until the yellow color disappeared. The corresponding dialdehydes (see reactions 1 and 2) were the only products detected. ^{1}H NMR (CCl_4): 1,2-benzenediacetaldehyde (**6**), δ 3.68 (d, J = 2.0 Hz, 4 H), 7.23 (m, 4 H), 9.63 (t, J = 2.0 Hz, 2 H); 3-(2-formylphenyl)propanol (**7**), δ 2.7 (dt, J = 7 Hz, J = 0.8 Hz, 2 H), 3.28 (t, J = 7 Hz, 2 H), 7.38 (m, 4 H), 9.7 (t, J = 0.8 Hz, 1 H), 10.06 (s, 1 H). Dialdehyde **6** was converted to the corresponding bis(semicarbazone): light yellow crystals from ethanol/H_2O; mp 214-215 °C (lit.[14] mp 215 °C). Dialdehyde **7** was isolated as the bis(2,4-dinitrophenyl)hydrazone derivative: orange crystals from ethanol; mp 204-205 °C (lit.[15] mp 204 °C).

Thermolysis Studies. The chemiluminescence monitoring apparatus is essentially identical with that previously described.[16] The temperature (±0.3 °C) of the reaction mixture in the apparatus was monitored directly by use of a YSI Model 425C Tele-Thermometer with a #423 probe before and after each run. The jacketed cell was pretreated with aqueous Na_2EDTA solution. All experiments were carried out in xylenes (Aldrich) as solvent. In a typical run, 10 μL of a dioxetane solution (~0.1 M) in CCl_4 was added to 1.0 mL of xylenes containing a known concentration of DBA or DPA as added fluorescer. The solution was mixed by bubbling air via pipet. Experiments carried out without added fluorescer were of the first order for at least 3 half-lives and showed no dependence on the amount or type of added fluorescer. Initial dioxetane concentrations must be kept at 10^{-3} M or lower to avoid complications due to induced decomposition.[2]

Yields of Excited States. The relative yields of excited states produced upon dioxetane thermolysis were determined at 60.0 °C by variation of the concentration of the appropriate fluorescer (DBA/DPA method) at constant dioxetane concentration. The dioxetane concentration was determined by the ^{1}H NMR spectroscopic method with an added internal standard. Concentrations determined by the NMR method were in good agreement with those calculated on the basis of weight of sample. The instrument was calibrated by setting the yield of triplet products from the thermolysis of tetramethyl-1,2-dioxetane at 0.30. The method of calculation has been discussed in detail.[2]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, to the Camille and Henry Dreyfus Foundation, and to the GSU research fund.

(14) Huisgen, R.; Lasehtuvken, E.; Ugi, I.; Kammermeier, A. *Ann.* **1960**, *630*, *128*.
(15) Topalova, D. V.; Shabrova, L. A. *Zh. Org. Khim.* **1975**, *11*, 2444.
(16) Wilson, T.; Schaap, A. P. *J. Am. Chem. Soc.* **1971**, *93*, 4126.

Palladium-Catalyzed Reaction of 1,3-Diene Monoepoxides with β-Keto Acids. Allylic Alkylation and Isomerization of 1,3-Diene Monoepoxides

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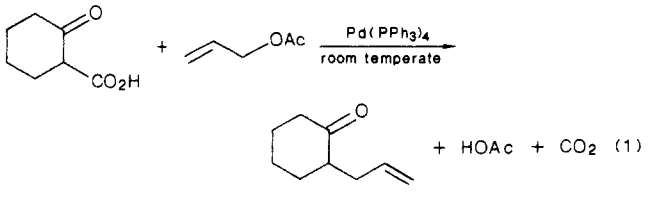
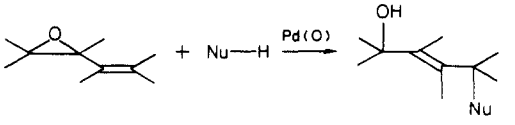
Tetrakis(triphenylphosphine)palladium catalyzed the decarboxylative allylic alkylation of 1,3-diene monoepoxides with β-keto acids at ambient temperature to produce keto allylic alcohols in moderate to good yields. 1,3-Diene monoepoxides employed in this reaction were 3,4-epoxy-1-butene (**2**), 3,4-epoxy-2-methyl-1-butene (**3**), 4,5-epoxy-2-hexene (**4**), and 3,4-epoxy-4-methyl-1-pentene (**5**). As β-keto acids, 1-oxocyclohexane-2-carboxylic acid, benzoylacetic acid (**1**), and 1,3-acetonedicarboxylic acid were used. The allylic alkylation of 1,3-diene monoepoxide took place regioselectively at the allylic carbon atom distal to the hydroxyl group. The stereochemistry of the resultant carbon-carbon double bond was predominantly to exclusively *E*. On the contrary, 3,4-epoxy-2,3-dimethyl-1-butene (**6**), 4,5-epoxy-2,5-dimethyl-2-hexene (**7**), and 3,4-epoxy-1-cyclohexene (**8**) took a different course of the reaction to undergo the palladium-catalyzed isomerization. The isomerization of **6** and **7** was accelerated by **1**, but that of **8** was not. The effect of the structure of 1,3-diene monoepoxides upon the reaction course and the role of β-keto acid in the isomerization were discussed.

