skeleton of the bicyclic reference olefin; the other comes from pyramidalization of the double bond in this skeleton. The olefin pyramidalization strain energy (OPSE) is the difference between the OSE of a pyramidalized alkene and that of the appropriate bicyclic reference compound.

In cubene (**11**) the majority of the calculated OSE is contained in bicyclo[2.2.0]hex-1(4)-ene (**13**). The 6-31G* TCSCF OPSE of 18.9 kcal/mol amounts to only 32% of the total OSE of 58.9 kcal/mol that is calculated for **11**. In **12**, of the computed OSE of 66.8 kcal/mol, the OPSE of 8.1 kcal/mol[43] amounts to just 12%. Thus, despite the fact that the large OSE predicted for **11** and **12** should confer on these molecules a high reactivity toward double-bond addition, most of the reactivity is expected to be found in the unbridged bicyclic alkenes **13** and **14**.

In contrast, MM2 predicts essentially no OSE for bicyclo-[3.3.0]oct-1(5)-ene (**9**), and the 6-31G* heat of hydrogenation of 23.6 kcal/mol that we estimate for **9** is nearly the same as that computed for cyclopentene. Since the OSE of **9** is zero, or close to it, the OPSEs for **10** and **1-3** are the same as the OSEs for these alkenes, which are given in Table IV. The unusual physical and chemical properties of these molecules can, therefore, be attributed entirely to pyramidalization of the doubly bonded carbons in them. Consequently, this series of alkenes provides an excellent opportunity to study the spectroscopic and chemical consequences of olefin pyramidalization, without a significant contribution from the OSE present in the unconstrained bicyclic alkene.

(43) An alternative definition of the OPSE would involve planar bicyclic alkenes as reference molecules. Since **14** has been computed to have a 12 kcal/mol barrier to planarity,[41] this definition would confer on **12** a small negative OPSE, amounting to −4 kcal/mol.

Acknowledgment. We thank the National Science Foundation for support of this research, including a generous grant of computer time at the San Diego Supercomputer Center, where many of the calculations reported here were performed. Some of the calculations were carried out on a Convex C-1 computer, whose purchase was made possible by a grant from the National Science Foundation. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Note Added in Proof. The prediction that cubene (**11**) should be preparable by the same type of reaction used for the synthesis of **1**[1] has been confirmed. Cubene has been synthesized by reductive dehalogenation by M. Maggini and P. F. Eaton (submitted for publication in *J. Am. Chem. Soc.*) and we have generated homocub-4(5)-ene in the same fashion (submitted for publication in *J. Am. Chem. Soc.*).

Supplementary Material Available: Cartesian coordinates for the 3-21G SCF optimized geometries of alkenes **1-3** and **9-14** and of the hydrogenation product of each alkene (14 pages). Ordering information is given on any masthead page.

The Three-Component Coupling Synthesis of Prostaglandins[†,1]

M. Suzuki, A. Yanagisawa, and R. Noyori*

Contribution from the Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan. *Received November 2, 1987*

Abstract: A convergent one-pot construction of the prostaglandin (PG) framework has been accomplished by the organocopper-mediated conjugate addition of the *S* configurated ω side-chain unit to a protected (*R*)-4-hydroxy-2-cyclopentenone followed by trapping of the enolate intermediate by α side-chain alkyl halides. Transmetalation with use of triphenyltin chloride at the enolate stage serves as key operation for the successful three-component coupling synthesis. The use of methyl (*Z*)-7-iodo-5-heptenoate as the α side-chain component allows short synthesis of PGE_2 and PGD_2. Introduction of a triple bond at the C-5–C-6 positions with methyl 7-iodo-5-heptynoate as the α side-chain synthon has opened a general entry of PGs. The protected 5,6-didehydro-PGE_2 derivatives are convertible to a variety of PGs of 1 and 2 series by the controlled hydrogenation of the C-5–C-6 unsaturated bonds and α-selective (100%) reduction of the C-9 keto function, if necessary. Lithium aluminum hydride reagents modified by (*R*)- and (*S*)-2,2′-dihydroxy-1,1′-binaphthyl exhibit a unique kinetic discrimination in reduction of PGE type compounds. A protected 5,6-didehydro-$PGF_{2\alpha}$ has been transformed stereoselectively to PGI_2 by using intramolecular alkoxypalladation/depalladation as the key step.

Prostaglandins (PGs) are now recognized as significant local hormones controlling a multitude of significant physiological processes.[2] Development of the efficient chemical synthesis has been strongly required, because organic synthesis is the only means to supply sufficient quantities of these important but naturally scarcely occurring substances[2d] and to create the medicinally more cultivated artificial compounds.[2d] Although the methods developed by Corey[3] and the Upjohn Co.[2d,4] among others[5] have already been commercialized, elaboration of the shorter, efficient entries to natural PGs and the analogues is still desirable.[2d] We have pursued the realization of the convergent three-component coupling process, viz. the simultaneous assembly of the five-membered cyclic ketone unit and two side chains, in view of the directness and flexibility.[6]

Obviously, the ultimate goal along this line is, as illustrated by eq 1 (M = metal, X = halogen), the one-pot construction of

[†] Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) Prostaglandin synthesis 16. Part 15: Suzuki, M.; Morita, Y.; Yanagisawa, A.; Baker, B. J.; Scheuer, P. J.; Noyori, R. *J. Org. Chem.* **1988**, *53*, 286.

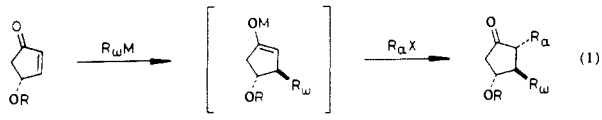
(2) (a) Vane, J. R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 741. (b) Samuelsson, B. *Ibid.* **1983**, *22*, 805. (c) Bergström, S. *Ibid.* **1983**, *22*, 858. (d) Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* **1982**, Aug. 16, p 30. (e) *Prostacyclin*; Vane, J. R., Bergström, S., Eds.; Raven: New York, 1979.

(3) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. Corey, E. J. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 24.

(4) Just, G.; Simonovitch, C. *Tetrahedron Lett.* **1967**, 2093. Just, G.; Simonovitch, C.; Lincoln, F. H.; Schneider, W. P.; Axen, U.; Spero, G. B.; Pike, J. E. *J. Am. Chem. Soc.* **1969**, *91*, 5364. Kelly, R. C.; VanRheenen, V.; Schletter, I.; Pillai, M. D. *Ibid.* **1973**, *95*, 2746. Kelly, R. C.; VanRheenen, V. *Tetrahedron Lett.* **1973**, 1709; **1976**, 1067.

0002-7863/88/1510-4718$01.50/0

the whole PG framework via organometallic-aided conjugate addition of the eight-carbon ω side-chain unit to 4-oxygenated 2-cyclopentenones followed by the trapping of the regiochemically defined enolate species by the seven-carbon *halides* having the α side-chain structures. Since the requisite optically active

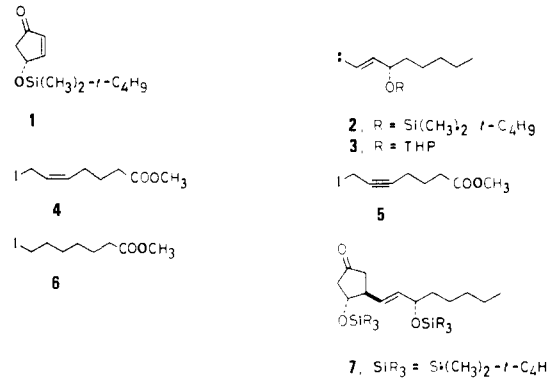


(1)

cyclopentenone[7] and ω side-chain units[8] are available in various ways, this scheme is designed to allow for the straightforward synthesis of optically active PGs. The organocopper-mediated conjugate addition of the ω side chain to the cyclopentenone unit proceeds smoothly,[9] but the trapping of the enolate intermediate by alkyl halides is most difficult, hampering this ideal route. Such difficulty, recognized earlier by many research groups,[10] urged us to use more powerful α side-chain electrophiles such as aldehydes[7c,11a,c] or nitro olefins,[11b,d] which realized, after functional group rectification, some modified three-component coupling PG syntheses.[11,12] This paper describes details of the success of the earnestly desired *direct alkylation* method. The synthesis disclosed herein constitutes a considerable improvement over the route published in preliminary forms.[13]

Results and Discussion

Tandem Organocopper Conjugate Addition/Alkylation Reaction. We have found that organocopper reagents prepared from equimolar amounts of copper(I) iodide and organolithiums and 2 to 3 equiv of tributylphosphine undergo high-yield conjugate addition to various α,β-unsaturated ketones by using a 1:1 reagent/substrate ratio.[9] Introduction of the ω side-chain unit to the five-membered ring was accomplished by this stoichiometry-controlled reaction in THF with the homochiral cyclopentenone **1** and the phosphine-complexed organocopper reagent formed from the homochiral vinylic iodide **2**. The complete stereoselectivity, generating the trans C-11/C-12 relationship (PG numbering), was proven by HPLC and ^{13}C NMR analysis of **7** obtained by aqueous quenching. Under such reaction and workup conditions the product was stable, and no cyclopentenone derivatives were detected. As well precedented,[10b] however, attempted trapping of the enolate intermediate with the α side-chain alkyl iodides was totally unsuccessful, giving complex mixtures.



The failure of the direct alkylative trapping (eq 1) is presumably due to the facile double-bond shift in the enolate via intermolecular protonation/deprotonation in the presence of some proton sources, which causes various side reactions.[6] We anticipated here that some transmetalation at the enolate stage could reduce its basicity, thereby retarding the equilibration, but still maintain the nucleophilicity toward alkyl halides. Among the various possibilities,[14,18] we were stimulated to investigate the transmetalation technique using triorganotin halides, which was originally ela-

(5) Reviews: (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic: New York, 1977. (b) Mitra, A. *Synthesis of Prostaglandins*; Wiley-Interscience: New York, 1977. (c) Garcia, G. A.; Maldonado, L. A.; Crabbe, P. *Prostaglandin Research*; Crabbe, P., Ed.; Academic: New York, 1977; Chapter 6. (d) Caton, M. P. L. *Tetrahedron* **1979**, *35*, 2705. (e) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293. (f) *Chemistry, Biochemistry, and Pharmaceutical Activity of Prostanoids*; Roberts, S. M., Scheinmann, F., Eds.; Pergamon: New York, 1979. (g) Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, *36*, 2163. (h) *New Synthetic Route to Prostaglandins and Thromboxanes*; Roberts, S. M., Scheinmann, F., Eds.; Academic: New York, 1982. (i) *Prostaglandins and Thromboxanes*; Newton, R. F., Roberts, S. M., Eds.; Butterworth Scientific: London, 1982.

(6) For an account on our earlier effort, see: Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847 and references cited therein.

(7) [Optical resolution] Chemical method: (a) Gill, M.; Rickards, R. W. *J. Chem. Soc., Chem. Commun.* **1979**, 121. (b) Gill, M.; Rickards, R. W. *Tetrahedron Lett.* **1979**, 1539. (c) Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Ibid.* **1982**, *23*, 4057. Chromatographic method: (d) Okamoto, Y.; Aburatani, R.; Kawashima, M.; Hatada, K.; Okamura, N. *Chem. Lett.* **1986**, 1767. [Transformation of natural products]: (e) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1976**, 759. (f) Mitscher, L. A.; Clark, G. W. III; Hudson, P. B. *Ibid.* **1978**, 2553. [Asymmetric reaction]: (g) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717. (h) Asami, M. *Tetrahedron Lett.* **1985**, *26*, 5803. [Kinetic resolution] Chemical method: (i) Kitamura, M.; Manabe, K.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4719. (j) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708. Enzymatic method: (k) Tanaka, T.; Kurozumi, S.; Toru, T.; Miura, S.; Kobayashi, M.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1713. (l) Dohgane, I.; Yamachika, H.; Minai, M. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 896. (m) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. (n) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875. (o) Deardorff, D. R.; Mattews, A. J.; McMeekin, D. S.; Craney, C. L. *Ibid.* **1986**, *27*, 1255.

(8) Optical resolution: (a) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827. (b) Fried, J.; Lin, C.; Mehra, M.; Kao, W.; Dalven, P. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 39. Pappo, R.; Collins, P.; Jung, C. *Ibid.* **1971**, *180*, 64. Sih, C. J.; Salomon, R. G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 857. Asymmetric reaction (chemical method): see ref 7g and (c) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (d) Vigneron, J. P.; Bloy, V. *Tetrahedron Lett.* **1980**, *21*, 1735. (e) Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255. (Enzymatic method): (f) Sih, C. J.; Heather, J. B.; Sood, R.; Price, P.; Peruzzotti, G.; Lee, L.-F. H.; Lee, S. S. *J. Am. Chem. Soc.* **1975**, *97*, 865. Kinetic resolution by chemical method: (g) Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 2033. Kitano, Y.; Matsumoto, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1987**, 1523.

(9) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Morita, Y.; Noyori, R. *Isr. J. Chem.* **1984**, *24*, 118.

(10) (a) Patterson, J. W., Jr.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2506. (b) Davis, R.; Untch, K. G. *Ibid.* **1979**, *44*, 3755 and references cited therein. For a review, see: Taylor, R. J. K. *Synthesis* **1985**, 364.

(11) Functionally modified methods: (a) Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 5563. (b) Tanaka, T.; Toru, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Ibid.* **1983**, 24, 4103. (c) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Ibid.* **1984**, *25*, 1383. (d) Tanaka, T.; Hazato, A.; Bannai, K.; Okamura, N.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Noyori, R. *Ibid.* **1984**, *25*, 4947. Tanaka, T.; Hazato, A.; Bannai, K.; Okamura, N.; Sugiura, S.; Manabe, K.; Toru, T.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron* **1987**, *43*, 813.

(12) Indirect method using shorter side-chain units: Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260. See also ref 10b.

(13) Preliminary reports: (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 1187. See also ref 6, 11a, and 11c.

(14) (a) Boeckmann, R. K., Jr. *J. Org. Chem.* **1973**, *38*, 4450. (b) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788. (c) Coates, R. M.; Sandefur, L. O. *J. Org. Chem.* **1974**, *39*, 275. (d) Posner, G. H.; Lentz, C. M. *Tetrahedron Lett.* **1977**, 3215. (e) Posner, G. H.; Whitten, C. E.; Sterling, J. J.; Brunelle, D. J.; Lentz, C. M.; Runquist, A. W.; Alexakis, A. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 249. (f) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934. (g) Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, *44*, 3661. (h) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886. (i) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *Ibid.* **1982**, *104*, 4180.

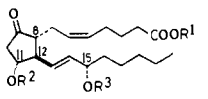
(15) (a) Tardella, P. A. *Tetrahedron Lett.* **1969**, 1117. (b) Nishiyama, H.; Sakuta, K.; Itoh, K. *Ibid.* **1984**, *25*, 223. (c) Nishiyama, H.; Sakuta, K.; Itoh, K. *Ibid.* **1984**, *25*, 2487. See also: (d) Yamamoto, Y.; Maruyama, K. *28th Symposium on Organometallic Chemistry*; Japan, Osaka, Nov. 1981; *Abstract* p 151.

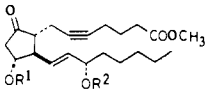
(16) For a similar observation, see: Binns, M. R.; Haynes, R. K.; Lambert, D. E.; Schober, P. A. *Tetrahedron Lett.* **1985**, *26*, 3385.

(17) Recently Johnson provided an alternative elegant solution to this problem. See: Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655.

(18) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

borated by Tardella[15a] and then Itoh to modify the reactivity of lithium enolates.[15b,c] Fortunately, the alkylation reaction of the regiodefined enolate did work most efficiently with the aid of triphenyltin chloride.[16,17] Thus sequential treatment of the organocopper reagent in THF with the enone **1** (1:1 molar ratio), HMPA (11 equiv), triphenyltin chloride (1 equiv) at −78 °C, and the *Z*-allylic iodide **4**[18,25c] (5 equiv) at −30 to −20 °C afforded the desired PGE_2-type product **8** in 78% yield together with a small

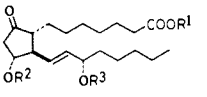




8, $R^1 = CH_3$, $R^2 = R^3 =$ $Si(CH_3)_2$-*t*-C_4H_9
9, $R^1 = CH_3$, $R^2 = Si(CH_3)_2$-*t*-C_4H_9, R^3 = THP
10, $R^1 = CH_3$, $R^2 = R^3 = H$
11, $R^1 = R^2 = R^3 = H$

12, $R^1 = R^2 = Si(CH_3)_2$-*t*-C_4H_9
13, $R^1 = Si(CH_3)_2$-*t*-C_4H_9, R^2 = THP

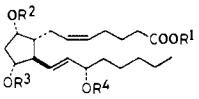
amount (3%) of the C-8 epimer. In a like manner, when the three-component coupling was conducted with the enone **1**, the ω side-chain precursor **2**, and the propargylic iodide **5**, the 5,6-didehydro-PGE_2 derivative **12**[19] was produced in 82% yield. Thus in our hands, up to 13 g of the PGE_2 derivative was obtained by the one-pot condensation. No PGA or PGB type compounds were formed. The only cautious operation for obtaining the reproducible results was the slow and constant addition of the enone **1** to the preformed copper reagent, which had been kept at low temperatures (see the Experimental Section for the apparatus). The satisfactory yields were obtained by excess use of the α side-chain halides, where over 75% of the unreacted halide was recovered after reaction. When only 1 equiv of **5** to **1** was utilized, the yield of **12** was lowered to 55%, accompanied with the production of simple 1,4-adduct **7** in 35% yield as the only major byproduct. 1,3-Dimethyl-2-imidazolidinone or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone was usable in place of HMPA but less effective. Besides triphenyltin chloride, various triorganotin halides were effective as promotors of the alkylation, but tributyltin triflate did not produce any desired products, suggesting that the lithium or copper to tin transmetalation was occurring but real reacting species could be a penta- or hexacoordinate stannate rather than the neutral tetracoordinate tin compound.[15,20,21] Saturated primary alkyl halides were less reactive than allylic or propargylic halides, and the alkylation with **6** resulted in the production of PGE_1 derivative **14** in only 20% yield.



14, $R^1 = CH_3$, $R^2 = R^3 =$ $Si(CH_3)_2$-*t*-C_4H_9
15, $R^1 = CH_3$, $R^2 = Si(CH_3)_2$-*t*-C_4H_9, R^3 = THP
16, $R^1 = CH_3$, $R^2 = R^3 = H$
17, $R^1 = R^2 = R^3 = H$

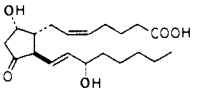
Short Synthesis of Prostaglandins of 2 Series. The device of the tandem conjugate addition/alkylation sequence has opened a simple, extremely short way to PGE_2. Removal of the silyl protective groups from **8** with pyridinium polyhydrogen fluoride, giving **10** (98%), followed by enzymatic ester hydrolysis,[8f,24] completes the synthesis of PGE_2 (**11**) (80%). Thus PGE_2 is now accessible from the cyclopentenone **1** in only three steps and in 61% overall yield. The starting chiral building blocks determine the 11*R* and 15*S* configuration and 8*R* and 12*R* stereochemistries are generated by the vicinal carbacondensation originating from the directing effect of the C-11 functionality.[25]

Synthesis of PGF_αs requires selective creation of the 9*S* configuration. To this end, reduction of **8** with 1.2 equiv of L-Selectride[26] (Aldrich) gave the 9α alcohol **18** exclusively in 95% yield. Deprotection of the hydroxyl group by a 10:3.3:1 mixture of acetic acid, water, and THF led to **22**, and the subsequent standard alkaline hydrolysis formed $PGF_{2\alpha}$ (**23**).

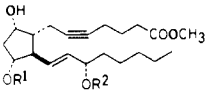


18, $R^1 = CH_3$, $R^2 = H$, $R^3 = R^4 =$ $Si(CH_3)_2$-*t*-C_4H_9
19, $R^1 = CH_3$, $R^2 = H$, $R^3 =$ $Si(CH_3)_2$-*t*-C_4H_9, R^4 = THP
20, $R^1 = CH_3$, $R^2 = R^4$ = THP, $R^3 = Si(CH_3)_2$-*t*-C_4H_9
21, $R^1 = CH_3$, $R^2 = R^4$ = THP, $R^3 = H$
22, $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
23, $R^1 = R^2 = R^3 = R^4 = H$

PGs of D series, unlike PGEs, bear a hydroxyl group at C-9 and a keto function at C-11. The reversal of such oxidation states is readily achievable by choosing appropriate defferentiable hydroxyl protective groups in the starting five-membered ring and ω side-chain synthons. The vincinal carbacondensation of the siloxy cyclopentenone **1** with the THP-protected ω side-chain precursor **3** and alkylating agent **4** by the organotin transmetalation technique gave the prostanoid skeleton **9** in 77% yield. This PGE_2-type compound was converted to PGD_2 (**24**) by the six-step sequence: (1) stereoselective (100%) reduction with L-Selectride (Aldrich) to **19**, (2) THP protection of the C-9 hydroxyl giving **20**, (3) desilylation to afford **21**, (4) saponification of the methyl ester, (5) Jones oxidation of the C-11 hydroxyl, and (6) removal of the THP protection. The ester hydrolysis should be conducted at the rather early stage rather than the final step because of the instability of the β-hydroxycyclopentanone structure.



24



25, $R^1 = R^2 = Si(CH_3)_2$-*t*-C_4H_9
26, $R^1 = Si(CH_3)_2$-*t*-C_4H_9, R^2 = THP

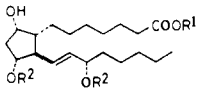
General Synthesis of Prostaglandins. Placement of an acetylenic bond at the C-5–C-6 positions has realized a general synthesis of naturally occurring PGs. The controlled hydrogenation of the triple bond, leading to PGs of 1 and 2 series, and the stereoselective reduction of the C-9 keto group giving the 9α alcohol, if necessary, result in a variety of PGs.

First, partial hydrogenation of the acetylenic bond in the common intermediate **12**, giving the *Z* double bond, was accomplished over 5% $Pd/BaSO_4$ catalyst to afford **8** (87%), a protected PGE_2, whereas the carefully controlled hydrogenation over Pd/C catalyst in methanol allowed the conversion to a protected PGE_1, **14** (71%), leaving the C-13–C-14 double bond intact.[27] The desilylation (95%) and enzymatic hydrolysis of the resulting **16** gave PGE_1 (**17**) (86%).

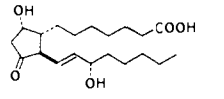
Reduction of **12** with 1.2 equiv of L-Selectride (Aldrich) in the presence of 3 equiv of methyl acetate[28] gave the 9α alcohol **25**

(19) Lin, C. H.; Stein, S. J.; Pike, J. E. *Prostaglandins* **1976**, *11*, 377.
(20) Odic, Y.; Pereyre, M. *J. Organomet. Chem.* **1973**, *55*, 273.
(21) Reaction of the cyclopentanone lithium enolate with 1-acetoxy-2-octyne in the presence of a Pd(0) complex and tributyltin chloride[22] or triethylborane[23] did not give any desired propargylation product.
(22) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591.
(23) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188. Negishi, E.; John, R. A. *Ibid.* **1983**, *48*, 4098. Luo, F.-T.; Negishi, E. *Tetrahedron Lett.* **1985**, *26*, 2177; *J. Org. Chem.* **1985**, *50*, 4762.
(24) Hazato, A.; Tanaka, T.; Toru, T.; Okamura, N.; Bannai, K.; Sugiura, S.; Manabe, K.; Kurozumi, S. *Nippon Kagaku Kaishi* **1983**, 1390.
(25) For related PGE_2 syntheses using (*R*)-4-hydroxy-2-cyclopentenone equivalents, see: (a) [oxime derivatives] Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199. (b) [4,5-dihydroxy-2-cyclopentenone] ref 17. (c) [sulfone derivatives] Donaldson, R. E.; Saddler, J. C.; Byrn, S.; McKenzie, A. T.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167.
(26) (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. (b) Corey, E. J.; Varma, R. K. *Ibid.* **1971**, *93*, 7319. (c) Stork, G.; Isobe, M. *Ibid.* **1975**, *97*, 4745. See also ref 10b.
(27) Corey, E. J.; Noyori, R.; Schaaf, T. K. *J. Am. Chem. Soc.* **1970**, *92*, 2586.

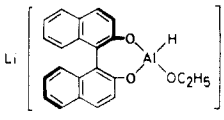
exclusively in 95% yield.[29] Some notable behavior was observed in reduction of **12** with BINAL-H, a chiral hydride reagent.[31] The (*R*)-BINAL-H reagent, **31** (empirical formula), appeared to match well with the chiral carbonyl environment of **12** to form the 9α alcohol **25** with a sufficiently high selectivity (9α/9β $\simeq$ 99:1), whereas the reaction of the enantiomeric reducing agent **32** proceeded very sluggishly (k_R/k_S > 130!) and exhibited somewhat lower diastereoselectivity (9α/9β $\simeq$ 95:5). This chiral disposition of the ring substituents appeared to play a particular role in such unprecedented high kinetic discrimination. When **25** was hydrogenated over the Lindlar catalyst, a protected $PGF_{2\alpha}$, **18**, was produced in 81% yield, while the use of 5% Pd/$BaSO_4$ catalyst was found to give the $PGF_{1\alpha}$ precursor **27** (60%). The latter was also obtainable by α-selective reduction of **14** with L-Selectride (Aldrich) in 92% yield. Deprotection of **27** with a mixture of acetic acid, water, and THF, giving **28** and standard alkaline hydrolysis of the ester group, leads to $PGF_{1\alpha}$ (**29**).[32]



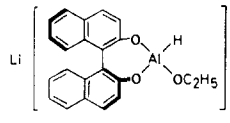
27, R^1 = CH_3, R^2 = $Si(CH_3)_2$-*t*-C_4H_9
28, R^1 = CH_3, R^2 = H
29, R^1 = R^2 = H



30



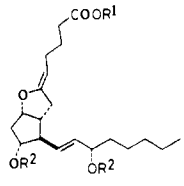
31



32

In a like manner, PGs of D series can be prepared. The organometallic mediated union of the siloxycyclopentenone **1**, THP-protected ω side chain **3**, and α side-chain iodide **5** afforded the acetylenic ketone **13** in 70% yield. The L-Selectride (Aldrich) reduction, resulting in exclusive formation of **26**, and partial hydrogenation of the acetylenic linkage over the Lindlar catalyst led to **19** (96%), which was converted, via **20**, to PGD_2 (**24**) in five steps as described above. Catalytic hydrogenation of **13** over 5% Pd/C catalyst formed a precursor of PGD_1 (**15**) (68%). The functional group transposition through a six-step sequence afforded PGD_1 (**30**).[33]

With the ready construction of the acetylenic compound **12** in hand, a stage was set for the synthesis of prostacyclin (PGI_2) (**35**), the most potent natural inhibitor of blood platelet aggregation and a powerful vasodilator.[2a] PGI_2 featured by the unique



33, R^1 = CH_3, R^2 = $Si(CH_3)_2$-*t*-C_4H_9
34, R^1 = CH_3, R^2 = H
35, R^1 = R^2 = H

(*Z*)-2-alkenyltetrahydrofuran structure is highly labile, particularly under acidic hydrolytic conditions. We now have found that such a sensitive compound is obtainable from **25** by a mild intramolecular alkoxypalladation/depalladation procedure. Thus cyclization of **25** with $PdCl_2(C_6H_5CN)_2$ in THF followed by depalladation with ammonium formate afforded the desired **33** in 71% yield (29% recovery of **25**) with excellent stereoselectivity, 5*Z*/5*E* > 33:1 (limit of NMR accuracy).[34,35] The structures of **33** and its 5*E* isomer were confirmed carefully by superposition of their 500-MHz ^{1}H NMR spectra with those of authentic materials.[36d] No evidence was provided for the formation of any double-bond positional isomers. It is clear that the intramolecular alkoxypalladation to the C-5–C-6 triple bond occurs in a 5-exo-dig manner[37] and in an anti fashion and that the reductive depalladation is accomplished with retention of the alkenyl ether stereointegrity. The present palladium-mediated procedure is superior to the previously discovered alkoxymercuration/demercuration recipe,[13b] giving the 5*Z*/5*E* ratio of 19:1.[38,39] Finally, deblocking of the hydroxyl groups of **33** by commercial tetrabutylammonium fluoride in THF, giving **34** (97%), followed by alkaline hydrolysis of the ester completes the synthesis of PGI_2 (**35**).[36d] No 6-oxo-$PGF_{1\alpha}$ derivatives were formed throughout the transformation. This short-cut synthesis, achievable in five steps from the cyclopentenone **1**, compares well with the existing approaches via $PGF_{2\alpha}$.[36]

The success of this PG synthesis relies on a variety of efficient organometallic methodologies effecting requisite selective reactions. Here we describe the entry to only naturally occurring PGs, but it is obvious that the three-component coupling approach allows the preparation of a wide range of physiologically significant analogues by choosing suitably modified side-chain units.[6]

Experimental Section

General Methods. Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted by using Florisil (Nakarai, M7P4145), silica gel (E. Merck 7734, 70–230 mesh, Fuji Devison BW-80, 80–200 mesh, or Katayama K230, 230–400 mesh), or deactivated silica gel (E. Merck) by mixing with water (5–10%). Medium-pressure column chromatography was conducted by using silica gel 60 (E. Merck, 230–400 mesh) with a Kiriyama ILC-PB column system consisting of a glass column and a pump. High-performance liquid chromatography (HPLC) was conducted by using Waters 6000A instrument on a column of Zorbax Sil (4.6 mm ϕ × 25 cm): solvent, 1:100 ethanol/hexane; flow rate, 1.0 mL/min; pressure, 140 kg/cm^2; detection, UV (210 nm).

Copper(I) iodide (Nakarai) was continuously extracted with THF in a Soxhlet extractor overnight and dried in vacuo at room temperature for several hours. Tributylphosphine (Nakarai) was purified by distillation before use. Commercial *n*-butyllithium (Mitsuwa or Nakarai) and *tert*-butyllithium (Aldrich) were stored at 4 °C and used directly from the bottles. Molarity of these alkyllithiums were determined by titration.[40] Optically pure (*S*,*E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene

(28) Reduction of **12** with 1 equiv of this reagent gave a mixture of desired **25** (86%), the over-reduced diol (2%) and unreacted **12** (8%). The unfavorable overreduction was avoided simply by addition of excess methyl acetate.

(29) Stereoselectivities (9α/9β ratio) with some other reducing agents were (i-C_4H_9)$_2$AlH–2,6-(t-C_4H_9)$_2$-4-$CH_3C_6H_4OH$[30] (toluene, −20 °C), 92:8[11a]; $LiAlH_4$ (THF, −78 °C), 85:15; $NaBH_4$ (CH_3OH, 0 °C), 75:25.

(30) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3033.

(31) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. See also ref 7g.

(32) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1972**, 3333.

(33) For the synthesis of PGE_1 and PGD_1, see ref 7c and 11c.

(34) Model alkoxypalladation with catalytic amounts of Pd(II) complexes failed; endo isomer was formed exclusively: (a) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842. (b) Utimoto, K. *J. Synth. Org. Chem. Jpn.* **1987**, *45*, 112. For related carboxylate-participating intramolecular oxypalladation, see: (c) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (d) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753.

(35) For reductive cleavage of Pd–C bond, see: (a) Roffia, P.; Gregorio, G.; Conti, F.; Pregaglia, G. F. *J. Organomet. Chem.* **1973**, *55*, 405. (b) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491. (c) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, 623 and references cited therein.

(36) (a) Corey, E. J.; Keck, G. E.; Szekely, I. *J. Am. Chem. Soc.* **1977**, *99*, 2006. (b) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *Ibid.* **1977**, *99*, 4182. (c) Nicolaou, K. C.; Barnette, W. E.; Gasic, G. P.; Magolda, R. L.; Sipio, W. J. *J. Chem. Soc., Chem. Commun.* **1977**, 630. (d) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem. Soc.* **1978**, *100*, 7690. (e) Nicolaou, K. C.; Barnette, E.; Magolda, R. L. *J. Chem. Res., Synop.* **1979**, 202; *J. Chem. Res., Miniprint* **1979**, 2444. (f) Newton, R. F.; Roberts, S. M.; Wakefield, B. J.; Woolley, G. T. *J. Chem. Soc., Chem. Commun.* **1981**, 922.

(37) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(38) Detection of a small amount of the 5*E* isomer in the 5*Z*/5*E* mixture by a 90- or 270-MHz ^{1}H NMR spectrometer was difficult.

(39) For model reaction, see ref 34a.

(40) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879. Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

(2), $[\alpha]^{23}_D$ −37.5° (c 0.97, CH_3OH), and (3S,E)-3-(tetrahydropyran-2-yloxy)-1-iodo-1-octene (3), $[\alpha]^{22}_D$ −65.9° (c 1.05, CH_3OH), were prepared via optical resolution[8a,b] of the corresponding racemic alcohol or purification of optically active alcohol obtained by asymmetric reduction[7g] of the enone through the crystalline (−)-α-methylbenzylamine salt of the hydrogen phthalate. These optically pure compounds were supplied from Teijin Co. (R)-4-(tert-Butyldimethylsiloxy)-2-cyclopentenone (1), $[\alpha]^{22}_D$ +67.4° (c 0.4, CH_3OH), was prepared by the reported procedure.[7c] The optical pure compound was supplied from Teijin Co. and Sumitomo Chemical Co. Methyl (Z)-7-iodo-5-heptenoate (4) was prepared by the reported procedure.[18] Methyl 7-iodo-5-heptynoate (5) was prepared in 70% yield by treatment of methyl 7-hydroxy-5-heptynoate[41] with a mixture of triphenyl phosphite, iodine, and pyridine (3 equiv each) in ether at 0 °C for 30 min. Methyl 7-iodoheptanoate (6) was prepared by reaction of the corresponding alcohol with I_2, $(C_6H_5)_3P$, and imidazole in ether.[42] Triphenyltin chloride and a THF solution of L-Selectride[26] were obtained from Aldrich. $PdCl_2(C_6H_5CN)_2$ was prepared according to the method of Doyle.[43] Five percent palladium on charcoal (lot no. 4540), 5% palladium on barium sulfate, and Lindlar catalyst (lot no. 29) were purchased from Nippon Engelhard Co.

The solution after extraction was dried over anhydrous sodium or magnesium sulfate and then evaporated under reduced pressure (aspirator).

Monitoring of Partial Hydrogenation of 5,6-Unsaturated PGs. Silica gel TLC plate were impregnated with silver nitrate by immersing TLC plates (E. Merck) into a 5% solution of silver nitrate in acetonitrile and then dried for 30 min under reduced pressure (aspirator).[44] Progress of partial hydrogenation of **12**, **25**, and **26** was monitored by TLC analysis on this silver nitrate impregnated plates. R_f values (5:1 hexane/ethyl acetate as solvent) of **8**, **12**, **14**, **18**, **25**, and **27** were 0.47, 0.43, 0.53, 0.32, 0.28, and 0.40, respectively.

Confirmation of the Homogeneity of the 1,4-Adduct 7. The conjugate addition was conducted by a similar reaction procedure to that described in the synthesis of **12** (see below) by using (S,E)-3-(tert-butyldimethylsiloxy)-1-iodo-1-octene (2) (354 mg, 0.96 mmol), a pentane solution of tert-butyllithium (1.76 M, 1.09 mL, 1.92 mmol), copper(I) iodide (183 mg, 0.96 mmol), tributylphosphine (0.62 mL, 2.5 mmol), and (R)-4-(tert-butyldimethylsiloxy)-2-cyclopentenone (1) (200 mg, 0.94 mmol). After ordinary extractive workup, the product was subjected to column chromatography on deactivated silica gel (1:16 water/silica gel, 40 g) by using a 40:1 mixture of hexane and ethyl acetate as eluant to give the single 1,4-adduct **7** (333 mg, 78%) as a colorless oil. The product was proven homogeneous by HPLC and ^{13}C NMR spectroscopy: HPLC t_R 13.06 min; TLC R_f 0.34 (20:1 hexane/ethyl acetate); IR ($CHCl_3$) 1742, 1460, 1080, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01, 0.04, 0.06, and 0.08 (s each, 12, 2 $Si(CH_3)_2$), 0.8–1.1 (m, 21, CH_3 and 2 $SiC(CH_3)_3$), 1.1–1.7 (m, 8, 4 CH_2), 1.9–2.9 (m, 5, 2 CH_2 and CH), 4.0–4.3 (m, 2, 2 CHO), 5.5–5.6 (m, 2, vinyls); ^{13}C NMR ($CDCl_3$) δ −4.7 (2 C), −4.2 (2 C), 14.0, 18.0, 18.3, 22.6, 25.0, 25.8 (3 C), 25.9 (3 C), 31.9, 38.4, 42.0, 46.8, 47.6, 73.0, 74.8, 128.9, 135.3, 214.8; MS, m/z 454 (M^+), 439, 397, 383, 281, 239, 202; HRMS, m/z calcd for $C_{25}H_{50}O_3Si_2$ (M^+) 454.3298, found 454.3277.

5,6-Didehydro-11,15-*O*-bis(*tert*-butyldimethylsilyl)PGE$_2$ Methyl Ester (12). Standard procedure for the conjugate addition/alkylation process is illustrated by synthesis of this compound.

The apparatus used for the synthesis is shown in Figure 1. Ampule F was used as the reaction vessel in order to avoid the air contamination and for efficient cooling. Cold spiral tube D was set for introduction of an organocopper reagent to an enone substrate that had been kept at low temperature. The slow and constant addition of the enone substrate was conducted by a syringe pump through A. Prior to introduction of solvents and materials, reaction vessel F was dried in vacuo by heating with a heat gun and then filled with argon. Vacuum lines were employed for the quick operation. Inlets A and J were capped with rubber septa (Aldrich) and sealed tightly by Parafilm (American Can Co.). Outlet C of three-way stopcock B was connected to a paraffin bubbler. Methanol sherbet (−95 °C), dry ice–methanol (−78 °C), or cold methanol (−30 °C) was used for cooling. Reaction vessel F was sank into Dewar bottle H until spiral tube D was entirely covered by a cold medium I.

In a 1-L large Pyrex ampule F was placed (S,E)-3-(tert-butyldimethylsiloxy)-1-iodo-1-octene (2) (10.149 g, 27.6 mmol) under argon atmosphere and then the material dissolved in dry ether (100 mL). After

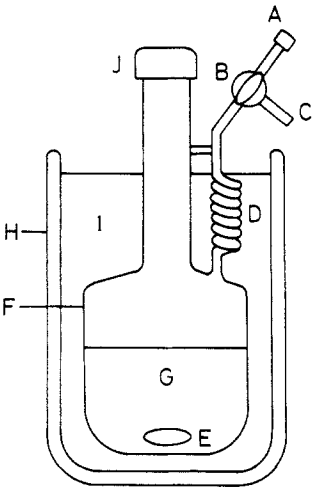


Figure 1. Apparatus for the organocopper conjugate addition/alkylation reaction. A, inlet for introducing an enone substrate; B, three-way stopcock; C, outlet; D, spiral tube; E, stirrer bar; F, ampule (reaction vessel); G, reaction mixture; H, Dewar cooling bath; I, cold medium; J, inlet for introducing reagents and solvents.

the solution was cooled to −95 °C, a pentane solution of t-C_4H_9Li (1.77 M, 31.13 mL, 55.1 mmol) was added through J at −95 °C. Then the mixture was stirred for 3 h at −78 °C, giving the suspension containing the lithiated ω side-chain component. In a separate 200-mL round-bottomed flask was placed copper(I) iodide (5.247 g, 27.6 mmol), which was heated with a heat gun in vacuo to remove any moisture, and the flask was filled with argon. Dry THF (100 mL) and tributylphosphine (17.85 mL, 71.6 mmol) were added to room temperature, and the mixture was stirred until the suspension became a clear solution (5 min). This mixture was cooled to −78 °C and then added to the lithium derivative in ampule F from inlet J through a stainless steel cannula under argon stream. The flask was rinsed with dry THF (100 mL), and the resulting THF solution was added to ampule F with cooling at −78 °C. The mixture was stirred for 10 min at −78 °C. To this organocopper reagent was added a solution of (R)-4-(tert-butyldimethylsiloxy)-2-cyclopentenone (1) (5.793 g, 27.3 mmol) in THF (200 mL) from inlet A through the cooled (−78 °C) spiral tube D over the period of 3.5 h by using a glass syringe under the drive with a syringe pump (*Caution*: slow addition is crucial for high-yield reaction). The syringe was rinsed with additional dry THF (10 mL), and the THF solution was added to ampule F with cooling at −78 °C. After the mixture was stirred for 10 min at −78 °C, HMPA (25 mL) was added via J, and the mixture was stirred for 30 min at −78 °C. Then a solution of triphenyltin chloride (10.741 g, 27.6 mmol) in THF (30 mL) was added at the same temperature. After the mixture was warmed to −30 °C, a solution of methyl 7-iodo-5-heptynoate (**5**) (36.29 g, 136 mmol) in HMPA (22.46 mL) was added from inlet J. Then the cold bath was quickly replaced by a CryoCool-controlled −30 °C bath. After being stirred at −30 °C for 39 h, the reaction mixture was poured into saturated aqueous ammonium chloride solution (300 mL). The organic layer was separated, washed with saturated aqueous sodium chloride solution (300 mL), dried over anhydrous sodium sulfate, and evaporated. TLC (5:1 hexane/ethyl acetate as solvent) showed seven spots having R_f values of 0.16 (triphenyltin derivatives, tailing spot), 0.45 (α side-chain unit **5**), 0.50 (desired product **12**), 0.58 (unknown product in very small quantity), 0.64 (organocopper phosphine complex), 0.67 (1,4-adduct **7**), and 0.82 (tributylphosphine). Isolation of the product **12** was conducted as follows: First, the crude mixture was chromatographed through a short column filled with silica gel (50 g) by using a 1:5 mixture of ethyl acetate and hexane as eluant (500 mL). By this rough chromatographic operation the organotin derivatives, organocopper phosphine complex, simple 1,4-adduct **7**, and tributylphosphine were mostly removed. Fractions containing **12** and **5** were further subjected to silica gel (600 g) column chromatography with a 1:60 and then 1:20 mixture of ethyl acetate and hexane as eluants (9.0 and 6.3 L each) to give **12** (12.31 g, 76%) a colorless oil and then **5** (23.24 g, 75% recovery). The three-component coupling product was proven homogeneous by ^{13}C NMR. **12**: TLC R_f 0.50 (1:5 ethyl acetate/hexane); IR (neat) 1746, 1246, 827, 767 cm^{-1}; $[\alpha]^{17}_D$ −13.2° (c 0.59, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.04 and 0.06 (s each, 12, 4 $SiCH_3$), 0.89 (s, 18, 2 $SiC(CH_3)_3$), 0.92 (t, 3, J = 6.5 Hz, CH_3), 1.1–1.5 (m, 8, 4 CH_2), 1.7–2.9 (m, 12, 5 CH_2 and 2 CH), 3.65 (s, 3, OCH_3), 4.05 (m, 2, 2 CHO), 5.4–5.7 (m, 2, vinyls); ^{13}C NMR ($CDCl_3$) δ −4.7, −4.5 (2 C), −4.2, 13.6, 14.0, 16.9, 18.0, 18.2, 22.6, 24.2, 25.0, 25.8 (3 C), 25.9 (3 C),

(41) Martel, J. Jpn. Tokkyo Koho 46-28153; Jpn. Kokai Tokkyo Koho 46-5625.
(42) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978; *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
(43) Doyle, J. R.; Slade, P. E.; Jonassen, H. B. *Inorg. Synth.* **1960**, *6*, 218.
(44) This method for silver nitrate impregnation of silica gel TLC plates was suggested by Professor H. Yamamoto of Nagoya University.

31.9, 32.7, 38.6, 47.7, 51.4, 51.9, 52.9, 72.7, 73.1, 77.3, 80.8, 128.2, 136.8, 173.4, 213.4; MS, *m/z* 592 (M^+), 577, 561, 535, 521; HRMS, *m/z* calcd for $C_{33}H_{60}O_5Si_2$ (M^+) 592.3979, found 592.3956.

The small-scale reaction was conducted as follows. A 150-mL ampule of the same type was used as reaction vessel. The reaction and workup procedure was similar to those described above. The vinyllithium derivative was prepared by adding a pentane solution of *tert*-butyllithium (1.92 M, 1.72 mL, 3.30 mmol) to a solution of **2** (607.8 mg, 1.65 mmol) in dry ether (6 mL) at −95 °C and then by stirring the mixture at −78 °C for 3 h. The organocopper complex was prepared by introducing a solution of copper(I) iodide (314.2 mg, 1.65 mmol) and tributylphosphine (1.07 mL, 4.29 mmol) in dry THF (12 mL) to the vinyllithium compound prepared above at −78 °C. The conjugate addition was conducted by slow addition of a solution of the enone **1** (318.5 mg, 1.50 mmol) in dry THF (12 mL) to the organocopper reagent at −78 °C over a period of 1 h. The alkylation of the enolate was performed by sequential addition of HMPA (1.5 mL, 8.62 mmol) at −78 °C, a solution of triphenyltin chloride (643.2 mg, 1.65 mmol) in dry THF (2 mL) at −78 °C, and a solution of the iodide **5** (2.00 g, 7.50 mmol) in HMPA (1.37 mL, 7.87 mmol) at −30 °C. The mixture was stirred at −30 °C for 20 h and worked up. The products were chromatographed on a short silica gel (5 g) column by using a 1:5 mixture of ethyl acetate and hexane as eluant. The semipurified product was further subjected to column chromatography with silica gel (50 g) and a 1:60 and then 1:20 mixture of ethyl acetate and hexane as eluants to give **12** (732.0 mg, 82%) and then **5** (1.50 g, 90% recovery).

11,15-*O*-Bis(*tert*-butyldimethylsilyl)PGE$_2$ Methyl Ester (8). This compound was synthesized by the similar reaction and workup procedure to the synthesis of **12**. The conjugate addition was conducted by addition of a THF solution of the cyclopentenone **1** (311 mg, 1.46 mmol) to the organocopper reagent prepared from **2** on 1.61-mmol scale as described above. The alkylation of the resulting enolate was performed by sequential addition of HMPA (1.5 mL, 8.62 mmol) at −78 °C, a solution of triphenyltin chloride (628 mg, 1.61 mmol) in THF (2 mL) at −78 °C, and a solution of methyl (*Z*)-7-iodo-5-heptenoate (**4**) (1.96 g, 7.30 mmol) in HMPA (1.37 mL, 7.87 mmol) at −20 °C and then by stirring the mixture at −20 °C for 17 h. The reaction mixture after aqueous workup was chromatographed on a column of a small amount of silica gel (5 g) eluted by a 1:5 mixture of ethyl acetate and hexane. The semipurified product was subjected to column chromatography on silica gel (50 g) with a 1:60 and then 1:20 mixture of ethyl acetate and hexane as eluants to give the C-8 epimer of **8** (23.7 mg, 3%, R_f 0.57 (1:5 hexane/ethyl acetate)) and then **8** (677 mg, 78%). Compound **8**: TLC R_f 0.55 (1:5 ethyl acetate/hexane); IR (neat) 1743, 1243, 1000, 964, 927, 828, 768 cm^{-1}; $[\alpha]^{19}_D$ −49.9° (*c* 1.02, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.03 and 0.06 (s, 12, 4 $SiCH_3$), 0.8–1.0 (m, 21, 2 $SiC(CH_3)_3$ and CH_3), 1.2–1.5 (m, 8, 4 CH_2), 1.6–2.9 (m, 12, 5 CH_2 and 2 CH), 3.67 (s, 3, OCH_3), 4.06 (m, 2, 2 CHO), 5.37 (m, 1, vinyl), 5.54 (m, 1, vinyl); ^{13}C NMR ($CDCl_3$) δ −4.6 (2 C), −4.2 (2 C), 14.1 (2 C), 18.0, 18.3, 22.7, 24.8, 25.1, 25.3, 25.9 (4 C), 26.7, 32.0, 33.5 (2 C), 38.6, 47.7, 51.3, 52.8, 54.0, 72.7, 73.3, 126.8, 128.8, 130.7, 136.5, 173.7, 214.7; HRMS, *m/z* calcd for $C_{33}H_{62}O_5Si_2$ (M^+) 594.4136, found 594.4142. The C-8 epimer was epimerized slowly to **8** while being put on the silica gel TLC plate.

The compound **8** was also synthesized by partial hydrogenation of the triple bond of **12**: The mixture of **12** (48.2 mg, 0.081 mmol), benzene (2.5 mL), cyclohexane (2.5 mL), 5% palladium on barium sulfate (75 mg), and synthetic quiloline (75 mg) was stirred at 25 °C for 3 h and at 40 °C for 4.5 h under hydrogen (1 atm). The catalyst was filtered through a Celite pad, and the filtrate was evaporated. Chromatography on silica gel (8 g) eluted by a 1:10 mixture of ether and hexane gave **8** (41.8 mg, 87%) as a colorless oil.

Unless otherwise stated, partial hydrogenation of other compounds was conducted by the similar procedure.

PGE$_2$ Methyl Ester (10). Compound **8** (40 mg, 0.067 mmol) was dissolved in dry acetonitrile (8 mL) and to this was added 15% hydrogen fluoride/pyridine mixture (0.1 mL) at 0 °C with stirring. The mixture was stirred at 24 °C for 30 min. Additional hydrogen fluoride/pyridine mixture (0.4 mL) was added, and the mixture was further stirred for 3 h at this temperature. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic extracts were dried over sodium sulfate and evaporated. The residual oil was subjected to a silica gel column chromatography (2 g) with a 1:1 mixture of ethyl acetate and hexane and then ethyl acetate as eluants to give **10** (24.1 mg, 98%): IR (neat) 3680–3080, 1744, 970 cm^{-1}; $[\alpha]^{22}_D$ −71.7° (*c* 1.04, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3, J = 6.5 Hz, CH_3), 1.1–2.9 (m, 20, 9 CH_2 and 2 CH), 3.08 (br s, 1, OH), 3.66 (s, 3, OCH_3), 4.06 (m, 3, 2 CHO and OH), 5.34 (m, 1, vinyl), 5.70 (m, 1, vinyl); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.7, 25.1, 26.6, 31.7, 33.5, 37.3, 46.1, 51.5, 53.7, 54.5, 72.0, 73.0, 126.6, 130.8, 131.5, 136.8, 174.0, 214.1. These optical and spectroscopic properties as well as chromatographic behavior were identical with those of the authentic sample prepared from commercial PGE$_2$ (Ono Pharmaceutical Co.) and diazomethane, $[\alpha]^{20}_D$ −71.1° (*c* 1.56, CH_3OH).

11,15-*O*-Bis(*tert*-butyldimethylsilyl)PGE$_1$ Methyl Ester (14). The conjugate addition was conducted by introducing a THF solution of the cyclopentenone **1** (319 mg, 1.50 mmol) to the organocopper reagent prepared from **2** on 1.65-mmol scale as described in the synthesis of **12**. The alkylation of the resulting enolate was performed by sequential addition of HMPA (1.5 mL, 8.62 mmol) at −78 °C, a solution of triphenyltin chloride (643 mg, 1.65 mmol) in THF (2 mL) at −78 °C, and a solution of methyl 7-iodoheptanoate (**6**) (2.09 g, 7.73 mmol) in HMPA (1.37 mL, 7.87 mmol) at −20 °C, and then by stirring the mixture at −20 °C for 16 h. After workup, the reaction mixture was chromatographed on a silica gel (5 g) short column by using a 1:5 mixture of ethyl acetate and hexane as eluant. The semipurified product was further chromatographed on a column of silica gel (50 g) eluted by a 1:60 and then 1:20 mixture of ethyl acetate and hexane to give **14** (178.7 mg, 20%): TLC R_f 0.52 (1:5 ethyl acetate/hexane); IR (neat) 1743, 1000, 970, 830, 770 cm^{-1}; $[\alpha]^{17}_D$ −34.2° (*c* 1.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.02 and 0.05 (s, 12, 4 $SiCH_3$), 0.88 (s, 9, $SiC(CH_3)_3$), 0.90 (s, 9, $SiC(CH_3)_3$), 0.85–0.95 (t, 3, J = 6.5 Hz, CH_3), 1.1–2.8 (m, 24, 11 CH_2 and 2 CH), 3.66 (s, 3, OCH_3), 4.08 (m, 2, 2 CHO), 5.54 (m, 2, vinyls); HRMS, *m/z* calcd for $C_{33}H_{64}O_5Si_2$ (M^+) 596.4292, found 596.4269.

The compound **14** was also synthesized by selective hydrogenation of the triple bond of **12** (8.1 mg, 0.014 mmol) by 5% palladium on charcoal (5 mg) in methanol (1 mL) (0 °C, 12.5 h). Chromatography on silica gel (3 g) with a 1:10 mixture of ethyl acetate and hexane as eluant gave **14** (5.8 mg, 71%).

PGE$_1$ Methyl Ester (16). To a solution of **14** (4.8 mg, 8.0 μmol) in acetonitrile (0.5 mL) was added 15% hydrogen fluoride–pyridine mixture (0.05 mL) at 0 °C. The mixture was stirred at 19 °C for 4 h and poured into saturated aqueous sodium hydrogen carbonate solution (5 mL). The extracted material with $CHCl_3$ (15 mL × 3) was subjected to chromatography on silica gel (1 g) with a 1:1 mixture of hexane and ethyl acetate as eluant to give **16** (2.8 mg, 95%): TLC R_f 0.22 (1:3 hexane/ethyl acetate); IR (neat) 3390, 1748, 970 cm^{-1}; $[\alpha]^{22}_D$ −52.0° (*c* 1.01, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, CH_3), 1.1–1.8 (m, 18, 9 CH_2), 1.8–2.6 (m, 7, 2 CH_2, CH, and 2 OH), 2.73 (dd, 1, J = 18.0 and 7.6 Hz, CH), 3.68 (s, 3, OCH_3), 3.9–4.3 (m, 2, 2 CHO), 5.63 (m, 2, vinyls). These spectral data and chromatographic behavior were identical with those of the authentic sample donated by Ono Pharmaceutical Co.

11-*O*-(*tert*-Butyldimethylsilyl)-15-*O*-(tetrahydropyran-2-yl)PGE$_2$ Methyl Ester (9). The conjugate addition was conducted by introducing a THF solution of the cyclopentenone **1** (319 mg, 1.50 mmol) to the organocopper reagent prepared from **3** on 1.65-mmol scale as described in the synthesis of **12**. The alkylation of the resulting enolate was conducted by sequential addition of HMPA (1.5 mL, 8.62 mmol) at −78 °C, a solution of triphenyltin chloride (643 mg, 1.65 mmol) in THF (2 mL) at −78 °C, and a solution of methyl (*Z*)-7-iodo-5-heptenoate (**4**) (2.01 g, 7.50 mmol) in HMPA (1.37 mL, 7.87 mmol) at −20 °C and then by stirring the mixture at −20 °C for 16.5 h. After workup, the mixture was chromatographed on a column of a small amount of silica gel (5 g) by using a 1:5 mixture of ethyl acetate and hexane as eluant to remove organotin compounds, organocopper phosphine complexes, and tributylphosphine. The semipurified product was further subjected to column chromatography on silica gel (50 g) eluted with a 1:60, 1:20, and then 1:10 mixture of ethyl acetate and hexane to give **9** (656 mg, 77%) as a colorless oil: TLC R_f 0.42 (1:5 ethyl acetate/hexane); IR (neat) 1744, 1240, 1102, 1013, 827, 767 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6, 2 $SiCH_3$), 0.88 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.0–3.0 (m, 26, 12 CH_2 and 2 CH), 3.3–4.3 (m, 7, OCH_3, CH_2O, and 2 CHO), 4.69 (br s, 1, OCHO), 5.3–5.7 (m, 4, vinyls); $[\alpha]^{16}_D$ −60.0° (*c* 1.02, CH_3OH); HRMS, *m/z* calcd for $C_{31}H_{53}O_6Si$ ($M^+ - CH_3$) 549.3611, found 549.3587.

11,15-*O*-Bis(*tert*-butyldimethylsilyl)PGF$_{2\alpha}$ Methyl Ester (18). In a 10-mL test tube was placed the ketone **8** (48.4 mg, 0.0813 mmol), and it was dissolved in dry THF (4 mL). After the mixture was cooled to −78 °C, a solution of L-Selectride (Aldrich) in THF (0.098 mL, 0.0976 mmol) was added. The mixture was stirred for 30 min at this temperature, and then 3% H_2O_2 (2 mL) was added to the mixture at −78 °C. Extractive workup followed by chromatography on a column of silica gel (5 g) eluted by a 1:10 mixture of ethyl acetate and hexane give **18** (46.4 mg, 95%) as a colorless oil: TLC R_f 0.32 (1:5 ethyl acetate/hexane); IR (neat) 3610–3280, 1745, 1250, 1000, 970, 938, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 and 0.05 (s each, 12, 4 $SiCH_3$), 0.8–1.0 (m, 21, 2 $SiC(CH_3)_3$ and CH_3), 1.2–2.4 (m, 20, 9 CH_2 and 2 CH), 2.69 (d, 1, J = 9.5 Hz, OH), 3.67 (s, 3, OCH_3), 4.05 (br, 3, 3 CHO), 5.40 (m, 2, vinyls); $[\alpha]^{23}_D$ +12.3° (*c* 1.04, CH_3OH); HRMS, *m/z* calcd for $C_{29}H_{55}O_5Si_2$ ($M^+ - C_4H_9$) 539.3588, found 539.3616.

The compound **18** was also synthesized by partial hydrogenation of **25** (28.7 mg, 0.048 mmol) in a mixture of benzene (1 mL) and cyclohexane (1 mL) containing Lindlar catalyst (28.7 mg) (23 °C, 12 h). Column chromatography on silica gel (6 g) by using a 1:15:2 mixture of ethyl acetate, hexane, and benzene as eluent gave **18** (23.2 mg, 81%).

$PGF_{2\alpha}$ Methyl Ester (22). The compound **18** (21 mg, 0.035 mmol) was dissolved in a 10:3.3:1 mixture of acetic acid, water, and THF (1.5 mL), and the mixture was stirred at 55 °C for 1.5 h. The mixture was concentrated in vacuo followed by the azeotropic evaporation with toluene (three times). Chromatography on silica gel (3 g) eluted with a 1:1 mixture of ethyl acetate and hexane and then ethyl acetate gave **22** (11 mg, 85%) as a colorless oil: R_f 0.2 (6:3:1 ethyl acetate/cyclohexane/THF); IR (neat) 3640–3040, 1738, 1435, 1160, 1042, 1020, 968, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, J = 6.5 Hz, CH_3), 1.2–2.4 (m, 20, CH_2CO, 6 CH_2, 2 CH_2C=, and 2 CH), 2.57 (br, 1, OH), 3.29 (br, 1, OH), 3.69 (s, 3, OCH_3), 4.03 (br m, 3, 3 CHO), 5.3–5.6 (m, 2, vinyls); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.8, 25.2, 25.6, 26.6, 31.8, 33.5, 37.3, 43.0, 50.5, 51.6, 55.8, 72.9, 73.0, 78.0, 129.1, 129.6, 132.6, 135.3, 174.3; $[\alpha]^{20}_D$ +31.4° (c 0.42, CH_3OH). These spectral data and chromatographic behavior were identical with those of the authentic sample, $[\alpha]^{20}_D$ +28.3° (c 1.2, CH_3OH), derived by reaction of diazomethane and commercial $PGF_{2\alpha}$ donated by Ono Pharmaceutical Co.

11-*O*-(*tert*-Butyldimethylsilyl)-15-*O*-(tetrahydropyran-2-yl)$PGF_{2\alpha}$ Methyl Ester (19). A THF solution of L-Selectride (Aldrich; 0.096 mL, 0.0958 mmol) was added to a solution of the ketone **9** (45.1 mg, 0.0798 mmol) in THF (4 mL) at −78 °C, and then the mixture was stirred at −78 °C for 15 min. Purification of the product by column chromatography on silica gel (5 g) eluted with a 1:5 mixture of ethyl acetate and hexane gave **19** (42.1 mg, 93%) as a colorless oil: TLC R_f 0.46 (1:4 ethyl acetate/hexane); IR ($CHCl_3$) 3740–3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6, 2 $SiCH_3$), 0.7–1.0 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.0–2.7 (m, 27, 12 CH_2, 2 CH, and OH), 3.3–4.2 (m, 8, OCH_3, CH_2O, and 3 CHO), 4.67 (m, 1, OCHO), 5.1–5.6 (m, 4, vinyls); $[\alpha]^{27}_D$ −20.6° (c 1.02, CH_3OH); HRMS, m/z calcd for $C_{28}H_{49}O_6Si$ ($M^+ - C_4H_9$) 509.3298, found 509.3289.

The compound **19** was also synthesized by partial hydrogenation of **26** (21.1 mg, 0.0374 mmol) in a 50:50:1 mixture of cyclohexane, benzene, and cyclohexene (2 mL) containing Lindlar catalyst (24.1 mg) (26 °C, 13 h). Column chromatography on silica gel (2.4 g) by a 1:12 mixture of ethyl acetate and hexane as eluant gave **19** (20.3 mg, 96%) as a colorless oil.

11-*O*-(*tert*-Butyldimethylsilyl)-9,15-*O*-bis(tetrahydropyran-2-yl)$PGF_{2\alpha}$ Methyl Ester (20). To a solution of the alcohol **19** (20.3 mg, 0.0358 mmol) in dry dichloromethane (5 mL) were added 3,4-dihydro-2*H*-pyran (6.0 mg, 0.0716 mmol) and pyridinium *p*-toluenesulfonate (4.5 mg, 0.0179 mmol) at 0 °C, and the mixture was stirred at this temperature for 10 min and then at 26 °C for 3 h. After being diluted with dichloromethane (5 mL), saturated brine (5 mL) was added to the mixture with vigorous shaking. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (5 mL × 2). The combined extracts were dried and evaporated. The residual oil was chromatographed on a silica gel (2 g) column by using a 1:15 mixture of ethyl acetate and hexane as eluant to give **20** (23.2 mg, 100%) as a colorless oil: TLC R_f 0.58 (1:4 ethyl acetate/hexane); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6, 2 $SiCH_3$), 0.7–1.0 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.0–2.6 (m, 32, 15 CH_2 and 2 CH), 3.3–4.2 (m, 10, OCH_3, 2 CH_2O, and 3 CHO), 4.5–5.0 (m, 2, OCHO), 5.2–5.6 (m, 4, vinyls); $[\alpha]^{27}_D$ −8.3° (c 0.92, CH_3OH). HRMS, m/z calcd for $C_{37}H_{66}O_7Si$ (M^+) 650.4578, found 650.4584.

9,15-*O*-Bis(tetrahydropyran-2-yl)$PGF_{2\alpha}$ Methyl Ester (21). To a solution of **20** (18.4 mg, 0.0283 mmol) in THF (0.4 mL) was added a commercial THF solution of tetrabutylammonium fluoride (0.42 mL, 0.42 mmol) at 26 °C, and the mixture was stirred at this temperature for 3 h and diluted with THF (5 mL). Saturated brine (5 mL) was added to the mixture with vigorous shaking. Extractive workup with ethyl acetate (10 mL × 2) followed by column chromatography silica gel (1.8 g) with a 1:3 mixture of ethyl acetate and hexane as eluant gave **21** (14.4 mg, 95%) as a colorless oil: TLC R_f 0.14 (1:2 ethyl acetate/hexane); IR ($CHCl_3$) 3700–3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 6.0 Hz, CH_3), 1.0–2.6 (m, 33, 15 CH_2, 2 CH, and OH), 3.3–4.3 (m, 10, OCH_3, 2 CH_2O, and 3 CHO), 4.5–4.8 (m, 2, 2 OCHO), 5.1–5.6 (m, 4, vinyls); $[\alpha]^{28}_D$ −6.76° (c 0.72, CH_3OH); HRMS, m/z calcd for $C_{26}H_{42}O_5$ ($M^+ - C_5H_{10}O_2$) 434.3033, found 434.3009.

PGD_2 (24). In a 10-mL test tube was placed **21** (16.3 mg, 0.0304 mmol), which was dissolved in methanol (1 mL) and cooled to 0 °C. To this was added 20% aqueous sodium hydroxide solution (1 mL). The mixture was stirred for 18.3 h at 16 °C and then acidified by adding 1 N aqueous oxalic acid solution (10 mL) at 0 °C. The mixture was extracted with ethyl acetate (10 mL × 3), and the combined extracts were dried and evaporated. The residual oil was placed in a 10-mL test tube and dissolved in acetone (0.8 mL) and cooled to −30 °C. Jones reagent (2.4 M, 19.1 mL, 0.0456 mmol) was added slowly to the mixture at −30 °C, and the mixture was stirred for 20 min at this temperature. Ethyl acetate (10 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL) were added to the mixture. The resulting mixture was acidified with 1 N aqueous oxalic acid (10 mL), and then the organic layer was separated. The aqueous layer was extracted with ethyl acetate (10 mL × 2), and the combined extracts were dried and evaporated. The residual oil was dissolved in a 3:1:1 mixture of acetic acid, water, and THF (2 mL), and the mixture was stirred at 16 °C for 1 h and at 27 °C for 29 h. The mixture was concentrated in vacuo at room temperature, and the residual material was dissolved in toluene. The toluene solution was evaporated under reduced pressure, and this azeotropic operation was repeated three times. Chromatography on silica gel (1.5 g) eluted by a 4:2:1 mixture of cyclohexane, ethyl acetate, and acetone and then acetone gave PGD_2 (**24**) (8.0 mg, 75%) as white crystals: mp 58.0–58.5 °C; TLC R_f 0.11 (4:1 ethyl acetate/hexane); IR ($CHCl_3$) 3740–2400, 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 6.0 Hz, CH_3), 1.1–2.2 (m, 15, 7 CH_2 and CH), 2.35 (t, 2, J = 5.7 Hz, CH_2CO), 2.43 (d, 2, J = 2.6 Hz, CH_2CO), 2.7–3.1 (m, 1, CHCO), 3.63 (br s, 3, 2 OH and CO_2H), 4.17 (br q, 1, J = 6.0 Hz, CHO), 4.51 (m, 1, CHO), 5.3–5.8 (m, 4, vinyls); $[\alpha]^{18}_D$ +8.8° (c 0.17, THF). These spectral data and chromatographic behavior were identical with those of the commercial authentic sample (Ono Pharmaceutical Co.). Rotation value, $[\alpha]^{21}_D$ +7.5° (c 1.0, THF), was given by Ono Pharmaceutical Co. for authentic PGD_2.

5,6-Didehydro-11-*O*-(*tert*-butyldimethylsilyl)-15-*O*-(tetrahydropyran-2-yl)PGE_2 Methyl Ester (13). The conjugate addition was conducted by addition of a THF solution of the cyclopentenone **1** (319 mg, 1.50 mmol) to the organocopper reagent prepared from **3** on 1.65-mmol scale as described in the synthesis of **12**. The alkylation of the resulting enolate was performed by sequential addition of HMPA (1.5 mL, 8.62 mmol) at −78 °C, a solution of triphenyltin chloride (643 mg, 1.65 mmol) in THF (2 mL) at −78 °C, and a solution of methyl 7-iodo-5heptynoate (**5**) (1.20 g, 4.50 mmol) in HMPA (1.37 mL, 7.87 mmol) at −30 °C and then by stirring the mixture at −30 °C for 20 h. Most of the organotin compounds, an organocopper phosphine complex, and tributylphosphine were removed by column chromatography on a small amount of silica gel (5 g) eluted by a 1:5 mixture of ethyl acetate and hexane. The semipurified product was further chromatographed on a column of silica gel (50 g) by using a 1:50, 1:20, and then 1:10 mixture of ethyl acetate and hexane to give **13** (592.6 mg, 70%, a colorless oil), the simple 1,4-adduct (123.9 mg, 19%, R_f 0.42 (1:4 ethyl acetate/hexane)), and unreacted **5** (582.2 mg, 73% recovery, R_f 0.43 (1:4 ethyl acetate/hexane)). **13**: TLC R_f 0.31 (1:4 ethyl acetate/hexane); IR ($CHCl_3$) 2920, 2850, 1740, 1360, 1100, 880, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0–0.1 (s, 6, 2 $SiCH_3$), 0.7–1.0 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.0–3.0 (m, 26, 12 CH_2 and 2 CH), 3.3–4.3 (m, 7, OCH_3, CH_2O, and 2 CHO), 4.69 (m, 1, OCHO), 5.4–5.7 (m, 2, vinyls); $[\alpha]^{26}_D$ −46.1° (c 0.38, CH_3OH); HRMS, m/z calcd for $C_{28}H_{45}O_6Si$ ($M^+ - C_4H_9$) 505.2986, found 505.2967.

11-*O*-(*tert*-Butyldimethylsilyl)-15-*O*-(tetrahydropyran-2-yl)PGE_1 Methyl Ester (15). To a solution of **13** (9.6 mg, 0.0171 mmol) in a 50:50:1 mixture of cyclohexane, benzene, and cyclododecene (1 mL) was added 5% Pd on charcoal (12.6 mg). The mixture was stirred at 27 °C for 3 h under hydrogen atmosphere (1 atm). Chromatography of the product on a silica gel (1 g) column eluted by a 1:10 mixture of ethyl acetate and hexane gave **15** (6.6 mg, 68%) as a colorless oil: TLC R_f 0.48 (1:4 ethyl acetate/hexane); IR ($CHCl_3$) 1740, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6, 2 $SiCH_3$), 0.7–1.0 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.0–2.8 (m, 30, 14 CH_2 and 2 CH), 3.3–4.2 (m, 7, OCH_3, CH_2O, and 2 CHO), 4.68 (m, 1, OCHO), 5.4–5.6 (m, 2, vinyls); $[\alpha]^{23}_D$ −66.2° (c 0.60, CH_3OH); HRMS, m/z calcd for $C_{32}H_{58}O_6Si$ (M^+) 566.4003, found 566.4012.

5,6-Didehydro-11,15-*O*-bis(*tert*-butyldimethylsilyl)$PGF_{2\alpha}$ Methyl Ester (25). A THF solution of L-Selectride (Aldrich; 0.128 mL, 0.128 mmol) was added to a solution of **12** (63.2 mg, 0.107 mmol) and methyl acetate (0.025 mL, 0.32 mmol) in THF (6 mL) at −78 °C. Then the mixture was stirred at −78 °C for 20 min. Purification of the product by column chromatography on silica gel (6 g) eluted with a 1:10 mixture of ethyl acetate and hexane gave **25** (60.3 mg, 95%, a colorless oil): TLC R_f 0.29 (1:5 ethyl acetate/hexane); IR (neat) 3640–3080, 1745, 1247, 1020, 970, 930, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 and 0.05 (s each, 12, 4 $SiCH_3$), 0.7–1.0 (m, 21, 2 $SiC(CH_3)_3$ and CH_3), 1.1–2.7 (m, 21, 9 CH_2, 2 CH, and OH), 3.67 (s, 3, OCH_3), 3.9–4.4 (br, 3, 3 CHO), 5.4–5.5 (m, 2, vinyls); $[\alpha]^{21}_D$ +0.37° (c 0.72, CH_3OH); HRMS, m/z calcd for $C_{33}H_{60}O_4Si_2$ ($M^+ - H_2O$) 576.4030, found 576.4018.

The compound **25** was also synthesized by reduction with (*R*)-BINAL-H (**31**): **31** was prepared in situ by addition of a solution of ethanol in THF (1.1 M, 0.47 mL, 0.5 mmol) and a solution of (*R*)-(+)-binaphthol (144.7 mg, 0.5 mmol) in THF (0.75 mL) to a solution of lithium aluminum hydride in THF (1.07 M, 0.47 mL, 0.5 mmol) at −78

°C.[31] This reducing agent was added to a solution of **12** (95.9 mg, 0.162 mmol) in THF (1 mL) at −100 °C. After being stirred for 0.5 h at −100 °C, the mixture was further stirred at −78 °C for 24 h and then quenched with methanol (0.1 mL), followed by the addition of water (0.2 mL) and ether (10 mL). The mixture was stirred for 30 min, dried over magnesium sulfate, and filtered through a Celite pad. The filtrate was concentrated in vacuo, and chromatography of the residual material on a silica gel (20 g) by elution with 1:10 mixture of hexane and ethyl acetate gave **12** (31.4 mg, 33% recovery), the 9α alcohol **25** (62.7 mg, 65%), and the 9β isomer (0.8 mg, 0.8%) (9α/9β 98.7:1.3). 9β isomer: R_f 0.19 (1:5 ethyl acetate/hexane); IR (CCl_4) 3700–3200, 1745, 1460, 1255, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 and 0.05 (s each, 12, 4 $SiCH_3$), 0.8–1.0 (m, 21, 2 $SiC(CH_3)_3$ and CH_3), 1.1–2.7 (m, 21, 9 CH_2, 2 CH, and OH), 3.67 (s, 3, OCH_3), 3.9–4.4 (m, 3, 3 CHO), 5.4–5.6 (m, 2, vinyls). HRMS, *m/z* calcd for $C_{33}H_{60}O_4Si_2$ ($M^+ - H_2O$) 576.4030, found 576.4047.

The reduction of **12** (102.7 mg, 0.173 mmol) with **32** (0.54 mmol) was very slow and under comparable conditions **25** and its 9β isomer were obtained in 5.3 and 0.25% yields, respectively.

The relative rates (k_R/k_S) were estimated by comparing product yields of the reduction at the early stage. The observed k_R/k_S ratios were 516:1 (5 min), 237:1 (20 min), 130:1 (1 h), and 85:1 (2 h). In addition, stereoselectivity (9α/9β) in reduction of **12** with **31** changed from 99.3:0.7 (3 h) to 98.7:1.3 (24 h).

5,6-Didehydro-11-*O*-(*tert*-butyldimethylsilyl)-15-*O*-(tetrahydropyran-2-yl)$PGF_{2\alpha}$ Methyl Ester (26). The reduction was run by adding a THF solution of L-Selectride (Aldrich; 0.113 mL, 0.113 mmol) to a solution of **13** (53.2 mg, 0.0945 mmol) in THF (4 mL) at −78 °C and then by stirring the mixture at −78 °C for 20 min. Extractive workup followed by column chromatography on silica gel (5 g) eluted with a 1:5 mixture of ethyl acetate and hexane gave **13** (1.6 mg, 3% recovery) and **26** (49.1 mg, 92%, a colorless oil). **26**: TLC R_f 0.53 (1:2 ethyl acetate/hexane); IR ($CHCl_3$) 3720–3300, 2920, 2850, 2210, 1730, 1430, 1100, 860, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6, 2 $SiCH_3$), 0.6–1.1 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.1–2.7 (m, 27, 12 CH_2, 2 CH, and OH), 3.3–4.4 (m, 8, OCH_3, CH_2O, and 3 CHO), 4.66 (m, 1, OCHO), 5.2–5.6 (m, 2, vinyls); $[\alpha]^{26}_D$ −28.8° (*c* 1.30, CH_3OH); HRMS, *m/z* calcd for $C_{32}H_{56}O_6Si$ (M^+) 564.3846, found 564.3828.

11,15-*O*-Bis(*tert*-butyldimethylsilyl)$PGF_{1\alpha}$ Methyl Ester (27). The reduction was carried out by addition of a THF solution of L-Selectride (Aldrich; 0.10 mL, 0.10 mmol) to a solution of **14** (49.7 mg, 0.0832 mmol) in THF (4 mL) at −78 °C and then by stirring the mixture at −78 °C for 30 min. Extractive workup and column chromatography on silica gel (5 g) eluted with 1:10 mixture of ethyl acetate and hexane gave **14** (1.1 mg, 2.2% recovery) and **27** (45.9 mg, 92%, a colorless oil). **27**: TLC *R* 0.40 (5:1 hexane/ethyl acetate); IR (neat) 3600–3200, 1743, 1000, 968, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 and 0.05 (s each, 12, 4 $SiCH_3$), 0.87 and 0.89 (s each, 18, 2 $SiC(CH_3)_3$), 0.87–0.92 (hidden in this region, 3, CH_3), 1.2–2.8 (m, 25, 11 CH_2, 2 CH, and OH), 3.66 (s, 3, OCH_3), 4.05 (br, 3, 3 CHO), 5.38 (m, 2, vinyls); $[\alpha]^{21}_D$ +7.7° (*c* 0.49, CH_3OH); HRMS, *m/z* calcd for $C_{33}H_{66}O_5Si_2$ (M^+) 598.4449, found 598.4441.

The compound **27** was also synthesized by selective hydrogenation of the triple bond of **25** (14.3 mg, 0.024 mmol) in a mixture of benzene (2 mL) and cyclohexane (2 mL) in the presence of 5% palladium on barium sulfate (24 mg) and synthetic quinoline (32 mg) (40 °C, 2.7 h). Column chromatography on silica gel (3 g) eluted by a 1:10 mixture of ethyl acetate and hexane gave **27** (8 mg, 60%).

$PGF_{1\alpha}$ Methyl Ester (28). The compound **27** (14.4 mg, 0.024 mmol) was dissolved in a 10:3.3:1 mixture of acetic acid, water, and THF (1.5 mL), and the mixture was stirred at 60 °C for 1.5 h. The reaction mixture was concentrated in vacuo, and the the residual material was subjected to azeotropic evaporation with toluene. Column chromatography on silica gel (3 g) eluted by a 1:1 mixture of ethyl acetate and hexane and then acetate gave **28** (6.8 mg, 76%) as a colorless oil: R_f 0.26 (6:3:1 ethyl acetate/cyclohexane/THF); IR ($CHCl_3$) 3630–3200, 1732, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, *J* = 6 Hz, CH_3), 1.1–3.0 (m, 27, 11 CH_2, 2 CH, and 3 OH), 3.66 (s, 3, OCH_3), 4.05 (br, 3, 3 CHO), 5.48 (m, 2, vinyls); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.4, 24.8, 25.0, 27.9 (2 C), 28.9, 29.3, 31.7, 34.0, 37.5, 43.3, 50.7, 51.0, 56.4, 72.7, 73.5, 78.5, 132.5, 134.7, 173.8; $[\alpha]^{21}_D$ +29.3° (*c* 0.30, CH_3OH). These spectral data and chromatographic behavior were identical with those of the authentic material derived from PGE_1 methyl ester by L-Selectride (Aldrich) reduction.[32,45]

11,15-*O*-Bis(*tert*-butyldimethylsilyl)PGI_2 Methyl Ester (33). In a 20-mL test tube was placed the acetylenic alcohol **25** (19.1 mg, 0.0321 mmol), which was dissolved in dry THF (2 mL). The atmosphere was replaced with argon, and the solution was cooled to −78 °C. To this was added a solution of $PdCl_2(C_6H_5CN)_2$ (13.5 mg, 0.0353 mmol) and triethylamine (0.0049 mL, 0.0353 mmol) in THF (2 mL) at −78 °C with stirring over a period of 1 min through a stainless steel cannula under argon atmosphere. The mixture was stirred at −78 °C for 0.5 h and then −50 °C for 5 h. The mixture was warmed to −28 °C and stirred for 19 h at this temperature. A solution of ammonium formate (13.4 mg, 0.212 mmol) and triethylamine (0.03 mL, 0.212 mmol) in methanol (0.7 mL) was quickly added to this mixture at −78 °C, and the mixture was stirred at −78 °C for 4 h. Triethylamine (0.02 mL) was added, and the resulting mixture was poured into a saturated aqueous sodium hydrogen carbonate solution (5 mL) with vigorous shaking. The mixture was diluted with ether (5 mL), and the organic layer was separated. The aqueous layer was extracted with ether (5 mL), and the combined ethereal extracts were dried over a 1:1 mixture of magnesium sulfate and potassium carbonate and evaporated. The residual material was chromatographed on a Florisil (2 g) column by elution with a 200:5:1 mixture of hexane, ethyl acetate, and triethylamine to give **33** (13.6 mg, 71%, 5*Z*/5*E* > 33:1) as a white solid and then **25** (5.5 mg, 29% recovery). The isomer ratio, 5*Z*/5*E*, was determined by comparing the signals at δ 4.55 and 4.50 due to the C-9 protons of the 5*Z* and 5*E* isomers, respectively. Chromatographic and spectral data measurements of acid-labile PGI_2 derivatives were done with added triethylamine. **33**: TLC R_f 0.54 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 1730, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.02 and 0.03 (s each, 12, 4 $SiCH_3$), 0.9–1.0 (m, 21, 2 $SiC(CH_3)_3$ and CH_3), 1.2–2.6 (m, 20, 9 CH_2 and 2 CH), 3.64 (s, 3, OCH_3), 3.80 (dd, 1, *J* = 16.3 and 8.7 Hz, CHO), 4.05 (dd, 1, *J* = 11.6 and 5.8 Hz, CHO), 4.09 (t, 1, *J* = 6.6 Hz, vinyl), 4.55 (dt, 1, *J* = 6.7 and 3.4 Hz, CHO), 5.42 (dd, 1, *J* = 15.6 and 7.3 Hz, vinyl), 5.51 (dd, 1, *J* = 15.6 and 5.5 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ −4.6, −4.5, −4.2, 11.7, 14.0, 18.1, 18.3, 22.6, 24.8, 25.1, 25.5, 25.9, 31.8, 33.3, 33.6, 38.6, 42.0, 44.7, 46.3, 51.3, 53.9, 73.0, 77.9, 83.4, 95.4, 129.1, 135.5, 154.8, 174.4; $[\alpha]^{21}_D$ +28.8° (*c* 0.4, $CHCl_3$); HRMS, *m/z* calcd for $C_{33}H_{62}O_5Si_2$ (M^+ 594.4136, found 594.4182. The ^1H NMR spectrum of this compound was identical with that of the authentic sample donated by Teijin Co. The authentic 5*E* isomer for comparison of the 5*Z*/5*E* ratio was prepared according to the Upjohn procedure[36d] followed by silylation (16 °C for 2 h in dichloromethane, 49% yield): 5*E* isomer of **33**: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.02 and 0.03 (s each, 12, 4 $SiCH_3$), 0.8–1.0 (m, 21, 2 $SiC(CH_3)_3$ and CH_3), 1.2–2.6 (m, 20, 9 CH_2 and 2 CH), 3.64 (s, 3 OCH_3), 3.82 (dd, 1, *J* = 16.5 and 8.2 Hz, CHO), 4.06 (dd, 1, *J* = 11.6 and 5.8 Hz, CHO), 4.50 (dt, 1, *J* = 6.7 and 3.1 Hz, CHO), 4.63 (t, 1, *J* = 7.8 Hz, vinyl), 5.44 (dd, 1, *J* = 15.4 and 7.5 Hz, vinyl), 5.52 (dd, 1, *J* = 15.4 and 5.3 Hz, vinyl); HRMS, *m/z* calcd for $C_{33}H_{62}O_5Si_2$ (M^+) 594.4136, found 594.4116. The use of formic acid (5 equiv) and triethylamine (5 equiv) in THF (0.5 mL) (−78 °C, 2.7 h) for the demetalation gave **33** in 85% yield with 5*Z*/5*E* = 21:1. When sodium borohydride (5 equiv) and sodium methoxide (10 equiv) in methanol (0.2 mL) (−78 °C, 2–3 h) were used, **33** was obtained in 83–92% yield, 5*Z*/5*E* ratio being 12:1–6:1. Attempted reactions with use of a $Pd(OCOCH_3)_2/NaBH_4/NaOCH_3$ or $Pd(OCOCF_3)_2/NaBH_4/NaOCH_3$ combination were much less effective.

The alkoxymercuration/demercuration was conducted as follows: In a 20-mL test tube was placed the acetylenic alcohol **25** (10.3 mg, 0.0173 mmol), which was dissolved in dry THF (2 mL). The atmosphere was replaced with argon, and the solution was cooled to −78 °C. To this was added a solution of mercuric trifluoroacetate (8.1 mg, 0.019 mmol) and triethylamine (1.9 mg, 0.019 mmol) in THF (2 mL) at −78 °C with stirring over a period of 5 min through a stainless steel cannula under argon atmosphere. A methanolic sodium methoxide solution (1 M, 0.19 mL, 0.19 mmol) containing sodium borohydride (3.6 mg, 0.0952 mmol) was added to the mixture through a stainless steel cannula at −78 °C under argon. After the mixture was stirred at this temperature for 1 h, triethylamine (0.01 mL) was added, and the resulting mixture was poured into a saturated aqueous sodium hydrogen carbonate solution (10 mL) with vigorous shaking and then diluted with ether (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (10 mL). The combined ethereal extracts were dried over a 1:1 mixture of magnesium sulfate and potassium carbonate and evaporated. The residual material was chromatographed on a column of Florisil (1 g) by using a 200:5:1 mixture of hexane, ethyl acetate, and triethylamine as eluant to give **33** (6.9 mg, 67%, 5*Z*/5*E* = 19:1 by 500 MHz ^1H NMR assay, a white solid) and **25** (3.1 mg, 30% recovery). When the oxymercuration/demercuration procedure was conducted at 0 °C in the absence of triethylamine, the Δ^6 isomer (double-bond positional isomer) was obtained exclusively.

PGI_2 Methyl Ester (34). In a 5-mL round-bottomed flask was placed **33** (11.6 mg, 0.0195 mmol), and this was dissolved in THF (0.5 mL). To this was added a commercial THF solution of tetrabutylammonium fluoride (1 M, 0.19 mL, 0.19 mmol) at 25 °C, and the mixture was

(45) Just, G.; Simonovitch, C.; Lincoln, F. H.; Schneider, W. P.; Axen, U.; Spero, G. B.; Pike, J. E. *J. Am. Chem. Soc.* **1969**, *91*, 5364.

stirred for 3 h at this temperature. A 0.1% solution of triethylamine in hexane (0.5 mL) was added, and the mixture was evaporated. The residual material was chromatographed on a column of Florisil (1.2 g) by using a 1:1:0.001 mixture of hexane, ethyl acetate, and triethylamine as eluant to give **34** (6.9 mg, 97%) as a white solid: mp 35.0 °C (lit.[36d] mp 30–33 °C); TLC R_f 0.36 (6:3:1 ethyl acetate/cyclohexane/THF); IR ($CHCl_3$) 3600, 3560–3280, 1730, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, J = 6.5 Hz, CH_3), 1.1–2.5 (m, 22, 9 CH_2, 2 CH and 2 OH), 3.67 (s, 3, OCH_3), 3.7–4.2 (m, 3, 3 CHO), 4.58 (m, 1, vinyl), 5.55 (m, 2, vinyls); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.7, 25.1 (2 C), 31.7, 33.0, 33.6, 37.0, 40.6, 45.3, 51.4, 54.7, 73.0, 77.0, 83.4, 95.8, 131.8, 136.4, 154.6, 174.5; $[\alpha]^{21}_D$ +79.8° (c 0.27, $CHCl_3$) [lit.[36d] $[\alpha]^{25}_D$ + 78° (c 0.88, $CHCl_3$]. These spectral data and chromatographic behavior were identical with those of authentic specimen donated by Ono Pharmaceutical Co. and Teijin Co.

Acknowledgment. We are grateful to Ono Pharmaceutical Co., Teijin Co., and Sumitomo Chemical Co. for providing various authentic samples of PGs and starting materials as well as valuable information. We also appreciate Dr. C. H. Lin of Upjohn Co. for sending us IR and ^1H NMR spectra of **12** and **25**.

Triply Convergent Synthesis of (−)-Prostaglandin E_2 Methyl Ester†

Carl R. Johnson* and Thomas D. Penning

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202. *Received December 4, 1987*

Abstract: Enone **1**, prepared from cyclopentadiene, was obtained in optically pure form by resolution with (+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine or by a procedure involving asymmetric semihydrolysis of *meso*-**3** catalyzed by electric eel acetylcholinesterase. The absolute configuration of (+)-**1** was assigned as *S*,*S* on the basis of a comparative optical rotary dispersion study. The lower prostanoid side chain was added to (+)-**1** as an organocopper reagent, the resulting enolate was alkylated with the upper side chain as the iodide, and the acetonide was reductively removed by treatment with Al(Hg) to produce the 11-hydroxy prostanoid, (−)-PGE_2, methyl ester.

A conceptually simple route to the biologically important 11-hydroxyprostaglandins (PGE's) is a triply convergent approach involving the coupling of the two side chains with a protected 4-hydroxy-2-cyclopentenone (Scheme I, path A).[1,2] Success of this convergent approach has been thwarted by equilibration of the initially generated enolate followed by elimination of the protected ring hydroxyl function under conditions conducive to alkylative introduction of the top side chain (Scheme I, path B).[3]

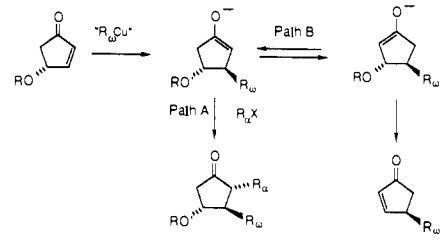
It appeared to us that a short and effective PGE synthesis might be achieved by design of a structural system that would suppress the offending enolate equilibration step. Our concept was to incorporate into the ring component a protecting group that would inhibit enolate equilibration to the undesired position. With this in mind, our attention turned to enone **1**. We postulated that the presence of the additional oxygen group constrained in the five-membered ring would eliminate enolate equilibration by a combination of dipole repulsion and angle strain, allowing alkylation to occur at the desired position. A selective deoxygenation at the 10-position would then furnish the PGE skeleton (Scheme II).

During the course of the work herein described, one solution to this equilibration/elimination problem appeared. Noyori and co-workers[4] found that the initially formed enolate (Scheme I) resulting from the addition of an organocuprate to a protected 4-hydroxy-2-cyclopentenone could be trapped at low temperatures as the *O*-(triphenylstannyl) derivative, which, in turn, could be directly alkylated[5] with a fivefold excess of $R_\alpha I$ in the presence of hexamethylphosphoramide. At about the same time as our preliminary disclosure[6] of the work herein described, an interesting, short, and convergent synthesis of PGE_2, based on the *O*-methyl derivative of the oxime of 4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopentenone, from the laboratories of Corey was revealed.[7]

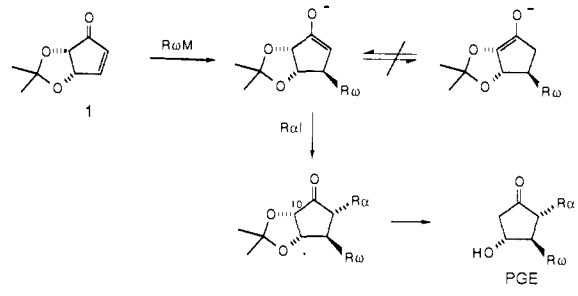
Results and Discussion

A. Synthesis of Enone 1. