, H_7), 1.72 (t, J = 7.2 Hz, H_4), 0.88 (s, 9H, *t*-BuSi), 0.05 (s, 3H, SiMe), 0.01 (s, 3H, SiMe).

Compound 58

^1H NMR ($CDCl_3$) δ 7.10 (dd, J = 15.9 and 8.7 Hz, 1H, H_{13}), 5.86 (d, J = 15.9 Hz, 1H, H_{14}), 5.12 (d, J = 4.8 Hz, 1H, H_6), 4.67 (t, J = 6.9 Hz, 1H, H_9), 4.19 (m, 1H, H_{11}), 3.72 (s, 3H, OCH_3), 3.65 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 3.39 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 2.99 (m, 1H), 2.58 (dt, J = 3.9 and 8.4 Hz, 1H), 2.35 (ddd, J = 12.3 and 8.7 and 4.8 Hz, 1H, H_7), 2.00 (d, J = 15.0 Hz, 1H, H_{10}), 1.91-1.74 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H, CH_3), 0.86 (s, 9H, *t*-BuSi), 0.02 (s, 3H, SiMe), 0.00 (s, 3H, SiMe).

Compound 59

^1H NMR ($CDCl_3$) δ 9.52 (d, J = 8.1 Hz, CHO), 6.98 (dd, J = 15.9 and 8.7 Hz, 1H, H_{13}), 6.17 (dd, J = 15.9 and 8.1 Hz, 1H, H_{14}), 5.14 (d, J = 4.8 Hz, 1H, H_6), 4.70 (t, J = 6.9 Hz, 1H, H_9), 4.27 (m, 1H, H_{11}), 3.67 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 3.41 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 3.06 (m, 1H), 2.74 (dt, J = 3.9 and 8.1 Hz, 1H), 2.34 (ddd, J = 12.3 and 8.7 and 5.1 Hz, 1H), 2.30 (d, J = 15.0 Hz, 1H, H_{10}), 1.98-1.84 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H, H_4), 0.87 (s, 9H, *t*-BuSi), 0.05 (s, 3H, SiMe), 0.00 (s, 3H, SiMe).

Compound 60

^1H NMR ($CDCl_3$) δ 7.32 (m, 5H, Ar), 6.43 (m, 2H, H_{13} and H_{14}), 5.16 (d, J = 4.8 Hz, 1H, H_6), 4.72 (t, J = 6.9 Hz, 1H, H_9), 4.23 (m, 1H, H_{11}), 3.64 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 3.41 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 3.02 (m, 1H), 2.62 (dt, J = 4.2 and 7.2 Hz, 1H), 2.47 (ddd, J = 12.6 and 8.7 and 4.8 Hz, 1H, H_7), 2.00 (d, J = 15.0 Hz,

1H, H_{10}), 1.95-1.83 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H, H_4), 0.87 (s, 9H, *t*-BuSi), 0.03 (s, 3H, SiMe), 0.00 (s, 3H, SiMe).

Compound 61

Clean separation of this compound was difficult, because the R_f value of compound 61 is very close to that of phenyl vinyl sulfone.

Compound 62

Since this compound was obtained as a mixture of diastereomers which are difficult to separate, a clean ^1H NMR spectrum was not obtained.

Compound 63

A clean ^1H NMR spectrum could not be obtained due to the presence of 4 diastereomers.

Compound 64

^1H NMR ($CDCl_3$) δ 5.43 (m, 2H, HC=CH), 5.09 (d, J = 4.5 Hz, 1H, H_6), 4.23 (t, J = 7.2 Hz, 1H, H_9), 4.07 (m, 1H, H_{11}), 4.67 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 3.39 (dq, J = 9.6 and 7.2 Hz, 1H, H_5), 2.90 (m, 1H, H_{10}), 2.30 (ddd, J = 10.8 and 7.8 and 4.8, 1H, H_7), 2.16 (m, 1H, H_{12}), 2.01-1.89 (m, 4H), 1.81-1.70 (m, 3H), 1.31 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H, H_4), 0.87 (m, 12 H, *t*-BuSi and CH_3), 0.03 (s, 3H, SiMe), 0.00 (s, 3H, SiMe).

Typical procedure for the epimerization reaction shown in Table 3

To a solution of aldehyde 38 (10 mg, 0.03 mmol) in 1.5 ml of dry methanol was added with stirring 1.0 g of silica gel . After standing one or two days at room temperature, the reaction mixture was diluted by adding methanol, then filtered and concentrated. The crude product was analyzed by ^1H NMR spectroscopy for the characteristic aldehyde peaks (Compound 38: 9.86 ppm, d, J = 1.8 Hz. Compound 47: 9.70 ppm, d, J = 1.8 Hz. Compound 48: 9.76 ppm, s).

Typical procedure for the epimerization reaction shown in Table 4

To a solution of morpholine (96 mg, 1.1 mmol), and HOAc (199 mg, 3.3 mmol) in a mixed solvent (4.5 ml DME plus 2.2 ml H_2O) was added aldehyde 38 (14 mg, 0.44 mmol) at room temperature. After the reaction mixture was stirred for 1 d at room temperature, the organic phase was decanted with 5:1 hexane/EtOAc. The reaction solution was washed with saturated $NaHCO_3$ (10 ml) and saturated NaCl (25 ml), then dried and concentrated. The crude product (19 mg) was analyzed by ^1H NMR spectroscopy as indicated above for Table 3.

References

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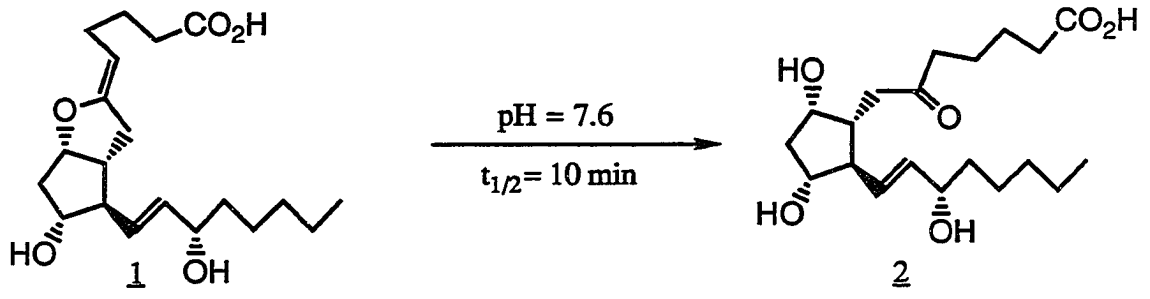
CHAPTER II. ORGANOPALLADIUM APPROACHES TO BENZOPROSTACYCLINS

INTRODUCTION

Prostacyclin (1), abbreviated PGI_2, was first discovered in 1976 by a research group at the Wellcome Laboratories[1a]. This new compound was found to be one of the most potent natural inhibitors of platelet aggregation yet discovered. Since platelet aggregation is a major risk factor for heart attack, PGI_2 is intimately involved in many of the cardiovascular disorders.

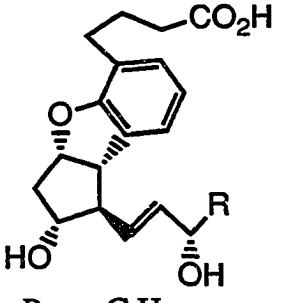


1 2

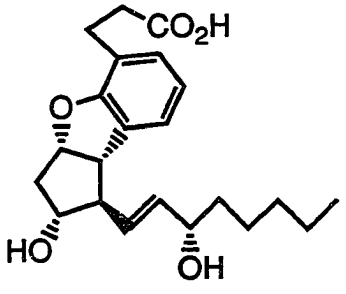
PGI_2 (1), however, is very unstable due to the labile cyclic enol ether moiety. Pharmacological evaluations revealed that PGI_2 is metabolized to biologically much less active 6-oxo-$PGF_{1\alpha}$ (2) under physiological conditions, having a half-life of 10 min[1b].

Since its discovery, many attempts have been made to synthesize chemically stable and biologically active PGI_2 analogues[2]. Some of the more important analogues involve the introduction of a phenyl ether in place of the enol ether (compounds 3[3], 4[3], 5[3] and 6[4]). Compounds 3-6 have been reported to exhibit substantial inhibition of platelet aggregation; compounds 3 and 4 inhibited ADP-induced aggregation with ED_{50}'s of 16 and 0.9 ng/mL respectively. The IC_{50} value for compound 6 against ADP-induced aggregation is 5.8 ng/mL. In addition, biological examination revealed that TRK-100 (5) has potent antiplatelet

activity and is orally and intravenously effective for a variety of thrombosis models, suggesting that it may have therapeutic value as an antithrombic drug[3b].



3 R = n-C_5H_{11}



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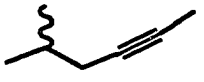
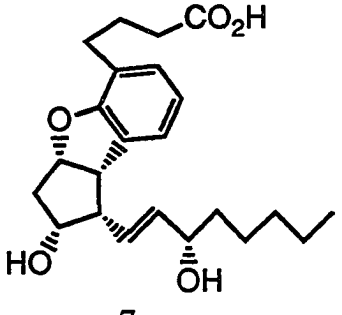
4 R = 

5 sodium salt of 4 (TRK-100)

In our continuing effort to synthesize prostaglandins utilizing palladium chemistry, we decided to examine the preparation of compound 3 and its 12-epi analogue 7. The

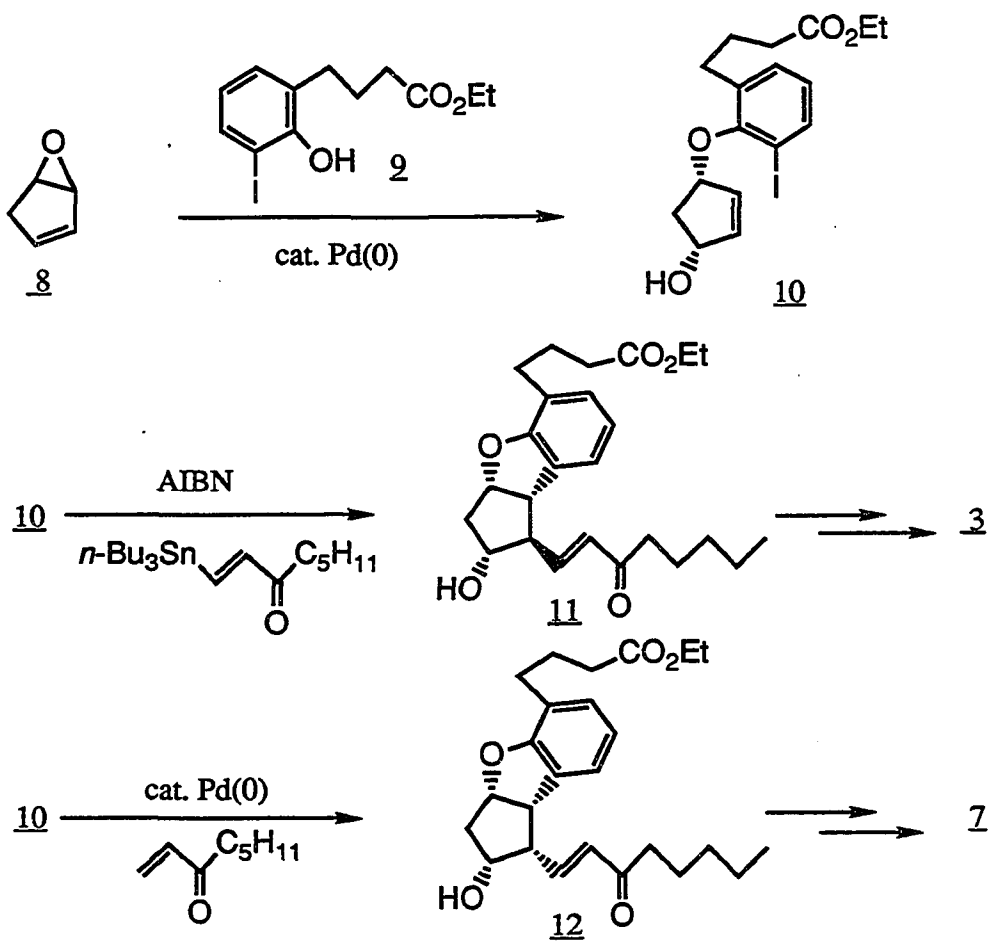


7

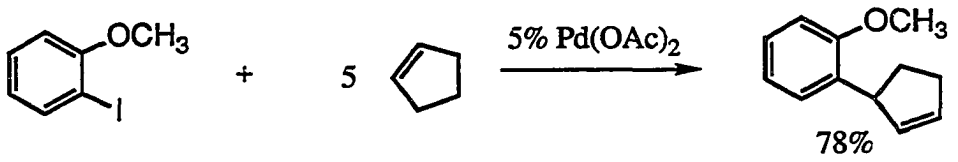
synthetic strategy is shown in Scheme I. It appeared that compound 10 could be prepared from cyclopentadiene monoepoxide (8) and functionalized phenol 9 employing palladium chemistry previously developed[5]. The key steps in these syntheses are the preparation of compounds 11 and 12 from intermediate 10. A radical promoted cyclization,

followed by β-stannyl enone trapping, previously employed in the synthesis of $PGF_{2\alpha}$[6] was envisioned for the efficient synthesis of compound 11 from compound 10.

Scheme I.

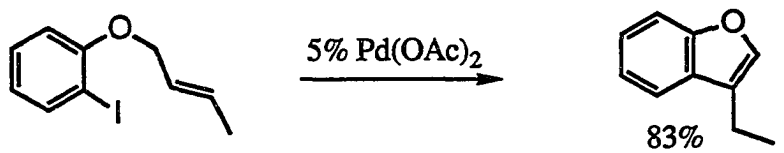


Previously, Larock and Baker[7] reported a cross-coupling reaction of aryl halides and cyclic alkenes using a catalytic amount of palladium (eq 1). Larock and Stinn[8] also utilized



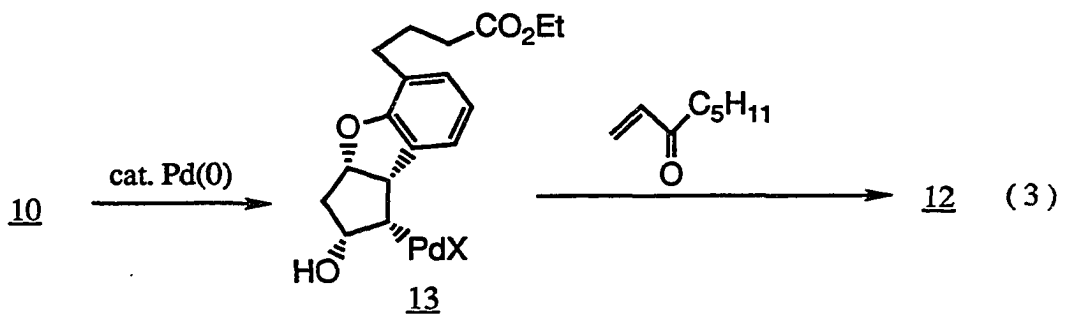
(1)

a palladium-promoted cyclization reaction for the synthesis of benzofurans (eq 2). Based on



(2)

the results in equations 1 and 2, an intramolecular organopalladium addition reaction was considered to be applicable to the synthesis of compound 12. Moreover, the resulting organopalladium intermediate 13 should be readily converted to compound 12 by trapping with 1-octen-3-one in a one-pot procedure (eq 3).

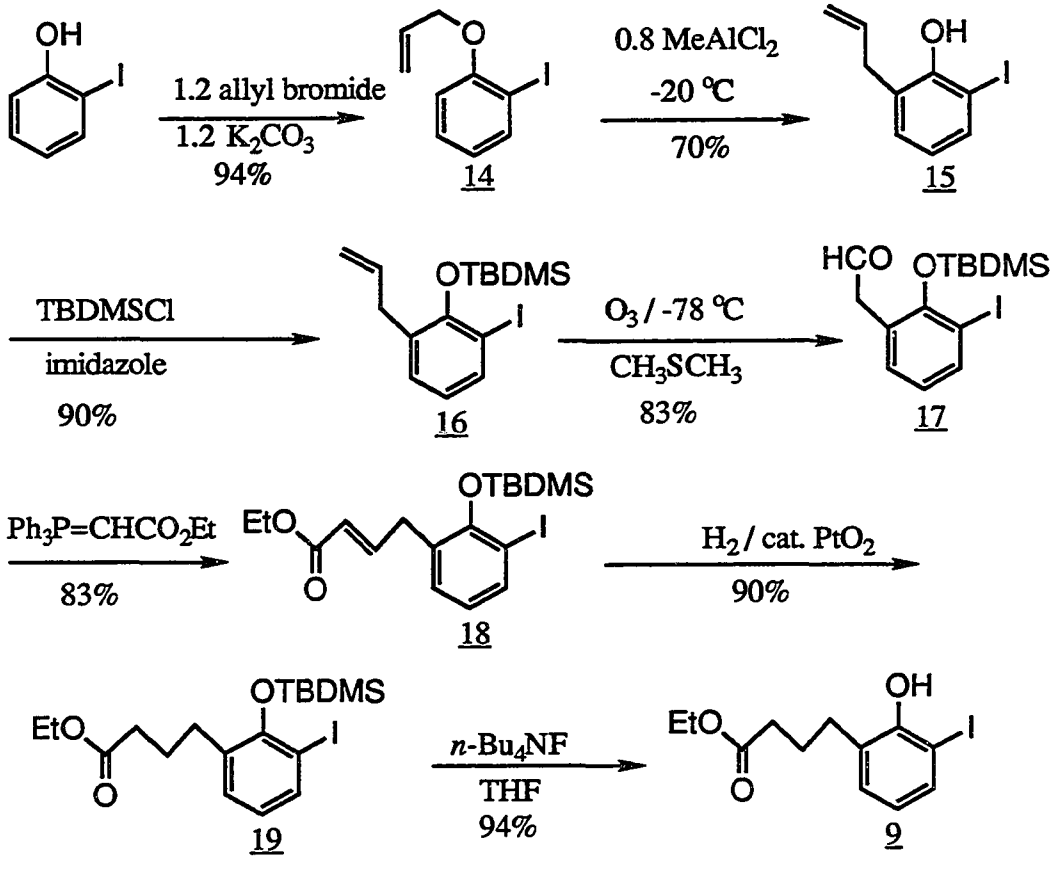


(3)

RESULTS AND DISCUSSION

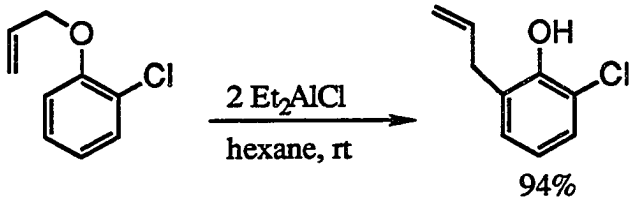
Compound 9 was synthesized by the sequence shown in Scheme II from *o*-iodophenol which is commercially available. While this approach is rather lengthy, our primary concern was to obtain sufficient amounts of compound 9 to explore subsequent chemistry. 6-Allyl-2-iodophenol (15) was obtained via Lewis acid-catalyzed Claisen

Scheme II.



rearrangement of ether 14. When compound 14 was subjected to thermal rearrangement either neat or in high boiling solvents, such as decalin or diphenyl ether, a 1:1 mixture of

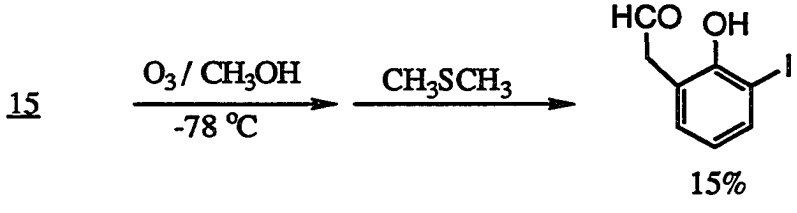
ortho- and para- rearranged products was obtained in about 20% yield. A literature survey showed[9] that allyl *o*-chlorophenyl ether undergoes clean rearrangement to only the ortho-isomer when promoted by diethylaluminum chloride (eq 4). This led us to examine Lewis



(4)

acids as possible catalysts. Employment of Et_2AlCl or $BF_3{\cdot}OEt_2$ provided no reaction. Only starting material was recovered. With $MeAlCl_2$ at -20 °C, however, the desired product 15 was obtained in a >20:1 isomeric ratio as indicated by ^1H NMR spectral analysis.

It was envisioned that ozonolysis of the terminal olefin in compound 15, followed by a Wittig reaction and hydrogenation of the resulting unsaturated ester would lead to compound 9. The major problem encountered was that treatment of compound 13 with ozone afforded only 15% of the desired product. Most of the starting material provided unidentified products (eq 5). To avoid the phenolic hydroxy group that may complicate the

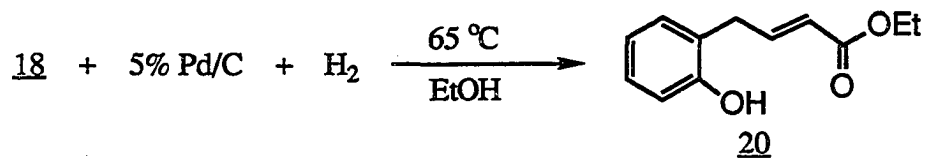


(5)

ozonolysis reaction, the silyl protected compound 16 was subjected to ozonolysis. Fortunately, good results were obtained with compound 16 providing the desired product 17

in 88% yield. The subsequent Wittig reaction was quite routine and gave compound 18 efficiently.

Attempts to reduce α,β-unsaturated ester 18 to saturated compound 19 failed using hydrogen and Pd/C as a catalyst; only compound 20 was obtained (eq 6). The use of PtO_2 as a catalyst, however, led to compound 19 along with reduced product 20 (eq 7). When a



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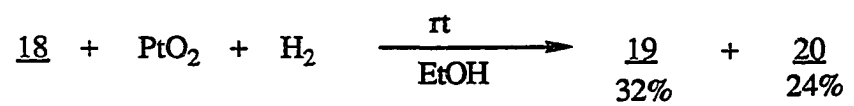
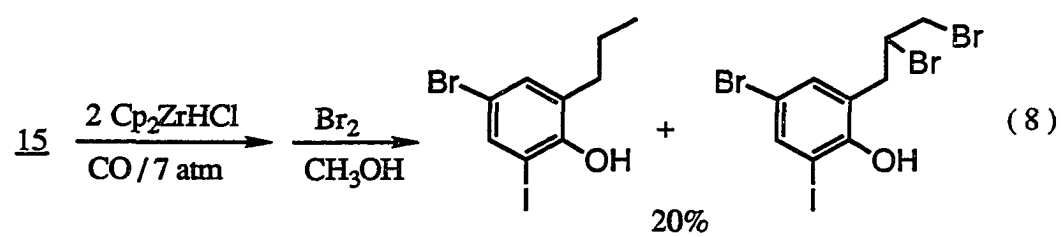


(7)

small amount of aqueous HCl was added, the reaction gave the desired product 19 in 90% yield. The subsequent deprotection was effected with *n*-Bu4NF in THF at -78 °C to give compound 9 in 94% yield.

In an effort to avoid the many steps utilized in going from compound 15 to compound 9 in Scheme II, hydrocarboxylation was attempted using either zirconium[10], borane[11] or palladium[12] reagents to obtain compound 9 in a single step (eqs 8-10). The desired product



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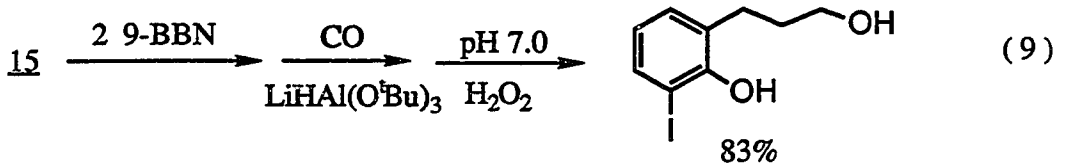

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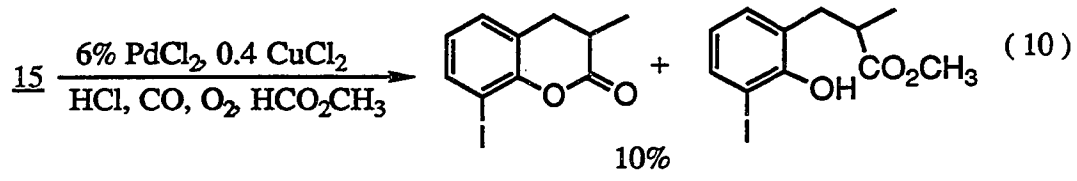
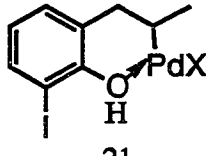


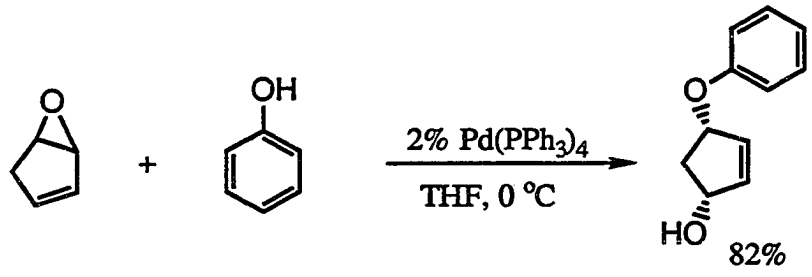
(10)

9, however, was not obtained, probably due to the poor hydrozirconation reaction in equation 8, and the ineffective carboxylation reaction in equation 9. In the reaction of equation 10, the carbonyl group was added to the internal carbon of the olefin. The phenolic oxygen was probably chelated to the Pd metal to form an organopalladium intermediate such as 21. No further attempts were made to shorten the synthesis of compound 9.



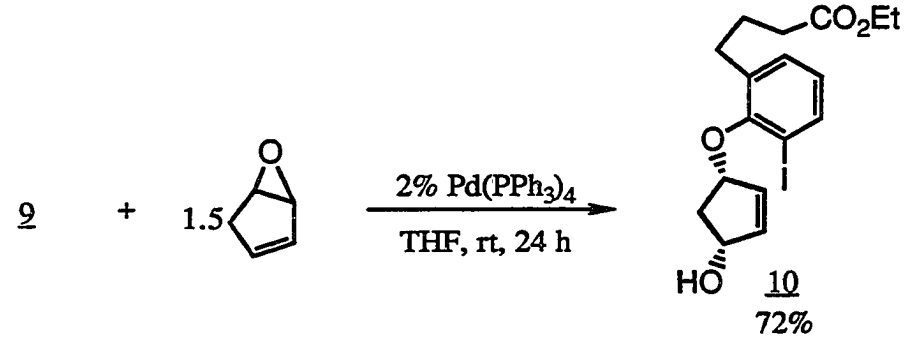
21

With compound 9 at hand, the preparation of compound 10 was examined. Deardorff and co-workers[5] in 1984 reported that treatment of cyclopentadiene monoepoxide and phenol in the presence of a catalytic amount of Pd(0) species provided *cis*-4-phenoxy-2-cyclopenten-1-ol (eq 11). The procedure illustrated in equation 11 proved to be quite efficient for the

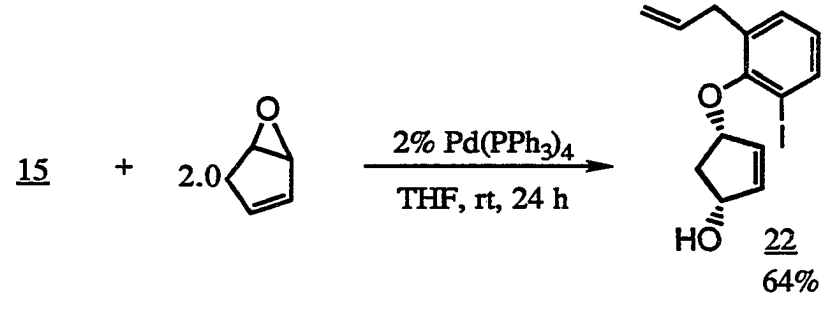


(11)

synthesis of compound 10 (eq 12). Compound 22 was also prepared employing the same procedure (eq 13). It is worth commenting that the iodide functionalities in compounds 10



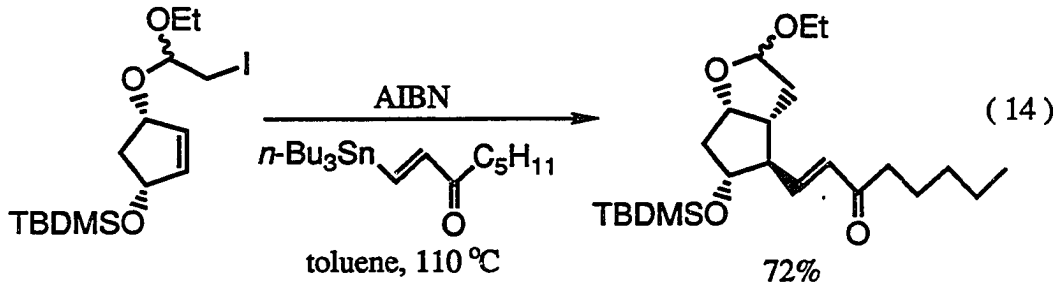
(12)



(13)

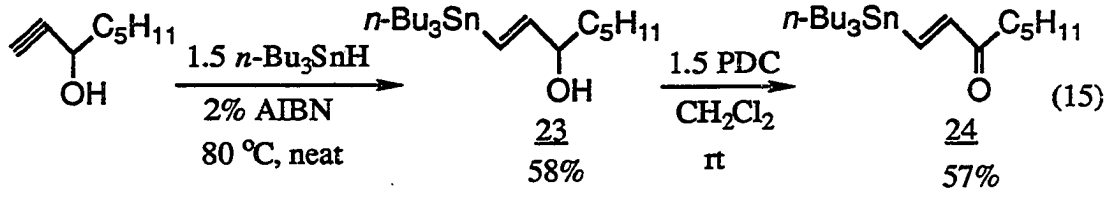
and 22 are unreactive toward Pd(0) attack under the reaction conditions.

Stork and co-workers[6a] reported a radical cyclization-trapping method for the construction of the $PGF_{2\alpha}$ framework. Keck and Burnett[6b] later improved this procedure employing a β-stannyl enone as a radical trapping reagent (eq 14).



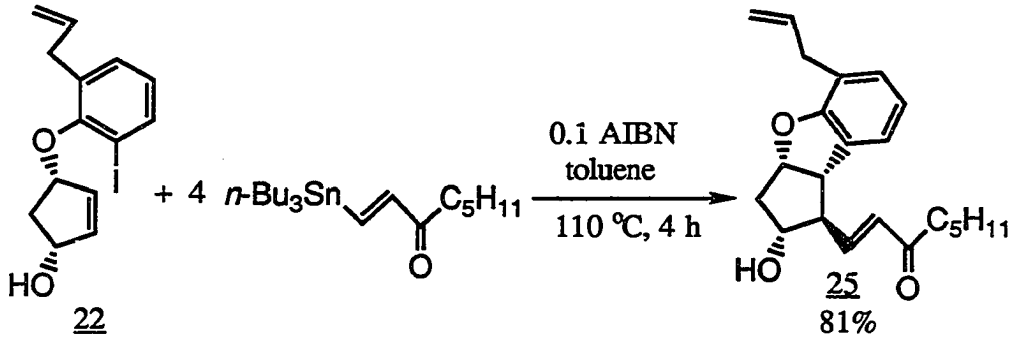
(14)

We decided to apply the basic procedure employed in equation 14 to the synthesis of compound 11. β-Stannyl enone 24 was prepared following the literature precedure[13] (eq 15).



(15)

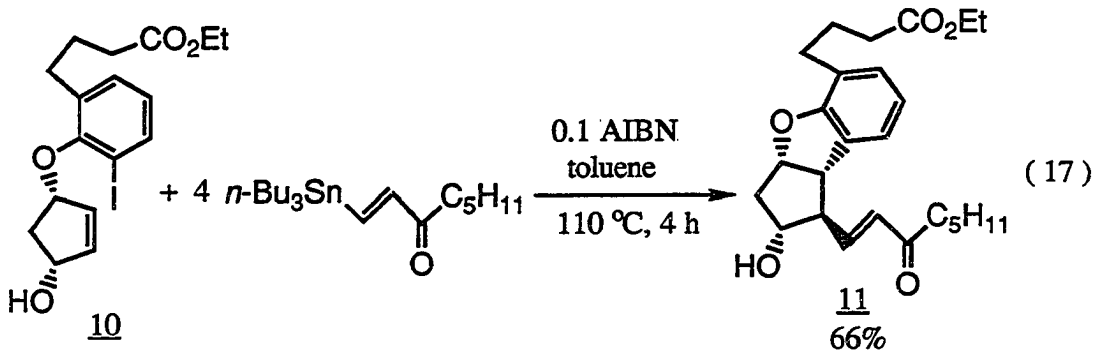
Compound 22 was subjected to Keck's reaction conditions as a model study. Quite pleasantly, the desired product 25 was obtained as a single diastereomer in 81% yield (eq 16). Considering that there are relatively few examples of the use of aryl radicals in organic



(16)

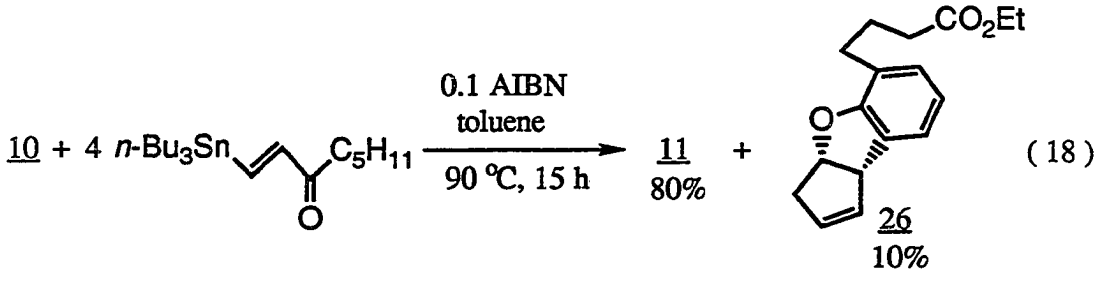
synthesis[14], it is of interest to find that compound 25 was prepared efficiently.

