PALLADIUM(0) CATALYZED REACTIONS OF 1,4-EPIPEROXIDES†

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Abstract - The $Pd(PPh_3)_4$ catalyzed reaction of 2,3-saturated and 2,3-unsaturated 1,4-epiperoxides proceeds by courses markedly different from those of the previously reported transition metal catalyses. The Pd(0)-promoted reaction of 2,3-saturated epiperoxides gives the corresponding 4-hydroxy ketones and 1,4-diols as the major products. From 2,3-dedihydroepiperoxides are formed the corresponding 4-hydroxy enones, syn-1,2;3,4-diepoxides, and 1,4-diols. The results are interpreted in terms of competing Pd(0)/Pd(II) and Pd(0)/Pd(I) exchange mechanisms. Exposure of prostaglandin (PG) H_2 methyl ester to $Pd(PPh_3)_4$ produces a mixture of methyl esters of PGD_2, PGE_2, $PGF_{2\alpha}$, and (5Z,8E,10E,12S)-12-hydroxy-5,8,10-heptadecatrienoic acid.

1,4-Epiperoxides (endoperoxides) serve as key substances in a variety of chemical[1] and biological[2,3] transformations. The O—O bond undergoes either homolytic or heterolytic cleavage depending on the reaction conditions.[1] Transition metal catalysis has been studied extensively only with metals such as Cu(I),[3f] Cu(II),[3f] Fe(II),[3e,g,4a,b,5] or Co(II),[4c,d] which have the ability to induce the reaction via a one-electron redox mechanism.[6] The catalysis of epiperoxides with Ru(II)-phosphine complexes, which exhibit unique reactivity,[7] also belongs to the same category. The study of catalysis with metals which cause the reaction to occur by a two-electron exchange mechanism is quite limited.[8] We have been intrigued by the catalytic decomposition of epiperoxides with a zero-valent Pd complex,[9] which has a tendency to recycle the metal through a two-equivalent change mechanism.[10] Behavior of prostaglandin (PG) endoperoxides in the presence of such a metal complex has also been examined.[11]

Results and Discussion

Palladium Catalyzed Reaction of 1,4-Epiperoxides. Both 2,3-saturated and 2,3-unsaturated 1,4-epiperoxides are stable in dichloromethane or benzene without catalyst. However, when a catalytic

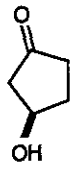
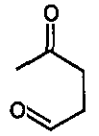
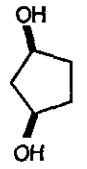
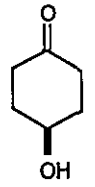
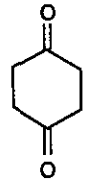
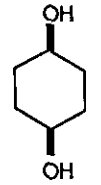
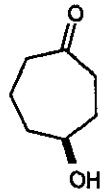
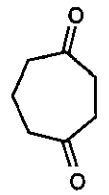
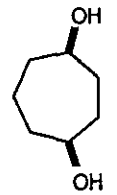
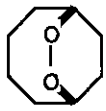
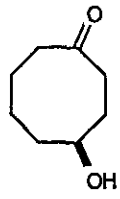
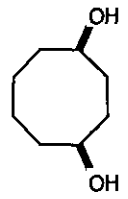
†This work is dedicated to the memory of Professor Tetsuji Kametani.

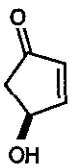
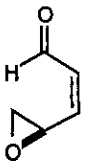
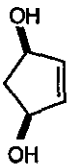
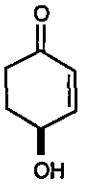
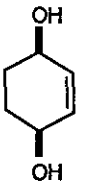
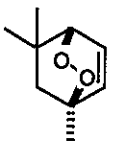
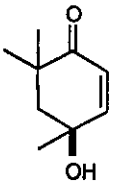
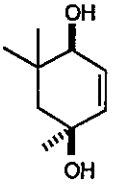
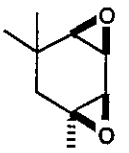
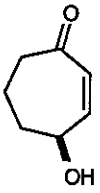
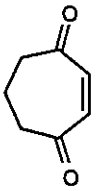
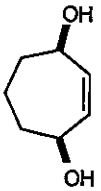
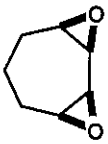
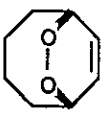
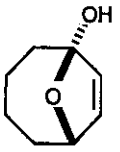
amount of $Pd(PPh_3)_4$ (5—10 mol %) was added to the solution, the O—O bond was cleaved under mild thermal conditions. Throughout the reaction the yellow to yellowish brown solution phase remained unchanged, and neither palladium mirror nor black precipitates were formed. Both monocyclic and bicyclic substrates are susceptible to such a redox catalyst under neutral conditions. The results are summarized in Table 1. The reaction pathways are highly affected by the ring systems and are different from those of the reported catalyses.[7] Bicyclic 2,3-saturated 1,4-epiperoxides gave the corresponding 4-hydroxy ketones and 1,4-diols as the major products. From bicyclic 2,3-didehydro-1,4-epiperoxides were obtained the 4-hydroxy enones, the 1,4-diols, and the diepoxides as the major products. Certain hydroxy enone products derived from the monocyclic substrates underwent further reaction to give the more stable E isomer, 1,4-diketone, or furan derivatives (entries 26—28). The relative reactivities of the bicyclic substrates are dependent on the ring size of the carbon frameworks. The relatively strained dioxabicyclo[2.2.1]heptane derivatives underwent a facile decomposition with $Pd(PPh_3)_4$ near or below room temperature (entries 1—3 and 14), whereas the substrates having larger ring systems required more forcing conditions (entries 4—13 and 16—25). The monocyclic substrates are less reactive than the bicyclic epiperoxides and consequently required harsh conditions for smooth decomposition (entries 26—28).

