Efficient Synthesis of Benzoprostacyclins Using Free-Radical and Palladium-Catalyzed Tandem Alkene Insertion Strategies

Nam Ho Lee[*] and Richard C. Larock[†]

Department of Chemistry and Research Institute for Basic Sciences, Cheju National University, Cheju 690-756, Korea
[†]Department of Chemistry, Iowa State University, Ames, IA 50011, U.S.A.
Received May 10, 2001

Efficient syntheses of PGI_2 analogue **2a** and its epimer **3** have been accomplished. Using aryl iodide **6** as the common intermediate, either radical or palladium-assisted tandem alkene insertion strategies have been employed for construction of the benzoprostacyclin framework.

Keywords : Prostaglandin, Benzoprostacyclin, Synthesis, Free radical, Palladium.

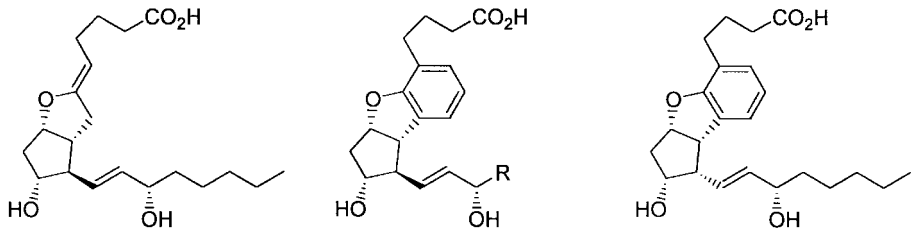
Introduction

Prostacycline (PGI_2, **1**) was discovered in 1976. It has attracted much attention as a potential medicine for cardiovascular disease, such as strokes and heart attacks, because of its potent antiplatelet and vasodilating effect.[1] However, due to the labile cyclic enol ether moiety, PGI_2 is readily metabolized to biologically much less active 6-oxo-$PGF_{1\alpha}$ under physiological conditions.[2] Since its discovery, many attempts have been made to synthesize chemically stable and biologically active PGI_2 analogues.[3] Some of the more important analogues posess a phenyl ether in place of the enol ether. Analogues, such as **2a** and **2b**, have been reported to exhibit substantial inhibition of platelet aggregation induced by ADP, collagen and arachidonic acid.[4] The sodium salt of beraprost (**2b**), the first commercial orally active PGI_2 drug has proven valuable in clinical use for its marked effect on arteriosclerosis obliterans.[5]

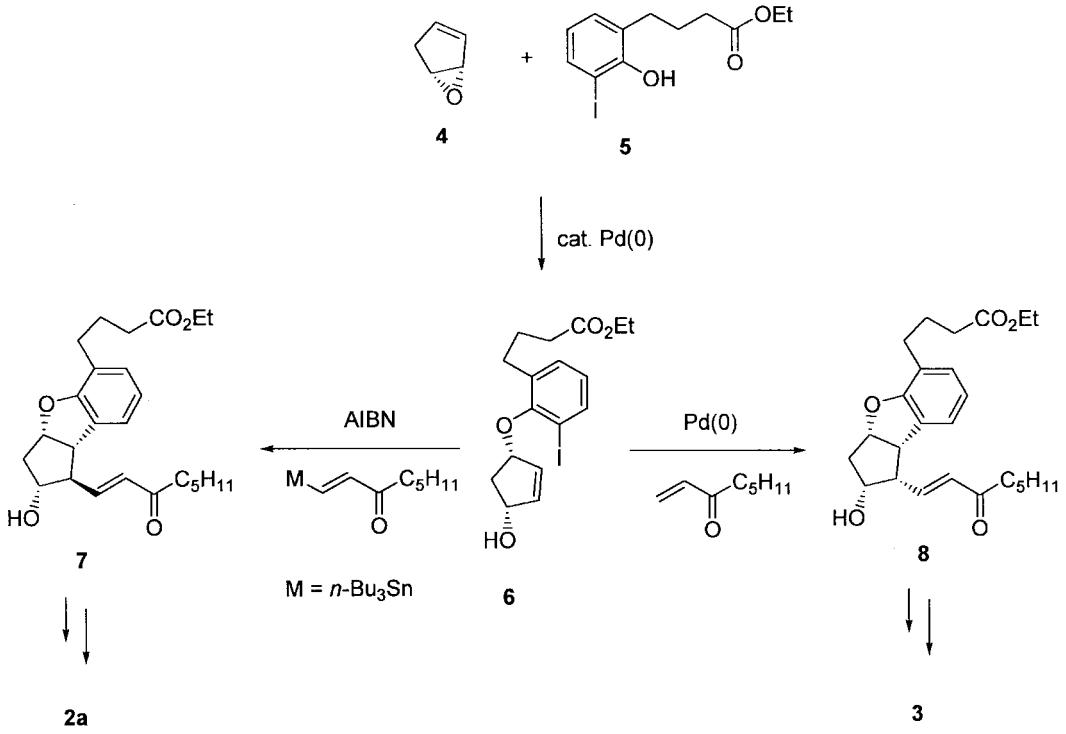
In our continuing effort to synthesize prostaglandins,[6] we decided to examine the preparation of compound **2a** and its 12-*epi* analogue **3**.[7] The synthetic strategy is shown in Scheme 1. It appeared that the compound **6** could be prepared stereoselectively from cyclopentadiene monoepoxide (**4**) and functionalized phenol **5** employing desired Pd(0) chemistry.[8] The key step in the syntheses of **2a** and **3** are the preparation of compounds **7** and **8**, from which the analogues could be easily obtained. A radical promoted cyclization, followed by β-stannyl enone trapping, previously employed in the synthesis of $PGF_{2\alpha}$ was envisioned for the efficient synthesis of **7**.[9] On the other hand, the 12-epimer **8** should also be readily available from the same starting material **6** using a palladium-catalyzed tandem alkene insertion strategy with 1-octen-3-one as the trapping agent.