Upon conducting the reaction with compound 10, product 11 was obtained in 66% yield (eq 17). Conducting the reaction at 90 °C, instead of at 110 °C, increased the yield of



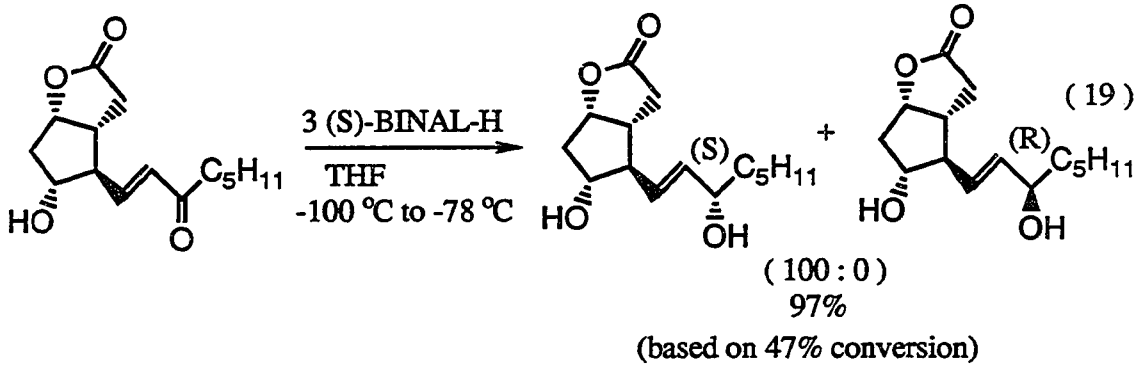
(17)

the product to 80% (eq 18). The only side-product was the eliminated product 26.



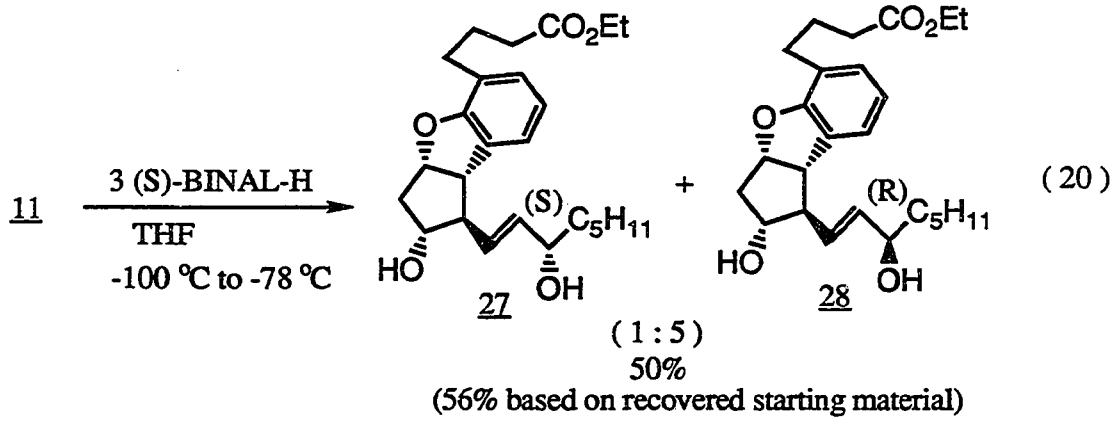
(18)

The diastereoselective reduction of the enone in compound 11 was attempted. Noyori and co-workers previously[15] reported that (S)-BINAL-H shows an excellent enantioselectivity in reducing α,β-unsaturated ketones in a predictable manner. They also showed[15] that (S)-BINAL-H can be applicable to the reduction of enone side chains in prostaglandins to provide the desired 15-(S) configuration (eq 19). Thus, we used



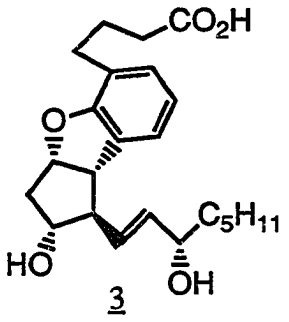
(19)

(S)-BINAL-H to obtain compound 29 by a diastereoselective reduction of ketone 11 (eq 20). To our surprise, the 15-(R) isomer 28 was apparently obtained as the major product from



(20)

compound 11. The stereochemistry at C_{15} was assigned based on the polarity of the products 3 and its 15-(R) diastereomer 29 already known in the literature[3c]. According to the



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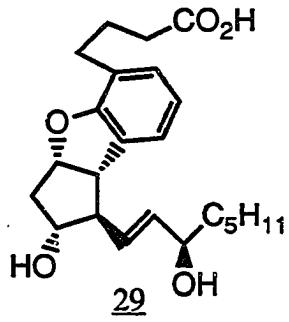


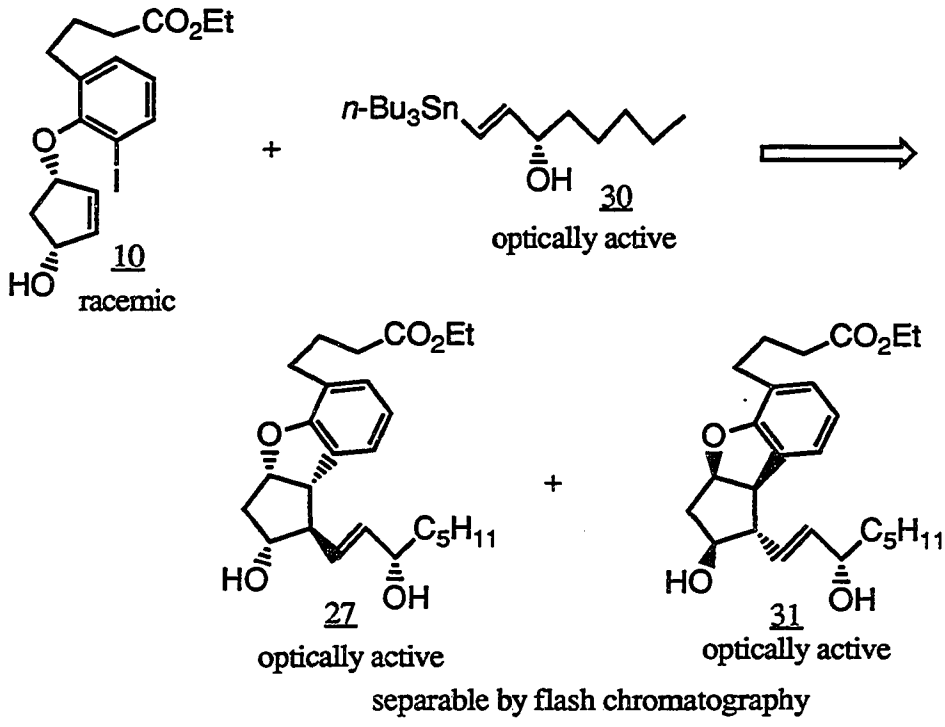
29

Literature[3c], the more polar isomer which has been assigned as the 15-(S) isomer 3 has more biological activity. They also cited an X-ray analysis underway. Eventually, the stereochemistry at C_{15} was assigned after compounds 27 and 28 were converted to acids 3 and 29. The 15-(S) isomer 27 and 15-(R) isomer 28 show a big difference in polarities (R_f = 0.17 for compound 27 and R_f = 0.38 for compound 28 in 1:2 hexane/EtOAc).

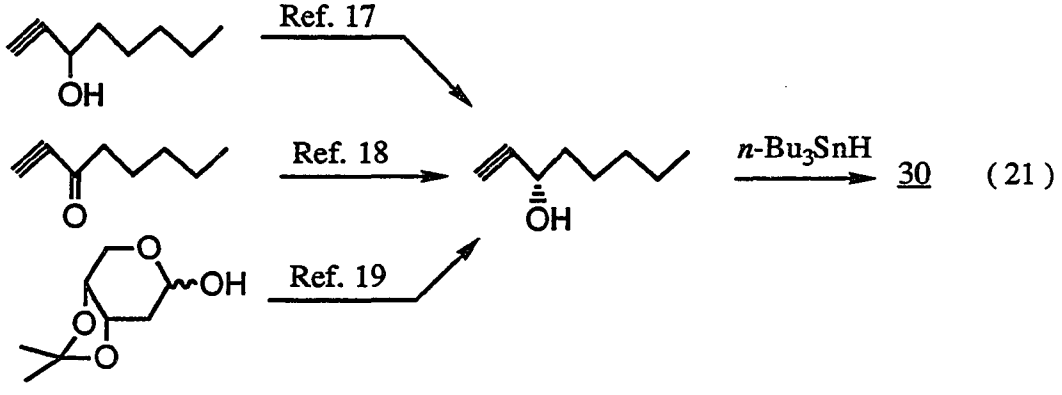
The unusual reversed stereoselectivity of (S)-BINAL-H in this reaction is interesting. It is known[16] that the reactivity of BINAL-H toward carbonyl substrates is influenced by steric effects and various electronic factors including the LUMO energy levels. One might suppose that the π-electrons present in the phenyl ring in compound 11 are responsible for the unexpected result shown in equation 20.

A more direct pathway to compound 27 would appear to involve the use of γ-stannyl allylic alcohol 30 as a radical trapping reagent. It was of great interest to ascertain whether optically active alcohol 30 would provide the optically active product 27 from the racemic compound 10 (Scheme III).

Scheme III.

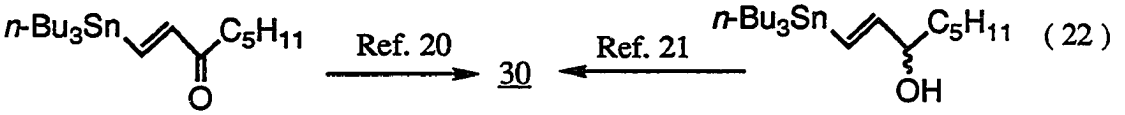


Several different procedures have been reported for the synthesis of allylic alcohol 30 in up to 99% ee. These include the preparation of optically pure 1-octyn-3-ol, followed by hydrostannylation (eq 21). In addition, the stereoselective reduction of the corresponding β-



(21)

stannyl enone or kinetic resolution of the β-stannyl allylic alcohol have been reported to afford enantiomerically pure alcohol 30 (eq 22).



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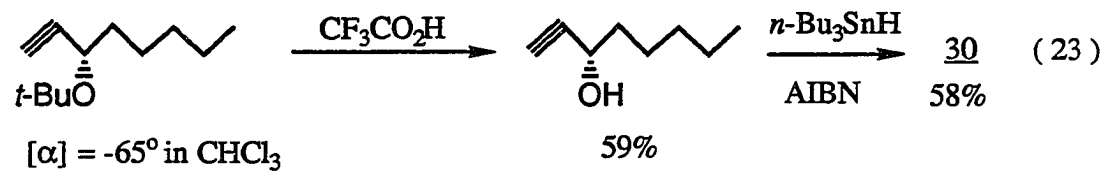
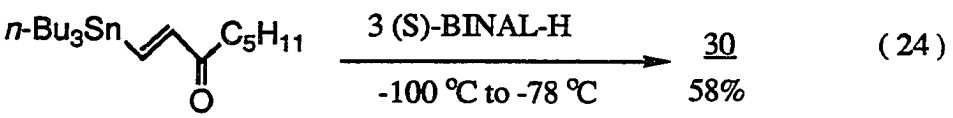
Indeed, optically pure alcohol 30 was prepared by deprotection of the corresponding ether which was generously provided by Professor Josef Fried at the University of Chicago (eq 23). Compound 30 was also prepared by the enantioselective reduction of the



(23)

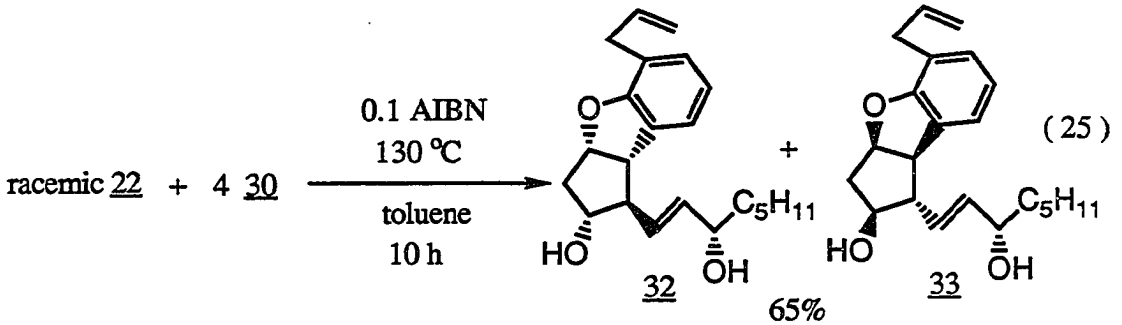
corresponding enone using the literature procedure[20] (eq 24). The optical purity of compound 30 has usually been determined using HPLC on a chiral phase after it was



(24)

converted to the corresponding diastereomeric ester[20,21]. Because of the lack of appropriate equipment, the optical purity of alcohol 30 was not determined. The literature[20] reports that stannane 30 was obtained in 98% ee by an enantioselective reduction with (S)-BINAL-H.

With the γ-tri-*n*-butylstannyl allylic alcohol 30 at hand, the radical-promoted cyclization-trapping method was examined (eqs 25 and 26). When the racemic compound 22



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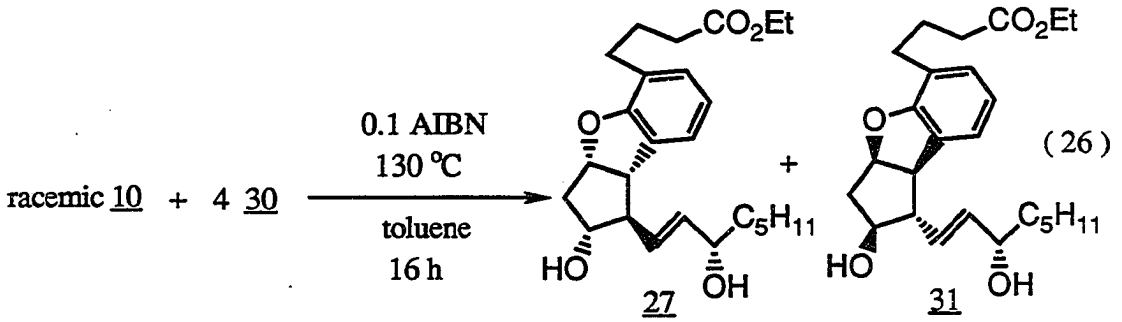
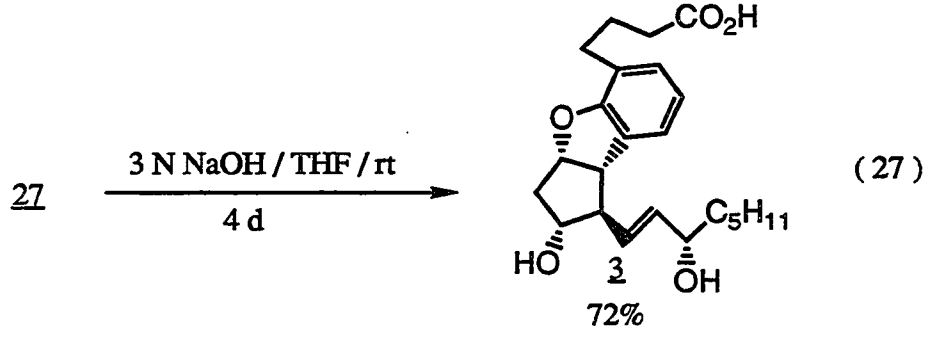


(26)

was reacted with optically active 30 in the presence of AIBN at 110 °C, TLC analysis showed that the starting material 22 was almost unchanged after 4 h stirring. Therefore, the reaction temperature was raised to 130 °C. Pleasantly, products 32 and 33 were obtained as separable diastereomers (eq 25). Subjection of racemic 10 to the reaction conditions shown in equation 26 led to the desired product 27 along with its diastereomer 31 in 41% yield. The compounds 27 and 31 are cleanly separable by flash chromatography.

Many examples have been reported of the radical addition to π-systems, followed by β-scission of trialkylstannyl radicals. Most of the reactions have focused on activated stannanes, such as allylic compounds[22], propargylic compounds[23] and α,β-unsaturated compounds[6b,24]. It is interesting to note that few examples have been reported on simple vinylic stannanes, such as compound 30.

The hydrolysis of compounds 27 and 31 with aqueous NaOH led to optically active carboxylic acids 3 and 34 (eqs 27 and 28).



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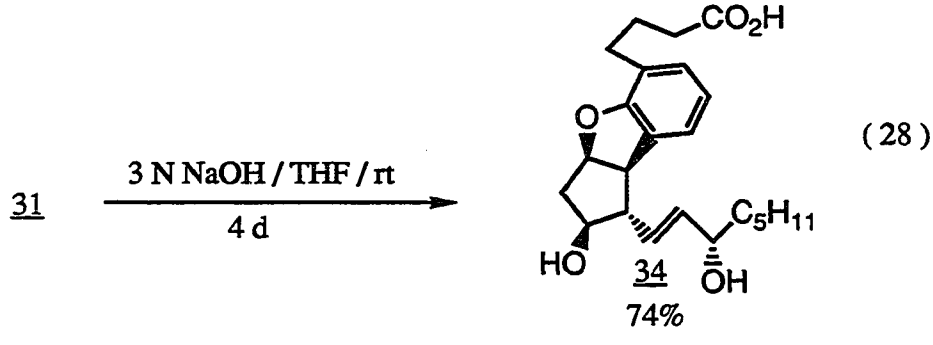

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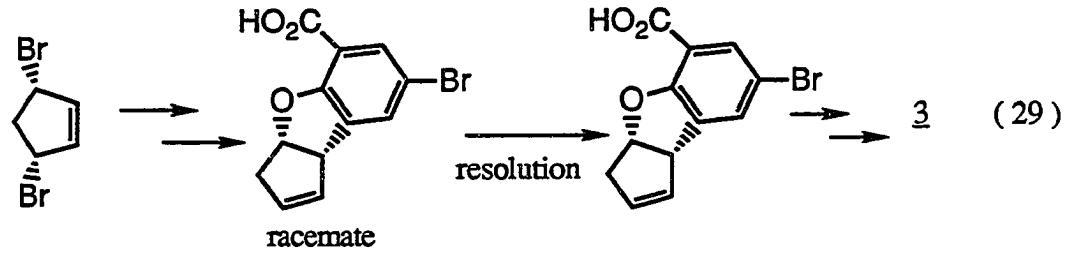
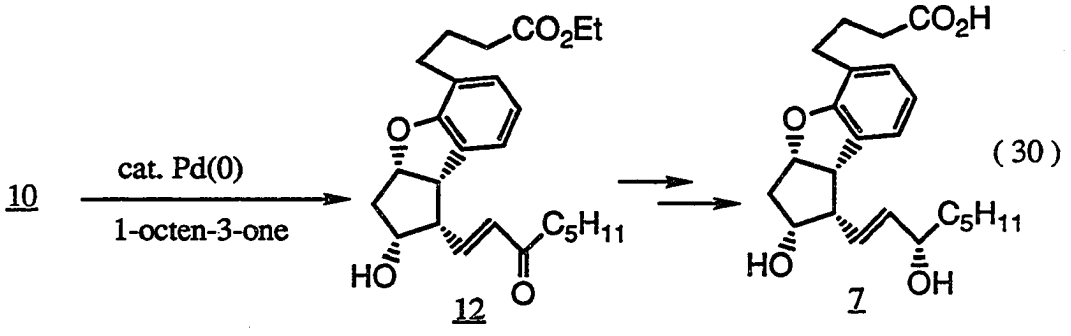
Considering that the previous synthesis of the PGI_2 analogue 3 outlined in equation 29 required 23 steps[3d], the synthetic sequence developed here is quite efficient.

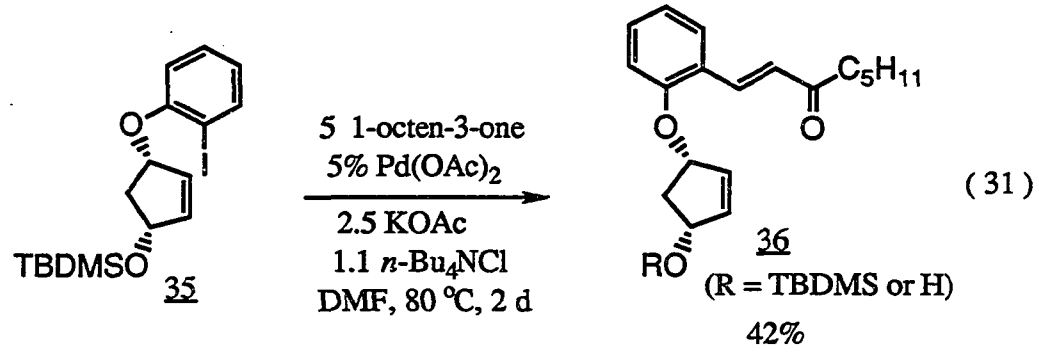


In our continuing effort to synthesize prostaglandins, it was desirable to synthesize 12-epi-benzoprostacyclin 7 using a palladium-promoted cyclization, followed by enone trapping, a proctocol developed in Chapter I of this dissertation (eq 30). It has previously



been reported[7,8] that aryl halides have been added to alkenes in an inter- or intramolecular process under the influence of a catalytic amount of a Pd(0) species.

As a model study, compounds 35 and 38 were subjected to similar reaction conditions[7,8] in the presence of an organopalladium trapping reagent such as 1-octen-3-one, 1-heptene or ethyl vinyl ketone (eqs 31-33). To our disappointment, none of the desired product was obtained from any of the reactions after examination of various reaction conditions. The intermolecular Heck-type product 36 or 39 was obtained along with the



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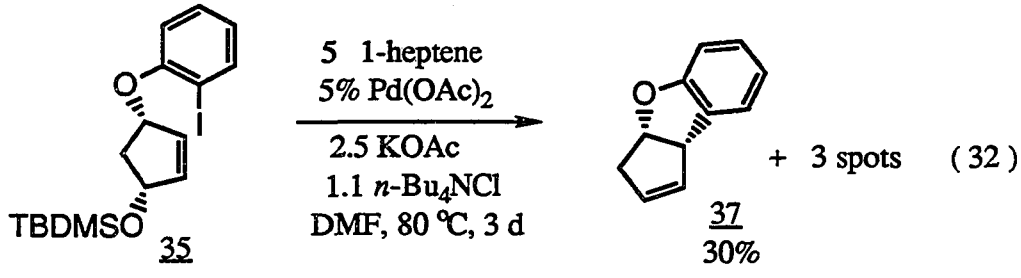
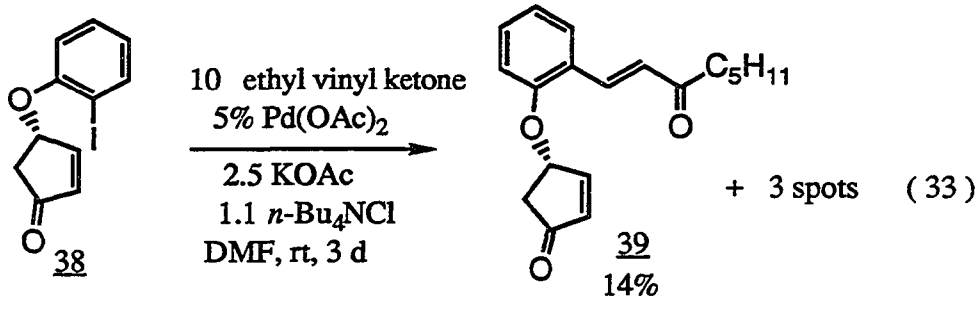


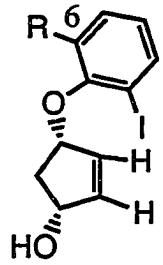
(32)



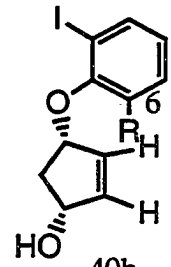
(33)

starting enone, while the eliminated product 37 was obtained as a major product with the less reactive olefin 1-heptene (eq 32).

It was envisioned that a change of steric or electronic environment around the phenyl ring might provide a better result. Indeed, it is reasonable to assume that introduction of a bulky group at C-6 in place of a hydrogen in compound 40 will favor rotamer 40a over 40b. To induce the desired cyclization, it is required that rotamer 40a be formed. Furthermore, the



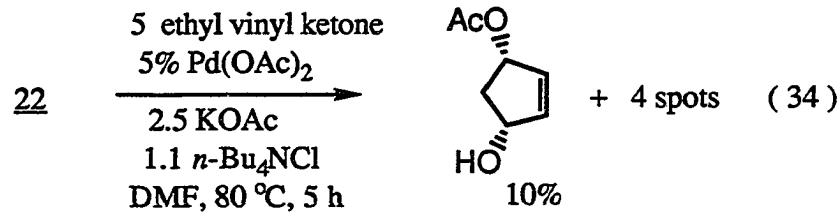
40a



40b

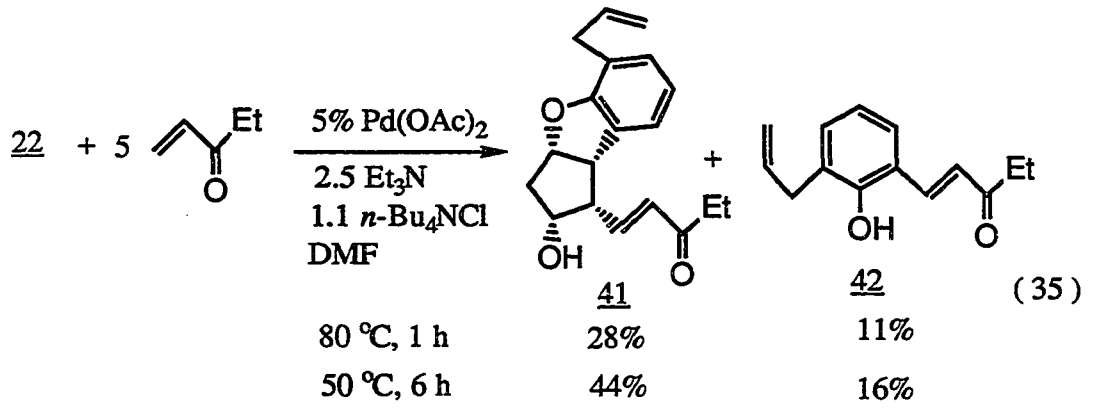
final product 7 we are attempting to prepare has an alkyl group at C_6. Thus, we decided to examine the reaction with substrates which have alkyl functionality at the C-6 position.

Upon subjection of compound 22 to the reaction conditions shown in equation 31, it was found that compound 22 is much more reactive than compound 35. The starting material spot upon TLC analysis disappeared within 5 h, while 2 days were needed to complete the reaction of compound 35. Upon reaction, five spots showed up on TLC analysis. One of them was identified to be *cis*-4-acetoxy-2-cyclopenten-1-ol which is probably formed by the nucleophilic attack of acetate on a π-allylpalladium complex (eq 34). Therefore, the organic



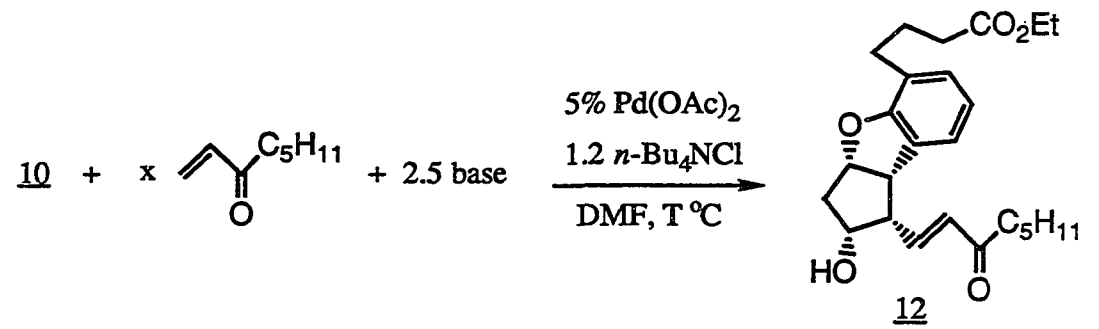
(34)

base Et_3N was tried in order to eliminate this side-product. Surprisingly, the desired product 41 was obtained as a major product, along with the cleavage product 42. An examination of the reaction temperature revealed the optimum temperature is around 50 °C (eq 35). For construction of the prostaglandin framework, compound 10 was subjected to this



intramolecular addition, followed by cross-coupling with 1-octen-3-one. The reaction conditions examined are presented in Table 1.

Table 1. The synthesis of compound 12



Entry	x	Base	T °C	Time (h)	% Isolated Yield 12	10
1	5	Et_3N	50	9	21	-
2			40	18	21	-
3		KOAc	50	24	0	-
4		Na_2CO_3		12	24	-
5		K_2CO_3		12	<5	-

Table 1. Continued

Entry	x	Base	T °C	Time (h)	% Isolated Yield 12	10
6		*i*-Pr2NEt		9	34	-
7	10			12	42	-
8		2,6-di-*t*-butylpyridine		36	0	70
9		Ph3N	65	30	0	68
10		proton sponge	50	24	0	61
11	10	dicyclohexylethylamine	53	12	42	15
12	15	*i*-Pr2NEt	42	22	39	-
13	20		50	30	41	-
14[a]	10		70	19	25	-
15[b]			100	24	0	59
16[c]			65	48	17	-
17[d]			60	16	29	-
18		1.5 *i*-Pr2NEt	48	12	38	-
19		3.5 *i*-Pr2NEt	55	36	30	-

[a]The reaction was conducted using DMSO as the solvent, instead of DMF.

[b]The reaction was conducted using CH3CN as the solvent, in place of DMF.

[c]The reaction was conducted with 5% of PPh3 as an additive.

[d]The reaction was conducted with 5% of Pd(dba)2, instead of Pd(OAc)2.

The best result was obtained by using a hindered organic base, such as diisopropylethylamine (entry 7) or dicyclohexylethylamine (entry 11). In entry 11, the product 12 was obtained in 42% yield, along with the recovery of starting material 10 in 15% yield. A longer reaction time resulted in a decrease in the yield of product for some reason.

The temperature dependence was examined in entries 1 and 2. With triethylamine as the base, no difference was observed in the yield of the product.

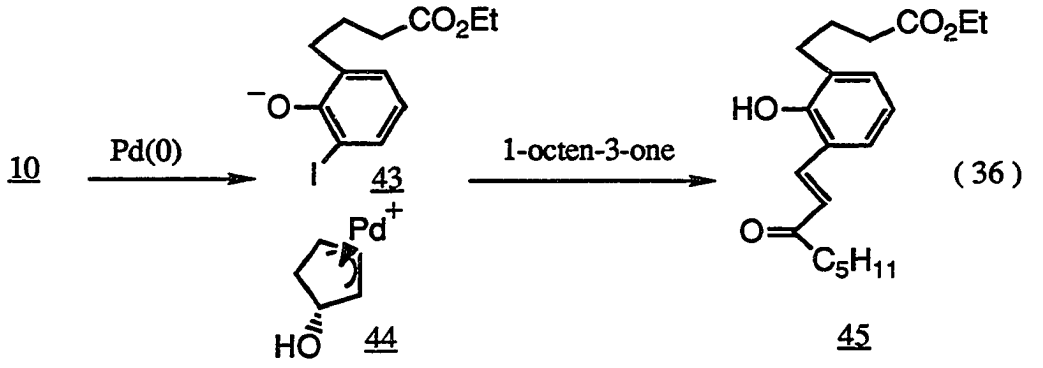
The variations of base are presented in entries 2 to 11. Hindered aliphatic amines seem to be a better choice in this reaction. It is noteworthy that the aromatic amines in entries 8, 9 and 10 gave no reaction. The starting material upon examination by TLC analysis was left unchanged.

In entries 12 and 13, along with entry 7, the optimum number of equivalents of 1-octen-3-one was examined. The use of 15 or 20 equivalents of 1-octen-3-one, in place of 10 equivalents, didn't increase the product yield significantly.

The solvent effect was checked in entries 14 and 15. With DMSO as the solvent, the reaction was very slow. Actually, the reaction temperature had to be raised up to 70 °C to get a reasonable rate of reaction. With CH_3CN as the solvent, no reaction occurred even though the reaction temperature was raised to 100 °C.

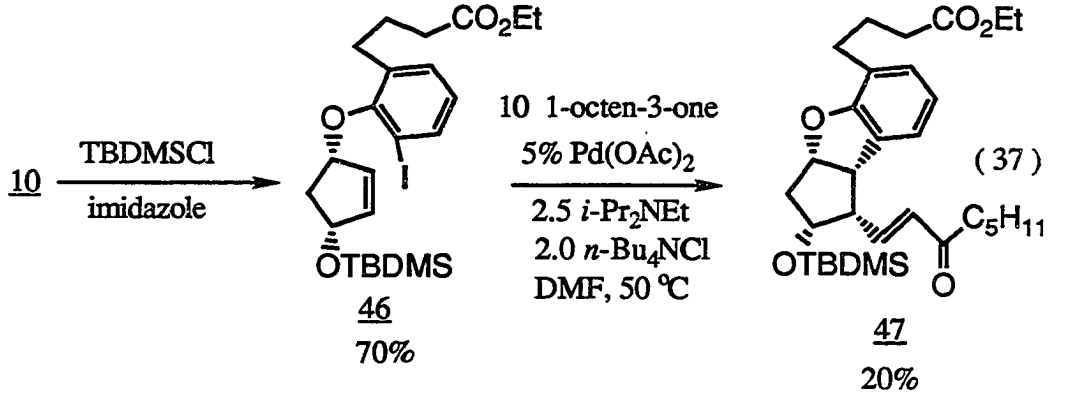
A reaction with 5% PPh_3 was conducted (entry 16). Both the reaction rate and product yield decreased. In entry 17, a reaction was examined in which 5% $Pd(dba)_2$ replaced 5% $Pd(OAc)_2$. This resulted in a decrease in product yield, as well as the reaction rate. The optimum amount of *i*-Pr_2NEt was examined in entries 18 and 19. With 1.5 equivalents of base, instead of 2.5 equivalents, a comparable result was obtained. Increasing the amount of *i*-Pr_2NEt to 3.5 equivalents, however, provided a slight decrease in reaction rate and yield of product.

As previously described, the major side-product was compound 45. Compound 45 is presumably formed via Pd(0)-promoted generation of phenoxide 43, followed by enone cross-coupling (eq 36). Compound 10 seems to be very susceptible to Pd(0) attack to generate intermediates 43 and 44, which is undoubtedly the major reason we obtain a low yield of the product 12 in this reaction.