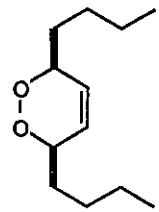
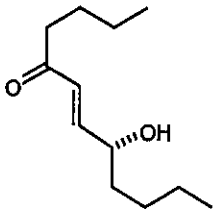
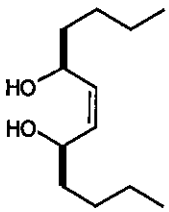
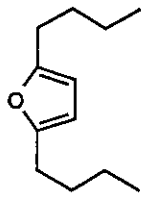
In the presence of a catalytic quantity of $PdCl_2(PPh_3)_2$ the epiperoxides, **5**, **6**, and **8**, formed (Z)-4,5-epoxy-2-pentenal (**26**), syn-1,2;3,4-diepoxycyclohexane (**30**), and syn-1,2;3,4-diepoxycycloheptane (**37**) respectively in high yields (entries 15, 19, and 24). Without catalyst, decomposition of **6** or **8** occurred in dichloromethane only by heating at 100—120 °C, giving diepoxides in rather low yield together with some byproducts.[7c]

Mechanistic Consideration. $Pd(PPh_3)_4$ dissociates into triphenylphosphine and $Pd(PPh_3)_n$ (n = 3 or 2) in solution[10e] and such in situ generated coordinatively unsaturated Pd(0) complexes could be responsible for the catalytic reactions.[10] Although triphenylphosphine does act as a stoichiometric reducing agent of cyclic peroxides giving the diols,[3e,12] participation of the dissociated phosphine ligand is unimportant in the present catalytic conditions because of the following reasons. (1) Catalyst concentration does not affect the product ratio and yield to any notable extent. Actually the catalysis of **3** with 2.5 to 20 mol % of $Pd(PPh_3)_4$ under the standard conditions consistently gave the 1,4-diol in 25—30% yield (entries 6—9, 21 and, 22). The yield, 29%, obtained by using 2.5 mol % of the catalyst is much higher than that expected from the stoichiometric reaction of triphenylphosphine and **3** (entry 6). (2) When the reaction of triphenylphosphine and the epiperoxide **8** was conducted in dichloromethane at 60 °C for 6 h, 1,2-epoxy-3-cycloheptene was obtained quantitatively (90% conversion).[1g] However, the $Pd(PPh_3)_4$-catalyzed reaction of the same epiperoxide produced the corresponding 1,4-diol in ca. 20% yield (entries 21—23) together with other disproportionation products. No, or very little, epoxycycloheptene (< 3%, if any) was obtained (entries 21—23). (3) Generally, coordinatively un-

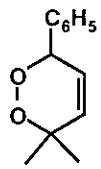
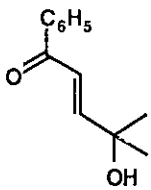
Table 1. Palladium(0)-Catalyzed Reaction of 1,4-Epiperoxides[a]

entry	epiperoxide weight, mg (mmol)	conditions $Pd(PPh_3)_4$ μ mol	CH_2Cl_2 mL	temp (time) °C (h)	products % yield[b]		
							
1	**1**, 30 (0.3)	15	3.5	28 (2)	**14**, 40[c]	**15**, 25[c]	**16**, 20[c]
2	**1**, 14.7 (0.15)	7.5	1[d]	17 (3)	**14**, 41[c]	**15**, 29[c]	**16**, 20[c]
3	**1**, 27.1 (0.27)	13.5	1.5	28[e] (2.5)	**14**, 54[c]	**15**, 18[c]	**16**, 27[c]
							
4	**2**, 25 (0.22)	11	1	60 (5)	**17**, 44	**18**, 4	**19**, 39
5	**2**, 25 (0.22)	11	1	60 (5[f])	**17**, 49	**18**, 3	**19**, 37
							
6	**3**, 25.6 (0.2)	5	2	60 (10)	**20**, 56	**21**, 6	**22**, 29
7	**3**, 25.6 (0.2)	10	2	60 (10)	**20**, 62	**21**, 13	**22**, 25
8	**3**, 25.6 (0.2)	20	2	60 (10)	**20**, 63	**21**, 11	**22**, 26
9	**3**, 25.6 (0.2)	40	2	60 (10)	**20**, 65	**21**, 10	**22**, 25
10	**3**, 25.6 (0.2)	10	2	60 (10[g])	**20**, 60	**21**, 12	**22**, 28
11	**3**, 25.6 (0.2)	10	2	60 (10[f])	**20**, 68	**21**, 10	**22**, 22
12	**3**, 25.6 (0.2)	10	2	60 (10[e])	**20**, 77	**21**, 2	**22**, 21[h]
							
13	**4**, 44.6 (0.31)	14	1.5[d]	65 (15)	**23**, 73, 70[i]	**24**, 23, 20[i]	

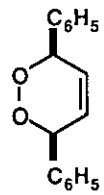
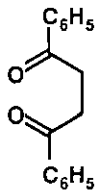
							
14	**5**, 60 (0.61)	61.2	3	4[j] (20)	**25**, 54[c]	**26**, 0	**27**, 16[c]
15	**5**, 18 (0.18)	14[k]	1[l]	4[j] (50)	**25**, 0	**26**, 62[c]	**27**, 0
							
16	**6**, 20 (0.18)	9	1.5	50–60 (5)	**28**, 39	**29**, 30	**30**, 8
17	**6**, 20 (0.18)	9	1.5	50–60 (5[f])	**28**, 42	**29**, 32	**30**, 9
18	**6**, 20 (0.18)	9	1.5	50–60 (5[e])	**28**, 37	**29**, 50[m]	**30**, 6
19	**6**, 19 (0.17)	14[k]	1.5	60 (20)	**28**, 0	**29**, 0	**30**, 88[c]
							
20	**7**, 61.7 (0.4)	20	3	60 (46)	**31**, 68[t]	**32**, 6[t]	**33**, 24[t]
								
21	**8**, 22.7 (0.18)	7	1.5	60 (29)	**34**, 40	**35**, 3	**36**, 19	**37**, 26
22	**8**, 22.7 (0.18)	18	1.5	60 (29)	**34**, 45	**35**, 10	**36**, 17	**37**, 28
23	**8**, 22.7 (0.18)	18	1.5	60 (29[f])	**34**, 44	**35**, 9	**36**, 17	**37**, 29
24	**8**, 19.5 (0.17)	14[k]	1.5	60 (35)	**34**, 0	**35**, 0	**36**, 0	**37**, 78[c]
								
25	**9**, 140.2 (1)	50	5[d]	60 (29)	**38**, 51[t]			

26	**10**, 29.7 (0.15)	7.5	1.5	60 (39)	**39**, 34[f]	**40**, 59[f]	**41**, 5[f]

27	**11**, 91.1 (0.5)	25	3	100 (15)	**42**, 66[f]	

28	**12**, 10.8 (0.07)	3.9	1.5	70 (12)	**43**, 74[c]	