Very recently we reported palladium-catalyzed decarboxylative allylic alkylation of allylic acetates with β-keto acids (eq 1).[1] Use of other allylic compounds may expand



the scope of this type of decarboxylative allylic alkylation reaction.[2] Palladium-catalyzed reactions of 1,3-diene monoepoxides as allylic ethers are a recent subject of considerable interest.[3] The palladium-catalyzed regio- and stereoselective allylic alkylation of 1,3-diene monoepoxides with the stabilized nucleophiles generated in situ from carbon acids (NuH) has been reported (eq 2).[3b,c] The



allylic alkylation takes place at the allylic carbon atom distal to the hydroxyl group, and the allylic alkylation

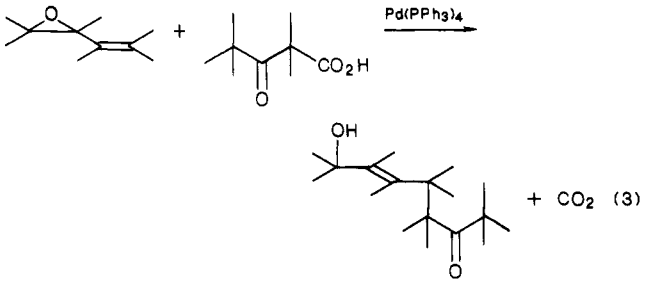
(1) Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421.
(2) (a) Tsuda, T.; Chujo, T.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (b) Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199.
(3) (a) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623. (b) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (c) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575. (d) Fujinami, T.; Suzuki, T.; Kamiya, M.; Fukuzawa, S.; Sakai, S. *Chem. Lett.* **1985**, 199. (e) Trost, B. M.; Angle, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 6123.

0022-3263/86/1951-5216$01.50/0

product is predominantly the (*E*)-allylic alcohol. In this paper, we have studied the palladium-catalyzed reaction of 1,3-diene monoepoxides with β-keto acids.

Results and Discussion

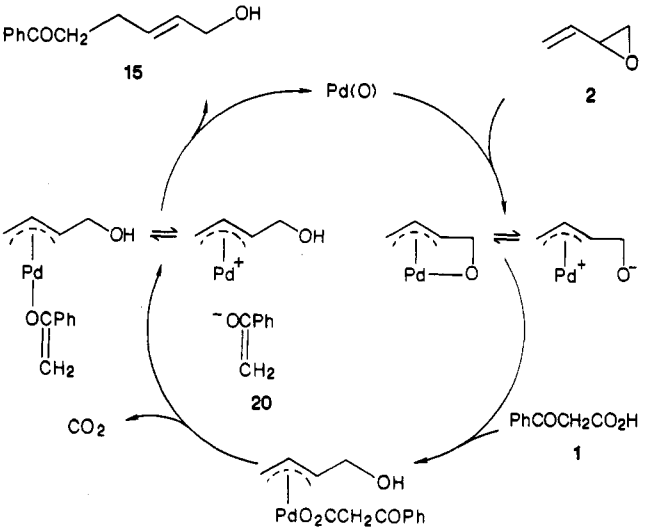
In the presence of 5 mol % of tetrakis(triphenylphosphine)palladium, β-keto acids reacted with 1,3-diene monoepoxides in benzene or tetrahydrofuran (THF) at ambient temperature with quantitative evolution of CO_2 to produce keto allylic alcohols in moderate to good yields (eq 3). The keto allylic alcohols are the decarboxylative