Results and Discussion

For the synthesis of the key intermediate **6**, we needed to prepare the substituted phenol **5**. Iodophenol was used as the starting material for the preparation of the required phenol **5** (Scheme 2). The allylation of iodophenol and subsequent Lewis acid-catalyzed Claisen rearrangement gave the 2-allyl-6-iodophenol (**11**) with high efficiency. While Lewis acids such as Et_2AlCl[10] or $BF_3 \cdot OEt_2$ provided no Claisen rearrangement product, $MeAlCl_2$ at –20 °C proved to be an efficient and selective catalyst for this transformation, giving the *ortho* allylation over *para* rearrangement in a > 20 : 1 isomeric ratio. Protection of phenol **11**, followed by ozonolysis provided the aldehyde **13**, which was then subjected to a Wittig reaction to give the adduct **14**. Direct ozonolysis of the unprotected phenol **11** gave poor results, suggesting that the hydroxyl group was the source of the problem. Selective reduction of the unsaturated ester to the corresponding saturated substrate **15** using H_2 and a Pd/C catalyst failed. This reduction gave the iodide-reduced unsaturated ester as the only product. The use of PtO_2 as the catalyst, however, led to the desired product **15,** but in only 32% yield, along side product with the iodide reduced off. This problem was solved by using a small amount of aq. HCl as an additive. This gave the desired product in 90% yield. The compound **5** was then obtained by deprotection with *n*-Bu_4NF in THF.