(36)

Oxidation of the hydroxy group in compound 10 by Pd(II) in this reaction might be responsible for the lower yield of product 12. Therefore, the silyl-protected compound 46 was subjected to the optimum reaction conditions (eq 37). The result was no different from

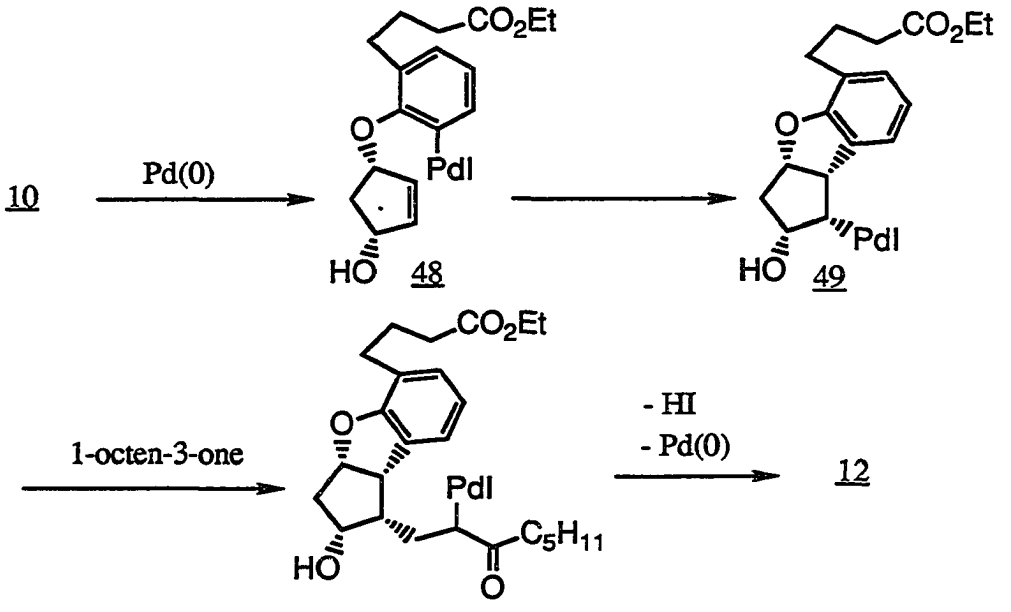


(37)

the reaction with the free hydroxy substrate 10. The desired product 47 was obtained in only a 20% yield.

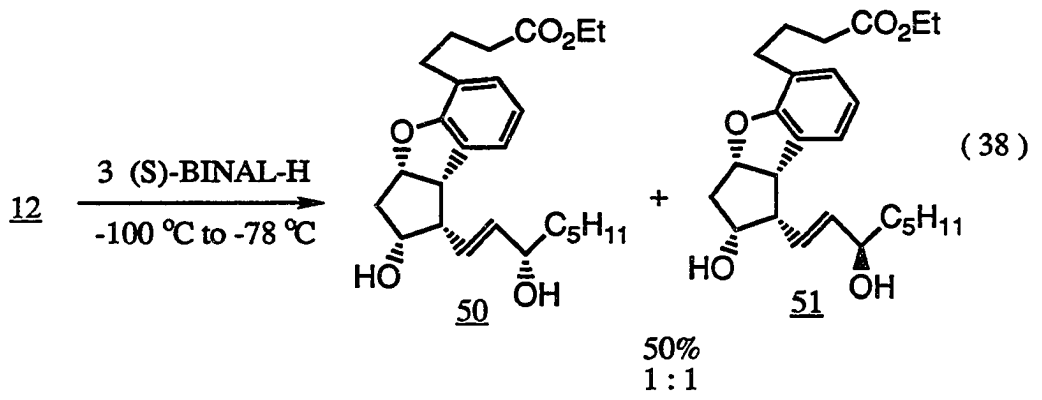
A reaction mechanism for the formation of the desired product 12 is proposed in Scheme IV. Aryl iodide 10 is oxidatively added to palladium(0) to generate organopalladium

Scheme IV.



intermediate 48, which undergoes cyclization, followed by coupling with 1-octen-3-one, to produce the product 12 in a single synthetic step.

The next step in the synthesis of compound 7 required the stereoselective reduction of the enone (ω-side chain) in compound 12. The diastereoselective reduction was conducted using Noyori's (S)-BINAL-H[15] (eq 38). The reaction was quite clean; only two spots were observed upon TLC analysis with a big difference in polarity (R_f = 0.25 for compound 50, 0.48 for compound 51 in 1:2 hexane/EtOAc). The more polar component was tentatively

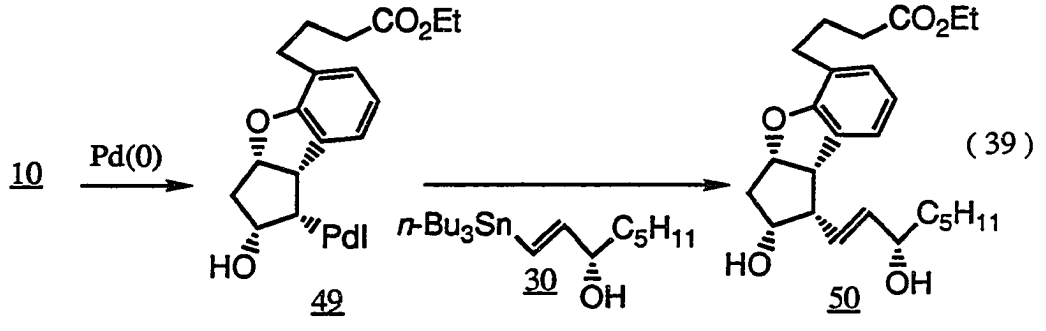


(38)

assigned as the desired 15-(S) isomer. It is generally recognized[25] that the more polar isomer has the 15-(S) configuration in prostaglandins. Comparison of the NMR spectra of the final products 3 and 7, which will be described later, also supports this assignment.

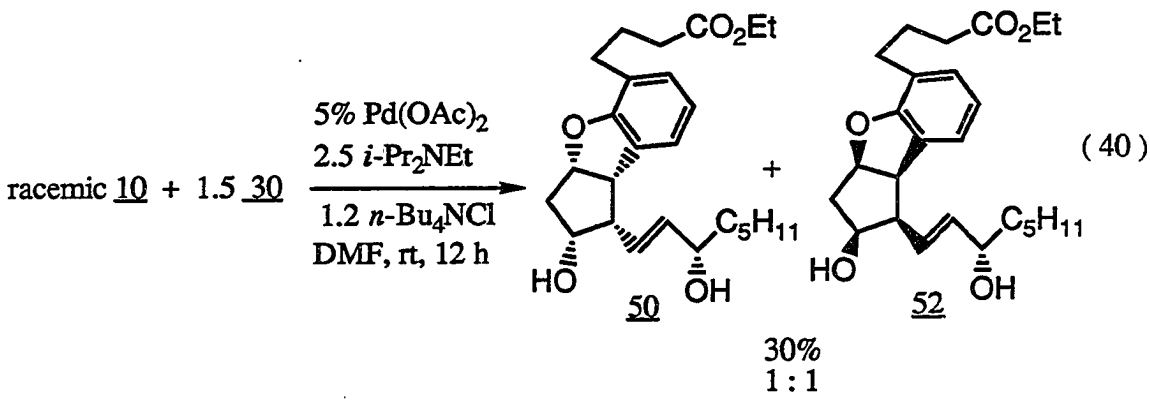
While BINAL-H has been reported to reduce α,β-unsaturated ketones with very high diastereoselectivity (usually >80% ee)[15,16], no selectivity was observed in this reaction. As previously described in the reduction of compound 11, π-electrons present in the phenyl ring might be responsible for the poor selectivity.

The reaction mechanism in Scheme IV suggests that the use of optically pure tri-*n*-butylstannyl allylic alcohol 30 might lead to optically active diol 50 directly from compound 10 (eq 39). Cross-coupling reactions between organopalladium and organotin reagents have



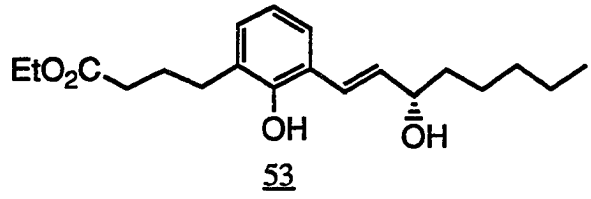
(39)

been well studied[26]. Thus, the racemic compound 10 was subjected to palladium-assisted cyclization in the presence of the vinylic tin compound 30 (eq 40). The desired product 50



(40)

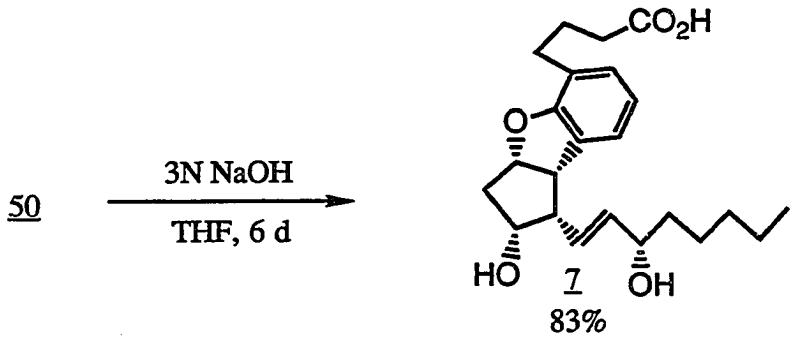
along with its diastereomer 52 were obtained in 30% yield. Compound 52 is separable from compound 50 by flash chromatography. Like in the reaction in equation 36, compound 53 was obtained as a major side-product. When the reaction was conducted with LiCl as an



53

additive or with Na_2CO_3 as a base, it gave the same results as in equation 40. Upon adding 5% PPh_3, the yield of the desired product was reduced and the amount of compound 53 increased. It is noteworthy that the reaction is much faster with compound 30, than with 1-octen-3-one, as a trapping reagent. While more than 12 h was needed at 50 °C to complete the reaction with 1-octen-3-one (Table 1), it took only 1 h at 50 °C for completion of the reaction with organotin reagent 30.

The final products 7 and 54 were obtained upon hydrolysis of racemic compounds 50 and 51 (eqs 41 and 42).



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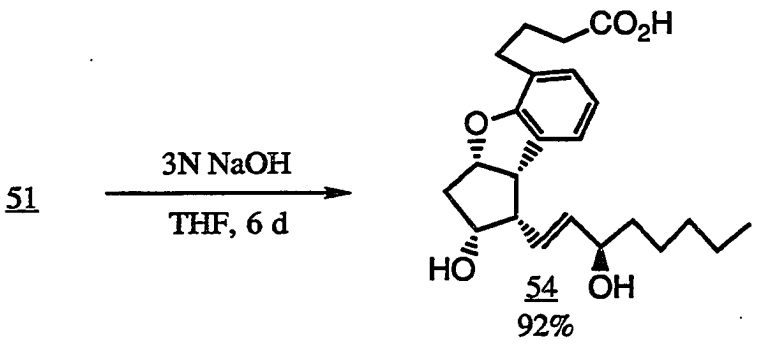
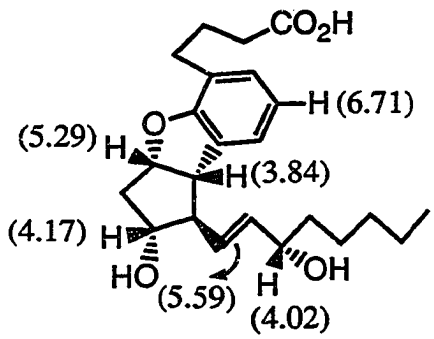


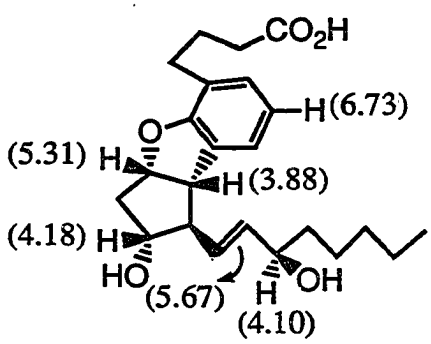
(42)

As described earlier, the stereochemistry of C-15 was assigned based on the polarity of the compounds 7 and 54. The ^1H NMR spectral data for compounds 3, 7, 29 and 54 are shown in Scheme V. The chemical shifts of H_{13}, H_{14} and H_{15} in 15-(S) isomers 3 and 7 consistently appear at higher field than those in 15-(R) isomers 29 and 54.

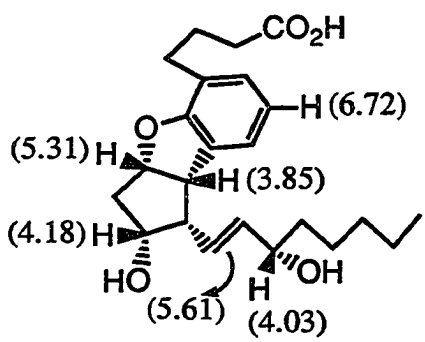
Scheme V.



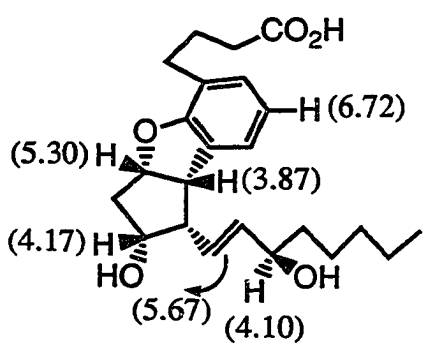
3
(more polar)



29
(less polar)



7
(more polar)



54
(less polar)

CONCLUSION

An efficient synthesis of PGI_2 analogue 3 which is known to have potent inhibitory activity for platelet aggregation has been accomplished. Compound 10 was prepared from cyclopentadiene monoepoxide (8) and the functionalized phenol 9 employing Pd(0) chemistry. The desired cyclization and subsequent enone trapping of compound 10 was effected in one step by radical chemistry to give compound 11 which can be readily converted to prostaglandin 3.

Even more efficiently, the use of optically active γ-stannyl allylic alcohol 30 as a trapping reagent directly led to optically active 27 which was converted to compound 3 upon hydrolysis.

The epimer 7 and its diastereomer 54 were also synthesized via one-step Pd(0)-mediated cyclization and subsequent enone coupling to give intermediate 12 which has been carried on to prostanoids 7 and 54. Employment of optically active organotin reagent 30 provided an even more direct synthetic pathway to optically active prostaglandin 7.

EXPERIMENTAL SECTION

Equipment

NMR spectra were recorded on a Nicolet NT-300 spectrometer (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz), and chemical shifts are reported in ppm relative to TMS (δ 0.00) as an internal standard. IR spectra were obtained on an IBM IR 98. High-resolution mass spectra were recorded on a Kratos MS-50 spectrometer.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. Tetrahydrofuran was distilled over sodium benzophenone ketal and used immediately. Methanol was distilled over sodium methoxide and stored over 4Å molecular sieves. Methylene chloride was distilled over phosphorous pentoxide and stored over 4Å molecular sieves. Ethanol was distilled azeotropically by adding a small amount of benzene and stored over 4Å molecular sieves. Toluene was distilled over sodium hydride. Hexane was distilled over sodium hydride. DMF was distilled over sodium hydride and stored over 4Å molecular sieves.

Preparation of (+)-5,6,7-trinor-4,8-inter-*m*-phenylene PGI$_2$ (3)

To a solution of compound 27 (40 mg, 0.10 mmol) in 1.2 ml of THF was added 0.6 ml of 3N aqueous NaOH. After the reaction mixture was stirred for 4 d at room temperature, it was neutralized with 2N aqueous HCl. The organic phase was decanted with ethyl acetate (3 x 5 ml), then dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography with 20:1 EtOAc/MeOH gave the title product: 27 mg, 72% yield; R_f = 0.21 (20:1 EtOAc/MeOH); ^{1}H NMR ($CDCl_3$) δ 6.91-6.87 (m, 2H, Ar), 6.70 (t, J = 7.5 Hz, 1H, Ar), 5.59 (m, 2H, HC=CH), 5.29 (t, J = 6.9 Hz, 1H, CHOAr), 4.95 (br s, 2H, OH's), 4.17 (m, 1H, C<u>H</u>OH), 4.03-3.99 (m, 1H, C=CH-C<u>H</u>OH), 3.84 (t, J = 8.7 Hz, 1H, CHAr), 2.75-2.64 (m, 2H),

2.57-2.48 (m, 1H), 2.34 (d, J = 15.3 Hz, 1H, CH_2 in cyclopentane), 2.25 (t, J = 6.6 Hz, 2H), 2.16-1.99 (m, 2H), 1.88-1.76 (m, 1H), 1.48 (m, 3H), 1.31 (m, 6H, CH_2's), 0.91 (t, J = 6.9 Hz, 3H, CH_3). This compound has ^1H NMR spectral data very close to those reported in the literature[3c]; ^{13}C NMR ($CDCl_3$) δ 178.14, 158.02, 136.25, 128.87, 128.38, 127.64, 123.94, 122.75, 119.86, 88.30, 77.00, 73.03, 52.10, 49.87, 41.92, 36.89, 32.89, 31.80, 28.79, 25.24, 24.79, 22.72, 14.14; IR (neat) 3510 (OH), 2935, 1703 (C=O) cm^{-1}; HRMS m/z calculated for $C_{23}H_{32}O_5$ 388.22497, found 388.22530. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 69.21; H, 8.43. The poor elemental analysis is possibly due to insufficient drying of compound 3.

Preparation of 12-epi-5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 (7)

To a solution of compound 50 (22 mg, 0.06 mmol) in 0.74 ml of THF was added 3N aqueous NaOH (0.37 ml) at room temperature. After the mixture was stirred for 6 d at room temperature, it was neutralized by 2N aqueous HCl. The organic phase was decanted with EtOAc, and then dried over $MgSO_4$. Concentration, followed by flash chromatography with 20:1 EtOAc/MeOH, gave product 7: 17 mg, 83% yield; R_f = 0.29 (20:1 EtOAc/MeOH); ^1H NMR ($CDCl_3$) δ 6.90 (d, J = 7.5 Hz, 1H, Ar), 6.89 (d, J = 7.5 Hz, 1H, Ar), 6.72 (t, J = 7.5 Hz, 1H, Ar), 5.61 (m, 2H, HC=CH), 5.31 (dd, J = 0.9 and 7.8 Hz, 1H, CHOAr), 4.30 (br, 2H, OH's), 4.18 (m, 1H, CHOH), 4.03 (m, 1H, C=CCHOH), 3.85 (t, J = 9.0 Hz, 1H, CHAr), 2.75-2.65 (m, 2H), 2.53 (m, 1H), 2.36 (d, J = 15.0 Hz, 1H, CH_2 in cyclopentane), 2.26 (m, 2H), 2.17-2.01 (m, 2H), 1.81 (m, 1H), 1.53 (m, 3H), 1.32 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.93, 157.99, 136.35, 128.91, 128.29, 127.65, 123.97, 122.80, 119.98, 88.37, 77.00, 73.04, 52.18, 49.95, 42.02, 36.96, 32.89, 31.83, 28.83, 25.28, 24.85, 22.73, 14.12; IR (neat) 3383 (OH), 2928, 1709 (C=O), 1595, 1454 cm^{-1}; HRMS m/z calculated for $C_{23}H_{32}O_5$ 388.22497,

found 388.22406. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.75; H, 8.92.

Preparation of cyclopentadiene monoepoxide (8)[27]

To an ice-cold, mechanically stirred mixture of 35 ml (0.47 mol) of freshly cracked cyclopentadiene and 203 g of powdered, anhydrous sodium carbonate in 520 ml of CH_2Cl_2 was added dropwise over 1.5 h 100 ml (0.47 mol) of 32% peracetic acid which has been pretreated with 2 g of sodium acetate. The mixture was stirred at room temperature until a negative test was obtained with moist starch-iodine paper. The solid salts were removed by suction filtration and washed with CH_2Cl_2. The solvent was removed from the filtrate by distillation through a Vigreux column. Then distillation continued under partial vacuum pressure (bath temperature, 50 °C, 15 mm Hg) to give a mixture of the product and CH_2Cl_2, and the vacuum was increased to 4.5 mm Hg to give the product 8. The mixture (product 8 plus CH_2Cl_2) was redistilled under atmospheric pressure and then with partial vacuum pressure (15 mm Hg). The combined yield was 15 g (38% yield): ^{1}H NMR ($CDCl_3$) δ 6.12 (m, 1H, HC=C), 5.96 (dt, J = 5.7 and 2.1 Hz, 1H, C=CH), 3.89 (dd, J = 5.4 and 3.0 Hz, 1H, CHOR), 3.78 (m, 1H, CHOR), 2.61 (ddd, J = 19.2 and 3.9 and 1.8 Hz, 1H, CH_2), 2.37 (ddt, J = 19.2 and 3.6 and 1.8 Hz, 1H, CH_2).

Preparation of compound 9

To a solution of compound 19 (2.85 g, 6.2 mmol) in 60 ml of THF at -78 °C was added *n*-Bu4NF (Aldrich, 1.0 M in THF, 6.2 ml, 6.2 mmol). The reaction mixture was stirred for 1 h at -78 °C, then allowed to warm to 0 °C, and quenched by adding H_2O (10 ml). The mixture was poured into 50 ml of EtOAc, washed with H_2O (25 ml) and brine (20 ml). The organic phase was dried and concentrated. The residue was purified by flash chromatography with 4:1 hexane/EtOAc to give the title compound: 2.02 g, 94% yield; R_f = 0.37 (5:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, J = 7.8 and 1.2 Hz, 1H, Ar), 7.05

(dd, J = 7.8 and 1.2 Hz, 1H, Ar), 6.58 (t, J = 7.8 Hz, 1H, Ar), 6.18 (s, 1H, OH), 4.15 (q, J = 7.2 Hz, 2H, CH_2), 2.69 (t, J = 7.2 Hz, 2H, CH_2), 2.36 (t, J = 7.2 Hz, 2H, CH_2), 1.91 (m, 2H, CH_2), 1.27 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (CDCl3) δ 174.15, 152.96, 136.44, 130.64, 128.05, 122.06, 86.28, 60.59, 33.28, 30.54, 24.68, 14.24; IR (neat) 3373 (OH), 2980, 2957, 1707 (C=O), 1445 cm^{-1}. HRMS m/z calculated for $C_{12}H_{15}O_3I$ 334.00660, found 334.00617.

Preparation of compound 10

To a dried flask was added $Pd(PPh_3)_4$ (18 mg, 0.016 mmol). To this was added compound 9 (264 mg, 0.79 mmol) in 2 ml of THF, and the reaction mixture was stirred in an ice-water bath. Cyclopentadiene monoepoxide (97 mg, 1.18 mmol) in 2 ml of THF was added dropwise at 0 °C, and stirring was continued for 20 min at this temperature and another 24 h at room temperature. The reaction mixture was concentrated. The residue was purified by flash chromatography with 2:1 hexane/EtOAc to give product 10: 235 mg, 71% yield; R_f = 0.27 (2:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.58 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 7.15 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 6.77 (t, J = 7.8 Hz, 1H, Ar), 6.09 (m, 1H, HC=C), 6.01 (m, 1H, HC=C), 5.11 (m, 1H, CHOAr), 4.68 (m, 1H, CHOH), 4.12 (q, J = 7.2 Hz, 2H, OCH_2), 2.85 (m, 2H), 2.60 (ddd, J = 15.3 and 9.6 and 6.0 Hz, 1H, CH_2 in cyclopentane), 2.30 (dt, J = 1.8 and 6.9 Hz, 2H), 2.06 (dt, J = 14.7 and 3.9 Hz, 1H, CH_2 in cyclopentane), 1.88 (m, 2H), 1.25 (t, J = 6.3 Hz, 3H, CH_3), 0.88 (m, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 173.69, 156.22, 138.09, 137.98, 136.65, 133.55, 130.56, 125.87, 92.45, 85.71, 74.97, 60.52, 41.28, 33.50, 30.86, 25.47, 14.28; IR (neat) 3350 (OH), 2959, 1720 (C=O), 1599, 1462, 1352 cm^{-1}; HRMS m/z calculated for $C_{17}H_{21}O_4I$ 416.04847, found 416.04747.

Preparation of compound 11

To a solution of compound 10 (70 mg, 0.17 mmol) in 1.7 ml of toluene were added compound 24 (279 mg, 0.67 mmol) and AIBN (Aldrich, 2.8 mg, 0.017 mmol). The resulting mixture was placed into an oil bath preheated to 90 °C and stirred for 12 h. After cooling to room temperature, the mixture was purified by flash chromatography with 1:1 hexane/EtOAc to give product 11 as a yellow oil: 65 mg, 80% yield; R_f = 0.32 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.93 (d, J = 7.5 Hz, 1H, Ar), 6.86 (d, J = 7.5 Hz, 1H, Ar), 6.84 (dd, J = 16.2 and 9.6 Hz, 1H, HC=C), 6.73 (t, J = 7.5 Hz, 1H, Ar), 6.19 (d, J = 16.2 Hz, 1H, C=CH), 5.38 (dd, J = 7.5 and 6.3 Hz, 1H, CHOAr), 4.28 (m, 1H, CHOH), 4.09 (m, 2H, OCH_2), 3.98 (t, J = 8.7 Hz, 1H), 2.86 (dt, J = 3.9 and 9.6 Hz, 1H), 2.66-2.43 (m, 4H), 2.25 (m, 2H), 2.17 (ddd, J = 15.3 and 6.4 and 4.1 Hz, 1H), 2.09 (d, J = 5.7 Hz, 1H), 2.02 (m, 1H), 1.86 (m, 1H), 1.59 (m, 3H), 1.41-1.22 (m, 7H), 0.88 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 200.99, 173.84, 157.67, 144.28, 132.82, 129.09, 127.05, 123.65, 123.23, 120.11, 88.58, 76.77, 60.30, 52.65, 50.70, 43.03, 38.93, 33.38, 31.48, 28.93, 24.84, 24.02, 22.48, 14.30, 14.00; IR (neat) 3466 (OH), 2930, 1666 (C=O), 1372, 1456 cm^{-1}; HRMS m/z calculated for $C_{25}H_{34}O_5$ 414.24062, found 414.24080.

Preparation of compound 12

In a vial were placed compound 10 (94 mg, 0.23 mmol), 1-octen-3-one (285 mg, 2.3 mmol), *n*-Bu_4NCl (Lancaster, 70 mg, 0.25 mmol), *i*-Pr_2NEt (98 μl, 0.58 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) and DMF (0.46 ml). After the reaction was stirred for 12 h at 50 °C, it was poured into 40 ml of EtOAc. The mixture was washed with saturated NH_4Cl (15 ml) and then the aqueous phase was back-extracted with EtOAc (15 ml). The overall organic phase was washed with brine (15 ml), and then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to give product 12: 37 mg, 42% yield; R_f = 0.44 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 7.5 Hz,

1H, Ar), 6.88 (d, J = 7.5 Hz, 1H, Ar), 6.85 (dd, J = 15.9 and 9.9 Hz, 1H, C=CH), 6.75 (t, J = 7.5 Hz, 1H, Ar), 6.21 (d, J = 15.9 Hz, 1H, HC=C), 5.39 (dd, J = 8.1 and 6.0 Hz, 1H, CHOAr), 4.30 (m, 1H, CHOH), 4.12 (m, 2H), 3.99 (t, J = 8.4 Hz, 1H), 2.85 (dt, J = 3.9 and 9.6 Hz, 1H), 2.55 (m, 4H), 2.26 (m, 2H), 2.18 (ddd, J = 15.3 and 6.0 and 4.5 Hz, 1H, CH_2 in cyclopentane), 2.02 (m, 2H), 1.88 (m, 1H), 1.63 (m, 2H), 1.28 (m, 7H, CH_2's and OCH_2CH_3), 0.89 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 200.94, 173.79, 157.68, 144.27, 132.17, 129.05, 127.05, 123.61, 123.20, 120.06, 88.92, 76.69, 60.26, 52.63, 50.69, 43.01, 38.94, 33.36, 31.46, 28.94, 24.81, 24.00, 22.42, 14.22, 13.90; IR (neat) 3464 (OH), 2932, 1732 (C=O), 1688 (C=O), 1465 cm^{-1}; HRMS m/z calculated for $C_{25}H_{34}O_5$ 414.24063, found 414.24118.

Preparation of compound 14

A solution of *o*-iodophenol (6.6 g, 30 mmol), allyl bromide (4.0 g, 33 mmol) and potassium carbonate (4.6 g, 33 mmol) in 7.5 ml of acetone was refluxed for 8 h. The reaction mixture was diluted with 40 ml of H_2O, and extracted with ether (2 x 25 ml). The organic phase was washed with brine (25 ml), and then dried over $MgSO_4$. Concentration, followed by flash chromatography, gave compound 14 as a colorless oil: 6.8 g, 94% yield; ^1H NMR ($CDCl_3$) δ 7.77 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 7.27 (dt, J = 1.8 and 7.8 Hz, 1H, Ar), 6.80 (dd, J = 7.8 and 1.2 Hz, 1H, Ar), 6.70 (dt, J = 7.8 and 1.2 Hz, 1H, Ar), 6.06 (ddt, J = 17.4 and 10.5 and 7.8 Hz, 1H, HC=C), 5.52 (dd, J = 17.4 and 1.8 Hz, 1H, HC=C), 5.31 (dd, J = 10.5 and 1.2 Hz, 1H, HC=C), 4.59 (dt, J = 4.8 and 1.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 157.09, 139.51, 132.57, 129.35, 122.66, 117.59, 112.58, 86.72, 69.68; IR (neat) 1582, 1477 cm^{-1}.

Preparation of 6-allyl-2-iodophenol (15)

To a solution of compound 14 (7.0 g, 27 mmol) in 130 ml of hexane was added $MeAlCl_2$ (Aldrich, 1.0 M in hexane, 22 ml, 22 mmol) dropwise at -20 °C. After the reaction

was stirred for 2 h at -20 °C under N_2, it was quenched by adding H_2O (40 ml) and slowly warmed to room temperature with swirling. EtOAc (30 ml) was added to the reaction mixture; then stirring was continued for 5 min. After separating phases, the organic phase was washed with H_2O (30 ml) and brine (30 ml), then dried and concentrated. The residue was purified by flash chromatography with 15:1 hexane/EtOAc to give product 15: 4.9 g, 70% yield; R_f = 0.38 (20:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.51 (dd, J = 1.2 and 7.8 Hz, 1H, Ar), 7.07 (d, J = 7.8 Hz, 1H, Ar), 6.62 (t, J = 7.8 Hz, 1H, Ar), 5.98 (ddt, J = 17.4 and 9.6 and 6.6 Hz, 1H, HC=C), 5.37 (s, 1H, OH), 5.12 (m, 1H, HC=C), 5.07 (m, 1H, HC=C), 3.43 (d, J = 6.6 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.60, 136.33, 136.01, 130.73, 126.81, 122.42, 116.22, 86.41, 35.56; IR (neat) 3487 (OH), 1593, 1234 cm^{-1}; LRMS m/z (relative intensity) 51.1 (34), 77.1 (47), 105.1 (58), 118.1 (41), 133.1 (42), 260.0 (M^+, 100).

Preparation of compound 16

To a solution of compound 15 (4.9 g, 18.7 mmol) and imidazole (3.2 g, 47.1 mmol) in 20 ml of DMF was added *t*-butyldimethylsilyl chloride (3.1 g, 20.5 mmol) dissolved in 15 ml of DMF at room temperature under N_2. After the mixture was stirred for 12 h at room temperature, it was extracted with hexane (50 ml x 8). The hexane phase was concentrated and then flash chromatographed to give compound 16: 6.3 g, 90% yield; R_f = 0.52 (hexane); ^1H NMR ($CDCl_3$) δ 7.63 (dd, J = 7.8 and 1.8 Hz, 1H, Ar), 7.11 (dd, J = 7.8 and 1.8 Hz, 1H, Ar), 6.66 (t, J = 7.8 Hz, 1H, Ar), 5.86 (ddt, J = 17.4 and 9.6 and 6.6 Hz, 1H, C=C<u>H</u>CH_2), 5.08 (m, 2H, H_2C=C), 3.39 (d, J = 6.9 Hz, 2H, CH_2), 1.06 (s, 9H, *t*-BuSi), 0.331 (s, 6H, $SiMe_2$).

Preparation of compound 17

Ozone was passed through a solution of compound 16 (722 mg, 1.9 mmol) in 19 ml of methanol at -78 °C until the deep blue color persisted (about 15 min). The reaction was

flushed with N_2 gas and 8 ml of CH_3SCH_3 was added at -78 °C. The reaction mixture was then allowed to stir for 30 min at -78 °C, for 1 h at 0 °C and for another 30 min at room temperature. The methanol solvent was evaporated under reduced pressure, and 60 ml of ether was then added to the residue. After the mixture was washed with water (10 ml) and brine (20 ml x 2), it was dried and concentrated. Flash chromatography gave product 17: 638 mg, 83% yield; R_f = 0.63 (3:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 9.63 (t, J = 2.1 Hz, 1H, CHO), 7.74 (dd, J = 8.1 and 1.5 Hz, 1H, Ar), 7.09 (dd, J = 7.5 and 1.5 Hz, 1H, Ar), 6.72 (t, J = 7.5 Hz, 1H, Ar), 3.68 (d, J = 2.1 Hz, 2H, CH_2), 1.05 (s, 9H, *t*-BuSi), 0.32 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 199.34, 153.92, 139.70, 131.54, 124.26, 123.81, 91.23, 46.16, 26.37, 18.85, -1.52.

Preparation of compound 18

To a solution of (carbethoxymethylene)triphenylphosphorane (Aldrich, 3.88 g, 11.5 mmol) dissolved in 30 ml of CH_2Cl_2 was added dropwise at room temperature aldehyde 17 (3.57 g, 9.3 mmol) dissolved in 14 ml of CH_2Cl_2. After the reaction was stirred for 12 h at room temperature, it was concentrated in vacuo and purified by flash chromatography with 5:1 hexane/EtOAc to give ester 18: 3.52 g, 83% yield; R_f = 0.46 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.67 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 7.05 (dd, J = 7.5 and 1.5 Hz, 1H, Ar), 6.99 (dt, J = 15.6 and 6.6 Hz, 1H, HC=C), 6.66 (t, J = 7.5 Hz, 1H, Ar), 5.80 (d, J = 15.6 Hz, 1H, HC=C), 4.18 (q, J = 7.2 Hz, 2H, OCH_2), 3.53 (dd, J = 6.9 and 1.5 Hz, 2H, CH_2), 1.27 (t, J = 7.2 Hz, 3H, CH_3), 1.05 (s, 9H, *t*-BuSi), 0.32 (s, 6H, Me_2Si); ^{13}C NMR ($CDCl_3$) δ 166.32, 153.31, 146.18, 138.75, 130.60, 129.52, 123.61, 122.93, 91.09, 60.36, 33.94, 26.42, 18.94, 14.32, -1.49.