allylic alkylation products of 1,3-diene monoepoxides with β-keto acids. β-Keto acids employed in this reaction were 1-oxocyclohexane-2-carboxylic acid, 6-methyl-1-oxocyclohexane-2-carboxylic acid, benzoylacetic acid (**1**), and 1,3-acetonedicarboxylic acid. 3,4-Epoxy-1-butene (**2**) and methyl-substituted 3,4-epoxy-1-butenes **3**–**5** underwent this decarboxylative allylic alkylation with β-keto acids. The results are summarized in Table I. The reaction is featured by high regioselectivity. The carbon–carbon bond formation occurred regioselectively at the allylic carbon atom distal to the hydroxyl group to lead to a single allylic alkylation product (**9**–**16**). This high regioselectivity is similar to that observed in the palladium-catalyzed reaction of 1,3-diene monoepoxides with the stabilized carbanions (eq 2).[3b,c] The result of the reaction of 6-methyl-1-oxocyclohexane-2-carboxylic acid with **2** shows that the carbon–carbon bond formation at the β-keto acid took place regioselectively at the carbon atom originally bearing a carboxyl group to produce **13**. The ^1H NMR spectrum of **13** exhibited two kinds of the methyl signal at δ 1.01 (d, J = 6.5 Hz) and 1.08 (d, J = 6.8 Hz), which may be assigned to the methyl groups of the *cis*- and *trans*-2-(4-hydroxy-2-butenyl)-6-methylcyclohexanones, respectively, on the basis of the methyl signals of the *cis*- and *trans*-2,6-dimethylcyclohexanones, i.e., δ 1.01 (d, J = 6.0 Hz) and 1.10 (d, J = 6.5 Hz), respectively.[4] The trans/cis ratio determined by ^1H NMR was 1.5. 1,3-Acetonedicarboxylic acid reacted with **2** to give the monoallylation product of **14**. Thus, 1,3-acetonedicarboxylic acid behaves as an equivalent of acetoacetic acid which is thermally unstable at room temperature. The E/Z stereochemistry of the resultant carbon–carbon double bond of the allylic alkylation product was found to be predominantly to exclusively E. The E/Z stereochemistry was determined by the 400-MHz ^1H NMR coupling constant (J) of the two olefinic protons, i.e., J = ca. 15 Hz for the E isomer and J = ca. 11 Hz for the Z isomer. The absorption of the methylene or methine proton on the carbon atom bearing the hydroxyl group was also used for determining the E/Z stereochemistry. The results are shown in Tables I and II. The allylic alkylation products unsubstituted at the allylic methylene groups, i.e., **9** and **13**–**15**, have the predominant E stereochemistry (E/Z = 4.5–6.0). On the other hand, the allylic alkylation products

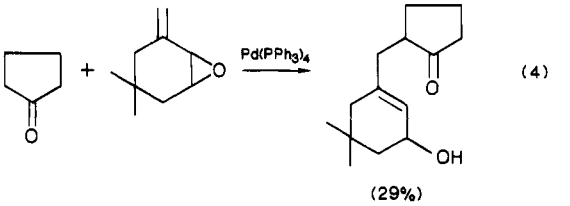
(4) D'Silva, T. D. J.; Ringold, H. J. *Tetrahedron Lett.* **1967**, 1505.

Scheme I



substituted with the methyl group on the allylic carbon atoms, i.e., **11**, **12**, **16**, have the exclusive E stereochemistry.

A recent paper[3b] reported that the palladium-catalyzed allylic alkylation of 1,3-diene monoepoxides with the stabilized carbanions generated from β-diketone, malonate, and β-keto sulfide proceeds smoothly to give the allylic alkylation products in good yields, but the reaction with the enolate anion generated from simple ketone produces the allylic alkylation product only in a low yield (eq 4).

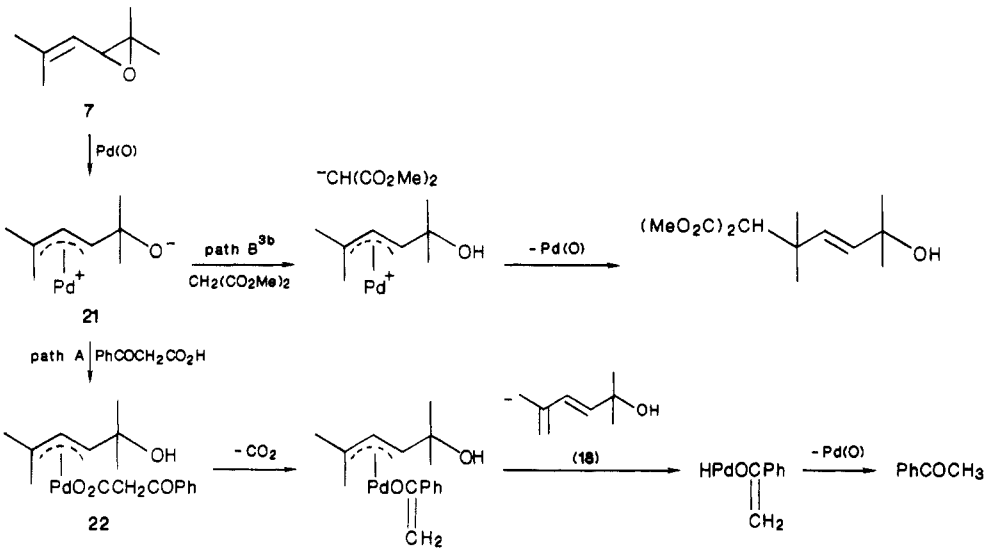


Thus, the present palladium-catalyzed regio- and stereoselective allylic alkylation of 1,3-diene monoepoxides with the simple ketone enolate anions produced by the decarboxylation of β-keto acids provides a convenient way of the preparation of keto allylic alcohols, which complements the palladium-catalyzed allylic alkylation methodology.[5]