1 **2a** R = *n*-C_5H_{11} **3**
2b R = $CH(Me)CH_2C{\equiv}CCH_3$

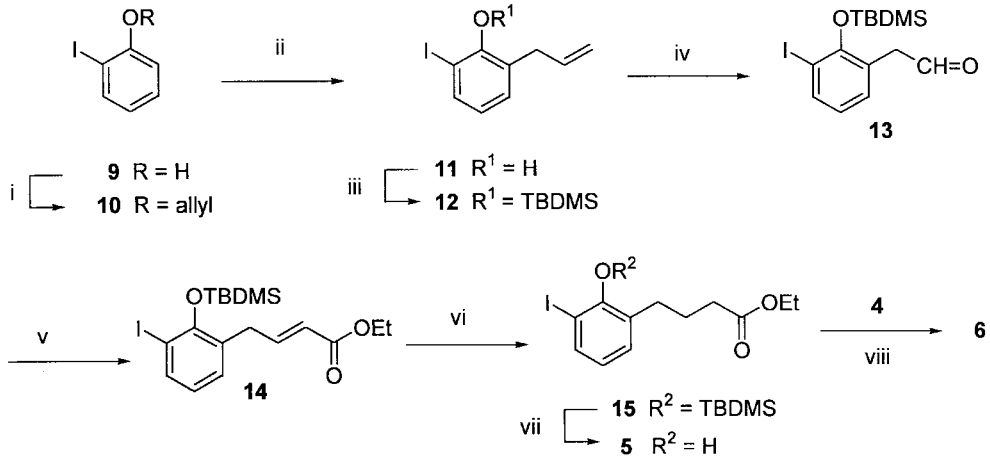


Scheme 1

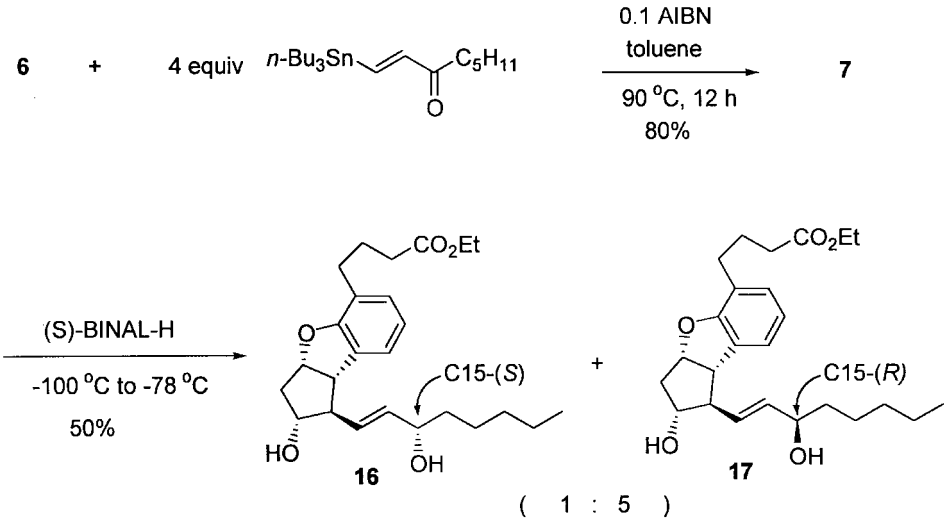
With the compound **5** at hand, stereoselective synthesis of the cyclopentenol **6** was cleanly carried out using cyclopentadiene monoepoxide (**4**) and known π-allylpalladium chemistry.[8] It is worth commenting that the iodide functionality in compound **5** remained intact under the reaction conditions employed.

Stork and co-workers have previously reported a radical cyclization-trapping method for construction of the $PGF_{2\alpha}$ framework.[9] Keck and Burnett later improved upon the Stork procedure by employing a β-stannyl enone as a radical trapping reagent.[11] Employment of this strategy using the radical precursor **6** proved successful. Using 4 equiv. of stannyl enone with a reaction temperature of 110 °C, the desired product **7** was obtained in 80% yield (Scheme 3).

The diastereoselective reduction of the enone in compound **7** was attempted using Noyori's (*S*)-BINAL-H, which has been documented to reduce the enone side chains of PGs to give the desired 15-(*S*) configuration.[12] When the reduction was conducted, to our surprise, the 15-(*R*) isomer **17** was apparently obtained as the major product from compound **7**. The stereochemistry at C15 was assigned based on the hydrolysis product **2a** and its 15-(*R*) diastereomer **20**, already known in the literature,[4c] The more polar isomer has been assigned as the 15-(*S*) isomer and measured to be



Scheme 2. [a]Reaction conditions: (i) 1.2 allyl bromide, 1.2 K_2CO_3, 94%; (ii) 0.8 $MeAlCl_2$, −20 °C, 70%; (iii) TBDMSCl, imidazole, 90%; (iv) O_3, −78 °C, then Me_2S, 83%; (v) $Ph_3P{=}CHCO_2Et$, 83%; (vi) H_2, PtO_2, HCl, 90%; (vii) *n*-Bu_4NF, THF, 94%; (viii) **4** (1.5 equiv), THF, rt, 24 h, 72%.