Preparation of compound 19

To a three neck flask equipped with a H_2 gas balloon were added α,β-unsaturated ester 18 (619 mg, 1.36 mmol), ethanol (20 ml), 2N aqueous HCl (0.4 ml) and PtO_2

(Aldrich, 60 mg). The reaction was flushed with H_2 gas using an aspirator, and then stirred for 1 h at room temperature under the H_2 balloon pressure. After the reaction was neutralized with 3N aqueous NaOH (0.27 ml), it was poured into 100 ml of ethyl acetate. The solution was washed with brine (50 ml, 25 ml) and concentrated in vacuo. The residue was purified by flash chromatography to give compound 19: 562 mg, 90% yield; R_f = 0.52 (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.62 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 7.10 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 6.64 (t, J = 7.8 Hz, 1H, Ar), 4.11 (q, J = 7.2 Hz, 2H, OCH_2), 2.66 (t, J = 7.8 Hz, 2H, CH_2), 2.27 (t, J = 7.5 Hz, 2H, CH_2), 1.88 (m, 2H, CH_2), 1.25 (t, J = 7.2 Hz, 3H, CH_3), 1.04 (s, 9H, *t*-BuSi), 0.32 (s, 6H, $SiMe_2$).

Preparation of compound 22

A solution of cyclopentadiene monoepoxide (1.4 g, 17.1 mmol) in 20 ml of THF was added dropwise over 10 min to an ice-cooled solution of $Pd(PPh_3)_4$ (Johnson Matthey, Inc., 173 mg, 0.15 mmol) and compound 15 (3.0 g, 11.5 mmol) in 20 ml of THF. After stirring for 30 min at 0 °C, the reaction was allowed to warm to room temperature, and stirring was continued for 24 h. After being filtered through a silica gel pad, the reaction mixture was concentrated in vacuo and flash chromatographed to give product 22: 2.5 g, 64% yield; R_f = 0.38 (2:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.67 (dd, J = 1.2 and 7.8 Hz, 1H, Ar), 7.18 (dd, J = 1.2 and 7.8 Hz, 1H, Ar), 6.80 (t, J = 7.8 Hz, 1H, Ar), 6.11 (m, 2H, HC=CH), 5.92 (ddt, J = 16.8 and 10.2 and 6.6 Hz, 1H, C=C<u>H</u>CH_2), 5.11 (m, 2H, H_2C=C), 5.00 (m, 1H, CHOAr), 4.69 (m, 1H, C<u>H</u>OH), 3.48 (t, J = 6.0 Hz, 2H, CH_2Ar), 2.84 (dt, J = 14.4 and 7.2 Hz, 1H, CH_2 in cyclopentane), 2.08 (dt, J = 14.1 and 4.2 Hz, 1H, CH_2 in cyclopentane), 1.89 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 156.22, 130.02, 137.78, 136.36, 134.45, 133.96, 130.90, 125.79, 116.59, 92.83, 86.35, 74.84, 41.66, 35.06; IR (neat) 3464 (OH), 1433, 1360, 1250 cm^{-1}; HRMS m/z calculated for $C_{14}H_{15}O_2I$ 342.01168, found 342.01149.

Preparation of γ-stannyl allylic alcohol 23[13]

To a solution of 1-octyn-3-ol (Aldrich, 5.0 g, 40 mmol) and AIBN (130 mg, 0.8 mmol) under N_2 atmosphere was added *n*-Bu_3SnH (Aldrich, 16 ml, 60 mmol) by a syringe. The reaction mixture was heated at 80 °C and stirred for 2 h, then cooled to room temperature. The reaction mixture was purified by flash chromatography to give compound 23: 9.6 g, 58% yield; ^1H NMR ($CDCl_3$) δ 6.12 (d, J = 19.2 Hz, 1H, HC=C), 5.98 (dd, J = 19.2 and 5.1 Hz, 1H, C=CH), 4.06 (m, 1H), 1.52 (m, 12H), 1.30 (m, 13H), 0.97 (m, 3H), 0.89 (t, J = 7.2 Hz, 12H).

Preparation of β-stannyl enone 24[6b]

To a solution of alcohol 23 (7.2 g, 17 mmol) in 24 ml of CH_2Cl_2 was added PDC (Aldrich, 9.7 g, 26 mmol) at room temperature. After being stirred for 8 h, the reaction mixture was filtered through Celite, and the flask was rinsed with ether (40 ml x 5). The filtrate was concentrated in vacuo and flash chromatographed with 15:1 hexane/EtOAc to give enone 24: 4.1 g, 57% yield; R_f = 0.48 (15:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.55 (d, J = 19.8 Hz, 1H, HC=C), 6.54 (d, J = 19.8 Hz, 1H, C=CH), 2.58 (t, J = 7.5 Hz, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.54-1.42 (m, 6H), 1.31 (m, 12H), 0.97 (m, 4H), 0.89 (t, J = 7.2 Hz, 12H).

Preparation of compound 25

In a 4 dram vial were placed compound 22 (106 mg, 0.31 mmol), β-stannyl enone 24 (514 mg, 1.24 mmol) and 3.1 ml of toluene. To this was added AIBN (Aldrich, 5.1 mg, 0.031 mmol), and then the reaction was stirred for 3 h at 110 °C. After the reaction mixture was allowed to cool to room temperature, it was purified by flash chromatography to give product 25: 85 mg, 81% yield; R_f = 0.37 (1:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.97 (d, J = 7.5 Hz, 1H, Ar), 6.89 (d, J = 7.5 Hz, 1H, Ar), 6.81 (dd, J = 15.6 and 9.6 Hz, 1H, HC=CHCO), 6.77 (t, J = 7.5 Hz, 1H, Ar), 6.19 (d, J = 15.6 Hz, 1H, C=CHCO), 6.03-

5.90 (m, 1H, HC=C), 5.41 (dd, J = 7.5 and 6.0 Hz, 1H, CHOAr), 5.06 (m, 2H, HC=CH), 4.27 (m, 1H, CHOH), 3.99 (t, J = 8.4 Hz, 1H), 3.32 (d, J = 6.0 Hz, 2H, CH_2Ar), 2.86 (dt, J = 4.2 and 9.6 Hz, 1H), 2.55-2.45 (m, 3H), 2.19 (dt, J = 15.3 and 4.8 Hz, 1H), 1.74 (br s, 1H, OH), 1.64-1.57 (m, 2H), 1.42-1.25 (m, 4H), 0.89 (m, 3H).

Compound 26

^1H NMR ($CDCl_3$) δ 7.05 (d, J = 7.5 Hz, 1H, Ar), 6.91 (d, J = 7.5 Hz, 1H, Ar), 6.76 (t, J = 7.5 Hz, 1H, Ar), 5.75 (m, 2H, HC=CH), 5.45 (t, J = 7.5 Hz, 1H, CHOAr), 4.35 (d, J = 7.8 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H, OCH_2), 2.88 (dd, J = 18.0 and 6.0 Hz, 1H), 2.75 (d, J = 17.4 Hz, 1H), 2.59 (dt, J = 3.3 and 7.5 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.98-1.88 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H, CH_3).

Preparation of compounds 27 and 28

1). Procedure A (via reduction of compound 11)[15]

To a solution of $LiAlH_4$ (Aldrich, 0.91 ml, 1.0 M in THF, 0.91 mmol) was added ethanol (0.46 ml, 2.0 M in THF, 0.91 mmol) dropwise at room temperature. To this was added (S)-binaphthol (Aldrich, 258 mg, 0.91 mmol) in 1.5 ml of THF, and the resulting mixture was stirred for 30 min. Enone 11 (126 mg, 0.30 mmole) in 1.2 ml of THF was added dropwise over 3 min at -100 °C. The resulting mixture was stirred for 2 h at -100 °C, and then another 2 h at -78 °C. Methanol (0.5 ml) was added at -78 °C to destroy the excess reducing agent and the mixture was allowed to warm to room temperature. After the addition of water (20 ml) and diethyl ether (25 ml), stirring was continued for 10 min. The solution was neutralized with 2N aqueous HCl, and then extracted with ether (3 x 30 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography using 1:2 hexane/EtOAc to give compound 27 (11 mg, 9% yield) and compound 28 (52 mg, 41% yield) as an oil. Starting material 11 (14 mg, 11% yield) was also recovered. Compound 27: R_f = 0.17 (1:2 hexane/EtOAc); ^1H NMR ($CDCl_3$)

δ 6.92 (d, J = 7.5 Hz, 2H, Ar), 6.73 (t, J = 7.5 Hz, 1H, Ar), 5.69-5.67 (m, 2H, HC=CH), 5.34 (t, J = 7.2 Hz, 1H, CHOAr), 4.20 (m, 1H, C<u>H</u>OH), 4.15-4.07 (m, 3H, OCH_2 and C=CC<u>H</u>OH), 3.90 (t, J = 9.0 Hz, 1H, CHAr), 2.79-2.71 (m, 1H), 2.66-2.51 (m, 2H), 2.38 (d, J = 15.0 Hz, 1H, CH_2 in cyclopentane), 2.27 (dt, J = 1.5 and 7.2 Hz, 2H), 2.15 (dt, J = 15.0 and 5.4 Hz, 1H, CH_2 in cyclopentane), 2.04-1.81 (m, 2H), 1.63 (m, 4H), 1.34 (m, 6H), 1.25 (t, J = 7.2 Hz, 3H, CH_3), 0.92 (t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.92, 157.81, 136.39, 128.71, 128.19, 127.75, 123.90, 122.960, 119.803, 88.267, 76.920, 72.951, 60.315, 52.213, 49.981, 42.299, 36.982, 33.50, 31.80, 29.06, 25.23, 24.87, 22.69, 14.24, 13.62; IR (neat) 3396 (OH), 2930, 1734 (C=O), 1458 cm^{-1}; HRMS m/z calculated for $C_{25}H_{36}O_5$ 416.25627, found 416.25574. Compound <u>28</u>: R_f = 0.38 (1:2 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.96 (d, J = 7.5 Hz, 1H, Ar), 6.91 (d, J = 7.5 Hz, 1H, Ar), 6.73 (t, J = 7.5 Hz, 1H, Ar), 5.69 (m, 2H, HC=CH), 5.32 (t, J = 7.5 Hz, 1H, CHOAr), 4.14 (m, 1H, C<u>H</u>OH), 4.07 (m, 3H), 3.88 (t, J = 9.3 Hz, 1H), 2.74 (m, 1H), 2.57 (m, 2H), 2.35 (d, J = 15.0 Hz, 1H, CH_2 in cyclopentane), 2.27 (m, 2H), 2.14 (dt, J = 15.0 and 5.7 Hz, 1H, CH_2 in cyclopentane), 1.99 (m, 1H), 1.91-1.81 (m, 3H), 1.49 (m, 2H), 1.28 (m, 6H), 1.24 (t, J = 7.5 Hz, 3H, CH_3), 0.88 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.84, 157.72, 136.39, 128.76, 127.79, 127.20, 124.04, 123.02, 119.91, 88.27, 77.00, 72.64, 60.28, 52.44, 50.12, 42.59, 37.32, 33.55, 31.82, 29.09, 25.21, 24.90, 22.66, 14.28, 14.10; IR (neat) 3443 (OH), 2987, 1732 (C=O), 1593, 1456 cm^{-1}; HRMS m/z calculated for $C_{25}H_{36}O_5$ 416.25627, found 416.25591.

2). Procedure B (via direct conversion from compound <u>10</u>)

In a vial were placed racemic compound <u>10</u> (100 mg, 0.24 mmol), optically active γ-stannyl allylic alcohol <u>30</u> (401 mg, 0.96 mmol), toluene (2.4 ml) and AIBN (Aldrich, 3.9 mg, 0.024 mmol). The resulting mixture was cooled to room temperature, and purified by flash chromatography using 1:1 to 1:2 hexane/EtOAc to give optically active <u>27</u> (22 mg, 21%

yield) and 31 (19 mg, 20% yield); The spectral data of this compound is the same as its racemic mixture 28.

Compound 29

See preparation of compound 34. The spectral data of this compound is the same as those of compound 34.

Preparation of optically active γ-tri-*n*-butylstannyl allylic alcohol 30[20]

To a solution of $LiAlH_4$ (6.0 ml, 1M in THF, 6.0 mmol) was added ethanol (3.0 ml, 2M in THF, 6.0 mmol) dropwise at room temperature. To this was added (S)-binaphthol (Aldrich, 1.7 g, 6.0 mmol) in 5 ml of THF, and the resulting mixture was stirred for 30 min. The enone 24 (830 mg, 2.0 mmol) in 2 ml of THF was added dropwise at -100 °C. The reaction mixture was stirred for 2 h at -100 °C, and then another 2 h at -78 °C. The reaction was quenched by adding 1 ml of methanol at -78 °C. After the reaction was warmed to room temperature, water (2 ml) and ether (30 ml) were added. Anhydrous $MgSO_4$ was added to the reaction mixture, and stirring was continued for 30 min at room temperature. The solution was filtered through Celite by adding ethyl acetate. The filtrate was concentrated. Hexane was added to the residue to remove the binaphthol as a crystalline solid. The filtrate was concentrated and flash chromatographed to give compound 30: 677 mg, 82% yield. The optical purity of compound 30 was not determined [literature report (98% ee)][20].

Compound 31

See preparation of compounds 27 and 28. The spectral data of this compound is the same as its racemic mixture 28.

Preparation of compounds 32 and 33

In a vial were placed compound 22 (93 mg, 0.27 mmol), alcohol 30 (454 mg, 1.1 mmol), AIBN (4.5 mg, 0.03 mmol) and 2.7 ml of toluene. The vial was placed in an oil bath preheated to 130 °C and the reaction mixture was stirred for 10 h. After the mixture was

cooled to room temperature, it was purified by flash column chromatography to give compounds 32 and 33. Compound 32: 29 mg, 32% yield; R_f = 0.17 (1:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.94 (d, J = 7.2 Hz, 1H, Ar), 6.92 (d, J = 7.2 Hz, 1H, Ar), 6.75 (t, J = 7.2 Hz, 1H, Ar), 5.94 (m, 1H, H_2C=C<u>H</u>), 5.68-5.54 (m, 2H, <u>H</u>C=C<u>H</u>CHOH), 5.34 (t, J = 6.9 Hz, 1H, CHOAr), 5.05-4.99 (m, 2H, H_2C=C), 4.15 (m, 1H, C<u>H</u>OH), 4.03 (m, 1H, C=CHC<u>H</u>OH), 3.86 (t, J = 8.7 Hz, 1H), 3.31 (d, J = 6.3 Hz, 2H, CH_2Ar), 2.76 (m, 1H), 2.36 (d, J = 15.3 Hz, 1H, CH_2 in cyclopentane), 2.15 (dt, J = 15.3 and 5.7 Hz, 1H, CH_2 in cyclopentane), 1.87 (m, 1H), 1.64-1.49 (m, 4H), 1.42-1.23 (m, 8 H), 0.90 (t, J = 6.9 Hz, 3H, CH_3). Compound 33: R_f = 0.37 (1:1 hexane/EtOAc): ^1H NMR ($CDCl_3$) δ 6.99 (d, J = 7.5 Hz, 1H, Ar), 6.95 (d, J = 7.5 Hz, 1H, Ar), 6.77 (t, J = 7.5 Hz, 1H, Ar), 5.97 (m, 1H, H_2C=C<u>H</u>), 5.70 (m, 2H, <u>H</u>C=C<u>H</u>CHOH), 5.36 (t, J = 6.9 Hz, 1H, CHOAr), 5.05-4.99 (m, 2H, H_2C=C), 4.16 (m, 1H, C<u>H</u>OH), 4.10 (m, 1H, C=CHC<u>H</u>OH), 3.31 (d, J = 6.3 Hz, 2H, CH_2Ar), 2.77 (m, 1H), 2.38 (d, J = 15.3 Hz, 1H, CH_2 in cyclopentane), 2.16 (ddd, J = 15.3 and 6.0 and 4.8 Hz, 1H, CH_2 in cyclopentane), 1.72-1.48 (m, 4H), 1.42-1.25 (m, 8 H), 0.89 (t, J = 6.9 Hz, 3H, CH_3).

<u>Preparation of compound 34</u>

To a solution of compound 31 (37 mg, 0.09 mmol) in 1.2 ml of THF was added 0.6 ml of 3N aqueous NaOH. After the reaction mixture was stirred for 4 d at room temperature, it was neutralized with 2N aqueous HCl. The organic phase was decanted with EtOAc (3 x 5 ml), then dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography with 20:1 EtOAc/MeOH gave compound 34: 26 mg, 74% yield; R_f = 0.29 (20:1 EtOAc/MeOH); ^1H NMR ($CDCl_3$) δ 6.94 (d, J = 7.5 Hz, 1H, Ar), 6.91 (d, J = 7.5 Hz, 1H, Ar), 6.73 (t, J = 7.5 Hz, 1H, Ar), 5.71 (dd, J = 15.6 and 5.4 Hz, 1H, HC=C), 5.64 (dd, J = 15.6 and 7.8 Hz, 1H, C=CH), 5.31 (m, 1H, CHOAr), 4.80 (br s, 2H, OH's), 4.18 (m, 1H, C<u>H</u>OH), 4.10 (dd, J = 11.7 and 6.3 Hz, 1H, C=CC<u>H</u>OH), 3.88 (t, J = 5.4 Hz, 1H, CHAr), 2.77 (m,

1H), 2.67 (m, 1H), 2.55 (m, 1H), 2.35 (d, J = 15.0 Hz, 1H, CH_2 in cyclopentane), 2.29 (dt, J = 3.0 and 7.2 Hz, 2H), 2.15 (dt, J = 15.0 and 5.7 Hz, 1H, CH_2 in cyclopentane), 2.06 (m, 1H), 1.84 (m, 1H), 1.49 (m, 3H), 1.29 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.17, 157.94, 136.42, 128.99, 127.66, 126.78, 124.19, 122.78, 119.98, 88.03, 76.97, 72.48, 52.31, 49.96, 42.16, 37.27, 33.01, 31.83, 29.02, 25.21, 24.66, 22.67, 14.18; IR (neat) 3362 (OH), 2926, 2851, 1701 (C=O), 1593, 1454 cm^{-1}; HRMS calculated for $C_{23}H_{32}O_5$ 388.22497, found 388.22512. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 62.38; H, 7.52. The poor elemental analysis for this compound is possibly due to insufficient drying of the sample.

Preparation of compound 35

A solution of cyclopentadiene monoepoxide (820 mg, 10.0 mmol) in THF (3 ml) was added dropwise over 20 min to an ice-cooled solution of $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and 2-iodophenol (Lancaster, 2.2 g, 10.0 mmol) in THF (7 ml). The reaction mixture was warmed to room temperature and stirred for 15 h. The reaction mixture was passed through a silica gel pad, and concentrated. The residue was purified by flash chromatography to give the product *cis*-4-(2-iodophenoxy)-2-cyclopenten-1-ol: 1.88 g, 62% yield; ^1H NMR ($CDCl_3$) δ 7.78 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 7.29 (dt, J = 1.5 and 7.8 Hz, 1H, Ar), 6.88 (dd, J = 7.8 and 1.2 Hz, 1H, Ar), 6.72 (dt, J = 1.2 and 7.1 Hz, 1H, Ar), 6.21 (dd, J = 5.7 and 1.5 Hz, 1H, HC=C), 6.17 (dd, J = 5.7 and 1.2 Hz, 1H, HC=C), 5.14 (m, 1H, CHOAr), 4.75 (m, 1H, C<u>H</u>OH), 2.83 (dt, J = 14.4 and 6.9 Hz, CH_2 in cyclopentane), 1.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 156.13, 139.05, 138.25, 131.34, 128.96, 122.09, 113.03, 86.89, 81.10, 73.72, 40.87. To a solution of *cis*-4-(2-iodophenoxy)-2-cyclopenten-1-ol (900 mg, 3.0 mmol) and imidazole (507 mg, 7.5 mmol) in CH_2Cl_2 (10 ml) was added dropwise over 10 min at room temperature TBDMSCl (583 mg, 3.6 mmol) dissolved in 5 ml of CH_2Cl_2. After being stirred 1 h, the reaction mixture was quenched by adding 5 ml of

H_2O, and extracted with hexane. The organic phase was dried, concentrated and flash chromatographed to give compound 35: 1.18 g, 95% yield; ^1H NMR ($CDCl_3$) δ 7.77 (dd, J = 7.8 and 1.5 Hz, 1H, Ar), 7.27 (dt, J = 2.1 and 7.1 Hz, 1H, Ar), 6.85 (dd, J = 8.4 and 1.2 Hz, 1H, Ar), 6.70 (dt, J = 1.2 and 7.5 Hz, 1H, Ar), 6.07 (m, 1H, HC=C), 6.02 (m, 1H, HC=C), 5.07 (m, 1H, CHOPh), 4.78 (m, 1H, CHOSi), 2.91 (dt, J = 13.8 and 6.9 Hz, 1H, CH_2), 1.88 (dt, J = 13.5 and 5.1 Hz, 1H, CH_2), 0.91 (s, 9H, *t*-BuSi), 0.11 (s, 3H, SiMe), 0.10 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$) δ 156.96, 139.73, 138.64, 131.26, 129.13, 122.45, 113.52, 87.54, 81.49, 74.85, 42.05, 25.74, 18.14, -4.69.

Compound 36 (R = TBDMS)

^1H NMR ($CDCl_3$) δ 7.87 (d, J = 16.5 Hz, 1H, HC=CHCO), 7.53 (dd, J = 7.8 and 1.2 Hz, 1H, Ar), 7.30 (dt, J = 1.2 and 7.8 Hz, 1H, Ar), 6.93 (m, 2H, Ar), 6.74 (d, J = 16.5 Hz, 1H, HC=CHCO), 6.04 (m, 2H, HC=CH), 5.12 (t, J = 6.0 Hz, 1H, CHOAr), 4.78 (t, J = 6.0 Hz, 1H, CHOSi), 2.93 (dt, J = 13.8 and 6.9 Hz, 1H, CH_2 in cyclopentane), 2.64 (t, J = 7.2 Hz, 2H, CH_2CO), 1.81 (dt, J = 13.5 and 5.4 Hz, 1H, CH_2 in cyclopentane), 1.65 (m, 2H), 1.31 (m, 4H), 0.89 (m, 12H, CH_3 plus *t*-BuSi), 0.09 (s, 3H, SiMe), 0.08 (s, 3H, SiMe).

Compound 37

^1H NMR ($CDCl_3$) δ 7.18 (d, J = 7.8 Hz, 1H, Ar), 7.07 (t, J = 7.8 Hz, 1H, Ar), 6.81 (t, J = 7.8 Hz, 1H, Ar), 6.73 (d, J = 7.8 Hz, 1H, Ar), 5.74 (m, 2H, HC=CH), 5.45 (t, J = 6.3 Hz, 1H, CHOAr), 4.37 (d, J = 7.5 Hz, 1H, CHAr), 2.87 (dd, J = 19.2 and 6.3 Hz, 1H, CH_2), 2.75 (d, J = 17.7 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$) δ 131.23, 129.07, 128.22, 128.04, 124.43, 124.11, 120.32, 109.47, 86.49, 54.37, 40.73; LRMS (relative intensity) m/z 115.0 (9), 131.0 (42), 158.3 (M^+, 100).

Compound 38

^{1}H NMR ($CDCl_3$) δ 7.80 (dd, J = 8.1 and 1.5 Hz, 1H, Ar), 7.73 (dd, J = 5.4 and 2.1 Hz, 1H, HC=CHCO), 7.32 (dt, J = 1.5 and 8.1 Hz, 1H, Ar), 6.89 (dd, J = 8.1 and 1.2 Hz, 1H, Ar), 6.77 (dt, J = 1.8 and 8.4 Hz, 1H, Ar), 6.39 (dd, J = 6.0 and 1.5 Hz, 1H, C=CHCO), 5.45 (m, 1H, CHOAr), 2.90 (dd, J = 18.3 and 6.0 Hz, 1H, CH_2), 2.54 (dd, J = 18.3 and 2.1 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$) δ 204.38, 158.96, 156.27, 139.98, 136.72, 129.55, 123.74, 113.85, 87.62, 76.95, 41.81; IR (neat) 1722 (C=O) cm^{-1}.

Compound 39

^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 16.5 Hz, 1H, PhHC=CHCO), 7.74 (dd, J = 5.7 and 2.4 Hz, 1H, HC=CCO), 7.60 (d, J = 7.8 Hz, 1H, Ar), 7.38 (t, J = 7.8 Hz, 1H, Ar), 7.04 (t, J = 7.8 Hz, 1H, Ar), 6.86 (d, J = 7.8 Hz, 1H, Ar), 6.75 (d, J = 16.5 Hz, 1H, PhC=CHCO), 6.30 (d, J = 5.7 Hz, 1H), 5.53 (m, 1H), 2.96 (dd, J = 18.3 and 6.0 Hz, 1H, CH_2 in cyclopentane), 2.80-2.61 (m, 3H), 1.65 (m, 2H), 1.31 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H, CH_3).

Preparation of compound 41

In a vial were placed compound 22 (68 mg, 0.2 mmol), ethyl vinyl ketone (84 mg, 1.0 mmol), triethylamine (50 mg, 0.5 mmol), *n*-Bu_4NCl (Lancaster, 61 mg, 0.22 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and 0.4 ml of DMF. After the mixture was stirred for 6 h at 50 °C, it was poured into 60 ml of ether and the overall solution was washed with saturated NH_4Cl (20 ml) and brine (20 ml). The solution was dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by flash chromatography with 2:1 to 1:1 hexane/EtOAc to give compound 41: 26 mg, 44% yield; ^{1}H NMR ($CDCl_3$) δ 6.97 (d, J = 7.5 Hz, 1H, Ar), 6.90 (d, J = 7.5 Hz, 1H, Ar), 6.82 (dd, J = 16.2 and 9.6 Hz, 1H, HC=CHCO), 6.79 (t, J = 7.5 Hz, 1H, Ar), 6.21 (d, J = 16.2 Hz, 1H, C=CHCO), 5.97 (m, 1H, H_2C=CH), 5.42 (dd, J = 7.8 and 5.7 Hz, 1H, CHOAr), 5.02 (m, 2H, H_2C=C), 4.28 (m, 1H, CHOH), 3.99 (t, J

= 8.4 Hz, 1H, CHAr), 3.32 (d, J = 6.3 Hz, 2H, CH_2Ar), 2.86 (dt, J = 4.2 and 9.6 Hz, 1H, $C\underline{H}CH$=CHCO), 2.57 (dq, J = 3.0 and 7.5 Hz, 2H, $OCC\underline{H}_2CH_3$), 2.49 (d, J = 15.3 Hz, 1H, CH_2 in cyclopentane), 2.20 (dt, J = 15.3 and 5.4 Hz, 1H, CH_2 in cyclopentane), 1.64 (d, J = 7.5 Hz, 1H, OH), 1.08 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 201.17, 157.22, 143.88, 136.23, 132.66, 129.17, 127.07, 123.90, 122.29, 120.53, 115.66, 88.98, 77.25, 52.60, 50.60, 42.87, 38.99, 32.26, 8.18; IR (neat) 3468 (OH), 1668 (C=O) cm^{-1}; HRMS m/z calculated for $C_{19}H_{22}O_3$ 298.15690, found 298.15741.

Compound 46

^1H NMR ($CDCl_3$) δ 7.65 (dd, J = 1.5 and 7.8 Hz, 1H, Ar), 7.17 (dd, J = 1.5 and 7.8 Hz, 1H, Ar), 6.77 (t, J = 7.8 Hz, 1H, Ar), 5.99 (m, 2H, HC=CH), 5.02 (m, 1H, CHOAr), 4.68 (m, 1H, CHOSi), 4.11 (q, J = 7.2 Hz, 2H), 2.84 (m, 2H), 2.66 (ddd, J = 15.3 and 9.6 and 6.0 Hz, 1H), 2.29 (t, J = 7.2 Hz, 2H), 2.00 (dt, J = 13.5 and 5.7 Hz, 1H), 1.90 (t, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H, CH_3), 0.92 (s, 9H, *t*-BuSi), 0.11 (s, 6H, $SiMe_2$).

Preparation of compounds 50 and 51

1). Procedure A (via reduction of compound 12)

To a solution of $LiAlH_4$ (Aldrich, 2.8 ml, 0.539 M in THF, 1.52 mmol) was added ethanol (0.76 ml, 2M in THF, 1.52 mmol) dropwise over 10 min at room temperature. Subsequently, a THF solution of (S)-binaphthol (Aldrich, 429 mg, 1.52 mmol in 2.4 ml of THF) was added dropwise, and the resulting mixture was stirred for 30 min. Enone 12 (199 mg, 0.51 mmol) in 2 ml of THF was added dropwise over 3 min at -100 °C, and stirring was continued for 2 h at -100 °C and for another 2 h at -78 °C. The reaction was quenched by adding methanol (0.5 ml) at -78 °C and warmed to room temperature. After addition of water (0.5 ml) and ether (15 ml), stirring was continued for an additional 30 min. To this was added anhydrous $MgSO_4$ and the mixture was filtered through Celite. Concentration,

followed by flash chromatography with 1:2 hexane/EtOAc, gave compounds 50 (49 mg, 25% yield) and 51 (50 mg, 25% yield). Compound 50: R_f = 0.25 (1:2 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.91 (d, J = 7.5 Hz, 2H, Ar), 6.73 (t, J = 7.5 Hz, 1H, Ar), 5.66 (m, 2H, HC=CH), 5.33 (t, J = 7.8 Hz, 1H, CHOAr), 4.20 (m, 1H, C<u>H</u>OH), 4.10 (m, 3H, OCH_2 and C=CHC<u>H</u>OH), 3.87 (t, J = 8.7 Hz, 1H, CHAr), 2.74 (m, 1H), 2.64 (dd, J = 12.9 and 6.6 Hz, 1H), 2.55 (dt, J = m, 1H), 2.38 (d, J = 15.0 Hz, 1H, CH_2 in cyclopentane), 2.27 (dt, J = 2.1 and 1.8 Hz, 1H), 2.15 (ddd, J = 15.0 and 6.0 and 4.5 Hz, 1H, CH_2 in cyclopentane), 2.04-1.78 (m, 4H), 1.67 (br s, 2H, OH's), 1.54 (m, 1H), 1.33 (m, 6H), 1.25 (t, J = 7.5 Hz, 3H, CH_3), 0.92 (t, J = 6.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.90, 157.81, 136.44, 128.73, 128.15, 127.76, 123.91, 122.99, 119.82, 88.28, 76.93, 72.96, 60.30, 52.28, 50.04, 42.37, 37.04, 33.52, 31.81, 29.06, 25.25, 24.89, 22.69, 14.29, 14.10; IR (neat) 3486 (OH), 1732 (C=O) cm^{-1}; HRMS m/z calculated for $C_{25}H_{36}O_5$ 416.25628, found 416.25541. Compound 51: R_f = 0.48 (1:2 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.97 (d, J = 7.2 Hz, 1H, Ar), 6.92 (d, J = 7.5 Hz, 1H, Ar), 6.74 (t, J = 7.5 Hz, 1H, Ar), 5.71 (m, 2H, HC=CH), 5.34 (t, J = 6.9 Hz, 1H, CHOAr), 4.19 (m, 1H, C<u>H</u>OH), 4.11 (m, 3H, OCH_2 and C=CHC<u>H</u>OH), 3.90 (t, J = 11.7 Hz, 1H, CHAr), 2.75 (m, 1H), 2.59 (m, 1H), 2.38 (d, J = 15.0 Hz, 1H, CH_2 in cyclopentane), 2.27 (m, 2H), 2.16 (ddd, J = 15.0 and 6.0 and 4.5 Hz, 1H, CH_2 in cyclopentane), 2.05-1.82 (m, 4H), 1.72 (d, J = 6.0 Hz, 1H), 1.53 (br s, 2H, OH's), 1.29 (m, 6H), 1.25 (t, J = 7.5 Hz, 3H, CH_3), 0.88 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.87, 157.69, 136.34, 128.70, 127.76, 127.08, 124.04, 122.95, 119.85, 88.23, 77.02, 72.53, 60.27, 52.38, 50.06, 42.52, 37.27, 33.49, 31.80, 29.04, 25.19, 24.86, 22.63, 14.27, 14.10; IR (neat) 3416 (OH), 3053, 2845, 1732 (C=O), 1599, 1447 cm^{-1}; HRMS m/z calculated for $C_{25}H_{36}O_5$ 416.25628, found 416.25711.

2). Procedure B (via direct conversion from compound 10)

In a vial were placed compound 10 (109 mg, 0.26 mmol), γ-stannyl alcohol 30 (164 mg, 0.39 mmol), *i*-Pr2NEt (85 mg, 0.66 mmol), *n*-Bu4NCl (Lancaster, 88 mg, 0.31 mmol), Pd(OAc)2 (2.9 mg, 0.013 mmol) and DMF (0.52 ml) as a solvent. After the resulting mixture was stirred for 12 h at room temperature, it was passed through a silica gel pad with 1:2 hexane/EtOAc. The solution was concentrated, and the residue was purified by flash chromatography with 1:2 hexane/EtOAc to give compounds 50 (15 mg, 14% yield) and 52 (17 mg, 16% yield).

Compound 52

See preparation of compound 51. The spectral data of this compound is the same as those of compound 51.

Preparation of 12,15-epi-5,6,7-trinor-4,8-inter-*m*-phenylene PGI2 (54)

To a solution of compound 51 (55 mg, 0.14 mmol) in 1.8 ml of THF was added 3N aqueous NaOH (0.9 ml) at room temperature. After the reaction was stirred for 6 d at room temperature, it was neutralized by 2N aqueous HCl. The organic phase was decanted with ethyl acetate and dried over MgSO4. Concentration in vacuo followed by flash chromatography with 20:1 EtOAc/MeOH gave compound 55: 47 mg, 92% yield; R_f = 0.37 (20:1 EtOAc/MeOH); ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 7.5 Hz, 1H, Ar), 6.90 (d, J = 7.5 Hz, 1H, Ar), 6.74 (t, J = 7.5 Hz, 1H, Ar), 5.72 (dd, J = 15.3 and 5.1 Hz, 1H, HC=C), 5.65 (dd, J = 15.3 and 7.8 Hz, 1H, C=CH), 5.62 (br s, 2H, OH's), 5.32 (t, J = 6.9 Hz, 1H, CHOAr), 4.20 (m, 1H, CHOH), 4.12 (dd, J = 12.0 and 9.0 Hz, 1H, C=CHCHOH), 3.89 (t, J = 8.7 Hz, 1H), 2.80 (dt, J = 4.2 and 9.0 Hz, 1H), 2.70 (m, 1H), 2.54 (m, 1H), 2.38 (d, J = 15.9 Hz, 1H, CH_2 in cyclopentane), 2.29 (dd, J = 14.1 and 6.3 Hz, 2H), 2.22-2.04 (m, 2H), 1.84 (m, 1H), 1.49 (m, 3H), 1.29 (m, 6H), 0.89 (t, J = 6.3 Hz, 3H, CH_3);

^{13}C NMR ($CDCl_3$) δ 178.54, 157.87, 136.26, 128.88, 127.64, 126.73, 124.15, 122.72, 119.92, 88.00, 76.93, 72.39, 52.27, 49.92, 42.12, 37.19, 33.07, 31.81, 28.97, 25.17, 24.64, 22.64, 14.13; IR (neat) 3412 (OH), 3271 (OH), 3063, 2924, 2858, 1709 (C=O), 1456, 1254 cm^{-1}; HRMS m/z calculated for $C_{23}H_{32}O_5$ 388.22497, found 388.22589. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.36; H, 8.09.