On the basis of the available information on the palladium-catalyzed allylic alkylation including 1,3-diene monoepoxides,[1-3,5] the reasonable reaction path of the palladium-catalyzed allylic alkylation of **2** with **1** as a representative is depicted in Scheme I. First, the Pd(0) complex reacts with **2** to form the π-allylpalladium alkolate complex, which abstracts a proton from **1** to generate the π-allylpalladium β-keto carboxylate complex. The π-allylpalladium β-keto carboxylate complex decarboxylates rapidly to form the π-allylpalladium enolate complex **20**.[2a] The hydroxyl group of the π-allylpalladium enolate intermediate **20** dictates the enolate anion with its regiochemical integrity to attack the allylic carbon atom distal to the hydroxyl group, which explains the regioselectivity of the reaction. The directing effect of the hydroxyl group in the nucleophilic attack onto the π-allylpalladium complexes is known.[3b,c] Concerning the mechanism of the coupling reaction between the ketone enolate moiety and the π-allyl group, the intermolecular nucleophilic trans attack of the free ketone enolate anion on the π-allyl group from the opposite side of palladium is generally accepted.[1]

(5) (a) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: New York, 1980. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

Scheme II

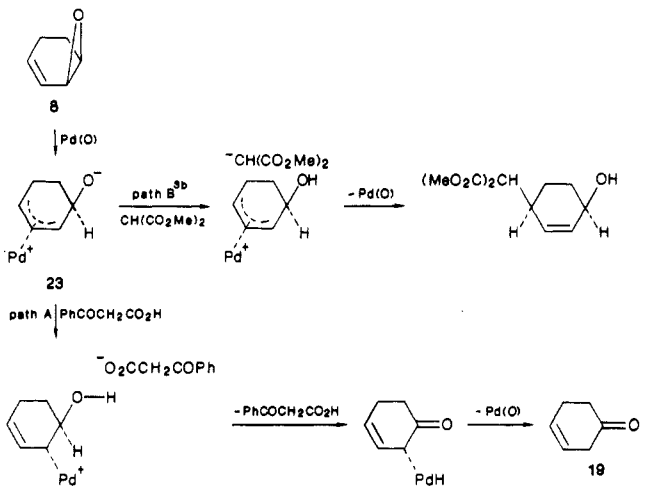


In our very recent study of the palladium-catalyzed decarboxylative allylic alkylation of allylic acetates with β-keto acids, where the ketone enolate moiety couples with the π-allyl group in the presence of carboxylic acids, we pointed out the possibility of the more complex nature of the coupling reaction.[1] Also, in the present reaction, the ketone enolate moiety couples with the π-allyl group in the presence of β-keto acid which may destroy the free enolate anion. Thus, these two palladium-catalyzed decarboxylative coupling reactions of β-keto acids with allylic acetates and 1,3-diene monoepoxides may provides a clue to elaborate the mechanism of the reaction of the π-allylpalladium complex and the ketone enolate anion.[6] The predominant to exclusive *E* stereochemistry of the resultant carbon–carbon double bond of the allylic alkylation product indicates that the coupling of the π-allyl group with the enolate anion proceeds relatively slowly (vide post) via the thermodynamically more stable syn π-allylpalladium complex **20**.

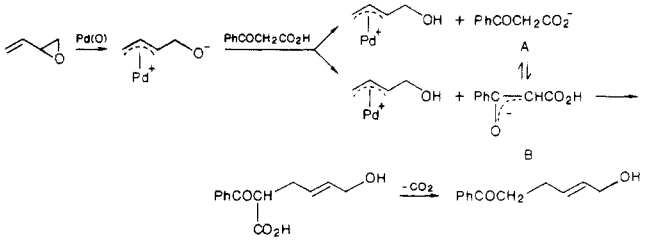
The 1,3-diene monoepoxides **3** and **4**, which are monomethyl substituted at C_1, C_2, and C_4 of **2**, and the 1,3-diene monoepoxide **5**, which is dimethyl substituted at C_4 of **2**, underwent the palladium-catalyzed allylic alkylation with the β-keto acids. On the contrary, the methyl substitution at C_3 (**6**) and the dimethyl substitution at C_1 (**7**) lead to a completely different course of the reaction; i.e., **6** and **7** were isomerized to dienols **17** and **18**, respectively, without the allylic alkylation with **1** (Table I). The palladium-catalyzed reaction of **7** and **1** in THF at room temperature produced the isomerization product of **18** in 81% yield after 4 h with the concomitant quantitative decarboxylation of **1**. The palladium-catalyzed isomerization of 1,3-diene monoepoxides themselves has already been reported, where the isomerization of **7** in THF requires a relatively severe reaction condition of 100 °C for 42 h.[3a] Thus, it is interesting to note that the β-keto acid **1** accelerated the palladium-catalyzed isomerization of **7** to proceed at room temperature in a short reaction time. The isomerization of **6** in the presence of **1** also took place at ambient temperature. On the other hand, the 1,3-diene monoepoxides **6** and **7** were found to accelerate the decarboxylation of **1**. Thus, the decarboxylation of **1** alone in THF at ambient temperature in the presence of 5 mol % of $Pd(PPh_3)_4$ proceeded slowly to require 30 h for the completion but was completed in 4 h in the presence of an equimolar amount of **6** or **7**.[6]

The explanation for the accelerating effect of the β-keto acid upon the isomerization of **7** is shown in path A in Scheme II. The β-keto acid donates a proton to the

Scheme III

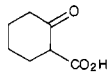
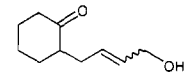
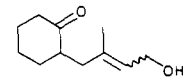
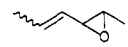
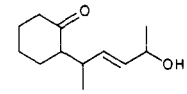
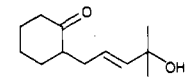
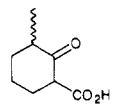
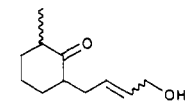
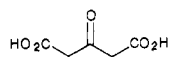
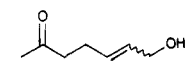
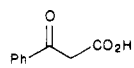
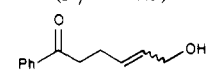
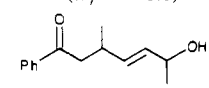
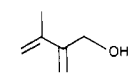
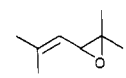
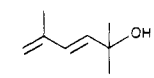


(6) The referee suggested a possibility of the following mechanism of the decarboxylative allylic alkylation of 1,3-diene monoepoxide with β-keto acid, which involves the nucleophilic attack of the enolate anion B of the β-keto acid to the π-allylpalladium cation followed by the spontaneous decarboxylation of the allylated β-keto acid. Considering the



acidity of protons of the β-keto acid, the predominant species is not B but the β-keto carboxylate anion A. We have recently reported the rapid decarboxylation of the π-allylpalladium β-keto carboxylate intermediate to generate the ketone enolate anion in the palladium-catalyzed decarboxylative allylic alkylation of allylic acetates with β-keto acids,[1] where the participation of the enolate anion B of the β-keto acid is excluded. Thus, it is reasonable to assume that the present allylic alkylation involves the palladium-catalyzed decarboxylation via the π-allylpalladium β-keto carboxylate complex (Scheme I). In addition, we have found that the decarboxylation of **1** alone in THF at ambient temperature proceeds very slowly in the presence of 5 mol % of $Pd(PPh_3)_4$ to require 30 h for its completion (see the text) in comparison with the rapid decarboxylative allylic alkylation of **2** with **1**. The latter reaction is ended in 0.5 h in THF at ambient temperature.

Table I. Palladium-Catalyzed Reaction of β-Keto Acids and 1,3-Diene Monoepoxides[a]

β-keto acid	1,3-diene monoepoxide	solv	time, h	allylic alkylation product or isomerization product (%)[b]
	 **2**	THF	0.5	 **9** (86) [88][c] (E/Z = 4.5)[d]
	 **3**	THF	3	 **10** (68)
	 **4**	C_6H_6	4	 **11** (59)[e]
	 **5**	C_6H_6	4	 **12** (54)[e]
	**2**	C_6H_6	0.5	 **13** (90)[f] (E/Z = 4.8)[d]
	**2**	THF	0.5	 **14** (73) (E/Z = 5.2)[d]
 **1**	**2**	THF	0.5	 **15** (90) (E/Z = 6.0)[d]
	4	THF	3.5	 **16** (67)[e]
	 **6**	THF	3	 **17** (27)[g]
	 **7**	THF	3.5	 **18** (81)[g]
	 **8**	THF	28	 **19** (73)[g]

[a] β-Keto acid, 1 mmol; 1,3-diene monoepoxide, 1 mmol; $Pd(PPh_3)_4$, 0.05 mmol; solvent, 5 mL; temperature, room temperature. [b] GLC yield. [c] The value in brackets is the isolated yield obtained in the reaction employing 15.0 mmol of the β-keto acid. [d] The E/Z ratio was determined by ^1H NMR (Table II). [e] Exclusive formation of the E isomer was determined by ^1H NMR (Table II). [f] The trans/cis stereochemistry of the methyl and the 4-hydroxy-2-butenyl groups was trans isomer/cis isomer = 1.5. [g] Acetophenone was produced in 75–100% yield.

palladium alkolate complex **21** to produce the π-allylpalladium β-keto carboxylate complex **22**, which generates the enolate anion via the decarboxylation. Due to the steric hindrance at the dimethyl-substituted C_1, the enolate anion cannot perform the allylic alkylation at C_1 directed by the hydroxyl group. Instead, the enolate anion abstracts the hydrogen atom from the methyl group at C_1 to yield the dienol **18** and acetophenone. Thus, the β-keto acid assists the palladium-catalyzed isomerization of 1,3-diene monoepoxide by both the proton donation and the proton abstraction.[7] The isomerization of **6**, which is unsubstituted at C_1, may be ascribed to the geometrical disposition of a hydrogen atom of the C_3 methyl group facing to the palladium, which facilitates the hydrogen abstraction from

(7) The preliminary experiment using deuteriated benzoylacetic acid ($PhCOCD_2CO_2D$, 75% D) shows that the palladium-catalyzed isomerization of 1,3-diene monoepoxides **7** and **8** in the presence of deuteriated benzoylacetic acid produced deuteriated acetophenone ($PhCOCD_3$) with 60% D and 74% D, respectively, which is compatible with Schemes II and III.

Table II. Spectral Data of Allylic Alkylation Products 9–16 and Isomerization Products 17–19

product	IR, cm^{-1} (liquid film)	^1H NMR (400 MHz, $CDCl_3$)	mass spectrum, m/e for M^+
9	1710, 980	1.30–2.20 (m, 6 H), 1.65 (m, 1 H), 1.95–2.05 (m, 1 H), 2.25–2.45 (m, 3 H), 2.45–2.60 (m, 1 H), 4.05–4.10 (m, CH_2O, 1.66 H),[b] 4.10–4.30 (m, CH_2O, 0.34 H),[c] 5.48 (d of t, J = 11.0, 7.9, CH=C, 0.18 H),[c] [5.64 (d of t, J = 15.4, 4.9, CH=C), 5.68 (d of t, J = 14.8, 4.0, CH=C)],[b] 5.68–5.73 (m, CH=C)[c]	168
10	1710, 810	1.62 (s, 3 H), 1.7–2.8 (m, 12 H) 4.13 (d, 2 H), 5.38 (t, 1 H)[a]	182
11	1700, 970	[0.997 (d, J = 6.8), 1.001 (d, J = 6.8), 1.24 (d, J = 6.3), 1.26 (d, J = 6.3), CH_3],[e] 1.40–2.05 (m, 6 H), 1.69 (br s, 1 H), 2.10–2.45 (m, 3 H), 2.60–2.75 (m, 1 H), 4.26 (br sextet, J = 6.4, 1 H), [5.48 (d of d, J = 15.5, 5.6), 5.49 (d of d, J = 15.5, 6.4), 5.53 (d of d), J = 15.5, 5.4), 5.63 (d of d, J = 15.5, 7.3), CH=C, 2 H]	196
12	1710, 975	1.30 (s, 6 H), 1.30–2.00 (m, 6 H), 1.65 (m, 1 H), 2.00–2.20 (m, 2 H), 2.25–2.45 (m, 2 H), 2.45–2.55 (m, 1 H), 5.58 (d of t, J = 15.5, 5.8, 1 H), 5.63 (d, J = 15.5, 1 H)	196
13	1700, 970	[1.01 (d, J = 6.5, 1.18 H), 1.08 (d, J = 6.8, 1.82 H), CH_3],[e] 1.25–2.05 (m, 6 H), 1.75 (m, 1 H), 2.05–2.60 (m, 4 H), 4.08 (d, J = 4.5, CH_2O, 1.65 H),[b] 4.10–4.35 (m, CH_2O, 0.35 H),[c] [5.45 (d of t, J = 10.9, 7.9), 5.47 (d of t, J = 10.9, 8.1), CH=C, 0.17 H],[c] [5.59 (d of t, J = 15.3, 6.3), 5.67 (d of t, J = 15.4, 5.4), CH=C],[b] 5.69–5.74 (m, CH=C)[c]	182
14	1720, 980	1.67 (s, 1 H), 2.15 (s, 3 H), 2.33 (t of d, J = 7.1, 5.1, 2 H), 2.54 (t, J = 7.3, 2 H), 4.09 (d, J = 4.5, CH_2O, 1.67 H),[b] 4.21 (d, J = 7.2, CH_2O, 0.33 H),[c] 5.45 (d of t, J = 10.9, 7.5, CH=C, 0.16 H),[c] [5.65 (d of t, J = 15.4, 4.5), 5.70 (d of t, J = 15.2, 5.1), CH=C],[b] 5.63–5.73 (m, CH=C)[c]	128
15	1680, 960	1.80 (br s, 1 H), 2.50 (q, J = 7.1, CCH_2C=C, 1.7 H),[b] 2.55 (q, J = 7.2, CCH_2C=C 0.3 H),[c] 3.08 (t, J = 7.3, 2 H), 4.09 (d, J = 5.4, CH_2O, 1.71 H),[b] 4.25 (d, J = 7.0, CH_2O, 0.29 H),[c] 5.54 (d of t, J = 10.9, 7.6, CH=C, 0.14 H),[c] [5.71 (d of t, J = 15.4, 5.4), 5.79 (d of t, J = 15.4, 6.1), CH=C][b]	190
16	1680, 960	[1.096 (d, J = 6.6), 1.100 (d, J = 6.5), 1.214 (d, J = 6.4), 1.219 (d, J = 6.5), CH_3, 3 H], 1.63 (br s, 1 H), 2.75–3.05 (m, 3 H), 4.24 (quint, J = 6.3, 1 H), 5.52 (d of d, J = 15.5, 6.5, 1 H), 5.65 (d of d, J = 15.5, 6.6, 1 H), 7.40–8.00 (m, 5 H)	218
17	1600, 895	1.67 (s, 1 H), 1.96 (s, 3 H), 4.38 (s, 2 H), 5.0–5.2 (m, 2 H), 5.2–5.4 (m, 2 H)[a]	98
18[d]	1650, 1600, 960, 880	1.38 (s, 6 H), 1.59 (s, 1 H), 1.87 (s, 3 H), 4.96 (s, 2 H), 5.77 (d, 1 H), 6.33 (d, 1 H)[a]	126
19	1720, 1642, 650	2.5 (s, 4 H), 2.88 (d, 2 H), 5.7–5.9 (m, 2 H)[a]	96