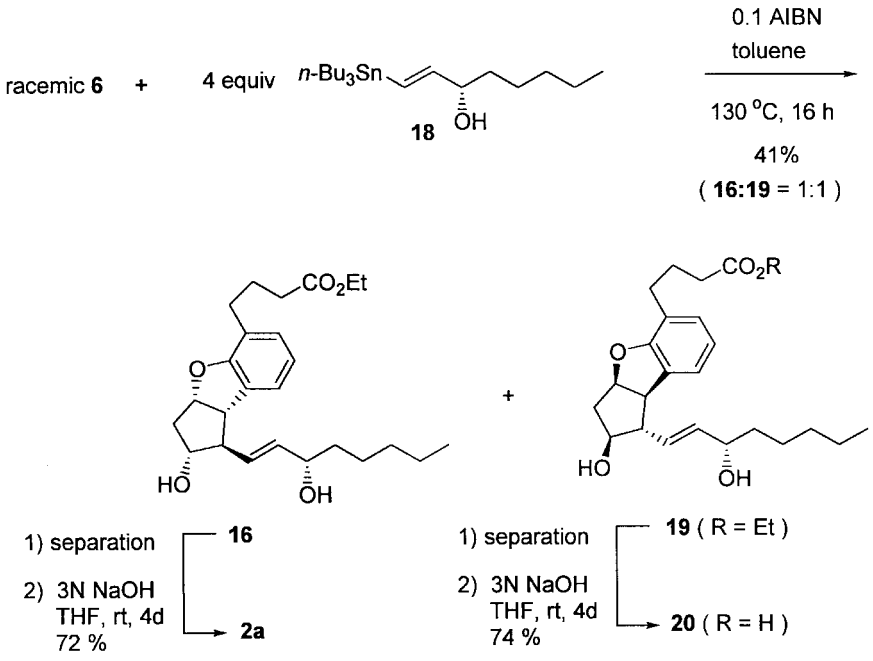


Scheme 3

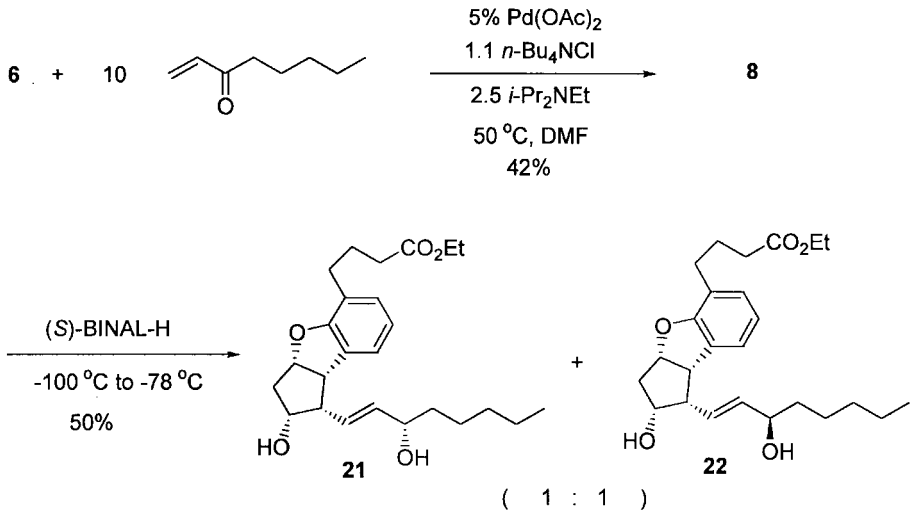
biologically more active. The chromatographic separation of diastereomers **16** and **17** was easy, because they show a large difference in polarities (R_f = 0.17 for **16** and R_f = 0.38 for **17** in 1 : 2 hexane/EtOAc). The unusual reversed stereoselectivity of (*S*)-BINAL-H in this reduction is interesting. It is reported that the reactivity of BINAL-H towards a carbonyl group is influenced by steric effects and various electronic factors, such as the LUMO energy levels.[12b] We assume that either steric or electronic factors introduced by the presence of an aromatic ring are responsible for this reversal of stereoselectivity.

A more direct pathway to compound **16** might be a radical reaction using γ-stannyl allylic alcohol **18** as a trapping agent. The allylic alcohol **18** is readily available in optically active form,[13] and utilization of the homochiral **18** should lead to the optically active diastereomer **16**. Thus, using the alcohol **18** as a trapping agent, the radical-promoted cyclization was conducted. Using the reaction conditions shown in Scheme 4 led to desired the product **16** along with its diastereomer **19** in 41% yield. The compounds **16** and **19** were cleanly separable by flash chromatography. Therefore, chromatographic separation, followed by the hydrolysis of compounds **16** and **19** with aq. NaOH, led to optically active PGI_2 analogues **2a** and **20**.

In our continuing effort to synthesize prostaglandins using a palladium-promoted cyclization-trapping strategy,[6] we decided to try to synthesize the key intermediate **8** for 12-*epi*-benzoprostacyclin **3**. Compound **6** was used as the organopalladium precursor, and 1-octen-3-one was used as the trapping agent. Various reaction conditions, including vari-



Scheme 4

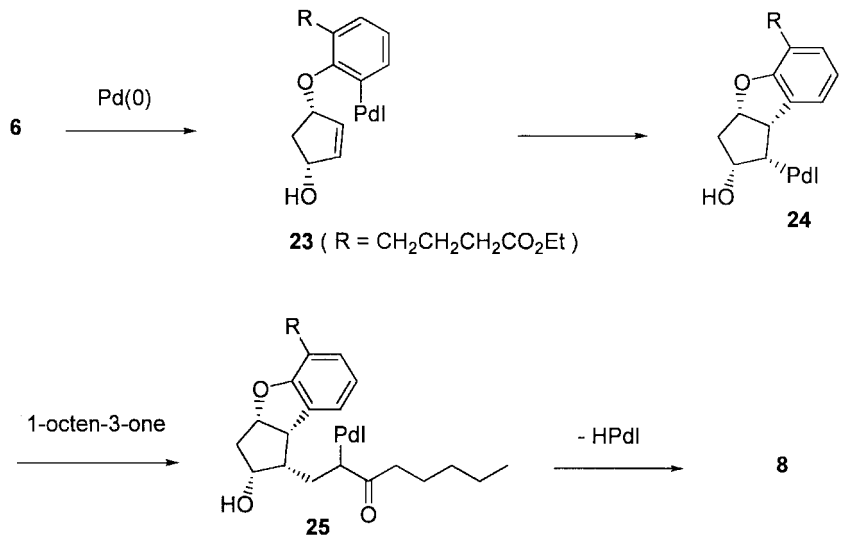


Scheme 5

ations in the base, temperature and solvent were examined to effect the tandem alkene insertions. We found that the desired product **8** could be obtained in 41% yield using the reaction conditions described in Scheme 5. It was found that the iodophenol **6** has low reactivity towards the Pd-assisted intramolecular cyclization under the reaction conditions. At a lower temperature, the product **8** was obtained usually along with the recovered **6**. At a higher temperature, however, the allyl aryl ether moiety in **6** was readily cleaved presumably *via* a π-allyl palladium intermediate to give a phenol as the major product.

A reaction mechanism for this interesting tandem alkene insertion process is proposed in Scheme 6. In this reaction, $Pd(OAc)_2$ is first reduced to Pd(0) species. To this Pd(0), aryl iodide **6** is oxidatively added to generate organopalladium intermediate **23**, which undergoes intramolecular *syn* addition to the cyclopentene to give **24**. The intermediate **24** is blocked from *syn* palladium β-hydride elimination by the hydroxy group. Enone insertion into the carbon-palladium bond and subsequent palladium β-hydride elimination provide the product **8** in a single step.

The next step in the synthesis of compound **21** required the stereoselective reduction of the α,β-unsaturated ketone in compound **8**. The diastereoselective reduction was examined using (*S*)-BINAL-H. The reaction was quite clean; only two spots were observed upon TLC analysis with a large polarity difference (R_f = 0.25 for compound **21**, R_f = 0.48 for compound **22** in 1 : 2 hexane/EtOAc). However, this reduction provided no selectivity, which might be ascribed to the presence of p-electrons in the phenyl ring in **8** as described previously in this text. The more polar component was tentatively assigned as the desired 15-(*S*) isomer. It is generally recognized that the more polar isomer has the 15-(*S*) configuration in prostaglandins. Comparison of the ^{1}H NMR spectra of the final products **3** and **27** also supports this assignment. The ^{1}H NMR spectral data for compounds



Scheme 6

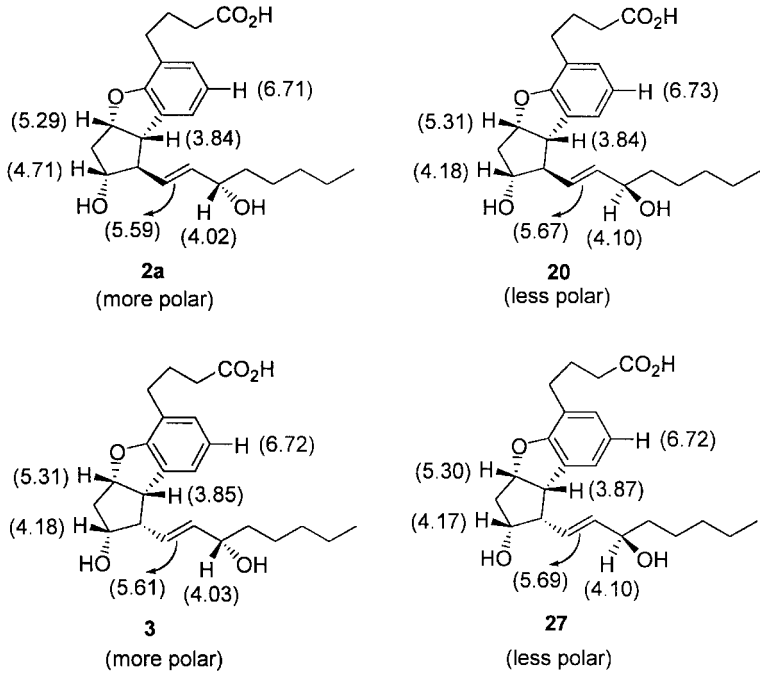
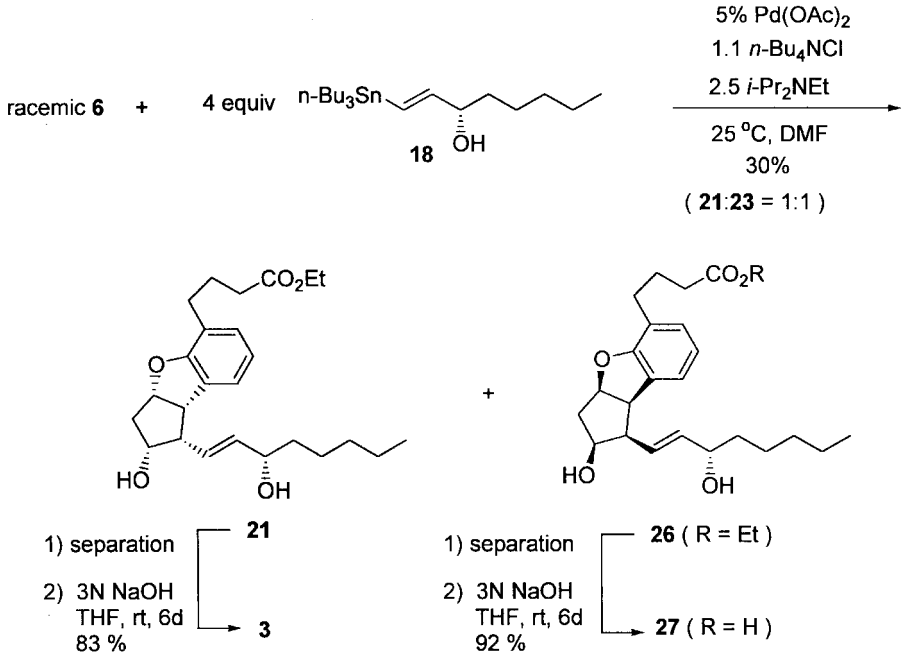


Figure 1. Comparison of the ^{1}H NMR δ values in compounds **2a**, **3**, **20**, and **27**.

2a, **3**, **20**, **27** are shown in Figure 1. The chemical shifts of H13, H14 and H15 in 15-(S) isomers **2a** and **3** consistently appear at higher field than those in the 15-(*R*) isomers **20** and **27**.

The reaction mechanism in Scheme 6 suggests that the use of optically pure stannyl alcohol **18** might lead to optically active diol **21** directly from compound **6**. Cross-coupling reactions between organopalladium and organotin reagents have been well studied.[14] Thus, the racemic compound **6** was subjected to Pd(0)-assisted cyclization in the presence of the vinylic tin compound **18** (Scheme 7). The desired product **21** along with its diastereomer **26** were obtained in 30% combined yield. Compound **21** was separable from compound **26** by flash chromatography. Finally, the products **3** and **27** were readily obtained upon hydrolysis of compounds **21** and **26** using aq. sodium hydroxide.

In conclusion, the preparation of biologically active PGI_2 analogue **2a** and its epimer **3** has been successfully achieved. In this synthesis, the compound **6** stereoselectively obtained using organopalladium chemistry was used as the key start-



Scheme 7

ing material, and either free radical or a palladium-assisted cyclization, followed by an alkene trapping proctocol, have been employed for construction of each prostaglandin framework. This tandem insertion strategy should find use in organic synthesis for the preparation of other alkyl branched aryl bicyclic compounds.

Experimental Section

General. 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 4A molecular sieves. Methylene chloride was distilled over phosphorous pentoxide and stored over 4A molecular sieves. Ethanol was distilled azeotropically by adding a small amount of benzene and stored over 4A molecular sieves. Toluene was distilled over sodium hydride. Hexane was distilled over sodium hydride. DMF was distilled over sodium hydride and stored over 4A molecular sieves.

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.

Preparation of (+)-5,6,7-trinor-4,8-inter-*m*-phenylene PGI$_2$ (2a). To a solution of compound **16** (40 mg, 0.10 mmol) in 1.2 mL of THF was added 0.6 mL of 3 N aqueous NaOH. After the reaction mixture was stirred for 4 d at room temperature, it was neutralized with 2 N aqueous HCl. The organic phase was decanted with ethyl acetate (3 × 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 = 6.9Hz, 1H, CHOAr), 4.95 (br s, 2H, OHs), 4.17 (m, 1H, CHOH), 4.03-3.99 (m, 1H, C=CH-CHOH), 3.84 (t, J = 8.7Hz, 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 ^{1}H NMR spectral data very close to those reported in the literature[4c]; ^{13}C NMR ($CDC1_3$) 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.

Preparation of 12-*epi*-5,6,7-trinor-4,8-inter-*m*-phenylene PGI$_2$ (3). To a solution of compound **21** (22 mg, 0.06 mmol) in 0.74 mL of THF was added 3 N aqueous NaOH (0.37 mL) at room temperature. After the mixture was stirred for 6 d at room temperature, it was neutralized by 2 N aqueous HCI. 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 **3**: 17 mg, 83% yield; R_f = 0.29 (20 : 1 EtOAc/MeOH); ^{1}H NHR ($CDC1_3$) 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 ($CDC1_3$) 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 compound 5. To a solution of compound **15** (2.85 g, 6.2 mmol) in 60 mL of THF at −78 °C was added *n*-Bu_4NF (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 ($CDC1_3$) 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 ($CDC1_3$) 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 6. To a dried flask was added $Pd(PPh_3)_4$ (18 mg, 0.016 mmol). To this was added compound **5** (264 mg, 0.79 mmol) in 2 mL of THF, and the reaction mixture was stirred in an ice-water bath. Cyclopentadiene monoepoxide[15] (**4**, 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 **6**: 235 mg, 71% yield; R_f = 0.27 (2 : 1 hexane/EtOAc); ^{1}H NMR ($CDC1_3$) 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, IH, 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 ($CDC1_3$) 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 7. To a solution of compound **6** (70 mg, 0.17 mmol) in 1.7 mL of toluene were added 1-stannyl-1-octen-3-one[16] (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 **7** 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 8. In a vial were placed compound **6** (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 **8**: 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 10. A solution of *o*-iodophenol (**9**, 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 (225 mL). The organic phase was washed with brine (25 mL), and then dried over $MgSO_4$. Concentration followed by flash chromatography, gave compound **10** as a colorless oil: 6.8 g, 94% yield; ^{1}H 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 (11). To a solution of compound **10** (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 the 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 **11**: 4.9g, 70% yield; R_f = 0.38 (20 : 1 hexane/EtOAc); ^{1}H 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 12. To a solution of compound **11** (4.9 g, 18.7 mmol) and imidazole (3.2 g, 47.l 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 × 2). The hexane phase was concentrated and then flash chromatographed to give compound **12**: 6.3g, 90% yield; R_f = 0.52 (hexane); ^{1}H 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=CHCH$_2$), 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 13. Ozone was passed through a solution of compound **12** (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 × 2), it was

dried and concentrated. Flash chromatography gave product **13**: 638mg, 83% yield; R_f = 0.63 (3 : 1 hexane/EtOAc); ^{1}H 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 14. 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 **13** (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 **14**: 3.52 g, 83% yield; R_f = 0.46 (5 : 1 hexane/EtOAc); ^{1}H 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}CNMR ($CDCl_3$) 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 15. To a three neck flask equipped with a H_2 gas balloon were added α,β-unsaturated ester **14** (619 mg, 1.36 mmol), ethanol (20 mL), 2 N 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 3 N 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 **15**; 562 mg, 90% yield; R_f = 0.52 (7 : 1 hexane/EtOAc); ^{1}H 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 compounds 16 and 17

Procedure in Scheme 3 (*via* reduction of compound 7): 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 **7** (126 mg, 0.30 mmol) 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 2 N aqueous HCl, and then extracted with ether (3 × 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 **16** (11 mg, 9% yield) and compound **17** (52 mg, 41% yield) as an oil. Starting material **7** (14 mg, 11% yield) was also recovered. Compound **16**: R_f = 0.17 (1 : 2 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.92 (d, *J* = 7.5 Hz, 1H, Ar), 5.69-5.67 (m, 2H, HC=CH), 5.34 (t, *J* = 7.5 Hz, 1H, CHOAr), 4.20 (m, 1H, CHOH), 4.15-4.07 (m, 3H, OCH_2 and C=CCHOH), 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, 122.96, 119.80, 88.27, 76.27, 76.92, 72.95, 60.32, 52.21, 49.98, 42.30, 36.98, 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 **17**; R_f = 0.38 (1 : 2 hexane/EtOAc); ^{1}H 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, CHOH), 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.

Procedure in Scheme 4 (*via* direct conversion from compound 6): In a vial were placed racemic compound **6** (100 mg, 0.24 mmol), optically active γ-stannyl allylic alcohol **18** (401 mg, 0.96 mmol), toluene (2.4 mL) and AIBN (Aldrich, 3.9 mg, 0.024 mmol). After the reaction was stirred for 16 h at 130 °C, 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 **16** (22 mg, 21% yield) and **19** (19 mg, 20% yield). The spectral data for **19** is the same as its racemic mixture **17**.

Preparation of optically active allylic alcohol 18. To a solution of $LiAlH_4$ (6.0 mL, 1 M in THF, 6.0 mmol) was added ethanol (3.0 mL, 2 M in THF, 6.0 mmol) dropwise at room temperature. To this was added (*S*)-binaphthol (Aldrich, 1.7 g, 6.0 mmol) in 2 mL of THF, and the resulting mixture was stirred for 30 min. The 1-tri-*n*-butylstannyl-1-octen-3-one[16] (830 mg, 2.0 mmol) in 2 mL of THF was added dropwise at –100 °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 purified by flash chromatography to give compound **18**: 677 mg, 82% yield. The optical purity of compound **18** was not determined [literature report (98% ee)].[13f]

Preparation of compound 20. To a solution of compound **19** (37 mg, 0.09 mmol) in 1.2 mL of THF was added 0.6 mL of 3 N aqueous NaOH. After the reaction mixture was stirred for 4 d at room temperature, it was neutralized with 2 N aqueous HCl. The organic phase was decanted with EtOAc (35 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography with 20 : 1 EtOAc/MeOH gave compound **20**: 26 mg, 74% yield; R_f = 0.29 (20 : 1 EtOAc/MeOH); ^{1}H 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, CHOH), 4.10 (dd, J = 11.7 and 6.3 Hz, 1H, C=CCHOH), 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, 32.27, 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 m/z 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.

Preparation of compounds 21 and 22

Procedure in Scheme 5 (*via* reduction of compound 8): 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. Compound **8** (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 **21** (49 mg, 25% yield) and **22** (50 mg, 25% yield). Compound **21**; R_f = 0.25 (1 : 2 hexane/EtOAc); ^{1}H 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, CHOH), 4.10 (m, 3H, OCH_2 and C=CHCHOH), 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 (m, 1H), 2.38 (d, J = 15.0 Hz, 1H, CH_2 in cycolpentane), 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 cycolpentane), 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 **22**: R_f = 0.48 (1 : 2 hexane/EtOAc); ^{1}H 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=CHCHOH), 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 (brs, 2H, OHs), 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.

Procedure in Scheme 7 (*via* direct conversion from compound 6): In a vial were placed compound **6** (109 mg, 0.26 mmol), γ-stannyl alcohol **18** (164 mg, 0.39 mmol), *i*-Pr_2NEt (85 mg, 0.66 mmol), *n*-Bu_4NCl (Lancaster, 88 mg, 0.31 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and DMF (52 mL) as 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 **21** (15 mg, 14% yield) and **26** (17 mg, 16% yield).

Compound 27. To a solution of compound **26** (55 mg, 0.14 mmol) in 1.8 mL of THF was added 3 N aqueous NaOH (0.9 mL) at room temperature. After the reaction was stirred for 6 d at room temperature, it was neutralized by 2 N aqueous HCl. The organic phase was decanted with ethyl acetate and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography with 20 : 1 EtOAc/MeOH gave compound **27** (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 (brs, 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.

References

1. Moncada, S.; Gryglewski, R. J.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663.
2. Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915.
3. (a) Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl*. **1982**, *21*, 751. (b) Newton, R. F.; Roberts, S. M.; Taylor, R. J. K. *Synthesis* **1984**, 449. (c) Skuballa, W.; Schillinger, E.; Sturzebecher, C. St.; Vorbruggen, H. *J. Med. Chem*. **1986**, *29*, 313.
4. (a) Ohno, K.; Nagase, H.; Matsumoto, K.; Nishiyama, H.; Nishio, S. *Adv. Prostaglandin Thromboxane Leukotriene Res*. **1985**, *15*, 279. (b) Umetsu, T.; Murata, T.; Tanaka, Y.; Osada, E.; Nishio, S. *Jpn. J. Pharmacol*. **1987**, *43*, 81. (c) Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett*. **1990**, *31*, 4489. (d) Nagase, H.; Matsumoto, K.; Yoshiwara, H.; Tajima, A.; Ohno, K. *Tetrahedron Lett*. **1990**, *31*, 4493. (e) Ohno, K.; Takahashi, T.; Ohtake, A.; Wakita, H.; Nishio, S. PTC Int. Appl. WO 89 03,378; *Chem. Abstr*. **1989**, *111*, 232453p.
5. Nishio, S.; Nagase, H.; Kanou, K.; Aoki, S.; Kanbayashi, Y. *Yakugaku Zasshi* **1997**, *117*, 509.
6. (a) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc*. **1991**, *113*, 7815. (b) Larock, R. C.; Lee, N. H. *Tetrahedron Lett*. **1991**, *32*, 5911. (c) Lee, N. H.; Larock, R. C. *Bull. Korean Chem. Soc*. **1995**, *16*, 859.
7. This results have been published as a communication, see: Larock, R. C.; Lee, N. H. *J. Org. Chem*. **1991**, *56*, 6253.
8. Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett*. **1985**, *26*, 5615.
9. Stork, G.; Sher, P. M.; Chen, H. L. *J. Am. Chem. Soc*. **1986**, *108*, 6384.
10. Sonnerberg, F. M. *J. Org. Chem*. **1970**, *35*, 3166.
11. Keck, G. E.; Burnett, D. A. *J. Org. Chem*. **1987**, *52*, 2958.
12. (a) Noyori, R.; Tomio, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc*. **1984**, *106*, 6717. (b) Noyori, R.; Tomio, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc*. **1984**, *106*, 6709.
13. (a) Fried, J.; Lin, C.; Mehra, M.; Kao, W.; Dalven, P. *Ann. N.Y. Acad. Sci*. **1971**, *180*, 38. (b) Larock, R. C.; Babu, S. *Tetrahedron* **1987**, *43*, 2013. (c) Midland, M. M.; Graham, R. S. *Org. Synth*. **1984**, *63*, 57. (d) Kang, S. K.; Lee, D. H.; Lee, J. M. *Synlett* **1990**, 591. (e) Suzuki, M.; Morita, Y.; Koyano, K.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809. (f) Kitano, Y.; Matsumoto, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett*. **1987**, 1523.
14. For a review of the cross-coupling of organostannanes and palladium compounds, see: Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508.
15. Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1973**, 790.
16. Jung, M. E.; Light, L. A. *Tetrahedron Lett*. **1982**, *23*, 3851.