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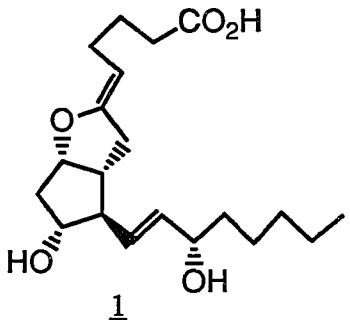
CHAPTER III. ORGANOPALLLADIUM APPROACHES TO 12-EPI-CARBACYCLINS

INTRODUCTION

Prostacyclin (1), abbreviated PGI_2, is the most powerful natural inhibitor of ADP-induced aggregation of human blood platelets. Due to the inherent chemical instability of the enol ether system in the natural PGI_2, intensive efforts have been made to prepare chemically stable and biologically potent prostacyclin analogues[1].

Among the prostacyclin analogues, carbacyclin (2) has attracted special attention, because of its potent biological activity[2d] and satisfactory chemical stability. Carbacyclin



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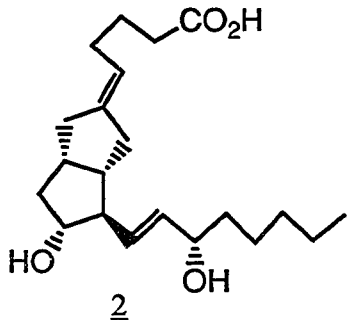
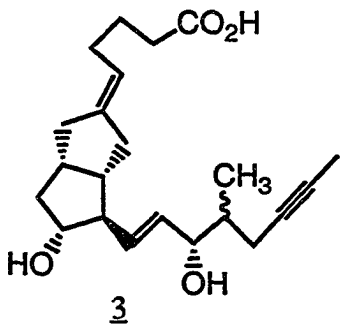


2

(2) was first synthesized in 1978 independently by Nicolaou et al.,[2a] Kojima and Sakai[2b], Shibasaki et al.,[2c] and Morton and Brokaw[2d]. Since then, several additional syntheses have appeared[3]. In addition, the significant biological activity of carbacyclin led to the synthesis of analogues. The therapeutically interesting analogues include ilopost (3)[4], ZK 96 480 (4)[5], ciprostene (5)[6] and OP 41 483 (6)[6].



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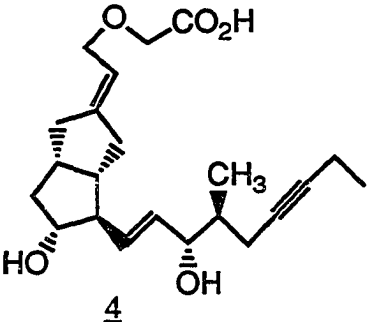

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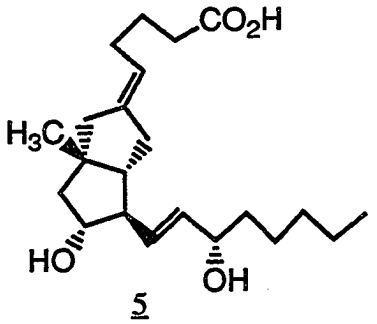

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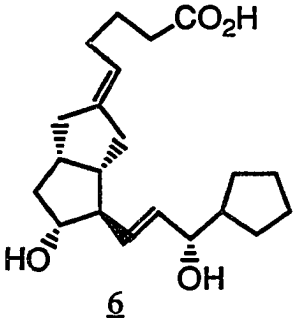

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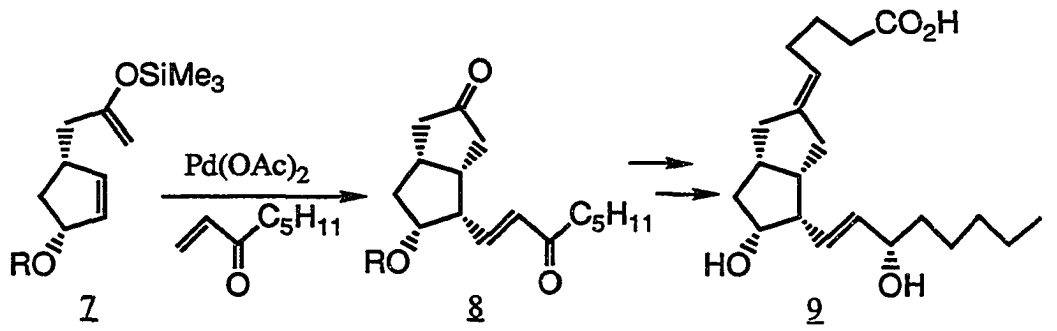
In our continuing effort to synthesize prostaglandins, compound 9 appeared to be an interesting carbacyclin analogue that we might approach using palladium chemistry (Scheme I). The cyclization of silyl enol ethers employing palladium acetate has previously been

Scheme I.



7 8 9

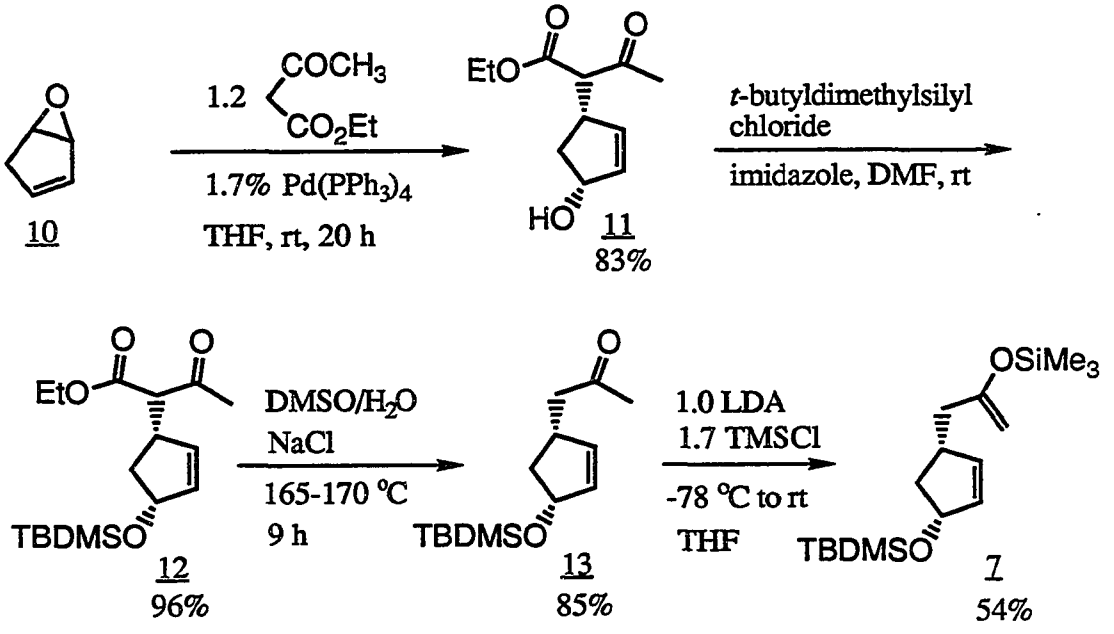
developed[7]. The coupling of 1-octen-3-one and the organopalladium intermediate generated by cyclization of compound 7 would give compound 8 in a single step procedure. Subsequent reactions including selective reduction of the α,β-unsaturated ketone and a Wittig reaction should provide the novel prostaglandin 9 in very few steps.

Unlike all of the carbacyclin analogues previously synthesized, compound 9 has an α-configuration at carbon 12. Thus, examination of the biological activity of compound 9 should be interesting.

RESULTS AND DISCUSSION

Compound 7 was prepared by the sequence shown in Scheme II. Compound 11

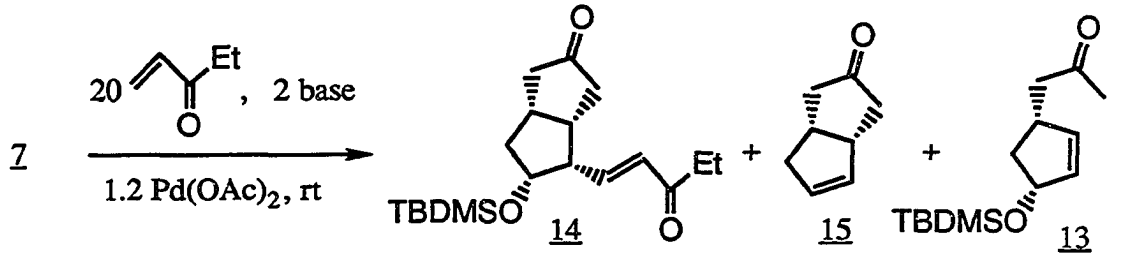
Scheme II.



was prepared from cyclopentadiene monoepoxide (10) by previously developed Pd(0) chemistry[8]. The decarboalkoxylation of compound 11 using Krapcho's method[9] provided only unidentified product. However, protection of the hydroxy group in compound 11, followed by Krapcho's thermal decarboalkoxylation[9] provided ketone 13 cleanly. Subsequent treatment of ketone 13 with LDA and trimethylsilyl chloride[10] afforded silyl enol ether 7.

The key step was examined using compound 7 and ethyl vinyl ketone as a model study. The Pd(II)-mediated cyclization, followed by enone coupling, was conducted under various conditions. The results are summarized in Table 1. The desired product 14 was

Table 1. Reaction conditions for the synthesis of compound 14



Entry	Base	Solvent	% Isolated Yield 14	15	13
1	NaOAc	-	23	5	20
2	Et_3N	-	0	5	52
3	NaOAc	THF	22	44	5
4	Na_2CO_3		21	30	5
5	Et_3N		9	8	42
6	K_2CO_3	acetone	26	33	?
7	$LiOAc{\cdot}2H_2O$		32	38	?
8[a]	NaOAc	THF	4	0	21
9[b]			0	0	21
10		CH_2Cl_2	7	38	5
11		CH_3CN	4	38	5
12		DMF	24	38	?

[a]The reaction was conducted with Li_2PdCl_4, instead of $Pd(OAc)_2$.

[b]The reaction was conducted with 10 PPh_3 as an additive.

Table 1. Continued

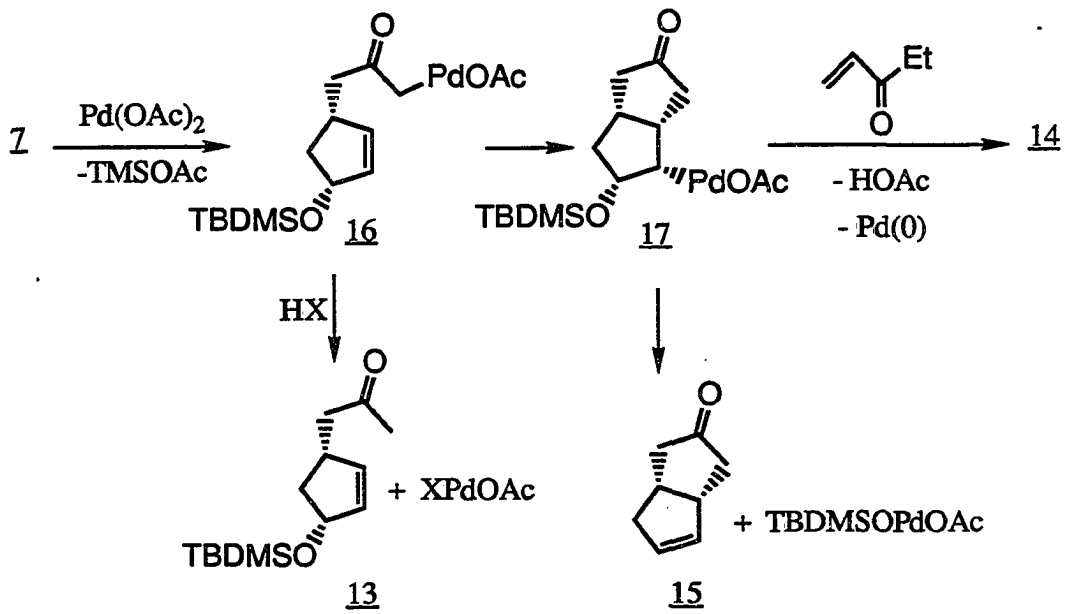
Entry	Base	Solvent	% Isolated Yield 14	15	13
13	NaOAc	DMSO	3	8	64
14		benzene	18	60	?
15		acetone	28	38	?
16[c]		CH_2Cl_2	19	24	?

[c]The reaction was conducted with 10 HMPA as an additive.

produced along with two side-products 13 and 15. The reaction was examined without any solvent in entries 1 and 2. With sodium acetate as a base, product 14 was obtained in 23% yield. None of the desired product was obtained with an organic base, such as triethylamine. From entries 3 to 7, variations of bases and solvents were examined. Inorganic bases gave better results than organic bases. Switching the Pd(II) species from $Pd(OAc)_2$ to Li_2PdCl_4 gave worse results (entry 8). Employment of PPh_3 as an additive gave none of the desired product; compound 13 was obtained as the only product (entry 9). Solvent variations were examined in entries 10 to 16. THF, DMF or acetone appeared to give the best results.

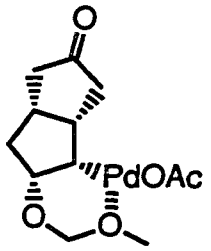
A possible reaction mechanism is proposed in Scheme III. Reactions with Et_3N as a base or PPh_3 as an additive led to the reduction product 13 over the cyclized intermediate 17. One might explain this by proposing that Et_3N or PPh_3 is coordinated to the acyl palladium intermediate 16, preventing olefin coordination, and thus favoring formation of compound 13

Scheme III.



over the competing pathway leading to intermediate 17. With inorganic bases, the desired cyclization proceeds well. However, the elimination reaction leading to compound 15 competes with the formation of the desired enone coupling leading to compound 14.

To prevent the elimination reaction from occurring in intermediate 17, we decided to employ other protecting groups in compound 7. The MOM protecting group was considered to be a better choice, because the organopalladium intermediate 17 might be stabilized by the coordination of a near-by oxygen as in intermediate 18. Then, the stabilized intermediate 18 might have sufficient time to undergo intermolecular enone insertion. However, that was not



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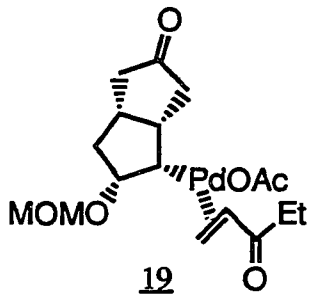
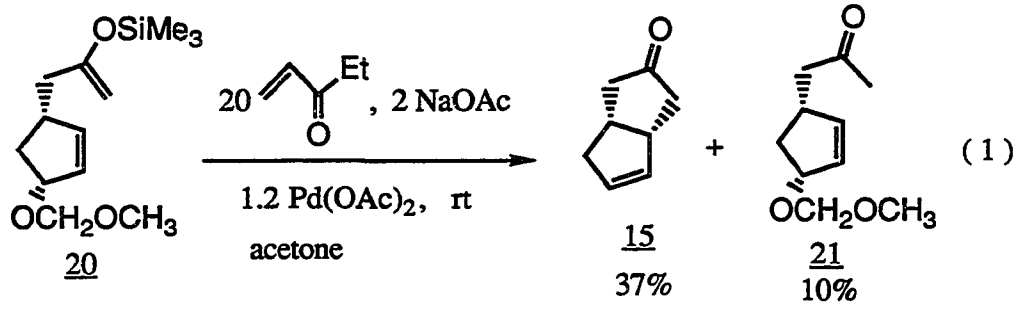


19

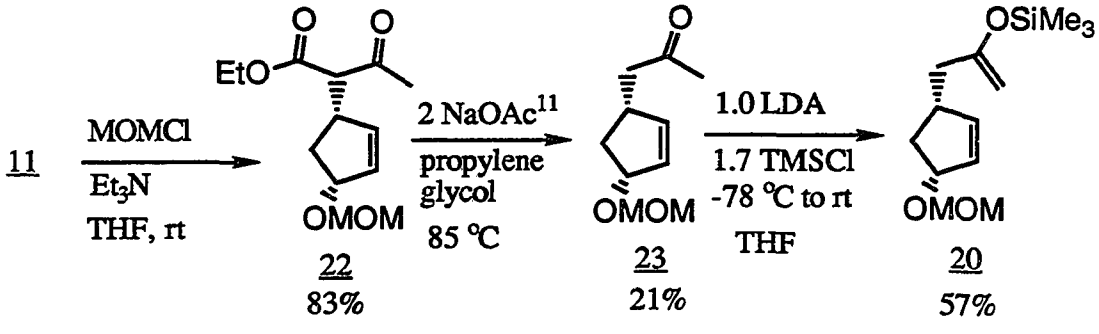
the case. The oxygen coordination apparently makes olefin coordination to form intermediate 19 more difficult. As a result, none of the desired product was obtained (eq 1).



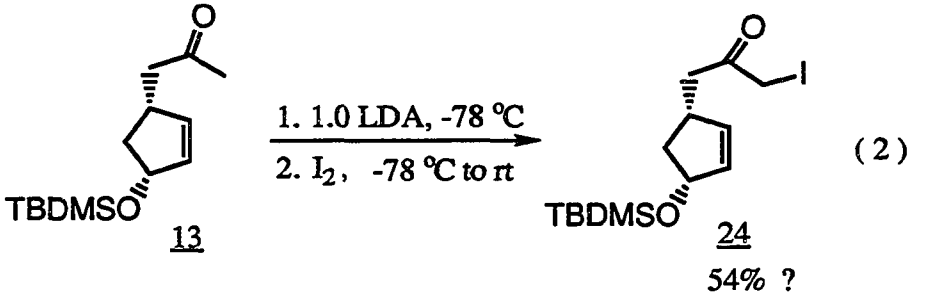
(1)

Compound 20 was prepared following the procedures shown in Scheme IV.

Scheme IV.



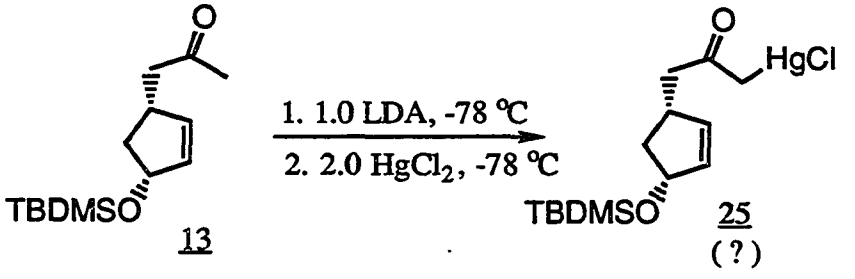
We decided to explore another starting material with which we might accomplish the key step more efficiently. α-Iodoketone 24 was considered as a possible starting material. No simple literature procedure for the α-iodination of ketones was found. Therefore, a procedure[12] for the synthesis of α-iodoesters was employed in the α-iodination of ketone 13 (eq 2). A compound which looked like product 24 by ^1H and ^{13}C NMR spectral analysis



(2)

was separated by flash chromatography. However, compound 24 seemed to be unstable. Compound 24 was found to decompose when it was subjected to ^1H NMR spectroscopic examination after overnight storage in a freezer.

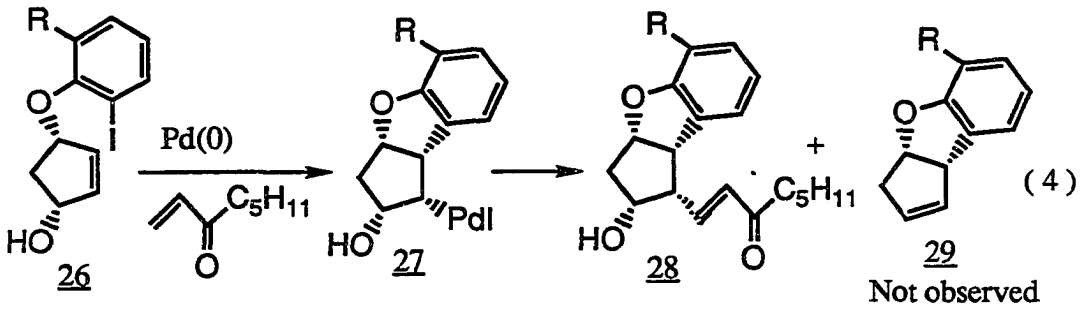
Another compound which might be used to synthesize compound 14 is organomercurial 25. When compound 13 was subjected to Stinn's procedure[13] for the mercuration of an ester, a relatively clean spot was observed upon TLC analysis (eq 3).



(3)

However, this compound could not be identified by ^1H NMR spectral analysis and high resolution mass spectroscopy.

While alkoxy palladium elimination in intermediate 17 appeared to be a major problem in this project, it was interesting that none of the side-product 29 was observed in the synthesis of compound 28 described in Chapter II of this dissertation (eq 4). The difference



(4)

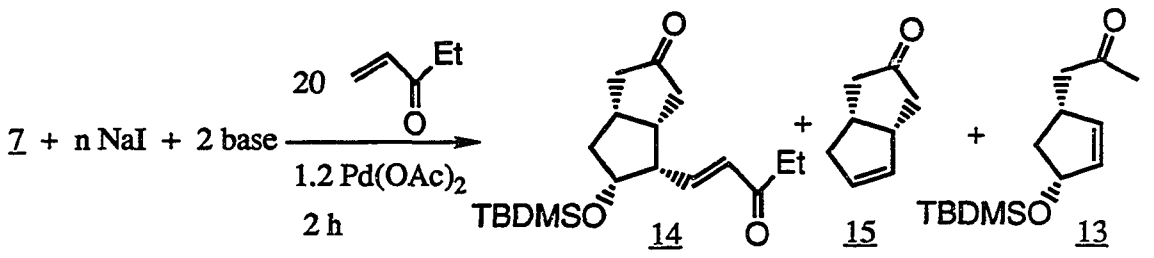
between organopalladium intermediates 17 and 27 lies partly in the ligand on palladium. Thus, substitution of an organopalladium iodide for an organopalladium acetate was considered to be worth examining. The reaction was conducted simply by adding sodium iodide to the reaction mixture. The results are summarized in Table 2.

As a preliminary experiment, sodium iodide was added to a solution of $Pd(OAc)_2$ dissolved in THF without any organic substrates. The color of $Pd(OAc)_2$ turned from brown to a dark purple as soon as NaI was added. One might suppose that the metathesis reaction described in equation 5 is occurring very fast.

$$Pd(OAc)_2 + NaI \longrightarrow IPdOAc + NaOAc \qquad (5)$$

As seen in Table 2, addition of NaI increased the yield of the product to some extent (compare entries 1 and 2, 9 and 10). The amount of sodium iodide employed didn't make

Table 2. Reaction conditions for the synthesis of compound 14



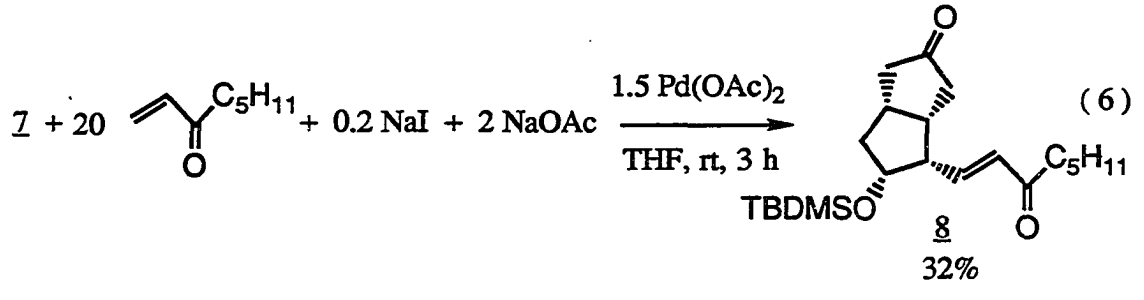
Entry	n	Temp. (°C)	Base	Solvent	% Isolated Yield 14	15	13
1	0	rt	NaOAc	THF	22	44	<5
2	1.2				45	30	20
3	0.6				43	38	?
4	0.2				42	50	<5
5[a]	0.2				55	?	?
6[b]	0.2				49	15	14
7	0.2		KOAc		34	30	30
8	0.2 KI		NaOAc		24	33	22
9	0			neat	23	15	20
10	0.2				44	19	34
11	0.2	0		THF	46	26	25
12	0.2	10			50	29	11

[a]The reaction was conducted employing 1.5 equivatents of $Pd(OAc)_2$.

[b]The reaction was conducted employing 1.5 equivalents of $Pd(OAc)_2$ and 20 equivalents of isobutylene oxide.

much difference in the product yield (entries 2-4). An increase in the amount of NaI afforded a slight decrease in the yield of the eliminated product 15. The use of 1.5 equivalents of $Pd(OAc)_2$ increased the yield of the product up to 55% (entry 5). A close look at the reaction mechanism in Scheme III suggests that we might reduce the amount of side-product 13 by elimination of acetic acid generated during the reaction. In entry 6, isobutylene oxide which has previously been used as a proton scavanger[14] was added to reduce the side-product 13. The attempt, however, proved fruitless. Contrary to NaI, no effect was observed when adding KI to this reaction (entry 8). The reaction mixture remained brown upon addition of KI implying that no metathesis reaction is occurring. Temperature variations were examined in entries 11 and 12. Little effect was observed.

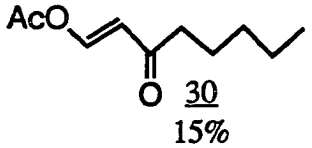
Based on the results in Tables 1 and 2, 1-octen-3-one was employed in place of ethyl vinyl ketone to carry through the synthesis of prostaglandin 9. It was observed that the yield of the product 8 decreased (eq 6). In addition, compound 30 was observed as a side product.



8
32%

(6)

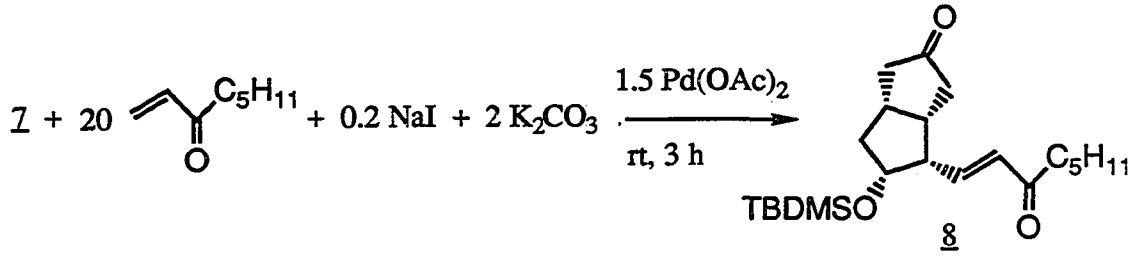
Thus, potassium carbonate was employed as a base to eliminate compound 30. Even though



30
15%

compound 30 still remained as a side-product, a slight increase in the product yield was observed (entry 1 in Table 3). The reaction was examined with potassium carbonate as a base in various solvents. The results were summarized in Table 3.

Table 3. Reaction conditions for the synthesis of compound 8

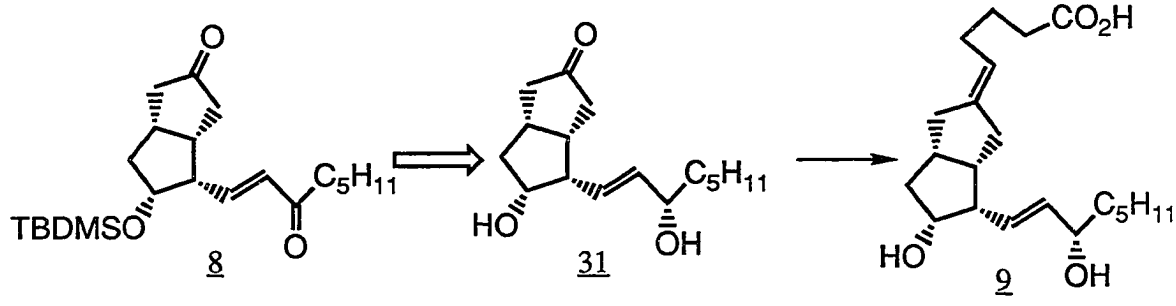


Entry	Solvent	% Isolated Yield of 8	Comment
1	THF	42	-
2	DME	40	-
3	*t*-BuOH	41	-
4	acetone	38	-
5	neat	30	-
6	$CHCl_3$	48	-
7		45	2 Na_2CO_3 was used as a base
8		49	0.2 LiI was used in place of NaI
9		49	0.5 NaI was used in place of 0.2 NaI
10	CH_2Cl_2	53	0.25 mmol of compound 7 was used
11		62	0.75 mmol of compound 7 was used

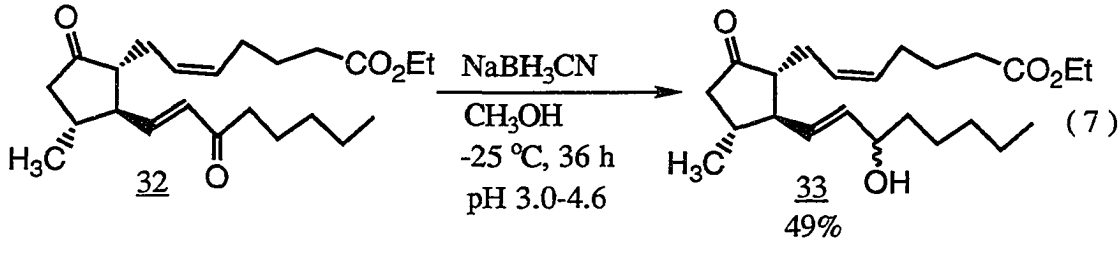
Among the solvents examined, CH_2Cl_2 (entries 10 and 11) appeared to be the best. By conducting the reaction on a larger scale, the product 8 could be obtained in up to 62% yield (entry 11). After this extensive examination of reaction conditions, the desired product 8 was obtained in good yield utilizing a Pd(II)-mediated cyclization, followed by enone coupling.

To carry through to the prostaglandin 9, we needed to convert compound 8 to compound 31 (Scheme IV). From a literature survey, no general method was found for the

Scheme IV.



selective reduction of an α,β-unsaturated ketone in the presence of a saturated ketone. One promising literature procedure involved the regioselective reduction of compound 32 to compound 33[15] (eq 7). After a systematic study of various reducing agents, Greene et al.,[15]

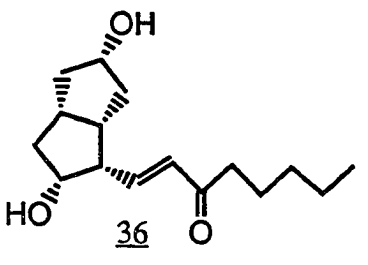


(7)

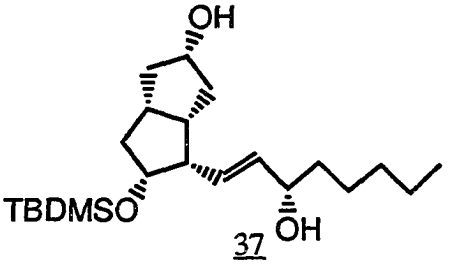
found that sodium cyanoborohydride was the most efficient reagent for the conversion of compound 32 to compound 33. However, this reaction was very sensitive to the reaction conditions. The reaction temperature had to be kept at -25 °C for 36 h, and also the pH had to be maintained between 3.0 and 4.6 by adding aqueous HCl. Moreover, diastereomeric alcohols at carbon-15 were obtained as 1:1 mixtures.

To overcome the problems in equation 7, we decided to examine Noyori's (S)-BINAL-H[16] as a stereo- and regioselective reducing agent. Even though BINAL-H has been well documented for the stereoselective reduction of α,β-unsaturated ketones in a predictable manner[16], no examples have been reported for the chemoselective reduction of enones in the presence of saturated ketones by BINAL-H.

We were pleased to observe that stereo- and chemoselective reduction of compound 8 was efficiently effected by (S)-BINAL-H (Scheme V). When compound 8 was subjected to reduction with (S)-BINAL-H, the desired product 34 was obtained selectively over compound 35 in a ratio of 9:1. The accidental overlapping of compounds 34, 35 and (S)-binaphthol on TLC made isolation of the product difficult. However, assignment of the olefinic hydrogens of compounds 34 and 35 in the crude product by ^{1}H NMR spectral analysis was possible. The olefinic hydrogens in compounds 34 and 35 were compared to those in compounds 31 and 36 which were isolated cleanly after desilylation. None of the



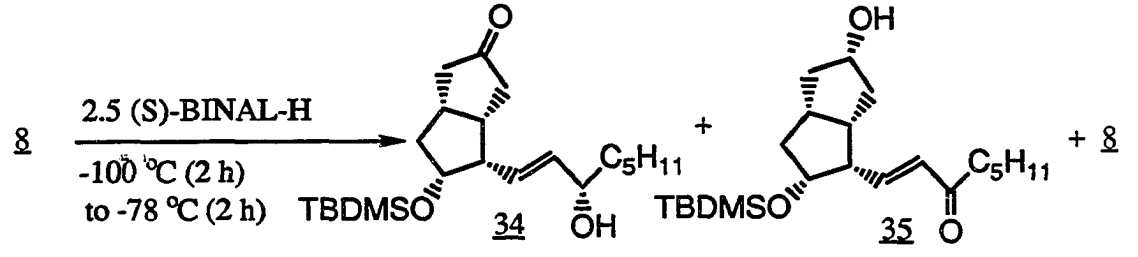
36



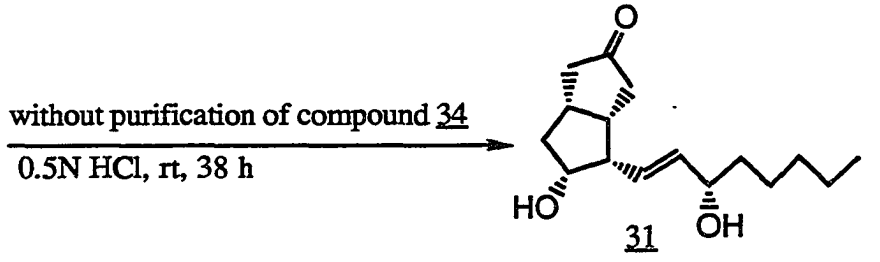
37

over-reduced product 37 was observed upon ^{1}H NMR spectral analysis. Even though an excess of the reducing agent was employed, some of the starting material 8 was left upon ^{1}H NMR spectral analysis. Since the R_f value of compound 8 was also close to (S)-binaphthol, no attempt was made to recover the starting material 8.