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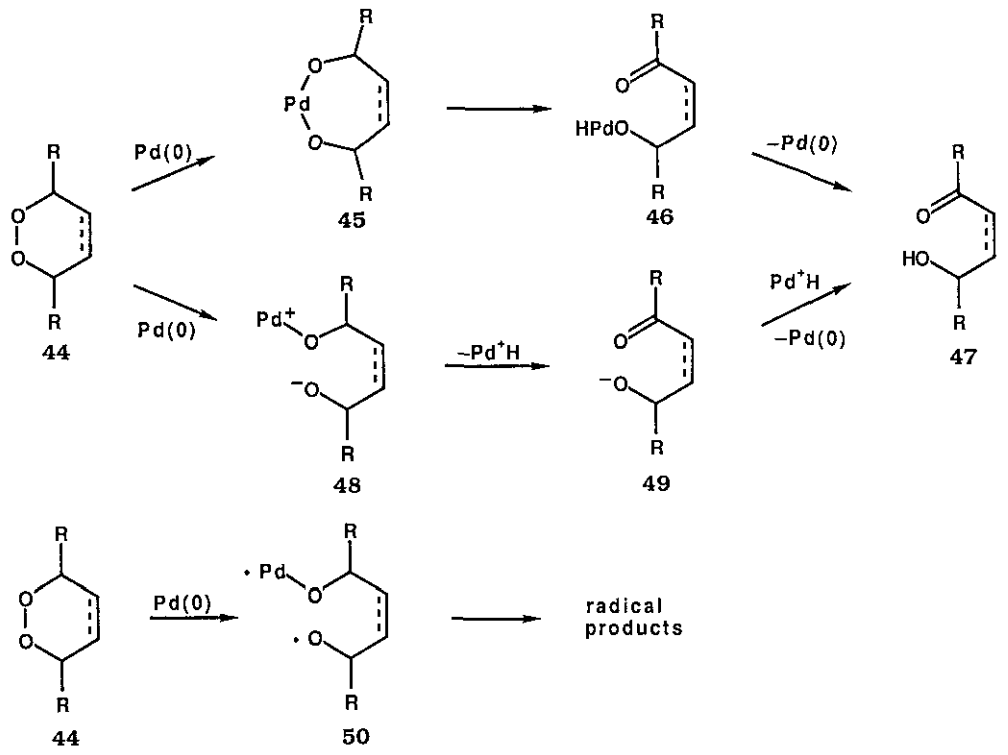
[a] Unless otherwise stated, reaction was conducted with $Pd(PPh_3)_4$ in dichloromethane under argon atmosphere. [b] Determined by glc analysis. [c] Determined by ^1H nmr analysis. [d] Benzene was used as solvent. [e] Ten equiv. of 2-propanol was added. [f] Reaction in the presence of 5 mol % of 2,4,6-tri-*tert*-butylphenol. [g] Reaction in the presence of 5 mol % of *m*-dinitrobenzene. [h] Acetone was formed in 19% yield. [i] Isolated yield after silica gel column chromatography. [j] The catalyst and substrate were mixed at -78 °C. [k] Decomposition in the presence of $PdCl_2(PPh_3)_2$. [l] THF was used as solvent. [m] Acetone was produced in 20% yield.

saturated Pd(0) complexes are much more nucleophilic than triphenylphosphine.[13] The product distribution of the reaction with $PdCl_2(PPh_3)_2$ (entries 15, 19, and 24) dismisses the possibility of the participation of Pd(II) catalyst species in the Pd(0)-promoted reaction.

The observations listed in Table 1 can be interpreted as being due to competing one- and two-equivalent change pathways, as outlined in Scheme I, in spite of the Pd(0) catalysis.[14] The epiperoxide

Scheme I. Two- and One-Electron Exchange Mechanisms



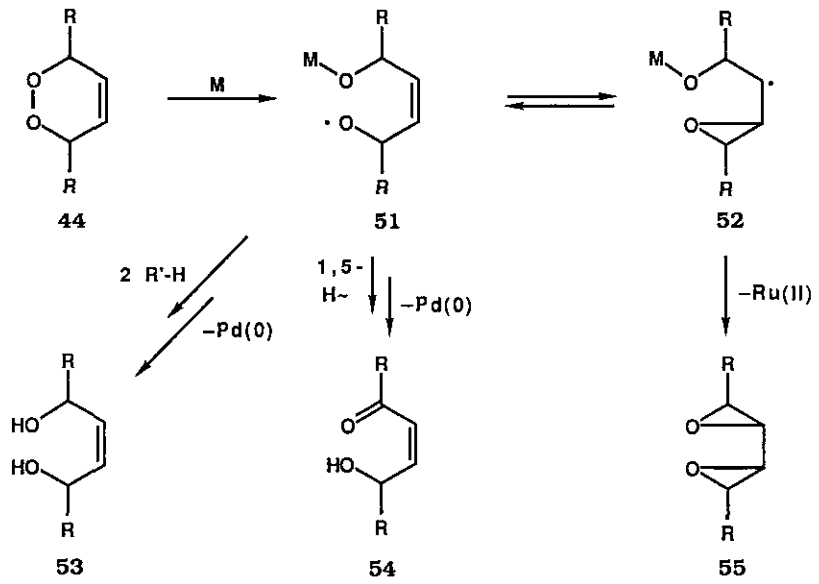
to hydroxy enone conversion, **44** → **47**,[15] is best accounted for in terms of the well-known Pd(0)/Pd(II) redox mechanism.[10] Thus oxidative addition of the O—O bond[16] of **44** to the coordinatively unsaturated Pd(0) species produces the seven-membered cyclic structure **45**. Subsequent β-elimination of a PdH element, giving **46**, followed by reductive elimination leads ultimately to the hydroxy enone **47** and Pd(0) species. Alternatively, the initial attack of Pd(0) species to an oxygen atom of **44** in an S_N2 manner[17] also cleaves the O—O linkage to generate the zwitterion **48**. Subsequent hydrogen reorganization via PdH species and the alkoxide **49** formed by β-elimination results in the same product, **47**. The conformationally flexible zwitterion **48** may be more appropriate for the PdH elimination than the cyclic intermediate **45**.[18] The efficiency of this catalytic process is attributable