[a] 60-MHz ^1H NMR data in $CDCl_3$. [b] Absorption due to the E isomer. [c] Absorption due to the Z isomer. [d] ^{13}C NMR ($CDCl_3$) 18.61, 29.90, 70.87, 116.50, 129.39, 137.54, 141.58. [e] Minor methyl signals appear additionally.

the C_3 methyl group by the palladium.

In the presence of **1**, the cyclic 1,3-diene monoepoxide **8** was also isomerized by $Pd(PPh_3)_4$ to give β,γ-unsaturated ketone **19**[3a] (Table I). But, in this case, **8** had no accelerating effect on the rate of the decarboxylation of **1**, which makes a contrast to the acyclic 1,3-diene monoepoxides **6** and **7** (vide ante). This finding suggests that the isomerization of **8** proceeds via the protonation of the π-allylpalladium alkolate complex **23** and the subsequent rapid hydrogen migration facilitated by the favorable geometrical disposition for the H–Pd interaction (path A in Scheme III).[7] Thus, there is no participation of the π-allylpalladium β-keto carboxylate complex in the isomerization of **8**.

It is interesting to note that the 1,3-diene monoepoxides **7** and **8**, which were isomerized in the present palladium-catalyzed reaction with β-keto acids, are known to undergo the smooth palladium-catalyzed allylic alkylation with dimethyl malonate (path B in Schemes II and III).[3b] This finding leads to an important conclusion that the carbon–carbon bond-forming reaction of the ketone enolate anion with the π-allylpalladium complex is much slower than that of the malonate anion, if it is reasonably assumed that the decarboxylation of the π-allylpalladium β-keto carboxylate complex is rapid.[2] The slow carbon–carbon bond formation of the ketone enolate anion favors the β-H elimination of the π-allylpalladium complex to result in the isomerization (path A in Schemes II and III).

Experimental Section

Infrared (IR) spectra were determined on a Hitachi EPI-G3 grating spectrophotometer. The ^1H nuclear magnetic resonance spectra were recorded at a Hitachi R-20B spectrometer (60 MHz) and a JEOL JNM-JX-400 instrument (400 MHz). ^{13}C NMR spectra were obtained on a Hitachi R-100 spectrometer. All chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane. Coupling constants (J) are reported in hertz. Mass spectra were obtained on a JEOL D-300 instrument. Gas chromatographic analyses (GLC) were made on Shimadzu 4APT and 4CPT instruments equipped with a thermal-conductivity detector. Quantitative GLC analyses of organic products were made with internal standards and calibration based upon authentic samples employing a 20% silicone DC 550 on Celite 545 column and a 20% PEG 20M on Celite 545 column. CO_2 gas was analyzed by GLC on an activated charcoal column by using methane as an internal standard.

All palladium-catalyzed reactions were conducted under an atmosphere of nitrogen. Tetrahydrofuran (THF) and benzene were distilled from calcium hydride under nitrogen. Tetrakis(triphenylphosphine)palladium was prepared by the reported procedure.[8] Commercially available 3,4-epoxy-1-butene (**2**) was used after deoxygenation by a stream of nitrogen. 3,4-Epoxy-2-methyl-1-butene (**3**) was synthesized by the published method.[9] Other 1,3-diene monoepoxides (**4**–**8**) were prepared on the basis of Crandall's[10] procedure using *m*-chloroperbenzoic acid and commercially available dienes of 2,4-hexadiene, 4-methyl-1,3-pentadiene, 2,3-dimethyl-1,3-butadiene, 2,5-dimethyl-2,4-hexadiene, and 1,3-cyclohexadiene. 1-Oxocyclohexane-2-carboxylic acid, 6-methyl-1-oxocyclohexane-2-carboxylic acid, and benzoylacetic acid (**1**) were prepared by the reported procedure.[11] 1,3-Acetonedicarboxylic acid was a commercial reagent.

General Procedure for the Palladium-Catalyzed Reaction of β-Keto Acids and 1,3-Diene Monoepoxides. To a stirred solution of β-keto acid (1.00 mmol) and $Pd(PPh_3)_4$ (0.0500 mmol) in 5 mL of solvent in a 200-mL two-necked flask equipped with a rubber septum and a three-way stopcock was added 1,3-diene monoepoxide (1.00 mmol) through the three-way stopcock under a countercurrent stream of nitrogen by using a microsyringe. The stopcock was closed and the reaction mixture was magnetically stirred at ambient temperature. Methane gas (20 mL, 0.83 mmol)

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was added through the rubber septum by using a hypodermic syringe. Carbon dioxide gas evolution was monitored by GLC analysis of a gaseous sample taken out through the rubber septum with a hypodermic syringe. After the quantitative carbon dioxide gas evolution was observed, a GLC internal standard was added. GLC analysis (a silicone DC 550 column or a PEG 20M column) of the reaction mixture gave the GLC yield of the allylic alkylation or isomerization product.

The allylic alkylation products **9**–**16** and the isomerization products **17**–**19** were isolated by GLC and were identified by the spectroscopic data in Table II. The allylic alkylation product **9** (2.22 g, 13.2 mmol, 88%), which was produced by the palladium-catalyzed reaction of 1-oxocyclohexane-2-carboxylic acid (2.13 g, 15.0 mmol) and **2** (1.21 mL, 15.0 mmol) in 120 mL of THF, was isolated by column chromatography on silica gel using ether as eluent.

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Registry No. **1**, 614-20-0; **2**, 930-22-3; **3**, 7437-61-8; **4**, 69429-05-6; **5**, 6812-25-5; **6**, 34485-82-0; **7**, 13295-59-5; **8**, 6705-51-7; (*E*)-**9**, 105182-95-4; (*Z*)-**9**, 33739-85-4; (*E*)-**10**, 105182-96-5; (*Z*)-**10**, 105183-01-5; **11**, 105182-97-6; **12**, 105182-98-7; **13**, 105182-99-8; (*E*)-**14**, 27267-99-8; (*Z*)-**14**, 27267-38-5; (*E*)-**15**, 33739-83-2; (*Z*)-**15**, 33739-82-1; **16**, 105183-00-4; **17**, 26431-13-0; **18**, 75082-96-1; **19**, 4096-34-8; $Pd(PPh_3)_4$, 14221-01-3; 2-oxocyclohexanecarboxylic acid, 18709-01-8; 3-methyl-2-oxocyclohexanecarboxylic acid, 52456-87-8; 3-oxoglutaric acid, 542-05-2.

Organopalladium Approaches to Prostaglandins. 5.[1] Synthesis of Bicyclic and Tricyclic Prostanoic Acids and Thiophene-Containing Prostaglandin Endoperoxide Analogues via Thienylpalladation of Bicyclic Alkenes[2]

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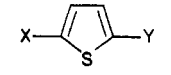
Thiophene-containing prostaglandin endoperoxide analogues **18**–**20** are readily available by addition of thienylpalladium species to norbornene and norbornadiene and subsequent reaction with the appropriate alkynyllithium reagent. Elaboration of the bicyclic palladium intermediate using alkenyltin or -copper reagents, or a carbonylation approach, affords endoperoxide analogue **25**. Hydrogenation and subsequent saponification of thiophenes **16** and **17** afford the first bicyclic (**31**) and tricyclic (**32**) prostanoic acids.

There has been considerable interest in introducing the thiophene and tetrahydrothiophene rings into prostaglandins.[3-10] While these sulfur-containing rings have been introduced into a variety of positions in the primary prostaglandins, there appear to be no examples of such analogues in the prostaglandin endoperoxide series. Our recent interest[1,2,11,12] in employing palladium chemistry in the synthesis of prostaglandin endoperoxide analogues encouraged us to examine possible methods for introducing the thiophene ring into the carboxylic acid side chain of such analogues. Unlike all previous work in this area, we desired to introduce the thiophene ring into the C_4–C_7 positions of the analogues, since that should mimic the normal olefinic C_5–C_6 cis stereochemistry common to most prostaglandins. Besides the obvious interest in exploring the biological activity of such thiophene-containing analogues, we also anticipated that hydrogenation of the thiophene ring might provide an easy entry into the first bicyclic and tricyclic prostanoic acids. At this time we report the details of our efforts in this area.

Results and Discussion

Our basic approach to the thiophene-containing endoperoxide analogues required the preparation of thienylmercurials **3** and **5**. Methyl (*E*)-3-(2-thienyl)acrylate (**2**)



1: X = H; Y = (*E*)-CH=CHCO$_2$H
2: X = H; Y = (*E*)-CH=CHCO$_2$CH$_3$
3: X = ClHg; Y = (*E*)-CH=CHCO$_2$CH$_3$
4: X = H; Y = CH$_2$CH$_2$CO$_2$CH$_3$
5: X = ClHg; Y = CH$_2$CH$_2$CO$_2$CH$_3$

was prepared from the commercially available acid **1**, by acid-catalyzed esterification, in 88% yield. Methyl 3-(2-thienyl)propanoate (**4**) was prepared by hydrogenation[13] of the unsaturated acid **1**, followed by esterification, in 79% overall yield. These heterocycles were then mercurated by a modification of Volhard's procedure,[14] involving 2 equiv of $HgCl_2$ and 10 equiv of NaOAc in aqueous ethanol, to afford thienylmercurials **3** and **5** in 86% and 83% yields, respectively.

While the addition of π-allyl, aryl, benzylic, and vinylic palladium species to bicyclic alkenes is well-known,[15] there have been no examples of the addition of heterocyclic

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