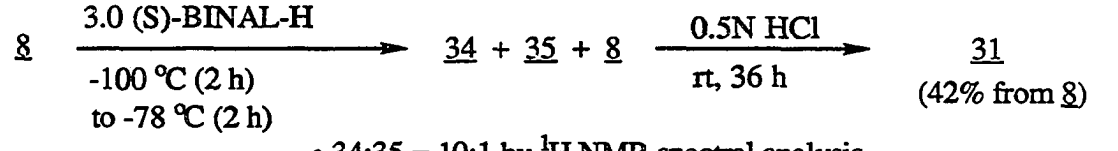
Scheme V.



- 34:35 = 9:1 by ^{1}H NMR spectral analysis
- 14-25% of starting material 8 left upon ^{1}H NMR spectral analysis



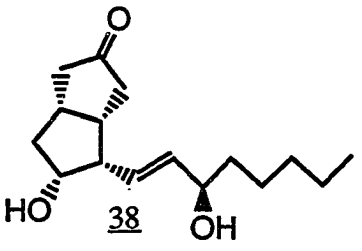
(50% from 8)



(42% from 8)

- 34:35 = 10:1 by ^{1}H NMR spectral analysis
- 16% of starting material 8 left upon ^{1}H NMR spectral analysis

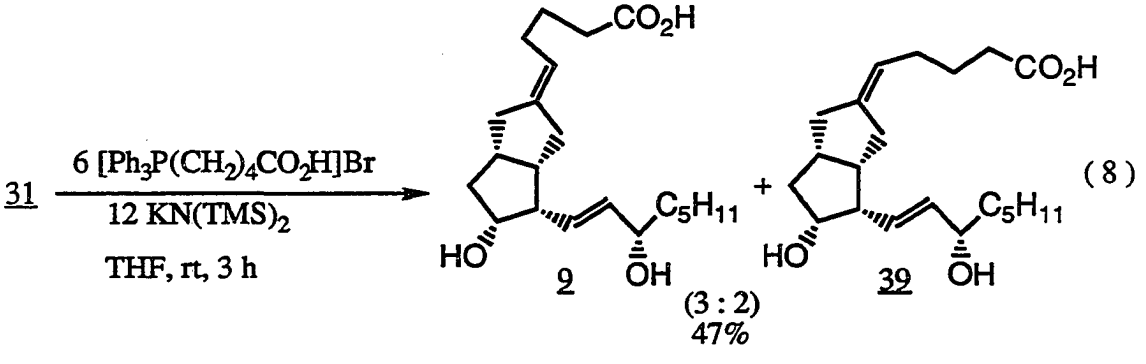
Deprotection of the silyl group in compound 34 was effected using aqueous hydrochloric acid to yield compound 31, which was then separable from (S)-binaphthol and compound 36. None of the C_{15}-(R) isomer 38 was observed. Since only one stereoisomer



38

at C_{15} was obtained, we assigned it as the desired C_{15}-(S) isomer based on the previous report using (S)-BINAL-H[16]. Therefore, compound 8 was reduced chemo- and stereoselectively to give crude product 34 which was, without further purification, subjected to hydrolysis to provide compound 31 in 50% yield from compound 8.

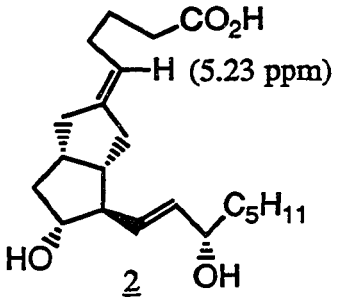
A subsequent Wittig reaction on conpound 31 provided the 12-epi-carbacyclin (9) along with its C_5-Z isomer 39 (eq 8). The E and Z configurational assignments at C-5 of



(8)

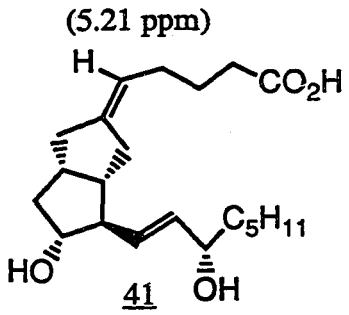
the final products has not been definitively established. The stereochemistry was tentatively assigned based on the polarity and product ratio of compounds 9 and 39. A literature survey revealed that the more polar isomers are generally those with the desired stereochemistry at C-5 (Scheme VI). The configuration of the trisubstituted olefin at C-5 in carbacyclin (2)[2] or its analogues, such as compounds 4[5] and 44[20], have been assigned by comparison of biological

Scheme VI.



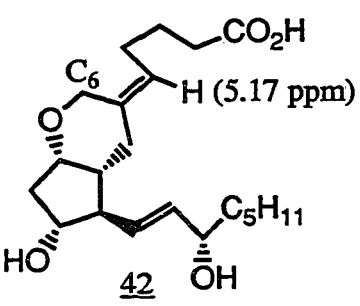
2

(more polar)



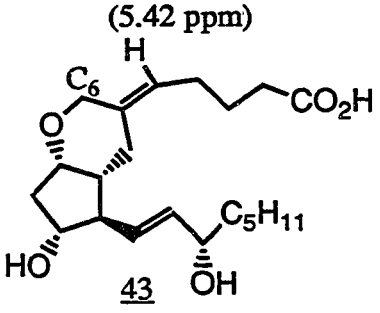
41

		Ref.
• product ratio via Wittig reaction	2 : 41 = 7 : 2	2c
	= 10 : 3	17
	= 7 : 3	18



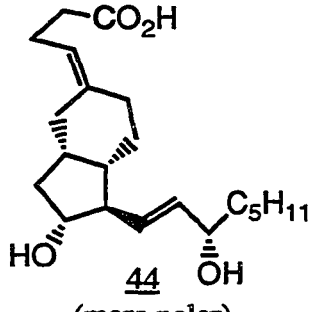
42

(more polar)



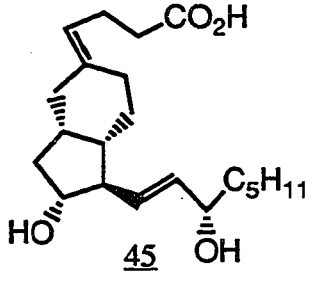
43

		Ref.
• product ratio via Wittig reaction	42 : 43 = 2 : 1	19
	= 9 : 1	18



44

(more polar)



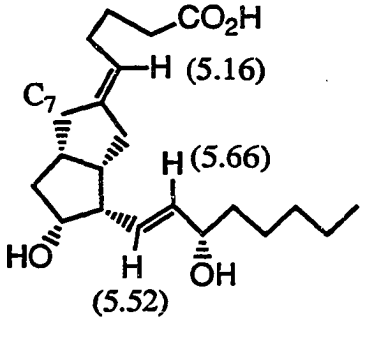
45

Ref.

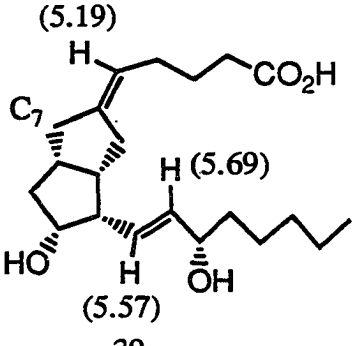
20

activities. The inhibitory activity of compound 2 toward human platelet aggregation was reported to be a hundred times stronger than 41[2c,2d]. The E and Z configurations in compounds 44 and 45 were also assigned based on polarities and biological activities. When tested in vitro against ADP-induced human platelet aggregation, compound 45 was found inactive (ED_{50} > 1000 ng/ml), whereas compound 44 showed slight activity (500 < ED_{50} <1500 ng/ml)[20]. On the other hand, the configuration of the C_5 double bond in compounds 42 and 43 was determined based on the difference in the chemical shift of the C_6 protons[19]. Due to the steric interaction with the upper side chain, the C_6 protons show a broad AB system (J = 12.5 Hz) in compound 42, whereas the corresponding signals in compound 43 are magnetically equivalent.

In the case of 12-epi-carbacyclin (9) and its isomer 39, however, the C_7 protons did not show up cleanly in the ^1H NMR spectra. Thus, unambiguous assignment of the configuration at C-5 was difficult. The olefin protons appeared cleanly, and their chemical shifts were assigned as indicated below.



9



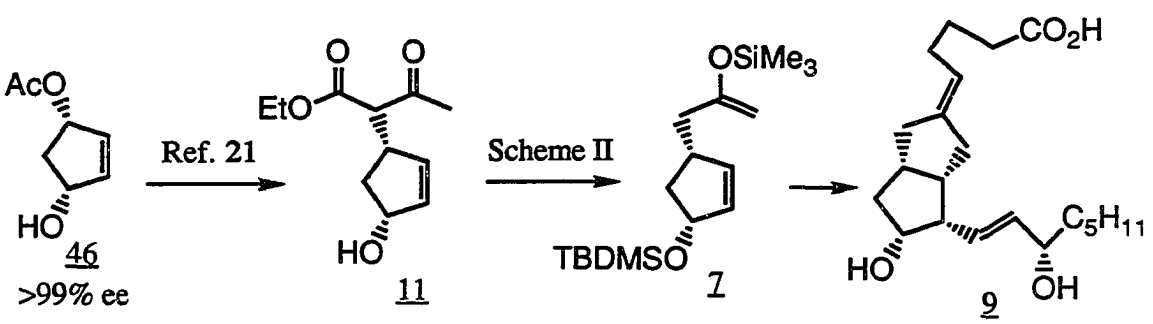
39

It is also noteworthy that the formation of compounds 2 and 42 over their isomers 41 and 43 respectively was found in the Wittig reaction (Scheme VI). We can explain this by proposing that the steric congestion in compounds 41 and 43 is larger than that present in

compounds 2 and 42. Upon the Wittig reaction of compound 31, compound 9 was obtained in larger quantity than compound 39. The spot of the more polar component 9 was much larger than that of the less polar component upon TLC analysis. Even though some difficulties were met in separation due to their close R_f values, compounds 9 and 39 were isolated in a 3 to 2 ratio. This product ratio also supports the assignment of the more polar component 9 as having the C_5-E configuration. Compounds 9 and 39 were characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy, plus high resolution mass spectrometry.

It is desirable to synthesize a compound in an enantiomerically pure form. In connection with the asymmetric synthesis of the prostaglandin analogue 9, it is worth noting that our key intermediate, compound 11, should be readily available in optically active form[21] (Scheme VII). The optically pure compound 46, which is available by enzymatic hydrolysis[22] of the diacetate, should be cleanly converted to compound 11 through π-allylpalladium chemistry[21]. Subsequent reactions described above should provide optically active 12-epi-carbacyclin (9).

Scheme VII.



CONCLUSION

A short synthesis of a novel prostanoid, 12-epi-carbacyclin (9), was accomplished using palladium chemistry as a key step. The silyl enol ether 7 prepared through organopalladium chemistry was treated with 1-octen-3-one in the presence of $Pd(OAc)_2$ to give compound 8 in a single step. The unusual chemo- and stereoselective reduction of the α,β-unsaturated ketone 8 was effected with (S)-BINAL-H. Subsequent desilylation and Wittig reaction have provided the PGI_2 analogue 9.

EXPERIMENTAL SECTION

Equipment

NMR spectra were recorded on a Nicolet NT-300 spectrometer (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz), and chemical shifts are reported in ppm relative to TMS (δ 0.00) as an internal standard. IR spectra were obtained on an IBM IR 98. High-Resolution mass spectra were recorded on a Kratos MS-50 spectrometer.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. Tetrahydrofuran was distilled over sodium benzophenone ketal and used immediately. Methylene chloride was distilled over phosphorous pentoxide and stored over 4Å molecular sieves. DMF was distilled over calcium hydride and stored over 4Å molecular sieves. Acetone was distilled over calcium hydride and stored over 4Å molecular sieves.

Preparation of compound 7[10]

To a solution of diisopropylamine (2.93 ml, 21.0 mmol) in 44 ml of THF was added *n*-BuLi (Aldrich, 2.5 M in hexane, 6.99 ml, 17.5 mmol) at -78 °C. The resulting mixture was stirred for 2 min at that temperature. To this was added ketone 10 (4.42 g, 17.5 mmol) over 10 min under N_2 at -78 °C. The solution was stirred for 1 h; then freshly distilled trimethylsilyl chloride (3.78 ml, 29.7 mmol) was added over 10 min. The solution was allowed to warm to room temperature and stirring was continued for an additional 1 h. The reaction mixture was concentrated under vacuum pressure, then hexane was added and the LiCl solid which precipitated was filtered off. After concentration, the residue was purified by vacuum distillation (110 °C/ 0.6 mm Hg) to give compound 7 as a light yellow oil: 3.1 g, 54% yield; R_f = 0.48 (15:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 1H, HC=C), 5.69 (m, 1H, HC=C), 4.82 (m, 1H, CHOSi), 4.06 (m, 2H, C=CH_2), 2.74 (m, 1H), 2.37 (dt, J

= 13.2 and 7.5 Hz, 1H), 2.18 (dd, J = 13.8 and 6.9 Hz, 1H), 2.03 (dd, J = 13.8 and 8.1 Hz, 1H), 1.32 (dt, J = 13.2 and 6.3 Hz, 1H), 0.90 (s, 9H, *t*-BuSi), 0.21 (s, 9H, $SiMe_3$), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 158.11, 136.80, 133.99, 90.86, 77.55, 43.47, 41.68, 40.67, 26.05, 18.33, 0.23, -4.47; IR (neat) 2957, 2930, 1252 cm^{-1}; HRMS calculated for $C_{17}H_{13}O_2Si_2$ 326.20974, found 326.20917.

Preparation of compound 8

In a vial were placed compound 7 (256 mg, 0.78 mmol), 1-octen-3-one (2.3 ml, 16 mmol), K_2CO_3 (216 mg, 1.6 mmol), NaI (23 mg, 0.16 mmol) and CH_2Cl_2 (2.3 ml). The resulting mixture was stirred for 2 min at room temperature. To this was added $Pd(OAc)_2$ (263 mg, 1.2 mmol); then stirring was continued for 2 h at room temperature. After the reaction mixture was filtered through a silica gel pad using 1:1 hexane/EtOAc, it was concentrated under reduced pressure. The residue was purified by flash chromatography with 3:1 hexane/EtOAc to give compound 8 as a yellow oil: 179 mg, 62% yield; R_f = 0.21 (3:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.96 (dd, J = 16.2 and 8.7 Hz, 1H, HC=CHCO), 6.11 (d, J = 16.2 Hz, 1H, HC=CHCO), 4.29 (t, J = 3.9 Hz, 1H, CHOSi), 2.94 (m, 2H), 2.70 (m, 1H), 2.61 (m, 1H), 2.53 (dt, J = 2.4 and 7.2 Hz, 2H), 2.30-2.20 (m, 3H), 1.67-1.55 (m, 3H), 1.34-1.22 (m, 5H), 0.88 (t, J = 6.3 Hz, 3H, CH_3), 0.85 (s, 9H, *t*-BuSi), 0.01 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 219.42, 200.47, 145.08, 132.23, 78.36, 60.30, 51.84, 46.23, 43.67, 40.05, 39.38, 36.10, 31.45, 25.66, 23.93, 22.41, 17.96, 13.90, -4.74; IR (neat) 2957, 2930, 1740 (C=O), 1672 (C=O), 1464, 1364 cm^{-1}; HRMS m/z 377.25070 [calculated for $C_{22}H_{37}O_3Si$ $(M-H)^+$, m/z 377.25119]; Ammonia CI Mass, m/z 396.3 for $M^+ + NH_4$.

Preparation of 12-epi-carbacyclin (9)

To a solution of (4-carboxybutyl)triphenylphosphonium bromide (Aldrich, dried for 12 h at 100 °C under reduced pressure, 1.15 g, 2.66 mmol) in 9 ml of freshly distilled THF

was added KHMDS (Aldrich, 0.5 M in THF, 10.7 ml, 5.32 mmol) at room temperature under N_2 atmosphere. At this point, the reaction mixture turned a deep red color. The reaction mixture was stirred for 15 min at room temperature. To this was added slowly ketone 31 (118 mg, 0.44 mmol) in 2 ml of THF. The reaction mixture turned a brown color. After stirring for 3 h at room temperature, the reaction was quenched by adding H_2O (25 ml). The reaction mixture was washed with ethyl acetate (25 ml) to remove any organic soluble side-product. The aqueous layer was acidified by adding 2N aqueous HCl (2.4 ml). The solution was extracted with CH_2Cl_2 (20 ml x 3). The organic phase was washed with water (15 ml), then dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with 500:1 EtOAc/acetic acid to give compounds 9 (44 mg) and 39 (29 mg) as oils in an overall 47% yield. Compound 9: R_f = 0.31 (500:1 EtOAc/AcOH); ^1H NMR ($CDCl_3$) δ 5.66 (dd, J = 15.3 and 9.0 Hz, 1H, HC=C), 5.52 (dd, J = 15.3 and 6.6 Hz, 1H, HC=C), 5.16 (t, J = 6.9 Hz, 1H, HC_5=C), 4.63 (br s, 2H, OH's), 4.09 (m, 2H), 2.71-2.45 (m, 3H), 2.45-2.23 (m, 5H), 2.23-2.08 (m, 2H), 2.08-1.95 (m, 2H), 1.78-1.63 (m, 2H), 1.63-1.42 (m, 3H), 1.42-1.18 (m, 7H), 0.89 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.87, 144.71, 136.69, 129.18, 119.96, 76.92, 73.18, 51.33, 44.50, 41.49, 40.54, 37.07, 36.04, 35.80, 33.50, 31.80, 28.79, 25.26, 24.74, 22.71, 14.12; IR (neat) 3414 (OH), 2930, 2858, 1709 (C=O), 1437 cm^{-1}; HRMS m/z 332.23463 [calculated for $C_{21}H_{32}O_3$ $(M-H_2O)^+$, m/z 332.23515]; Ammonia CI Mass, m/z 368.2 for $M^+ + NH_4$. Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 70.19; H, 8.77. The poor elemental analysis is possibly due to insufficient drying of compound 9. Compound 39: R_f = 0.38 (500:1 EtOAc/AcOH); ^1H NMR ($CDCl_3$) δ 6.00 (br s, 2H, OH's), 5.69 (dd, J = 15.3 and 7.8 Hz, 1H, HC=C), 5.57 (dd, J = 15.3 and 6.3 Hz, 1H, HC=C), 5.19 (t, J = 7.2 Hz, 1H, HC_5=C), 4.12 (m, 2H), 2.64-1.95 (m, 12H), 1.78-1.25 (m, 11H), 0.88 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.90, 144.57, 136.22,

129.69, 119.96, 76.47, 73.26, 51.28, 45.83, 41.45, 40.32, 37.05, 33.27, 31.81, 30.29, 28.55, 26.42, 25.25, 24.54, 22.69, 14.15; IR (neat) 3425 (OH), 1710 (C=O) cm^{-1}; HRMS m/z 332.23470 [calculated for $C_{21}H_{32}O_3$ $(M-H_2O)^+$, 332.23515]; Ammonia CI Mass, m/z 368.4 for $M^+ + NH_4$. Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 67.63; H, 9.93. The poor elemental analysis is possibly due to insufficient drying of compound 39.

Preparation of compound 11[8]

To a solution of $Pd(PPh_3)_4$ (1.18 g, 1.0 mmol) and ethyl acetoacetate (9.4 g, 72 mmol) in 50 ml of THF was added dropwise over 20 min at 0 °C cyclopentadiene monoepoxide (4.9 g, 60 mmol) dissolved in 10 ml of THF. After stirring for 40 min at 0 °C, the mixture was allowed to warm to room temperature, then stirring was continued for 24 h at room temperature. The reaction mixture was concentrated in vacuo, and the crude product was purified by flash chromatography with 1:1 hexane/EtOAc to give compound 11 as an inseparable mixture of diastereomers: 10.6 g, 83% yield; $R_f = 0.25$ (1:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.82 (m, 2H, HC=CH), 4.72 (m, 1H), 4.19 (dq, J = 1.8 and 7.2 Hz, 2H), 3.53 (dd, J = 8.1 and 6.0 Hz, 1H), 3.26 (m, 1H), 2.52 (dt, J = 17.1 and 7.8 Hz, 1H), 2.23 (ddt, J = 42.3 and 14.1 and 3.9 Hz, 1H), 2.24 (s, 3H), 1.44 (dd, J = 4.8 and 7.8 Hz, 1H), 1.26 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 202.36, 169.08, 168.72, 135.62, 135.29, 134.80, 134.31, 76.49, 64.59, 64.43, 61.52, 43.43, 43.22, 38.02, 37.28, 30.08, 29.72, 14.13; IR (neat) 3423 (OH), 1715 (C=O) cm^{-1}.

Preparation of compound 12

To a solution of alcohol 11 (2.90 g, 13.7 mmol) and imidazole (2.33 g, 34.3 mmol) in 20 ml of DMF was added with stirring at room temperature *t*-butyldimethylsilyl chloride (2.27 g, 15.1 mmol) dissolved in 16 ml of DMF. After stirring for 14 h at room temperature, the reaction was quenched by adding 20 ml of H_2O. The mixture was extracted with hexane (50 ml x 3), and the organic phase was washed with brine (50 ml), then dried and

concentrated. The residue was purified by flash chromatography using 4:1 hexane/EtOAc to give compound 12: 4.27 g, 96% yield; $R_f = 0.53$ (4:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.79 (m, 2H, HC=CH), 4.79 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.48 (dd, J = 10.5 and 3.6 Hz, 1H), 3.24 (m, 1H), 2.40 (m, 1H), 2.24 (s, 3H), 1.27 (m, 4H), 0.88 (s, 9H, *t*-BuSi), 0.06 (s, 6H, $SiMe_2$).

Preparation of compound 13

To a round bottomed flask attached with a reflux condenser were placed compound 12 (6.7 g, 20.6 mmol), DMSO (20.6 ml), H_2O (1.1 ml) and NaCl (1.8 g, 31.0 mmol). The reaction was placed in a hot oil bath (165-170 °C), and stirring was continued for 9 h. The mixture was cooled to room temperature, then poured into 150 ml of diethyl ether. The phases were separated, and the organic phase was washed with water (3 x 30 ml) and brine (30 ml). After being dried and concentrated in vacuo, the reaction mixture was purified by flash chromatography to give compound 13 as a colorless oil: 4.44 g, 85% yield; $R_f = 0.50$ (4:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.74 (m, 2H, HC=CH), 4.81 (m, 1H, CHOSi), 2.95 (m, 1H), 2.55 (m, 3H), 2.18 (s, 3H, O=CCH_3), 1.23 (ddd, J = 13.2 and 6.0 and 5.4 Hz, 1H), 0.89 (s, 9H, *t*-BuSi), 0.06 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 207.79, 135.83, 134.41, 76.43, 50.15, 40.71, 39.04, 30.22, 25.78, 18.02, -4.75; IR (neat) 1718 (C=O) cm^{-1}; HRMS m/z calculated for $C_{14}H_{25}O_2Si$ 253.16238, found 253.16260.

Typical procedure for the reactions in Table 1

In a vial were placed compound 7 (98 mg, 0.30 mmol), ethyl vinyl ketone (504 mg, 6.0 mmol), NaOAc (49 mg, 0.6 mmol), $Pd(OAc)_2$ (81 mg, 0.36 mmol) and THF (0.9 ml) as a solvent. After the resulting mixture was stirred for 2 h at room temperature, it was filtered through a silica gel pad. Concentration and flash chromatography with 3:1 hexane/EtOAc provided compounds 14, 15 and 13.

Typical procedure for the reactions in Table 2

In a vial were placed compound 7 (98 mg, 0.30 mmol), ethyl vinyl ketone (504 mg, 6.0 mmol), NaOAc (82 mg, 0.6 mmol), NaI (9 mg, 0.06 mmol) and THF (1.8 ml). The resulting mixture was stirred for 5 min at room temperature, then $Pd(OAc)_2$ (81 mg, 0.36 mmol) was added. After stirring for 2 h at room temperature, the reaction mixture was filtered through a silica gel pad. Concentration, followed by flash chromatography, gave compounds 14, 15, and 13.

Compound 14

R_f = 0.27 (3:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 6.95 (dd, J = 16.2 and 8.7 Hz, 1H, HC=CHCO), 6.12 (d, J = 16.2 Hz, 1H, HC=CHCO), 4.29 (m, 1H, CHOSi), 2.94 (m, 2H), 2.69 (m, 1H), 2.59 (m, 4H), 2.25 (m, 3H), 1.65 (m, 1H), 1.10 (t, J = 7.2 Hz, 3H, CH_3), 0.85 (s, 9H, *t*-BuSi), 0.02 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 219.57, 200.794 145.02, 132.05, 78.43, 51.94, 46.32, 44.15, 43.74, 40.16, 38.18, 32.58, 25.74, 18.04, 8.22, -4.63; IR (neat) 2955, 1748 (C=O), 1674 (C=O), 1256 cm^{-1}; HRMS m/z 321.18885 [calculated for $C_{18}H_{29}O_3Si$ $(M-CH_3)^+$, 321.18860].

Compound 15

R_f = 0.46 (3:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.82 (m, 1H, HC=C), 5.72 (m, 1H, C=CH), 3.40 (m, 1H), 2.95 (m, 1H), 2.69 (ddt, J = 16.5 and 5.1 and 2.4 Hz, 1H), 2.47 (m, 2H), 2.21 (m, 2H), 1.98 (dd, J = 18.9 and 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 220.49, 134.07, 130.43, 46.31, 44.93, 42.67, 40.15, 37.12; IR (neat) 2928, 2903, 1742 (C=O), 1402, 1159 cm^{-1}.

Preparation of compound 20

To a solution of LDA (0.65 mmol) was added compound 23 (120 mg, 0.65 mmol) at -78 °C. After stirring for 1 h at that temperature, TMSCl was added at -78 °C. The reaction mixture was warmed to room temperature, and stirring was continued for an additional 2 h.

The reaction mixture was concentrated, and then hexane was added and the LiCl solid which precipitated was filtered off. After concentration and flash chromatography using 4:1 hexane/EtOAc, compound 20 was obtained: 96 mg, 57% yield; R_f = 0.52 (4:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.93 (m, 1H, C=CH), 5.80 (m, 1H, HC=C), 4.69 (m, 3H), 4.06 (s, 2H), 3.37 (s, 3H), 2.78 (m, 1H), 2.42 (dt, J = 13.8 and 7.5 Hz, 1H), 2.18 (dd, J = 13.2 and 6.9 Hz, 1H), 2.04 (m, 1H), 1.44 (dt, J = 13.5 and 5.1 Hz, 1H), 0.22 (s, 9H, $SiMe_3$).

Preparation of compound 22

To a solution of alcohol 11 (1.0 g, 4.7 mmol) and triethylamine (2.0 ml, 14.1 mmol) in 10 ml of THF was added MOMCl (Aldrich, 0.72 ml, 9.4 mmol) dropwise over 5 min. After stirring for 9 h at room temperature, the mixture was filtered, and then concentrated. The residue was purified by flash chromatography to give compound 22: 1.04 g, 83% yield; R_f = 0.52 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 2H), 4.85 (m, 3H), 4.20 (q, J = 7.2 Hz, 2H), 3.45 (dd, J = 10.5 and 5.4 Hz, 1H), 3.35 (d, J = 2.1 Hz, 3H), 3.30 (m, 1H), 2.47 (m, 1H), 2.24 (s, 3H), 1.41 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H).

Preparation of compound 23[11]

A mixture of anhydrous propane-1,2-diol (16 ml) and sodium methoxide (343 mg, 6.4 mmol) was heated at 85 °C for 15 min. To this was added compound 22 (812 mg, 3.2 mmol) and heating was continued for 40 min. The reaction mixture was cooled to room temperature and H_2O (5 ml) was added, and then the reaction mixture was extracted with ether (30 ml x 3). The organic phase was washed with saturated NH_4Cl (20 ml) and brine (20 ml). Concentration, followed by flash chromatography, gave product 23: 122 mg, 21% yield; ^{1}H NMR ($CDCl_3$) δ 5.86 (m, 2H), 4.67 (m, 3H), 3.36 (s, 3H), 2.99 (s, 1H), 2.55 (s, 3H), 2.13 (s, 3H), 1.35 (dt, J = 13.8 and 7.5 Hz, 1H).

Preparation of compound 31[16]

To a solution of $LiAlH_4$ (Aldrich, 1.0 M in THF, 0.6 ml, 0.6 mmol) was added ethanol (2.0 M in THF, 0.3 ml, 0.6 mmol) dropwise over 10 min at room temperature. Subsequently a THF solution of (S)-binaphthol (Aldrich, 170 mg, in 1 ml of THF, 0.60 mmol) was added dropwise, and the resulting mixture was stirred for 30 min at room temperature. Enone 8 (91 mg, 0.24 mmol) in 1 ml of THF was added dropwise over 3 min at -100 °C (liquid N_2 and methanol bath). The reaction mixture was stirred for 2 h at -100 °C, and then another 2 h at -78 °C. Methanol (1 ml) was added at -78 °C to destroy the excess reducing agent, and the reaction mixture was allowed to warm to room temperature. After the addition of water (25 ml) and diethyl ether (30 ml) , stirring was continued for 10 min. The reaction solution was neutralized with 2N HCl, and then extracted with ether (30 ml x 3). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Crude product (247 mg) was obtained. The relative product ratio was calculated using ^1H NMR spectroscopy by integration of the following characteristic peaks: compound 8, 6.09 ppm (d, J = 15.9 Hz, C=CH-C=O); compound 34, 5.77 ppm (dd, J = 15.6 and 8.1 Hz, HC=C); compound 35, 6.06 ppm (d, J = 15.6 Hz, C=CH-C=O). The product ratio of compounds 34 and 35 was calculated to be 9 : 1. The crude product was dissolved in 3 ml of THF. To this was added 3 ml of 0.5 N aqueous HCl at room temperature. After stirring for 38 h at room temperature, the mixture was neutralized with 3N aqueous NaOH. Water (7 ml) was added to the mixture. After extraction with CH_2Cl_2, the organic phase was dried and concentrated. The residue was purified by flash chromatography to give compound 31: 32 mg, 50% overall yield; R_f = 0.19 (1:2 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 5.72 (dd, J = 15.3 and 7.5 Hz, 1H, HC=C), 5.61 (dd, J = 15.3 and 6.3 Hz, 1H, C=CH), 4.29 (m, 1H, CHOH), 4.09 (q, J = 6.3 Hz, 1H, CHOH), 2.88 (m, 2H), 2.68 (dt, J = 4.5 and 7.5 Hz, 1H), 2.61-2.51 (m, 2H), 2.32-2.20 (m, 3H), 2.03 (br s, 2H, OH's), 1.61 (dt, J = 14.4 and

3.0 Hz, 1H), 1.50 (m, 2H), 1.29 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 221.40, 136.80, 128.41, 76.83, 72.91, 51.17, 46.38, 42.20, 40.49, 37.33, 36.97, 31.73, 25.15, 22.60, 14.05, one aliphatic carbon is overlapped; IR (neat) 3404 (OH), 2930, 1734 (C=O), 1458 cm^{-1}; HRMS m/z calculated for $C_{16}H_{26}O_3$ 266.18819, found 266.18851.

Compound 36

R_f = 0.31 (1:2 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.14 (dd, J = 16.2 and 7.8 Hz, 1H, HC=CHCO), 6.69 (d, J = 16.2 Hz, 1H, C=CH-C=O), 4.32 (m, 1H, CHOH), 4.25 (m, 1H, CHOH), 3.20 (br s, 1H, OH), 2.72 (m, 4H), 2.59 (t, J = 7.8 Hz, 2H, $O=CCH_2$), 2.25 (ddd, J = 15.0 and 7.5 and 5.7 Hz, 1H), 2.14 (ddd, J = 13.8 and 8.4 and 5.7 Hz, 1H), 1.98 (m, 1H), 1.88-1.79 (m, 2H), 1.62 (m, 2H), 1.31 (m, 5H), 0.89 (t, J = 6.6 Hz, 3H, CH_3).

Compound 39

See preparation of compound 9.

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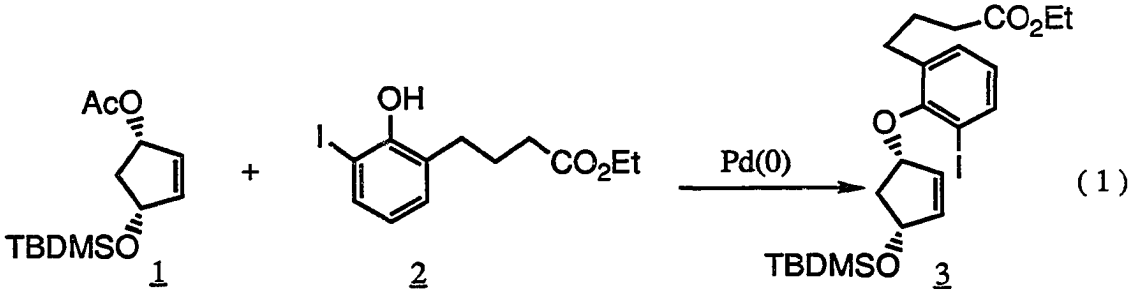
CHAPTER IV. PREPARATION OF ALLYLIC ARYL ETHERS VIA π-ALLYLPALLADIUM CHEMISTRY

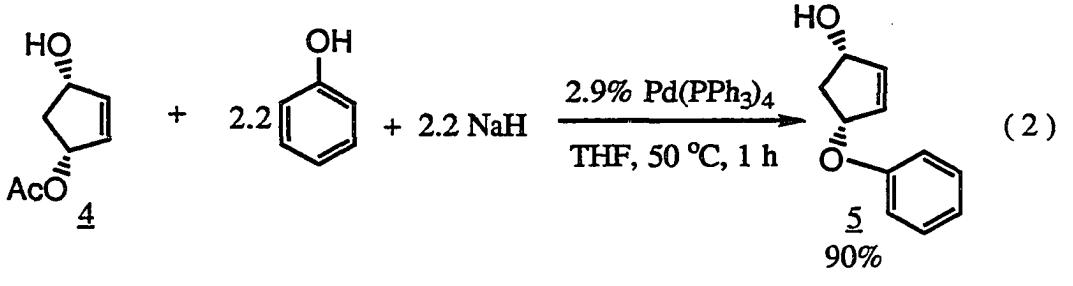
INTRODUCTION

As a part of our synthetic work directed toward the synthesis of optically pure benzoprostacyclins described in Chapter II of this dissertation, we found the need for optically pure allyl aryl ether 3 (eq 1). Thus, we decided to follow the procedure recently



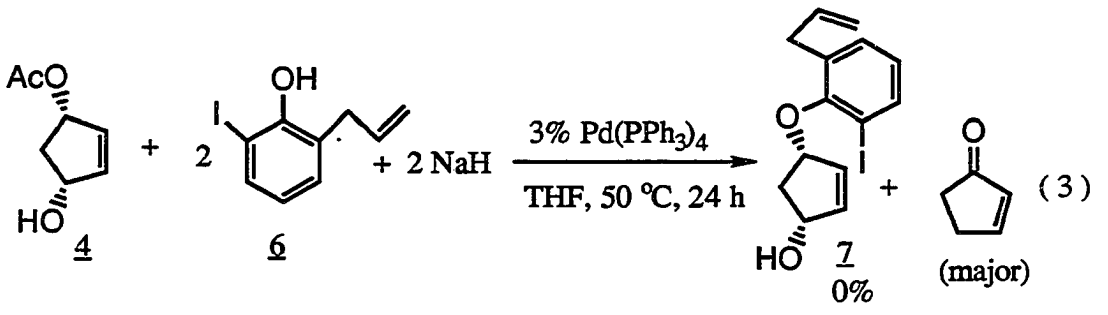
(1)

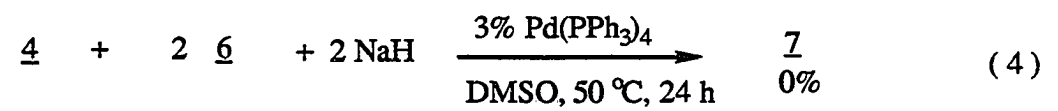
developed by Deardorff et al.[1]. It was reported that cyclopentanoid 5 was obtained stereoselectively via nucleophilic attack of phenoxide on a π-allylpalladium complex generated from allylic acetate 4 (eq 2). Unfortunately, none of the desired product 7 was

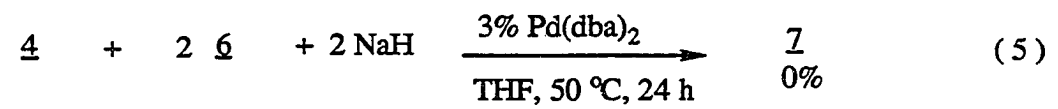


(2)

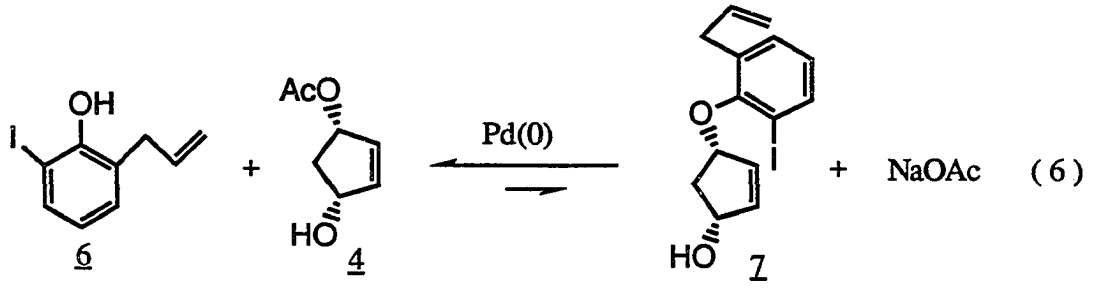
obtained when 2-allyl-6-iodophenol (6) was subjected to Deardorff's reaction conditions (eq 3). Several variations in the reaction conditions, including solvent and Pd(0) species, led to







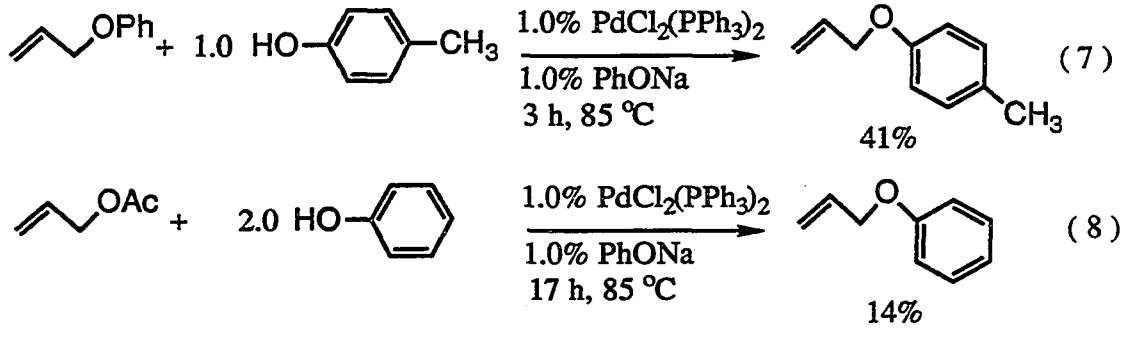
the same results (eqs 4 and 5). Failure to effect the desired phenoxide attack on the π-allylpalladium complex is probably due to steric hindrance around the phenoxide anion. In addition, product 7 may actually revert to starting material 4 in the presence of NaOAc through palladium chemistry (eq 6).



The above observations led us to survey literature procedures involving oxygen nucleophiles and π-allylpalladium complexes. Intramolecular attack of oxygen nucleophiles on π-allylpalladium complexes have proven useful in organic synthesis[2]. However, few

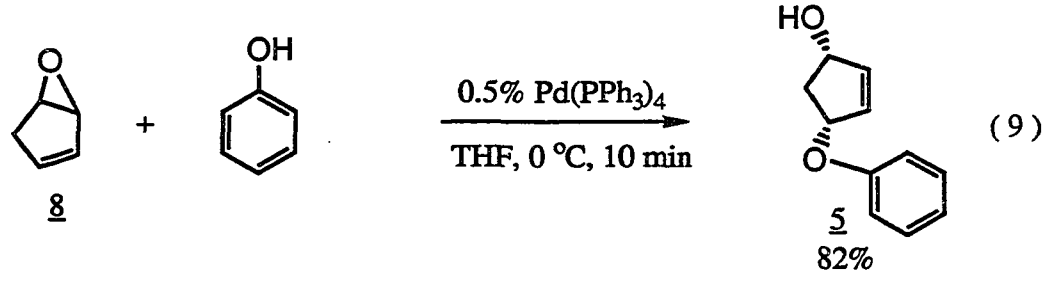
oxygen nucleophiles have proven useful for intermolecular attack on π-allylpalladium intermediates.

Takahashi and co-workers[3] reported that the phenoxy group in allyl phenyl ethers may be replaced by other phenoxy groups, such as *p*-methylphenoxy, employing $PdCl_2(PPh_3)_2$-NaOPh as the catalyst. Allyl acetate was also converted to allyl phenyl ether by phenoxide attack on π-allylpalladium complexes (eqs 7 and 8). Unfortunately, the yields



are low to moderate in most cases, with formation of allylic isomers. Thus, the synthetic value of this reaction is not high.

Deardorff and co-workers previously described[4] a palladium-catalyzed route to 4-phenoxy-2-cyclopenten-1-ol (5) based on the reaction of phenol with cyclopentadiene monoepoxide (8) (eq 9). Later they[5] extended this chemistry to the synthesis of

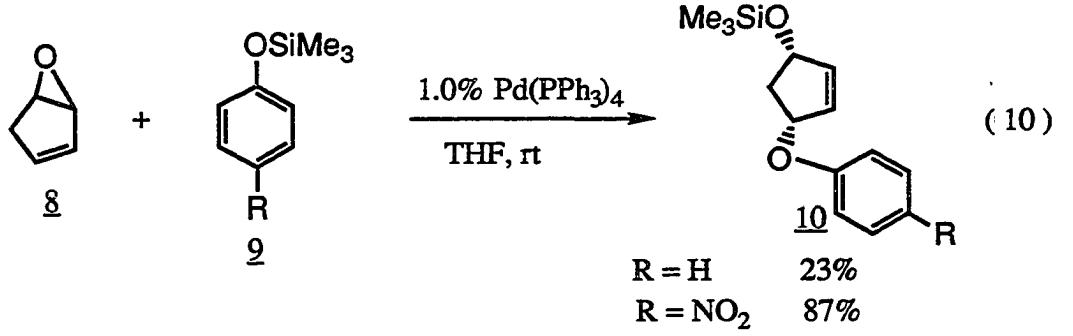


8

5

82%

unsymmetrically protected diol 10 using silyl-protected phenols 9 (eq 10). Even though a good example of the intermolecular attack of the phenoxide nucleophile in π-allylpalladium chemistry was presented, this reaction is limited to only cyclopentadiene monoepoxide (8) and sterically less congested phenols.



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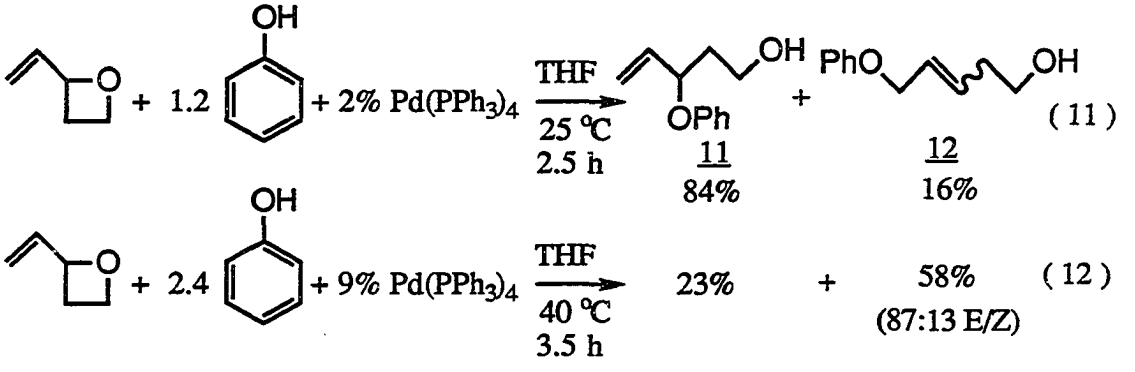
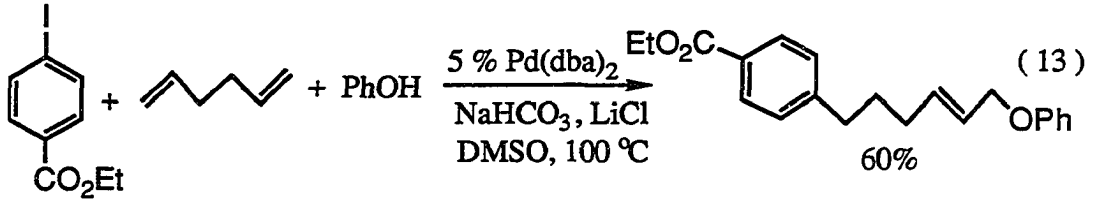
Larock and Stolz-Dunn recently reported[6] that mixtures of regio- and stereoisomers were obtained upon Pd(0)-catalyzed reaction of phenol and vinylic oxetanes (eqs 11 and 12).



With a low amount of the palladium catalyst and a low reaction temperature, the kinetic product 11 was obtained as the major product. With a higher amount of palladium catalyst and a higher reaction temperature, the thermodynamic product 12 was observed as the major product.

Larock and Lu also observed[7] the selective attack of phenoxide on π-allylpalladium complexes generated through palladium hydride migration (eq 13).

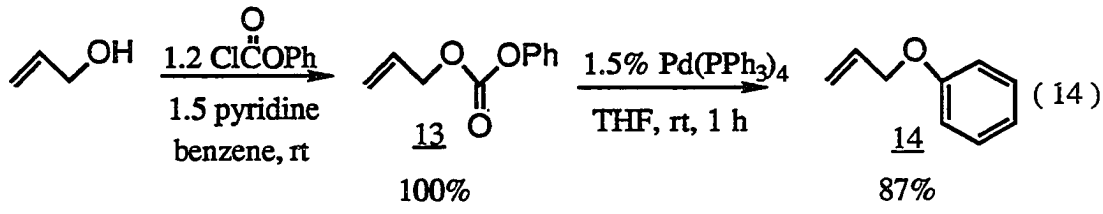


(13)

Thus far, no truly general, broadly useful synthetic method to prepare aryl allylic ethers from phenols and π-allylpalladium complexes has appeared. Since allyl aryl ethers are very important in organic synthesis as starting materials for thermal[8] or Lewis acid-catalyzed[9] Claisen rearrangements, we have attempted to develop just such a process.

RESULTS AND DISCUSSION

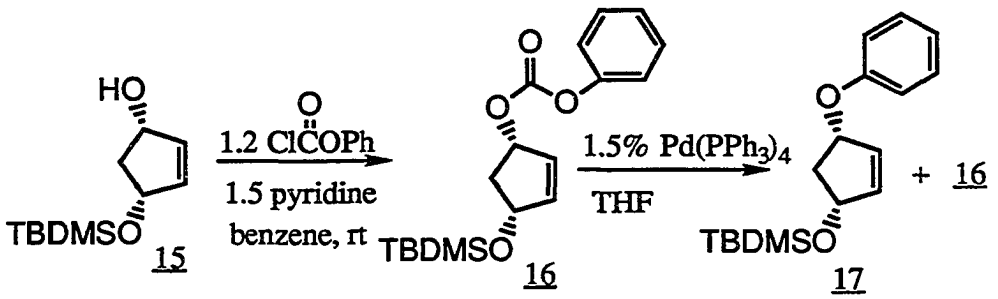
To overcome the problems described in equations 3-6, we decided to carry out the reaction employing a unimolecular process. Allylic carbonates appeared to be appropriate as starting materials in this reaction. Allylic carbonates are known to be more reactive than allylic acetates in π-allylpalladium chemistry, generally reacting with nucleophiles under mild conditions[10]. Since no examples have been found of oxygen nucleophiles being generated from allylic carbonates in π-allylpalladium chemistry, we simply examined the reaction with allyl alcohol (eq 14). Carbonate 13 was prepared quantitatively using commercially available



(14)

phenyl chloroformate and allyl alcohol. The desired decarboxylation, followed by phenoxide attack on the intermediate π-allylpalladium complex was cleanly effected using Pd(PPh3)4 to give allyl phenyl ether (14) in 87% yield.

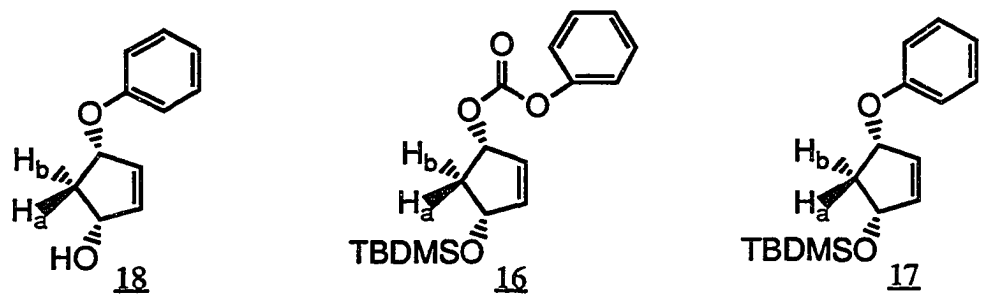
Cyclopentenyl carbonate 16 was also prepared and subjected to the same reaction conditions (eqs 15 and 16). The starting material 16 was recovered in 21% yield after 3 d stirring at room temperature (eq 15). However, the reaction could be completed by a slight increase of the reaction temperature to give phenyl ether 17 in 75% yield (eq 16).



89% • rt, 3 d 44% 21% (15)

• 47 °C, 2 h 75% - (16)

The product 17 was obtained as a single isomer. The stereochemistry of the product was assigned by comparing the ^1H NMR spectra to analogous compounds 16 and 18 shown below.

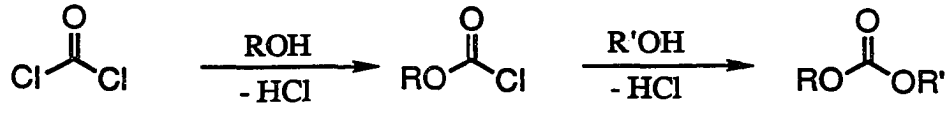


H_a δ 2.89 (dt, J=14.3, 7.0 Hz) δ 2.93 (dt, J=13.8, 7.2 Hz) δ 3.08 (dt, J=13.5, 7.2 Hz)

H_b δ 1.78 (dt, J=14.3, 3.8 Hz) δ 1.83 (dd, J=13.8, 4.8 Hz) δ 1.95 (dd, J=13.5, 5.1 Hz)

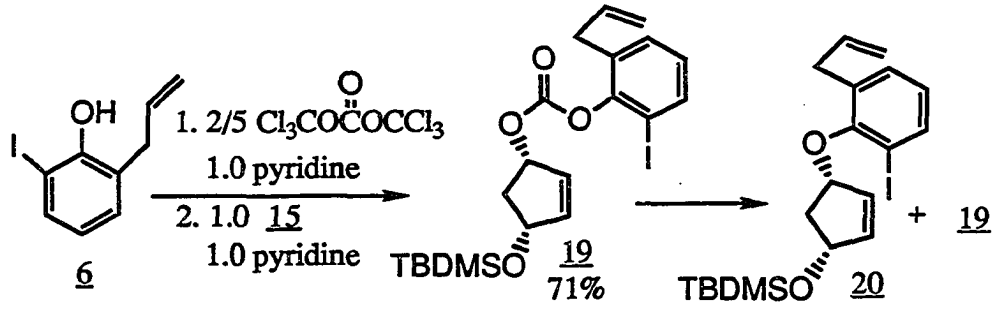
Since good results were obtained with simple phenyl carbonates, we decided to extend this chemistry to more complex carbonates, such as compound 19 (see equations 18 and 19). Since compound 19 has additional functional groups in the phenyl ring, we needed to develop a synthetic procedure to prepare compound 19 from the funtionalized phenol 6.

From a literature survey[11], no general method was found for the synthesis of unsymmetrical carbonates. However, we envisioned the step-by-step addition of two different alcohols to phosgene as an one-pot procedure (eq 17). Since phosgene is difficult to



(17)

handle, we considered instead the use of triphosgene which has been reported to generate three equivalents of phosgene upon reacting with bases[12]. We were pleased to find that consecutive addition of phenol 6 and alcohol 15 provided carbonate 19 in 71% yield in a one-pot procedure. With carbonate 19 in hand, we carried out the palladium reaction under the same conditions used in the reaction illustrated in equation 14 (eq 18). The desired product

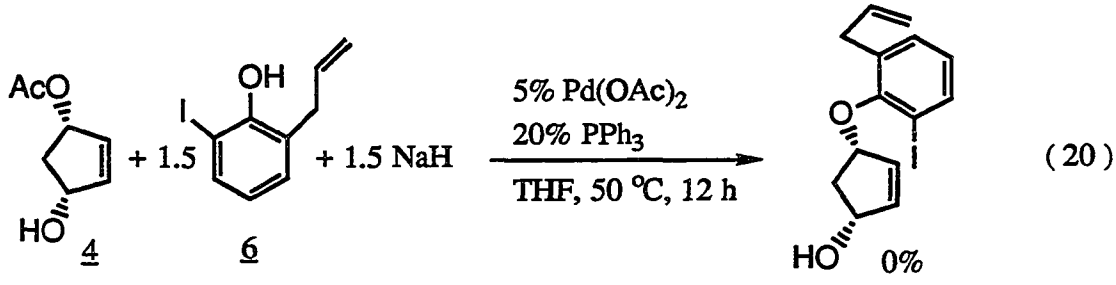


1.5% $Pd(PPh_3)_4$ THF, 50 °C, 20 h	5%	50%	(18)
5% $Pd(OAc)_2$ 20% PPh_3 rt, THF, 1 d	55%	10%	(19)

20 was obtained in only a 5% yield, accompanied by the starting material 19 in 50% yield. A literature report[13] that a tetrakis Pd(0) species generated in situ from $Pd(OAc)_2$ and PPh_3 gave better results than $Pd(PPh_3)_4$ in π-allylpalladium chemistry led us to try the reaction employing $Pd(OAc)_2$ and PPh_3 as a catalyst. Pleasantly, it was found that $Pd(OAc)_2$ and

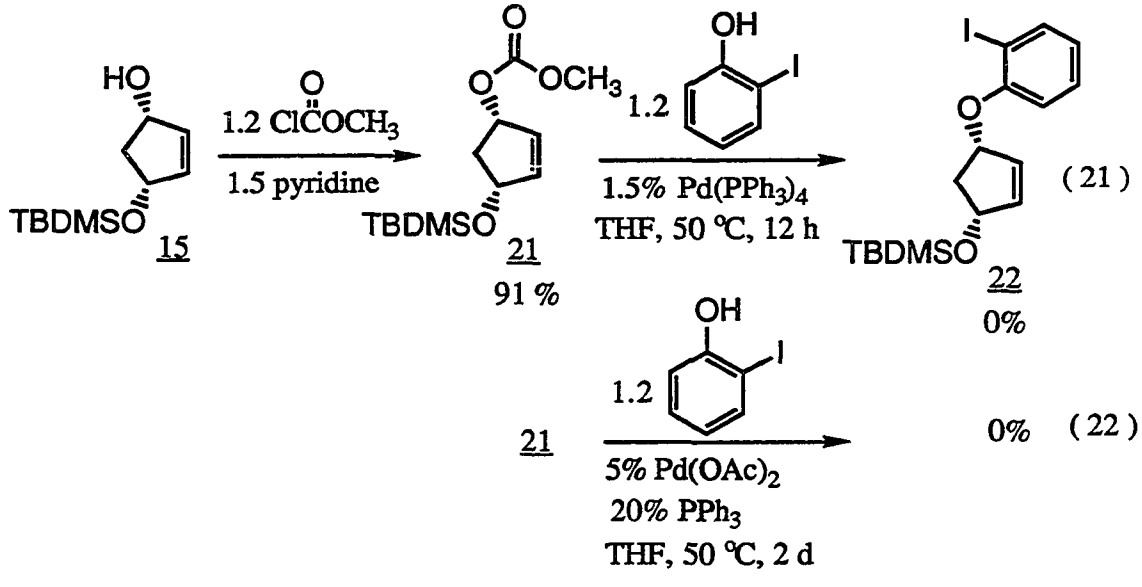
PPh3 were better than Pd(PPh3)4 in this reaction and gave compound 20 in 55% yield as a single isomer (eq 19). In addition, this reaction is operationally simpler, because Pd(OAc)2 and PPh3 can be handled with less difficulty than Pd(PPh3)4.

Since a better result was obtained using Pd(OAc)2 and PPh3, we re-examined the reaction of allylic acetate 4 and phenol 6 using this catalyst system (eq 20). However, none of the desired product was obtained.



(20)

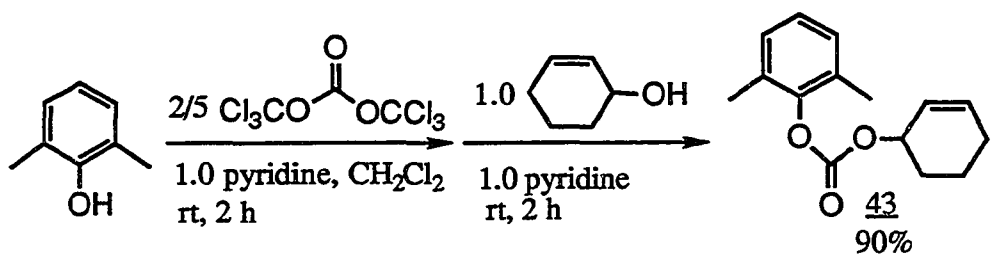
We also examined the reaction of methyl carbonate 21 and *o*-iodophenol under neutral conditions (eqs 21 and 22). Neither reaction gave any of the desired product 22. Only a



volatile product which seemed to be a low molecular weight cyclopentanoid was obtained as a side product.

With the results above, a number of carbonates were synthesized and subjected to the reaction conditions employed in equation 18. The results were summarized in Table 1.

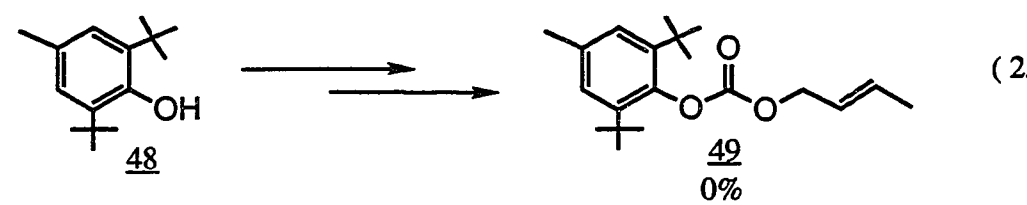
Phenyl carbonates were prepared from commercially available phenyl chloroformate and allylic alcohols usually in quantitative yield. Functionalized aryl carbonates, such as 19 and 43, were prepared efficiently from triphosgene and the corresponding alcohols in a one-pot procedure (eq 23).



(23)

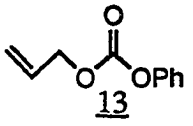
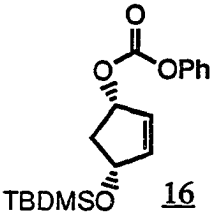
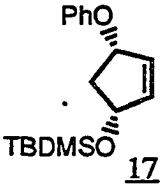
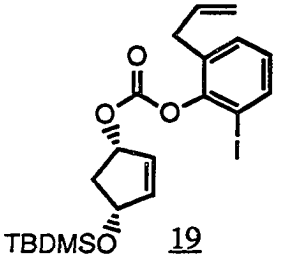
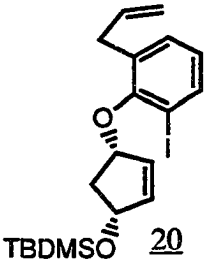
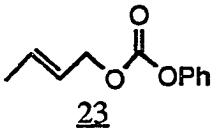
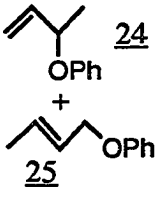
However, more sterically bulky phenols, such as compounds 2 and 48, failed to give carbonates, probably due to steric hindrance around the hydroxy group (eqs 24 and 25).

(24)



(25)

Table 1. Palladium-mediated synthesis of allyl aryl ethers[a]

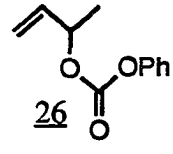
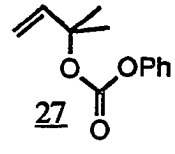
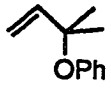
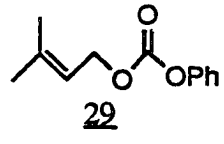
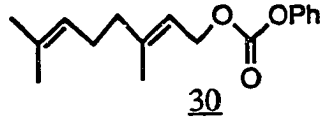
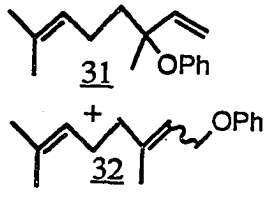
Entry	Substrate	Temp. (°C)	Time	Solvent	Product(s)	% Isolated Yield
1[b]	 13	rt	1 h	THF	 14	87
2[b]	 TBDMSO 16	47	2 h	THF	 TBDMSO 17	75
3	 TBDMSO 19	rt	1 d	THF	 TBDMSO 20	55 (61)[c]
4	 23	50	1 h	THF	 24 + 25 (24:25 = 86:14)	74

[a]All reactions were performed employing 5 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 1.0 mmol of substrate and 20 ml of solvent under N_2 unless otherwise stated.

[b]The reactions were conducted using 1.5 mol % of $Pd(PPh_3)_4$.

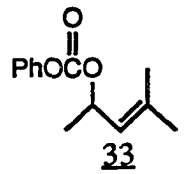
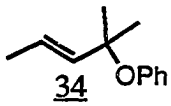
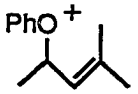
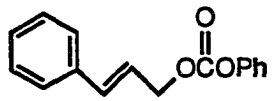
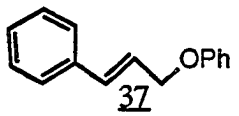
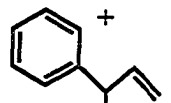
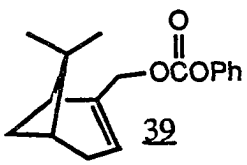
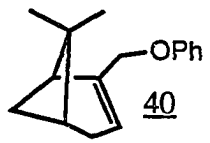
[c]Yields based on recovered starting material.

Table 1. Continued

Entry	Substrate	Temp. (°C)	Time	Solvent	Product(s)	% Isolated Yield
5	23	rt	12 h	THF	24:25 = 87:13	62
6	 26	rt	2 h	THF	24:25 = 86:14	80
7	 27	rt	5 h	THF	 28	60
8	 29	55	10 h	THF	28	27
9[d]	29	rt	1 d	CH_2Cl_2	28	42
10	 30	rt	5 d	CH_2Cl_2	 31 32 (31:32 = 86:14)	22

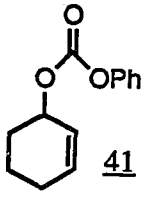
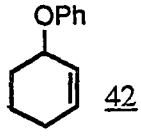
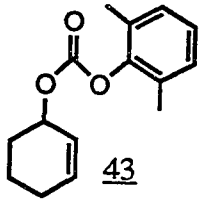
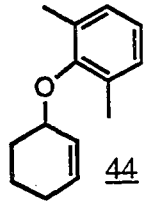
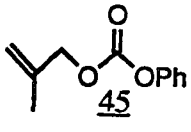
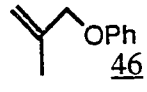
[d]In this reaction, an additional portion of catalyst [5% $Pd(OAc)_2$ and 20% PPh_3] was added after 12 h to attain complete conversion to products.

Table 1. Continued

Entry	Substrate	Temp. (°C)	Time	Solvent	Product(s)	% Isolated Yield
11[e]	 33	50	2 d	THF	 34 OPh  PhO + 35 (34:35 = 60:40)	43 (53)[c]
12	 36	rt	5 h	THF	 37 +  38 OPh (37:38 = 89:11)	89
13	 39	rt	30 h	THF	 40	65

[e]This reaction was conducted using 5 % $Pd(PPh_3)_4$.

Table 1. Continued

Entry	Substrate	Temp. (°C)	Time	Solvent	Product(s)	% Isolated Yield
14	39	rt	3 d	CH_2Cl_2	40	70
15	 41	50	12 h	THF	 42	62
16	 43	rt	3 d	CH_2Cl_2	 44	74
17	 45	rt	4 h	THF	 46	81

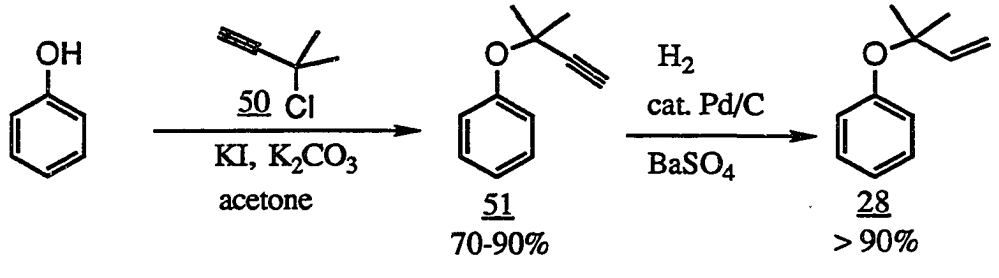
Although changing various reaction conditions, including solvent, reaction temperature and base, we were still unable to obtain any of the desired products 47 and 49.

As seen in Table 1, this reaction provides a general method for the preparation of allylic aryl ethers from allylic alcohols and phenols via carbonates. As described earlier, a high degree of regio- and stereoselectivity was observed with cyclopentenyl carbonates 16 and 19 to give compounds 17 and 20 with retention of stereochemistry (entries 2 and 3). The regioselectivity was examined in entries 2-14, and found to be excellent to good. The regioselectivity between primary and secondary centers was examined in entries 4-6. When

compounds 23 and 26 were subjected to the reaction conditions, regioisomers 24 and 25 were obtained in an 86:14 or 87:13 ratio. This shows that the regioselectivity is dependent on the charge distribution in the π-allylpalladium intermediate. Nucleophilic attack is favored at the more substituted allyl terminus. The reaction temperature didn't affect the regioselectivity (entries 4 and 5). The results in entries 4-6 show that the same π-allylpalladium complex was generated independent of the original position of the leaving group. Even though attempts were made to improve the regioselectivity in the reaction of carbonate 26, no improvement was observed. These efforts will be described later.

The regioselectivity between primary and tertiary centers was found to be excellent (entries 7-9). Only a single product 28 was obtained from carbonates 27 and 29 as indicated by ^{1}H NMR analysis, independent of the position of the leaving group. With compound 29, a slightly better yield was obtained using CH_2Cl_2 as the solvent.

Ethers, such as 1,1-dimethyl allyl phenyl ether (28) have been reported to be important substrates for Claisen rearrangement to *o*-isopentenyl phenols which are abundant in nature[14]. The compound 28 has been previously prepared[14a] by a partial hydrogenation of 1,1-dimethyl propargyl ether (51) which was prepared from phenol and 3-chloro-3-methylbut-1-yne (50) (eq 26). The method developed here can be an alternative route to

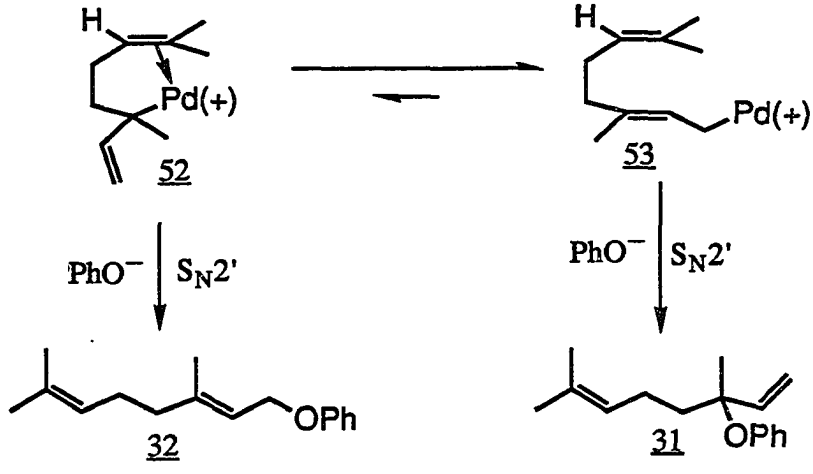


(26)

compound 28 from more readily available allylic alcohols. Moreover, our approach is advantageous in that we can obtain compound 28 from either starting material 27 or 29.

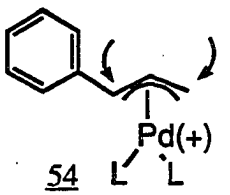
In the reaction of carbonate 30 derived from geraniol, the selectivity between the primary and tertiary positions was not as good, giving a 86:14 ratio of compounds 31 and 32 (entry 10). Comparing the results with those of substrates 27 and 29, we might expect that carbonate 30 would generate a more sterically congested tertiary center, thus giving less selectivity due to a competitive steric effect. As an alternative explanation, we might assume that some stabilization of the palladium in intermediate 52 by olefin coordination, which is not available in compounds 27 and 29, might favor formation of regioisomer 32 (Scheme I).

Scheme I.



We also examined the regioselectivities between secondary and tertiary carbons in the π-allylpalladium intermediates (entry 11). Even though nucleophilic attack favors the tertiary product over the secondary product, the selectivity is poor. In this reaction, the use of $Pd(PPh_3)_4$ as a catalyst provided a better result than $Pd(OAc)_2$-PPh_3. Since the starting material 33 is probably unstable to acidic conditions, the acetic acid generated by reduction of $Pd(OAc)_2$ might be destroying compound 33 when using the $Pd(OAc)_2$-PPh_3 catalyst system.

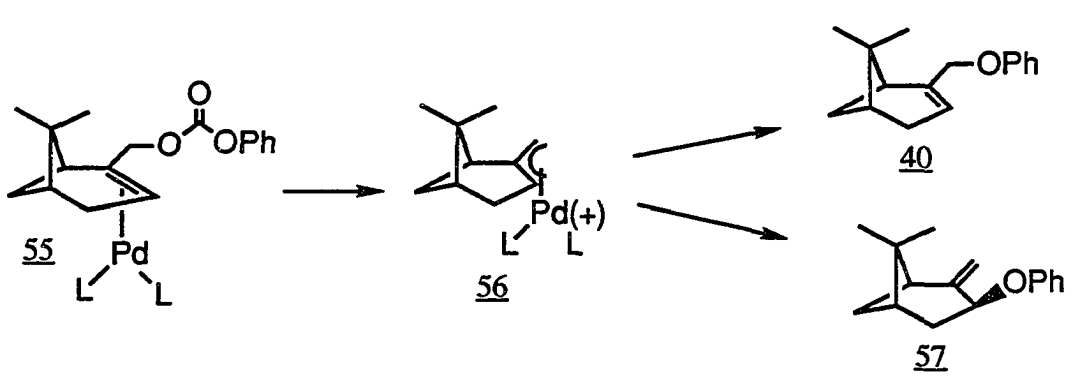
In entry 12, the reaction of carbonate 36 prepared from cinnamyl alcohol was examined. Due to the thermodynamic stability of conjugated carbon-carbon double bonds, phenoxide was found to attack the less hindered terminus of the π-allylpalladium intermediate 54 favoring formation of compound 37 as the major product in an 89:11 isomeric ratio.



54

In entry 13, carbonate 39 was prepared from (-)-myrtenol. It was considered to be of interest to examine the regio- and stereoselectivity of this reaction. Since π-allylpalladium complexes are reported to be generated via the intermediacy of an olefin-PdL_2 complex, such as 55[15], it was expected that the palladium should be directed toward the bottom of intermediate 56. Thus, we would expect regioisomers 40 and 57 in which the phenoxy group has attached itself to the upper face of the molecule, since the overall reaction has

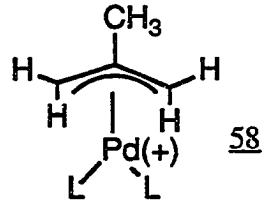
Scheme II.



already been shown to proceed with retention of stereochemistry (entries 2 and 3). However, subjection of carbonate 39 to the reaction conditions yielded compound 40 as the sole product, which shows that steric effects override the electronic effects in this reaction.

In entry 16, sterically bulky 2,6-dimethylphenoxide was employed as the nucleophile. Upon reaction, compound 43 gave the product 44 in 74% yield. This result shows that this methodology provides a useful route to introduce sterically congested phenols into an allylic position.

In entry 17, we examined carbonate 45 which has a methyl group at the C_2 position of the resulting π-allylpalladium complex 58. Nucleophilic attack of phenoxide proceeds well to give ether 46 in 81% yield.

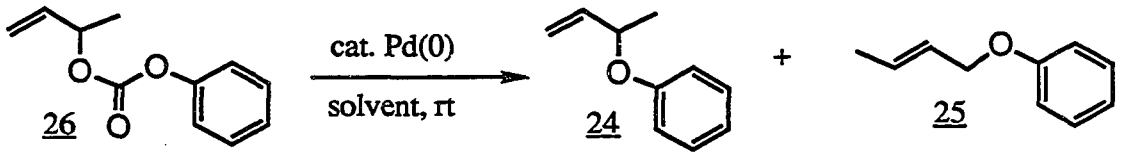


58

As mentioned earlier, we tried to improve the regioselectivity of the reaction represented by entry 6 in Table 1. The results were presented in Table 2.

Larock and Stolz-Dunn[6] reported that employing different amounts of Pd(0) provided different regioselectivities, implying that the resulting allylic phenyl ethers undergo Pd-assisted isomerization under the reaction conditions. Thus, we tried less $Pd(OAc)_2$ in entry 2. Although the reaction took longer, the yield remained high and there was no change in the regioselectivity observed. This indicates that isomerization doesn't occur under these reaction conditions. The effect of solvent was examined in entry 3. No effect on the regioselectivity

Table 2. Attempts to improve the regioselectivity of the reaction of compound 26



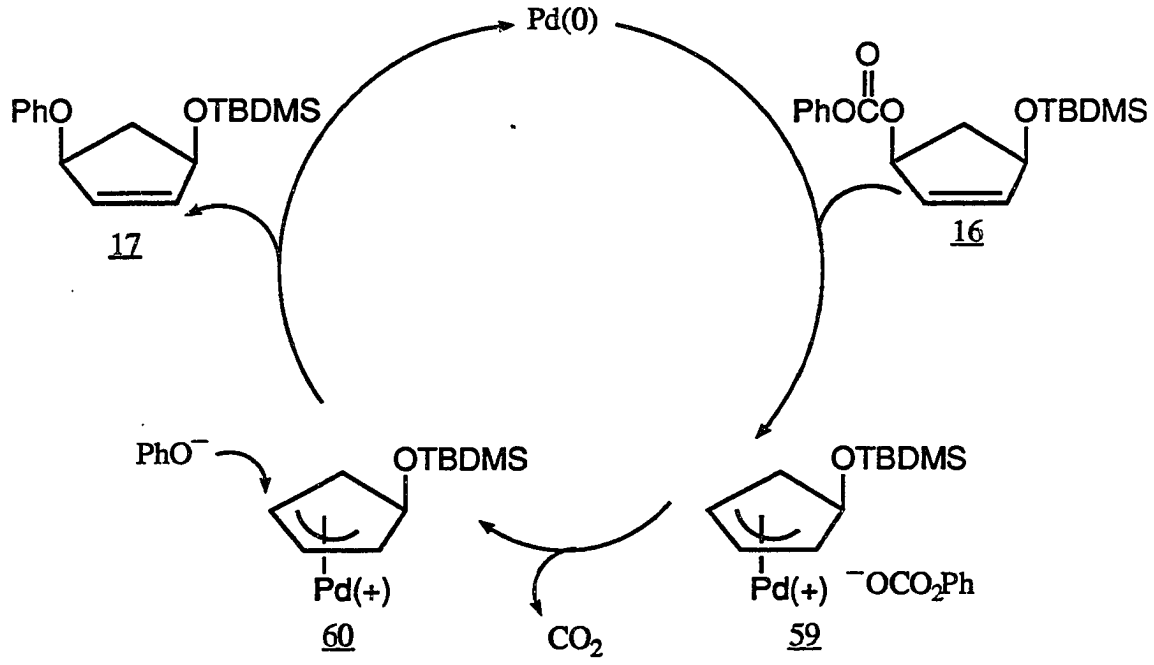
Entry	% $Pd(OAc)_2$	% PPh_3	Solvent	Time	Additive	24:25[a]	% Isolated Yield
1	5	20	THF	2 h	-	86:14	80
2	2	8	THF	12 h	-	86:14	81
3	5	20	CH_2Cl_2	20 h	-	86:14	68
4	5	10% dppe	THF	2 d	-	82:18	53
5	3	12% *n*-Bu_3P	THF	3 d	-	-	?
6[b]	5	20	DMF	3 d	1.0 $NaNO_2$	-	0

[a] Isomeric ratio was determined by ^1H NMR spectral analysis.
[b]This reaction was conducted at 33 °C.

was observed. Different phosphous ligands were examined in entries 4 and 5. With dppe, the regioselectivity and product yield decreased slightly. With *n*-Bu_3P, the reaction was found to be very slow. After stirring 3 days, only a very small product spot was observed upon TLC analysis. Tamura and co-workers[16] have recently reported that Pd(0)-assisted isomerization can be suppressed by adding sodium nitrite. This led us to try the reaction with addition of $NaNO_2$. Even though the starting material disappeared as indicated by TLC analysis, the reaction provided none of the desired product.

A reaction mechanism for our overall process is proposed in Scheme III with the compound 16 illustrated as the starting material. The palladium catalyst displaces the carbonate group in allylic carbonate 16 with inversion to give the π-allylpalladium complex

Scheme III.



59, which undergoes decarboxylation to complex 60 and phenoxide ion. The phenoxide ion, thus, attacks the anti face of the π-allylpalladium intermediate to form the allylic phenyl ether 17 with regeneration of the Pd(0) species, making the whole reaction catalytic in palladium.

Allylic aryl ethers have previously been synthesized from allylic halides or allylic alcohols[17]. However, these reactions are limited to sterically less congested primary or secondary allylic species or less bulky phenolic species. The method developed here exhibits a unique feature, that is, the sterically more congested product is obtained as the major

product. Due to the high regio- and stereoselectivity, along with the mild reaction conditions, this synthetic method should find considerable use in organic synthesis.

CONCLUSION

A simple 2-step method for the synthesis of allyl aryl ethers from allylic alcohols via allylic carbonates has been developed using Pd(0) chemistry. The allylic carbonates have been prepared either by using phenyl chloroformate or by employing triphosgene and substituted phenols. The palladium-mediated reaction of allylic carbonates gives high yields of allylic aryl ethers with high regio- and stereoselectivity.

EXPERIMENTAL SECTION

Equipment

NMR spectra were recorded on a Nicolet NT-300 spectrometer (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz), and chemical shifts are reported in ppm relative to TMS (δ 0.00) as an internal standard. IR spectra were obtained on an IBM IR 98. High-resolution mass spectra were recorded on a Kratos MS-50 spectrometer.

Reagents

All chemicals were used directly as obtained commercially unless otherwise noted. All starting materials were purchased from Aldrich (Triphosgene, phenyl chloroformate, 3-methyl-2-buten-1-ol, 2,6-dimethylphenol, 2-methyl-2-propen-1-ol, crotyl alcohol, geraniol, 2-cyclohexenol, allyl alcohol, 3-buten-2-ol, 2-methyl-3-buten-2-ol) and Pfaltz & Bauer, Inc. (4-methyl-3-penten-2-ol). Palladium acetate and Pd(PPh3)4 were generously supplied by Johnson Mattey, Inc. Tetrahydrofuran was distilled over sodium benzophenone ketal and used immediately. Methylene chloride was distilled over phosphorous pentoxide and stored over 4Å molecular sieves. Benzene was distilled azeotropically by adding a small amount ethanol.

General procedure for the preparation of carbonates: Allyl phenyl carbonate (13).

To a solution of allyl alcohol (1.2 g, 20 mmol) and pyridine (2.4 g, 30 mmol) in 40 ml of benzene was added phenyl chloroformate (3.8 g, 24 mmol) dropwise over 10 min at room temperature. After the reaction mixture was stirred for 30 min at room temperature, it was filtered and concentrated. The residue was purified by flash chromatography using 4:1 hexane/EtOAc to give the title product as a colorless oil: 3.6 g, 100% yield; $R_f = 0.50$ (4:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.41-7.16 (m, 5H, phenyl), 6.07-5.93 (m, 1H,

HC=C), 5.43 (d, J = 17.4 Hz, 1H, HC=C), 5.33 (d, J = 5.4 Hz, 1H, HC=C), 4.74 (d, J = 6.0 Hz, 2H, CH_2); IR (neat) 3090, 1759 (C=O), 1593, 1493, 1209 cm^{-1}.

Compound 16

This compound was obtained in 89% yield: R_f = 0.58 (4:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.47-7.20 (m, 5H, phenyl), 6.09-6.02 (m, 2H, HC=CH), 5.51 (m, 1H, CHOC=O), 4.77 (m, 1H, CHOSi), 2.92 (dt, J = 13.8 and 7.2 Hz, 1H, CH_2), 1.83 (dt, J = 13.8 and 4.8 Hz, 1H, CH_2), 0.94 (s, 9H, *t*-BuSi), 0.14 (s, 6H, $SiMe_2$); IR (neat) 2948, 1763 (C=O), 1211 cm^{-1}.

Compound 23

This compound was obtained in 76% yield: R_f = 0.54 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40-7.16 (m, 5H, phenyl), 5.89 (m, 1H, HC=C), 5.68 (m, 1H, HC=C), 4.66 (dt, J = 6.6 and 0.9 Hz, 2H, OCH_2), 1.76 (d, J = 6.6 Hz, 3H, CH_3); IR (neat) 2947, 1763 (C=O), 1495, 1238 cm^{-1}.

Compound 26

This compound was obtained in 86% yield: R_f = 0.50 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40-7.16 (m, 5H, phenyl), 5.93 (ddd, J = 17.4 and 10.5 and 6.3 Hz, 1H, HC=C), 5.39-5.22 (m, 3H, HC=CH and HCOC=O), 1.46 (d, J = 6.6 Hz, 3H, CH_3); IR (neat) 1761 (C=O), 1495, 1269, 1211 cm^{-1}.

Compound 27

This compound was obtained in 90% yield: R_f = 0.54 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.39-7.14 (m, 5H, phenyl), 6.15 (dd, J = 17.4 and 10.8 Hz, 1H, HC=C), 5.29 (d, J = 17.4 Hz, HC=C), 5.18 (d, J = 10.8 Hz, 1H, HC=C), 1.63 (s, 6H, 2 CH_3); IR (neat) 2996, 1755 (C=O), 1593, 1269 cm^{-1}.

Compound 29

This compound was obtained in 100% yield: $R_f = 0.50$ (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40-7.16 (m, 5H, phenyl), 5.45 (m, 1H, HC=C), 4.74 (d, J = 7.5 Hz, 2H, OCH_2), 1.79 (s, 3H, CH_3), 1.76 (s, 3H, CH_3); IR (neat) 2874, 2937, 1763 (C=O), 1495, 1234 cm^{-1}.

Compound 30

This compound was obtained in 85% yield: $R_f = 0.54$ (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40-7.16 (m, 5H, phenyl), 5.44 (m, 1H, HC=C), 5.09 (m, 1H, HC=C), 4.77 (d, J = 7.2 Hz, 2H, OCH_2), 2.09 (m, 4H, CH_2CH_2), 1.75 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.61 (s, 3H, CH_3); IR (neat) 2968, 2922, 1763 (C=O), 1495, 1236, 1211 cm^{-1}.

Compound 33

This compound was obtained in 50% yield. This product slowly decomposed during flash chromatography: $R_f = 0.44$ (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40-7.16 (m, 5H, phenyl), 5.55 (dq, J = 9.0 and 7.2 Hz, 1H, OCH), 5.25 (m, 1H, HC=C), 1.75 (s, 6H, 2 CH_3), 1.40 (d, J = 6.6 Hz, 3H, $OCHC\underline{H}_3$); IR (neat) 2936, 1763 (C=O), 1495, 1220 cm^{-1}.

Compound 36

This compound was obtained in 92% yield: $R_f = 0.34$ (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.43-7.18 (m, 10H, phenyl), 6.75 (d, J = 15.9 Hz, 1H, ArCH=C), 6.35 (dt, J = 15.9 and 6.3 Hz, 1H, ArC=CH), 4.89 (dd, J = 6.3 and 0.9 Hz, 2H, OCH_2); IR (neat) 3061, 3029, 1763 (C=O), 1593, 1495, 1263 cm^{-1}.

Compound 39

This compound was obtained in 93% yield: $R_f = 0.31$ (15:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40-7.14 (m, 5H, phenyl), 5.68 (m, 1H, HC=C), 4.61 (m, 2H, OCH_2), 2.44 (dt, J = 8.7 and 5.7 Hz, 1H), 2.30 (m, 2H), 2.23 (dt, J = 1.5 and 5.4 Hz, 1H), 2.12

(m, 1H), 1.31 (s, 3H, CH_3), 2.22 (d, J = 8.4 Hz, 1H), 0.85 (s, 3H, CH_3); IR (neat) 2928, 1763 (C=O), 1495, 1211 cm^{-1}.

Compound 41

This compound was obtained in 80% yield: R_f = 0.58 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.40-7.17 (m, 5H, phenyl), 6.03 (m, 1H, HC=C), 5.85 (m, 1H, HC=C), 5.21 (m, 1H), 2.16-1.64 (m, 6H); IR (neat) 2947, 1763 (C=O), 1236 cm^{-1}.

Compound 45

This compound was obtained in 100% yield: R_f = 0.46 (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.41-7.17 (m, 5H, phenyl), 5.09 (m, 1H, HC=C), 5.01 (m, 1H, HC=C), 4.66 (s, 2H, OCH_2), 1.83 (s, 3H, CH_3); IR (neat) 2973, 2945, 1763 (C=O), 1493, 1242 cm^{-1}.

Preparation of compound 19

To a solution of 2-allyl-6-iodophenol (260 mg, 1.0 mmol) and triphosgene (119 mg, 0.4 mmol) in 10 ml of CH_2Cl_2 was added pyridine (79 mg, 1.0 mmol) dropwise at room temperature. The resulting mixture was stirred for 20 h at that temperature. To this was added allylic alcohol 15 (214 mg, 1.0 mmol), followed by pyridine (79 mg, 1.0 mmol). After the reaction mixture was stirred for 5 h at room temperature, it was quenched by adding 20 ml of H_2O. The reaction mixture was extracted with CH_2Cl_2 (25 ml x 2), then dried and concentrated. The residue was purified by flash chromatography using 15:1 hexane/EtOAc to give compound 19: 355 mg, 71% yield; ^1H NMR ($CDCl_3$) δ 7.69 (dd, J = 7.8 and 1.5 Hz, 1H, aryl), 7.21 (dd, J = 7.8 and 1.5, 1H, aryl), 6.94 (t, J = 7.8 Hz, 1H, aryl), 6.04 (m, 2H, HC=CH), 5.89 (m, 1H, C=C<u>H</u>CH_2), 5.50 (t, J = 6.3 Hz, 1H, CHOC=O), 5.14-5.09 (m, 2H, H_2C=C), 4.75 (t, J = 5.4 Hz, 1H, CHOSi), 3.37 (d, J = 6.6 Hz, 2H, CH_2Ar), 2.91 (dt, J = 14.1 and 7.2 Hz, 1H, CH_2 in cyclopentane), 1.84 (dt, J = 14.1 and 5.1, 1H, CH_2 in cyclopentane), 0.91 (s, 9H, *t*-BuSi), 0.11 (s, 3H, SiMe), 0.11 (s, 3H, SiMe); ^{13}C NMR

($CDCl_3$) δ 151.80, 149.41, 140.01, 137.57, 135.04, 134.07, 130.49, 130.15, 128.00, 116.98, 91.33, 81.84, 74.66, 40.91, 35.31, 25.91, 18.18, -4.53; IR (neat) 2955, 2930, 1761 (C=O), 1244, 1213 cm^{-1}; HRMS m/z calculated for $C_{21}H_{28}O_4SiI$ $(M-H)^+$ 499.08016, found 499.07886.

Preparation of compound 43

To a solution of 2,6-dimethylphenol (2.4 g, 20 mmol) and triphosgene (2.3 g, 7.2 mmol) in 40 ml of CH_2Cl_2 was added pyridine (1.6 g, 20 mmol) dropwise at room temperature. The resulting mixture was stirred for 30 min at that temperature. To this was added 2-cyclohexenol (2.0 g, 20 mmol), followed by pyridine (2.0 g, 25 mmol), at room temperature. After the reaction was stirred for 2 h, it was quenched by adding 20 ml of H_2O, and the organic phase was separated, dried and concentrated. The residue was purified by flash chromatography with 7:1 hexane/EtOAc to give compound 43 as a colorless oil: 4.4 g, 90% yield; R_f = 0.48 (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.05 (m, 3H, aryl), 6.05-5.99 (m, 1H, HC=C), 5.86-5.81 (m, 1H, C=CH), 5.23 (m, 1H, CHOC=O), 2.21 (s, 6H, 2 CH_3), 2.10 (m, 1H), 2.04 (m, 1H), 1.99-1.89 (m, 2H), 1.83-1.77 (m, 1H), 1.70-1.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 152.67, 148.42, 133.75, 130.17, 128.63, 125.92, 124.59, 72.72, 28.17, 24.87, 18.59, 16.10; IR (neat) 3034, 2947, 2870, 1755 (C=O), 1479, 1259 cm^{-1}; HRMS m/z calculated for $C_{15}H_{18}O_3$ 246.12559, found 246.12555.

General procedure for the preparation of allylic aryl ethers: 1,1-dimethylallyl phenyl ether (28).

To a flask were added 1,1-dimethylallyl phenyl carbonate (27) (206 mg, 1.0 mmol), PPh_3 (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and THF (20 ml). The resulting mixture was stirred until the reaction was judged complete (5 h) by TLC analysis. Next, the reaction mixture was concentrated using a rotary evaporator and purified by flash chromatography to give compound 28 as a colorless oil: 98 mg, 60 % yield; R_f = 0.58 (8:1

hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.23-7.18 (m, 2H, phenyl), 6.99-6.95 (m, 3H, phenyl), 6.13 (dd, J = 17.7 and 10.5 Hz, 1H, HC=C), 5.25 (dd, J = 17.7 and 0.9 Hz, 1H, HC=C), 5.11 (dd, J = 10.5 and 0.9 Hz, HC=C), 1.44 (s, 6H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 155.97, 144.44, 128.76, 122.21, 121.72, 113.35, 79.42, 27.07; IR (neat) 3089, 2983, 1595, 1491, 1379 cm^{-1}; HRMS m/z calculated for $C_{11}H_{14}O$ 162.10447, found 162.10430. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found C, 81.11; H, 8.88.

Allyl phenyl ether (14)

This compound was obtained in 87% yield: R_f = 0.65 (4:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.32-7.22 (m, 2H, phenyl), 6.96-6.89 (m, 3H, phenyl), 6.04 (m, 1H, HC=C), 5.40 (d, J = 17.4 Hz, 1H, HC=C), 5.27 (d, J = 10.5 Hz, 1H, HC=C), 4.52 (d, J = 4.8 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 158.52, 133.32, 129.41, 120.80, 117.57, 114.69, 68.68; IR (neat) 3065, 3040, 1599, 1597, 1497 cm^{-1}; HRMS m/z calculated for $C_9H_{10}O$ 134.07317, found 134.07345. Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found C, 80.29; H, 7.83.

cis-4-*t*-butyldimethylsilyloxy-2-cyclpentenyl phenyl ether (17)

This compound was obtained in 75% yield: R_f = 0.60 (6:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.48-7.43 (m, 2H, phenyl), 7.14-7.08 (m, 3H, phenyl), 6.23-6.18 (m, 2H, HC=CH), 5.27 (m, 1H, CHOPh), 4.96 (m, 1H, CHOSi), 3.07 (dt, J = 13.5 and 7.2 Hz, 1H, CH_2), 1.95 (dt, J = 13.5 and 5.1 Hz, 1H, CH_2), 1.09 (s, 9H, *t*-BuSi), 0.28 (s, 3H, SiMe), 0.27 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$) δ 158.04, 138.50, 131.67, 129.48, 120.67, 115.42, 79.71, 75.06, 42.04, 25.95, 18.25, -4.59; IR (neat) 2955, 1599, 1495, 1371, 1240 cm^{-1}; HRMS m/z calculated for $C_{17}H_{25}O_2Si$ (M-H) 289.16238, found 289.16163; Ammonia CI Mass m/z 308.2 (M^++ NH_4). Anal. Calcd for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02. Found: C, 70.35; H, 9.14.

cis-4-*t*-Butyldimethylsilyloxy-2-cyclopentenyl (2-allyl-6-iodo)phenyl ether (20)

This compound was obtained in 55% yield: R_f = 0.54 (15:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.67 (dd, J = 7.8 and 1.5 Hz, 1H, aryl), 7.17 (dd, J = 7.5 and 1.5 Hz, 1H, aryl), 6.78 (t, J = 7.8 Hz, 1H, aryl), 6.04-5.85 (m, 3H), 5.10-4.99 (m, 3H), 4.69 (t, J = 5.4 Hz, 1H), 3.52-3.46 (m, 2H, CH_2Ar), 2.82 (dt, J = 13.5 and 7.2 Hz, 1H, CH_2 in cyclopentane), 2.03 (dt, J = 13.5 and 5.4 Hz, 1H, CH_2 in cyclopentane), 0.92 (s, 9H, *t*-BuSi), 0.11 (s, 6H, Me_2Si); ^{13}C NMR ($CDCl_3$) δ 156.26, 138.07, 137.99, 136.55, 134.94, 132.56, 130.67, 125.69, 116.41, 92.49, 86.09, 74.66, 42.09, 35.07, 25.99, 18.28, -4.44, -4.49; IR (neat) 2955, 2930, 1472, 1462, 1369, 1252 cm^{-1}; HRMS m/z calculated for $C_{20}H_{28}O_2SiI$ (M-H) 455.09033, found 455.08915. Anal. Calcd for $C_{20}H_{29}O_2SiI$: C, 52.63; H, 6.40. Found: C, 53.13; H, 6.65.

Compounds 24 and 25

These compounds were obtained as an inseparable 86:14 mixture of isomers: 62-80% yield; R_f = 0.65 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.28-7.22 (m, 2H, phenyl), 6.94-6.89 (m, 3H, phenyl), 5.91 (ddd, J = 16.5 and 10.5 and 5.7 Hz, 1H, HC=C in compound 24), 5.26 (dd, J = 16.5 and 1.2 Hz, 1H, HC=C in compound 24), 5.16 (dd, J = 10.5 and 1.2 Hz, 1H, HC=C in compound 24), 4.80 (t, J = 6.6 Hz, 1H, CHOPh in compound 24), 4.45 (d, J = 4.5 Hz, 0.3 H, CH_2OPh in compound 25), 1.43 (d, J = 6.6 Hz, 3H, CH_3 in compound 24); ^{13}C NMR ($CDCl_3$) δ 157.94, 139.20, 129.30, 120.67, 115.98, 115.52, 74.48, 21.39. Small peaks corresponding to compound 25 were not always evident; IR (neat) 2932, 1599, 1495 cm^{-1}.

Compounds 31 and 32

These compounds were obtained as an inseparable 86:14 mixture of isomers; 22% yield; R_f = 0.54 (15:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.27-7.17 (m, 2H, phenyl), 6.99-6.90 (m, 3H, phenyl), 6.08 (dd, J = 17.4 and 11.1 Hz, 1H, HC=C in compound 31),

5.19-5.13 (m, 3H). 4.53 (d, J = 6.6 Hz, 0.3 H, CH_2OPh in compound 32), 2.15-2.07 (m, 2H, CH_2), 1.83-1.73 (m, 3H), 1.68 (s, 3H, CH_3 in compound 31), 1.59 (s, 3H, CH_3 in compound 31), 1.39 (s, 3H, CH_3 in compound 31); ^{13}C NMR ($CDCl_3$) δ 156.07, 148.68, 131.67, 128.79, 124.19, 121.90, 121.30, 114.14, 81.44, 64.77, 41.64, 25.75, 22.58, 17.68. Small peaks corresponding to compound 32 were not always evident; IR (neat) 2978, 2916, 1599, 1491 cm^{-1}.

Compounds 34 and 35

These compounds were obtained as an inseparable 60:40 mixture of isomers: 44% yield; R_f = 0.63 (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.26-7.17 (m, 3.8 H, phenyl), 7.02-6.92 (m, 3.3H, phenyl), 5.74 (dd, J = 15.6 and 1.2 Hz, 1H, HC=C in compound 34), 5.56 (dq, J = 15.6 and 6.3 Hz, 1H, CH_3CH=C in compound 34), 5.52 (m, 0.7H, HC=C in compound 35), 4.98 (m, 0.7H, CHOPh in compound 35), 1.71 (m, 6.5H), 1.41 (s, 6H, 2 CH_3 in compound 34), 1.37 (d, J = 6.3 Hz, 2.3H, CH_3 in compound 35); ^{13}C NMR ($CDCl_3$) δ 158.09, 156.02, 137.28, 134.23, 129.30, 128.69, 127.08, 124.32, 122.11, 122.02, 120.43, 115.90, 79.19, 71.16, 27.46, 25.70, 21.48, 17.86; IR (neat) 3028, 2970, 1597, 1491 cm^{-1}.

Compounds 37 and 38

These compounds were obtained as an inseparable 89:11 mixture of isomers: 89% yield; ^1H NMR ($CDCl_3$) δ 7.59-6.90 (m, 10H, phenyl), 6.69 (d, J = 16.2 Hz, 1H, ArHC=C in compound 37), 6.37 (dt, J = 16.2 and 6.0 Hz, 1H, HC=CHAr in compound 37), 6.07 (m, 0.16 H, HC=C in compound 38), 5.60 (d, J = 6.0 Hz, 0.11 H, CHOPh in compound 38), 5.32 (d, J = 17.4 Hz, 0.12H , HC=C in compound 38), 5.21 (d, J = 10.5 Hz, 0.13H, HC=C in compound 38), 4.63 (dd, J = 5.7 and 1.5 Hz, 2H, CH_2OPh in compound 37); ^{13}C NMR ($CDCl_3$) δ 158.56, 136.38, 132.85, 129.45, 128.52, 127.83,

126.54, 124.16, 120.85, 114.71, 68.46. Small peaks corresponding to compound 38 were not always evident; IR (neat) 3028, 2903, 1599, 1495 cm^{-1}.

Compound 40

This compound was obtained in a 65% yield: R_f = 0.40 (15:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.32-7.22 (m, 2H, phenyl), 6.93-6.88 (m, 3H, phenyl), 5.59 (m, 1H, HC=C), 4.37 (m, 2H, CH_2OPh), 2.41 (dt, J = 8.8 and 5.7 Hz, 1H), 2.31-2.26 (m, 2H), 2.21 (dt, J = 1.2 and 8.7 Hz, 1H), 2.11 (m, 1H), 1.29 (s, 3H, CH_3), 1.20 (d, J = 8.4 Hz, 1H), 0.84 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 158.95, 144.00, 129.27, 120.53, 120.08, 114.87, 70.58, 43.29, 40.91, 38.12, 31.55, 31.31, 26.22, 21.09; IR (neat) 2910, 1599, 1497, 1242 cm^{-1}; HRMS m/z calculated for $C_{16}H_{20}O$ 228.15142, found 228.15126. Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.88; H, 8.94.

2-Cyclohexenyl phenyl ether (42)

This compound was obtained in 62% yield: R_f = 0.67 (5:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.29-7.23 (m, 2H, phenyl), 6.94-6.89 (m, 3H, phenyl), 5.98-5.84 (m, 2H, HC=CH), 4.79 (m, 1H, CHOPh), 2.16-2.02 (m, 2H), 1.96-1.80 (m, 3H), 1.68-1.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 157.83, 132.06, 129.47, 126.41, 120.62, 115.69, 70.83, 28.36, 25.17, 19.08; IR (neat) 3030, 2939, 2868, 1599, 1493, 1240 cm^{-1}; HRMS m/z calculated for $C_{12}H_{14}O$ 174.10447, found 174.10453. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.77; H, 8.33.

Compound 44

This compound was obtained in 74% yield: R_f = 0.50 (10:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.03 (d, J = 7.5 Hz, 2H, aryl), 6.93 (dd, J = 7.5 and 7.5 Hz, 1H, aryl), 5.97-5.86 (m, 2H, HC=CH), 4.40 (m, 1H, CHOPh), 2.32 (s, 6H, 2 CH_3), 2.21-1.86 (m, 5H), 1.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.12, 131.38, 131.28, 128.81, 127.37, 123.25, 75.32, 29.31, 25.31, 19.22, 17.32; IR (neat) 3029, 2932, 2864, 1474, 1261 cm^{-1};

HRMS m/z calculated for $C_{14}H_{18}O$ 202.13577, found 202.13557. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.24; H, 8.61.

Compound 46

This compound was obtained in 81% yield: R_f = 0.62 (7:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 7.32-7.23 (m, 2H, phenyl), 6.95-6.90 (m, 3H, phenyl), 5.08 (s, 1H, HC=C), 4.92 (s, 1H, HC=C), 4.41 (s, 2H, CH_2OPh), 1.82 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 158.74, 140.95, 129.37, 120.72, 114.76, 112.67, 71.62, 19.47; IR (neat) 3072, 2916, 1601, 1495 cm^{-1}; HRMS m/z calculated for $C_{10}H_{12}O$ 148.08882, found 148.08895. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found C, 81.13; H, 8.33.

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GENERAL SUMMARY

In this dissertation, the synthesis of prostaglandins has been accomplished using organopalladium chemistry in the key step. In addition, a method for the synthesis of allylic aryl ethers was developed.

In the first chapter of this dissertation, the formal synthesis of $PGF_{2\alpha}$ and the total synthesis of 12-epi-$PGF_{2\alpha}$ has been accomplished from optically active *cis*-4-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol. A Pd(II)-assisted three-component coupling reaction was employed as the key step.

In the second chapter of this dissertation, an efficient synthesis of the PGI_2 analogue (+)-5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 was accomplished. Radical chemistry was employed for the cyclization, followed by subsequent trapping by a tri-*n*-butylstannyl allylic alcohol in a one-step procedure. The epimer, 12-epi-5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2, was also synthesized by a one-step Pd(0)-mediated cyclization and subsequent enone coupling.

In the third chapter of this dissertation, a short synthesis of a novel prostanoid, 12-epi-carbacyclin, was accomplished. The Pd(II)-mediated cyclization of a silyl enol ether, followed by enone trapping, was used as a single step procedure.

In the last chapter of this dissertation, a Pd(0)-catalyzed synthetic approach to allylic aryl ethers was developed. Palladium-mediated reaction of allylic aryl carbonates gave allylic aryl ethers with high regio- and stereoselectivity. Allylic aryl carbonates were prepared from allylic alcohols either using phenyl chloroformate or triphosgene and functionalized phenols.

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