to the strong nucleophilicity of Pd(0)[13] and the hydrogen-carrying ability of Pd(II).[10] The formation of levulinaldehyde as a byproduct from 1,3-epiperoxycyclopentane (**1**) (entries 1—3) is considered to be a result of the intramolecular retro-aldol reaction of the intermediate **46** or **49** (R—R = CH_2).[3h] This leakage was supressed to some extent by the addition of an alcoholic substance to the reaction system (entry 3). Both this aldehyde and 3-hydroxycyclopentanone are not interconvertible under such neutral reaction conditions. The catalytic diol formation, diepoxide production, and perhaps hydroxy enone formation from a monocyclic substrate involve radical intermediates. A simple explanation for these reactions of a strong oxidizing substrate **44** can be made on the basis of the Pd(0)/Pd(I) one-equivalent redox mechanism,[14] producing an inner-sphere radical, depicted as **50**.[7,19] The addition of m-dinitrobenzene (5 mol %), an efficient anion radical quencher, neither inhibited the catalysis nor affected the product ratio (entry 10). This suggests that both one- and two-equivalent change reactions proceed via a direct atom-transfer process and not by an electron transfer mechanism.[20] In the reaction of dichloromethane, a trace amount of 1,1,2,2-tetrachloroethane was detected but chloroform was not formed. Therefore, the substrates or products are thought to be the major hydrogen sources. Secondary alcohols, among others, serve as efficient hydrogen donors for **50**. Thus, the reaction of 1,4-epiperoxycycloheptane (**3**) in the presence of ten equiv. of 2-propanol (entry 12) produced acetone in 19% yield at the expense of the 1,4-diketone formation. It is apparent that the initially formed hydroxylic products are partly dehydrogenated under the reaction conditions. Acetone (20% yield) was also formed in the decomposition of 1,4-epiperoxycyclohexene (**6**) in the presence of 2-propanol (10 equiv) (entry 18). Since addition of 2,4,6-tri-tert-butylphenol (0.5—5 mol %), an oxygen radical terminating agent, did not affect the reaction to any extent (entries 5, 11, 17, and 23),[14b] a chain mechanism is unlikely to be operative in the radical reaction.[20]

The reactivity of the oxy radical or radicaloids is subtly affected whether they are interacted with metals or not, and by the nature of the oxygen—metal bonding. Under purely thermal conditions the O—O bond tends to undergo homolytic cleavage giving the free radical but, depending on the substrate structures, neighboring conjugated bonds (either saturated or unsaturated) could participate in the O—O breakage to give non-radical type products via concerted, lower energy pathways. Thermolysis[21] of 1,3-epiperoxycyclopentane in benzene giving skeletally rearranged 4,5-epoxypentanal in 86% yield[21a] is a typical example. In the presence of certain metal complexes, the O—O bond may be ruptured even more readily to generate inner-sphere radicals,[7] whose behavior is markedly dependent on the nature of the metals. Some catalytic reactions may form more radical products than the uncatalyzed thermal processes. As outlined in Scheme II, Pd(0) catalysis of **44** for instance, tends to afford 1,4-diol **53** or hydroxy enone **54** predominantly, in sharp contrast with the Ru(II) catalysis[7] which gives the diepoxide **55** as the major product. The metal-bound diradical **51** equilibrates rapidly with the closed form **52**. The Pd—O bond in **51** or **52** would have to be rather strong to allow inter- or

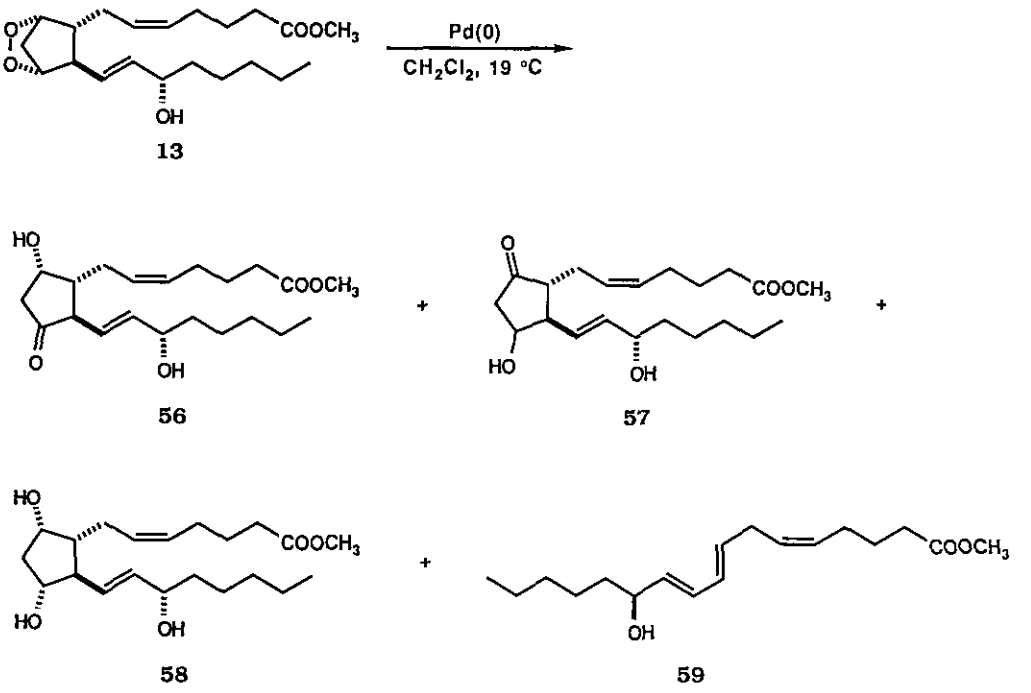
intramolecular hydrogen abstraction of the oxy radical **51** leading ultimately to **53** or **54**. On the other hand, the weak, nonpolar Ru—O bond in **52** is readily cleaved to form **55**.

Scheme II. Metal Dependency in One-Electron Exchange Mechanism



Conversion of a Prostaglandin Endoperoxide to Primary Prostaglandins. A well-defined transition metal catalysis provides a good chemical model for the bioconversion of PG endoperoxides to the PG family.[3] The present catalytic conversion of 1,4-epiperoxides to the hydroxy ketones and the diols is formally related to the biogenetic conversion of PG endoperoxides to primary PG derivatives.[2] Therefore, we have examined the behavior of a PG endoperoxide in the presence of the Pd(0) catalyst (Scheme III). Thus when PGH_2 methyl ester (**13**) was exposed to 10 mol % of $Pd(PPh_3)_4$ in dichloromethane at 19 °C for 3 h, a mixture of methyl esters of PGD_2 (**56**) (17%), PGE_2 (**57**) (11%), $PGF_{2\alpha}$ (**58**) (41%), and (5Z,8E,10E,12S)-12-hydroxy-5,8,10-heptadecatrienoic acid (HHT, **59**) (4%) was produced. The reaction pattern is markedly different from that observed with the Ru(II)-catalyzed reaction, which gives the HHT methyl ester (**59**) exclusively.[7]

Scheme III. Pd(0)-Catalyzed Reaction of PGH_2 Methyl Ester



EXPERIMENTAL

General Remarks. Infrared (ir) spectra were obtained with a JASCO IRA-1 spectrophotometer. ^1H Nuclear magnetic resonance (nmr) spectra were obtained with a Varian HA-100 or a JEOL PMX-60 spectrometer. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane ($\delta = 0$) in delta units. Multiplicity is expressed as s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, br s = broad singlet, etc. Mass spectra (ms) were determined on a JEOL D-10 or a Hitachi RMU-6C mass spectrometer with an ionization energy of 75 eV. Glc analysis was conducted on a Hitachi 063 or a Hitachi 163 gas chromatographic instrument. Elemental analyses were performed by the faculty of the Departments of Engineering of Nagoya University. Tlc analyses were conducted on E. Merck precoated (0.25 mm) Silica Gel 60 F_{254} plates. The products in the reaction of PGH_2 methyl ester with the Pd(0) complex were monitored by a Shimadzu CS-920 model high-speed TLC scanner. Column chromatography was conducted using Silica Gel 60 (E. Merck, 7734, 70—230 mesh). The bulb-to-bulb short-path distillation was performed by using a Büchi Kugelrohrofen.

Catalysts and Solvents. Tetrakis(triphenylphosphine)palladium(0) was prepared by the standard method

reported by Coulson[24] and the pale-green yellow crystals were recrystallized from a 3:1 mixture of THF and ether at 0 °C to give bright-yellow crystals. Although the complex can be handled in air for a short period without decomposition, it was stored in a sealed tube under argon to ensure its purity. Dichloromethane was distilled from P_4O_{10} under argon atmosphere and kept in a Schlenk tube. Benzene was purified by distillation from sodium benzophenone ketyl or CaH_2 under argon atmosphere and kept in a Schlenk tube. THF was distilled from sodium benzophenone ketyl under argon. Solvents for the catalysis were degassed by freeze/thaw cycles under high vaccum before use.

Epiperoxides. 1,3-Epiperoxycyclopentane (**1**), 1,4-epiperoxycyclohexane (**2**), 1,4-epiperoxycycloheptane (**3**), and 1,4-epiperoxycyclooctane (**4**) were prepared by diimide reduction of the corresponding 2,3-dehydro derivatives by the reported procedures.[25] 3,5-Epiperoxycyclopentene (**5**) was prepared by the reported method.[26] 3,6-Epiperoxycyclohexene (**6**),[27] 3,7-epiperoxycycloheptene (**8**),[28] 3,8-epiperoxycyclooctene (**9**),[29] and cis-3,6-diphenyl-1,2-dioxa-4-cyclohexene (**12**)[30,31] were prepared by photo-sensitized 1,4-dioxygenation of the corresponding 1,3-dienes. Irradiation was performed by using a 500W iodine lamp for several hours at 0 °C in the presence of rose bengal or meso-tetraphenylporphine while bubbling the solution with oxygen.[31] 3,5,5-Trimethyl-3,6-epiperoxycyclohexene (**7**) and cis-3,6-dibutyl-1,2-dioxa-4-cyclohexene (**10**)[7a,c] were prepared from the corresponding 1,3-dienes[32,33] by the standard dye-sensitized photooxygenation.[31] **7**: ^{1}H Nmr (CCl_4) δ 0.83 (s, 3H, CH_3), 1.20 (d, 1H, J = 12 Hz, a proton of CH_2), 1.25 (s, 6H, 2 CH_3), 1.62 (d, 1H, J = 12 Hz, a proton of CH_2), 3.90 (dd, 1H, J = 6 and 1.5 Hz, CHO), 6.20 (dd, 1H, J = 7 and 1.5 Hz, vinyl), 6.55 (dd, 1H, J = 7 and 6 Hz, vinyl); ms (m/z) 154 (M^+). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.82; H, 9.44. 3,3-Dimethyl-6-phenyl-1,2-dioxa-4-cyclohexene (**11**) was prepared as follows: To a suspension of Mg (2.5 g) in THF (100 ml) 1,2-dibromoethane (0.2 ml) was added under nitrogen atmosphere to activate the magnesium metal and then a solution of β-bromostyrene (8.23 g, 45 mmol) in THF (50 ml) was added over a period of 30 min. The mixture was refluxed for 1 h under nitrogen and then cooled to 0 °C, followed by the addition of isobutyraldehyde (4.1 ml, 45 mmol). After being stirred for 30 min at 0 °C, the mixture was quenched with saturated NH_4Cl aqueous solution (20 ml). After concentration of the mixture under reduced pressure, the residual material was shaken with a 2:1 mixture of ether and water (150 ml). The ethereal solution was separated, dried over $MgSO_4$, and evaporated. The residual oil was chromatographed on a column of silica gel (50 g) by using a 1:2 mixture of ethyl acetate and benzene as eluant. The obtained solution of the alcoholic product was concentrated and dissolved in CH_2Cl_2 (100 ml). To this was added pyridine (3.7 ml) and methanesulfonyl chloride (3.5 ml) at 0 °C under stirring. The mixture was stirred at 25 °C for 2 h and water (50 ml) was added. The organic layer was separated and washed with water (30 ml) and then with saturated $NaHCO_3$ aqueous solution (30 ml). After evaporation of the solvent, the crude mesylate was dissolved in benzene (100 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (13.4 ml, 90 mmol) was added at 25 °C.

The mixture was refluxed for 1 h and then washed twice with water (50 ml each), twice with dil H_2SO_4 (30 ml each), then with water (30 ml), and finally with saturated $NaHCO_3$ aqueous solution (30 ml). The benzene extract was dried over Na_2SO_4 and evaporated. The residual oil was subjected to bulb-to-bulb short-path distillation (110–120 °C/0.5–1 mmHg) to give 1-phenyl-4-methyl-1,3-pentadiene (2.75 g): ^{1}H Nmr (CCl_4) δ 1.79 (s, 6H, 2 CH_3), 5.86 (d, 1H, J = 11 Hz, vinyl), 6.26 (d, 1H, J = 16 Hz, vinyl), 6.86 (dd, 1H, J = 16 and 11 Hz, vinyl). This material (1.5 g) was dissolved in CH_2Cl_2 (400 ml) followed by the addition of meso-tetraphenylporphine (30 mg). The mixture was bubbled by introducing oxygen during irradiation with a 500W iodine lamp[32] at 0 °C for 5 h. The solvent was evaporated and the residual material was chromatographed on a column of silica gel (50 g) by using a 20:1:10 mixture of petroleum ether, ether, and benzene as eluant, giving the desired epiperoxide **11** (311 mg) and fractions containing impurities. The latter fractions containing impurities were further chromatographed on a column of silica gel (30 g) by using a 1:1 mixture of petroleum ether and benzene as eluant to afford **11** (200 mg). The combined epiperoxide was recrystallized from a mixture of hexane and ether, yielding pure **11** (383 mg): ^{1}H Nmr ($CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 5.50 (s, 1H, CH), 5.92 (br s, 2H, vinyl), 7.33 (s, 5H, phenyl); Ms (m/z) 190 (M^+), 176, 175, 174, 173, 172, 171, 159, 158, 157, 144, 143, 129, 128, 105. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.80; H, 7.41. PGH_2 methyl ester (**13**) was prepared from $PGF_{2\alpha}$ methyl ester according to the procedure reported by Porter.[34]

Authentic Samples for Product Analysis. The pure authentic materials used for glc or nmr analysis were obtained as follows: 3-Hydroxycyclopentanone (**14**) was prepared by catalytic hydrogenation (5% Pd/C, ethanol, 16 h) of 4-hydroxy-2-cyclopentenone (**25**),[9a] identical with the reported one.[35] Levulinaldehyde (**15**)[36] was prepared by the Pd(0)-catalyzed reaction of **1** followed by isolation by silica gel column chromatography using CH_2Cl_2 as eluant: ^{1}H Nmr (C_6D_6) δ 1.72 (s, 3H, CH_3), 2.18 (s, 4H, 2 CH_2), 9.36 (s, 1H, CHO). cis-1,3-Dihydroxycyclopentane (**16**) was prepared by catalytic hydrogenation of **1** by the reported procedure.[36b,37] 4-Hydroxycyclohexanone (**17**)[38] was prepared by the Pd(0)-catalyzed reaction of **2** followed by isolation by silica gel column chromatography using ether as eluant: Ir (neat) 3700–3000, 1700 cm^{-1}; ^{1}H nmr (CCl_4–$CDCl_3$) δ 1.8–2.1 (m, 5H, 2 CH_2 and OH), 2.2–2.9 (m, 4H, 2 CH_2), 4.16 (m, 1H, CHO); Ms(m/z) 114 (M^+). 1,4-Cyclohexanedione (**18**) was prepared by Jones oxidation (acetone, 0–25 °C, 30 min) of the diol **19** and purified by silica gel column chromatography using a 4:1 mixture of ether and hexane as eluant: mp 77.5–78 °C; ^{1}H nmr ($CDCl_3$) δ 2.73 (s, 8H, 4 CH_2), identical with the commercial sample (Aldrich). cis-1,4-Dihydroxycyclohexane (**19**) was prepared by $LiAlH_4$ reduction (ether, 0 °C, 30 min) of **2** followed by silica gel column chromatography using ethyl acetate as eluant: mp 112.5–113 °C (lit.[39] 113–114 °C); ^{1}H nmr (acetone-d_6) δ 1.3–1.9 (m, 8H, 4 CH_2), 2.80, 3.34, and 3.70 (s each, 2H, 2 OH), 3.5–3.8 (m, 2H, 2 CHO). 4-Hydroxycycloheptanone (**20**)[40] was prepared by the Pd(0)-catalyzed reaction of

3 (60%) or catalytic hydrogenation (5% Pd/C, ethanol, 13 h) of 4-hydroxy-2-cycloheptenone (**34**) and purified by silica gel column chromatography using a 4:1 mixture of ether and petroleum ether and then pure ether as eluant: Ir (neat) 3600, 3500–3200, 1697 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.6–2.9 (m, 11H, 5 CH_2 and OH), 3.94 and 4.50 (br each, 1H, CHO); ^1H nmr ($CDCl_3$ + D_2O) δ 1.6–2.3 (m, 8H, 4 CH_2), 2.4–2.9 (m, 2.3H, CH_2), 3.94 (br, 0.42H, CHO), 4.50 (br, 0.58H, CHO); Ms (m/z) 128 (M^+); thus **20** was an equilibrium mixture of the keto and hemiacetal forms. 1,4-Cycloheptanedione (**21**) was prepared from **20** by the reported procedure:[41] Ir (neat) 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.7–2.3 (m, 2H, CH_2), 2.5–2.9 (m, 8H, 4 CH_2); Ms (m/z) 126 (M^+). cis-1,4-Dihydroxycycloheptane (**22**) was prepared by catalytic hydrogenation of **8** (5% Pd/C, ethanol, 16 h, 27%): mp 68–69 °C identical with the reported value;[41] ^1H nmr ($CDCl_3$) δ 1.2–2.3 (m, 12H, 5 CH_2 and 2 OH), 3.7–4.2 (m, 2H, 2 CHO); Ms (m/z) 112 (M^+ - 18). 4-Hydroxycyclooctanone (**23**)[42] and cis-1,4-dihydroxycyclooctane (**24**)[43] were prepared by the Pd(0)-catalyzed reaction of **4** (entry 13) followed by silica gel column chromatography using a 4:1 to 10:1 mixture of ethyl acetate and benzene as eluant. **23**: Ir (neat) 3600–3000, 1697 cm^{-1}; ^1H nmr (CCl_4) δ 1.4–2.6 (m, 13H, 6 CH_2 and OH), 3.95 and 4.50 (br and br t, 1H, CHO). **24**: mp 84–85 °C (lit.[43] 83.2–84 °C); ^1H nmr (acetone-d_6) δ 1.6–1.9 (m, 12H, 6 CH_2), 2.80, 3.28, and 3.32 (s each, 2H, 2 OH), 3.6–3.9 (m, 2H, 2 CHO). 4-Hydroxy-2-cyclopentenone (**25**)[9a], (Z)-4,5-epoxy-2-pentenal (**26**),[22] and cis-3,5-dihydroxycyclopentene (**27**)[27] were prepared by the reported procedures. 4-Hydroxy-2-cyclohexenone (**28**)[23] was prepared through the three-step sequence from 3,4-epoxycyclohexene:[9a] (1) $Pd(PPh_3)_4$ (0.1 mol %), CH_2Cl_2, 25 °C, 3 h, 94%; (2) m-chloroperbenzoic acid, CH_2Cl_2, 0 °C, 23 h; (3) DBU, benzene, 25 °C, 1 h, 52% in two steps: Ir (neat) 3600–3200, 1675 cm^{-1}; ^1H nmr (CCl_4–$CDCl_3$) δ 1.7–2.7 (m, 4H, 2 CH_2), 3.70 (br, 1H, OH), 4.43 (br, 1H, CHO), 5.83 (dd, 1H, J = 10 and 2 Hz, vinyl), 6.86 (dt, 1H, J = 10 and 1.5 Hz, vinyl). cis-3,6-Dihydroxycyclohexene (**29**)[44] was prepared by $NaBH_4$ reduction of **6** (THF-H_2O, 25 °C, 22 h, 74%) followed by silica gel column chromatography using a 1:1 to 3:1 mixture of ethyl acetate and benzene as eluant: ^1H Nmr ($CDCl_3$) δ 1.7–2.0 (m, 4H, 2 CH_2), 2.17 (br s, 2H, 2 OH), 4.0–4.3 (m, 2H, 2 CHO), 5.86 (br s, 2H, vinyl). syn-1,2;3,4-Diepoxycyclohexane (**30**)[23] was prepared by thermolysis of **6** in CH_2Cl_2 in a sealed glass tube (120 °C, 20 h, 57%): ^1H Nmr ($CDCl_3$) δ 1.83 and 1.85 (s each, 4H, 2 CH_2), 3.0–3.2 (br, 2H, 2 CHO), 3.3–3.4 (dd, 2H, J = 3 and 2 Hz, 2 CHO). 4-Hydroxy-2-cycloheptenone (**34**) was prepared by the Pd(0)-catalyzed reaction of **8** followed by silica gel column chromatography using a 1:10 to 1:1 mixture of ethyl acetate and benzene as eluant: Ir (neat) 3680–3040, 1660 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.7–2.2 (m, 4H, 2 CH_2), 2.3–2.7 (m, 2H, CH_2), 3.15 (br, 1H, OH), 4.53 (br, 1H, CHO), 5.88 (dd, 1H, J = 12 and 2 Hz, vinyl), 6.60 (dd, 1H, J = 12 and 3 Hz, vinyl). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.48; H, 8.15. 3,7-Dioxocyclohexene (**35**)[45] was prepared by Jones oxidation of **34**: ^1H Nmr ($CDCl_3$) δ 2.0–2.3 (m, 2H, CH_2), 2.7–3.0 (m, 4H, 2 CH_2), 6.43 (s, 2H, vinyls). cis-3,7-Dihydroxycycloheptene (**36**) was prepared

by $LiAlH_4$ reduction of **8** according to the reported procedure:[44] ^1H Nmr ($CDCl_3$) δ 1.5—2.0 (m, 8H, 3 CH_2 and 2 OH), 4.2—4.5 (m, 2H, 2 CHO), 5.76 (d, 2H, J = 1.5 Hz, vinyl). syn-1,2;3,4-Diepoxycycloheptane (**37**) was prepared by thermolysis of **8** in refluxing toluene:[46] ^1H Nmr ($CDCl_3$) δ 1.2—2.5 (m, 6H, 3 CH_2), 3.1—3.3 (br, 4H, 4 CHO). 1,4-Diphenyl-1,4-butanedione (**43**) was prepared by the Pd(0)-catalyzed reaction of **12** followed by silica gel column chromatography using a 1:4 mixture of ether and hexane as eluant: ^1H nmr ($CDCl_3$) δ 3.46 (s, 4H, 2 CH_2), 7.4—7.6 and 8.0—8.2 (m each, 10H, phenyls).[30] The methyl esters of PGD_2 (**56**), PGE_2 (**57**), and $PGF_{2\alpha}$ (**58**) were products of Ono Pharmaceutical Co. HHT methyl ester (**59**) was obtained by the Ru(II)-catalyzed reaction of **13**.[7a,c]

Decomposition of 2,3-Didehydro-1,4-epiperoxides in the Presence of $PdCl_2(PPh_3)_2$. $PdCl_2(PPh_3)_4$ (10 mg, 0.014 mmol) and a THF (1 ml) solution of **5** (18 mg, 0.18 mmol) were mixed at -78 °C under argon atmosphere and then warmed to 4 °C. After being stirred for 50 h at this temperature, the mixture was submitted to ^1H nmr analysis (cyclododecane as internal standard), indicating the formation of (Z)-4,5-epoxy-2-pentenal (**26**) in 62% yield.

After a mixture of **6** (19.4 mg, 0.17 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 0.014 mmol), and CH_2Cl_2 (1.5 ml) was heated at 60 °C for 20 h under argon atmosphere, the resulting mixture was submitted to ^1H nmr analysis, indicating the formation of **30** in 88% yield. Similarly, heating a mixture of the epiperoxide **8** (19.5 mg, 0.16 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 0.014 mmol), and CH_2Cl_2 (1.5 ml) at 60 °C for 35 h gave **37** in 78% yield.

Pd(0)-Catalyzed Reaction of 1,4-Epiperoxides. Prior to the introduction of solvents and materials, the reaction vessels (glass syringe, flask, ampule, test (or glass) tube, or Schlenk tube) were treated with an aqueous solution of ethylenediaminetetraacetic acid (EDTA) disodium salt and washed with distilled water and then dried. The vessels were further evacuated under high vaccum by heating with a heat gun and then the atmosphere was replaced with argon before conducting the reaction. The typical procedure was exemplified by the reaction of 1,4-epiperoxycycloheptene (**3**).

Conversion of 3 to the Hydroxy Ketone 20, the 1,4-Dione 21, and the 1,4-Diol 22 (entry 7 in Table 1). $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) was placed in a glass tube and the atmosphere was replaced with argon. To this was added a solution of the peroxide **3** (25.6 mg, 0.2 mmol) in CH_2Cl_2 (2 ml) through a stainless steel cannula under slight argon stream. After sealing the glass tube at 0 °C, the mixture was heated at 60 °C for 10 h. The mixture was cooled and then the system was opened in air. The reaction mixture was concentrated under reduced pressure (aspirator) at 25 °C and to the resulting residue was added ethyl laurate (22.8 mg, 0.1 mmol, an internal standard for glc). The mixture was diluted with acetone and subjected to glc analysis (5% FFAP on Chromosorb W, 3 mmϕ x 3m, 2.6 Kg/cm^2, 200 °C), indicating the formation of 4-hydroxycycloheptanone (**20**) (t_r 6.50 min, 62%), cycloheptane-1,4-dione (**21**) (t_r 4.75 min, 13%), and cis-1,4-dihydroxycycloheptane (**22**)

(t_r 8.76 min, 25%).

Table 1 lists details of reaction conditions for other cases. Unless otherwise stated, the reaction was conducted by a similar reaction procedure.

Glc conditions and the retention time (t_r) of the products obtained in this Pd(0)-catalyzed reaction are as follows: **17**, t_r 5.65 min; **18**, t_r 4.42 min; **19**, t_r 4.15 min (10% Silicone XE-60 on Uniport HP, 3 mmϕ x 2 m, 1 Kg/cm^2, 135 °C, methyl caprate as internal standard). **20**, **21**, and **22** (see the values in the typical procedure); **23**, t_r 6.41 min; **24**, t_r 13.47 min (5% FFAP on Chromosorb W, 3 mmϕ x 3 m, 2.6 kg/cm^2, 200 °C, ethyl laurate as internal standard). **28**, t_r 4.21 min; **29**, t_r 3.59 min; **30**, t_r 1.76 min (10% FFAP on Chromosorb W, 3 mmϕ x 3 m, 1 kg/cm^2, 200 °C, ethyl myristate as internal standard). **34**, t_r 4.44 min, 220 °C; **35**, t_r 5.25 min, 175 °C; **36**, t_r 4.13 min, 220 °C; **37**, t_r 4.35 min, 175 °C (10% PEGS on Uniport B, 3 mmϕ x 3 m, 1.6 kg/cm^2).

The production of a trace amount of $CHCl_2CHCl_2$ (entry 7 in Table 1) was detected by glc (t_r 3.05 min, 5% FFAP on Chromosorb W, 3 mmϕ x 3 m, 2.4 Kg/cm^2, 150 °C). $CHCl_3$ was not formed (entry 7 in Table 1) in the reaction (30% liquid paraffin on Celite 545, 3 mmϕ x 3 m, 0.6 kg/cm^2, 70 °C).

The yield of acetone (entries 12 and 18 in Table 1) was determined by ^{1}H nmr analysis using toluene as the internal standard in $CDCl_3$.

Conversion of 7 to the Enone 31, the Diol 32, and the Diepoxide 33 (entry 20). Liquid chromatography (lc): SiO_2 (3.5 g), benzene/ethyl acetate (4:1) as eluant. **31**: Ir (neat) 3600–3100, 1760, 1620 (shoulder) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.16 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.04 (s, 2H, CH_2), 2.26 (s, 1H, OH), 5.87 (d, 1H, J = 10 Hz, vinyl), 6.64 (d, 1H, J = 10 Hz, vinyl); Ms (m/z) 154 (M^+), 139, 128, 126, 111, 99, 98. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.27; H, 9.24. **32**: mp 83–84 °C; Ir ($CHCl_3$) 3600–3000 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.00 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.6–2.0 (m, 4H, CH_2 and 2 OH), 3.79 (s, 1H, CHO), 5.63 (s, 2H, vinyl). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.46; H, 10.55. The diepoxide **33** was identical with the epoxy product by the Ru(II) catalyzed reaction of **7**.[7a,c] The diol **32** was identical with the compound derived from **7** with $LiAlH_4$ reduction according to the reported procedure.[44]

Conversion of 9 to the Hemiacetal 38 (entry 25). Lc: SiO_2 (8 g), benzene/ethyl acetate (20:1 to 5:1, gradient) as eluant. **38**: mp 94–95 °C (lit.[29] 93–94 °C); ^{1}H nmr (CCl_4) δ 1.2–2.2 (m, 8H, 4 CH_2), 3.94 (br, 1H, OH), 4.88 (dt, 1H, J = 6 and 2 Hz, CHO), 5.72 (dd, 1H, J = 6 and 1 Hz, vinyl), 5.88 (dd, 1H, J = 6 and 2 Hz, vinyl).

Conversion of 10 to the Enone 39, the Furan 40, and the Diol 41 (entry 26). Lc: SiO_2 (4 g), hexane/ether/benzene (20:1:5) and ethyl acetate/benzene (5:1 to 1:1, gradient) as eluant. **39**: Ir (neat) 3600–3100, 1670, 1620 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.94 (t, 6H, J = 6.5 Hz, 2 CH_3), 1.2–1.9 (m, 11H,

5 CH_2 and OH), 2.59 (t, 2H, J = 7 Hz, CH_2), 4.34 (m, 1H, CHO), 6.30 (dd, 1H, J = 16 and 1 Hz, vinyl), 6.81 (dd, 1H, J = 16 and 5 Hz, vinyl); Ms (m/z) 198 (M^+), 180, 169, 156, 147, 141. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.63; H, 11.20. The furan **40** was identical with the furan product by the Ru(II) catalyzed reaction of **10**.[7a,c,47] **41**: Ir (neat) 3600–3000 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.86 (t, 6H, J = 6 Hz, 2 CH_3), 1.1–2.0 (m, 12H, 6 CH_2), 2.63 (s, 2H, 2 OH), 4.2–4.7 (m, 2H, 2 CHO), 5.46 (dd, 2H, J = 5.5 and 2 Hz, vinyl). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.78; H, 12.14. The diol **41** was identical with the compound derived from **10** by $LiAlH_4$ reduction.[30,44]

Conversion of 11 to the Enone 42 (entry 27). Lc: SiO_2 (6 g), benzene/ethyl acetate (20:1 to 2:1, gradient) as eluant. **42**: Ir (neat) 3640–3240, 1660, 1620, 1600, 1580 cm^{-1}; ^1H nmr (CCl_4) δ 1.36 (s, 6H, 2 CH_3), 3.35 (br, 1H, OH), 6.95 (d, 1H, J = 15.5 Hz, vinyl), 7.13 (d, 1H, J = 15.5 Hz, vinyl), 7.2–8.0 (m, 5H, phenyl). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.79; H, 7.47.

Conversion of PGH_2 Methyl Ester (13) to the Methyl Esters of PGD_2 (56), PGE_2 (57), $PGF_{2\alpha}$ (58), and HHT (59). In a glass tube was placed $Pd(PPh_3)_4$ (0.31 mg, 0.27 μ mol) and the atmosphere was replaced with argon. To this was added a solution of PGH_2 methyl ester (**13**) (1 mg, 0.0027 mmol) in CH_2Cl_2 (0.5 ml) at 0 °C under argon atmosphere through a stainless steel cannula under a slight argon stream. The mixture was stirred at 19 °C for 3 h. The reaction mixture was put on a tlc plate and developed with a 6:3:1 mixture of ethyl acetate, cyclohexane, and THF as solvent. This solvent system is useful for monitoring PGs on tlc. The plate was then sprayed with a 3:20:80 mixture of $Cu(OAc)_2/H_2PO_4/H_2O$ (visualizing agent of PGs) and then heated until the spots became clearly visible. The concentration of all spots appearing on the tlc plate was counted by a high-speed tlc scanner. The formation of the methyl esters was indicated by the following R_f values: **56** (R_f 0.37, 17%), **57** (R_f 0.16, 11%), **58** (R_f 0.06, 41%), and **59** (R_f 0.79, 4%).

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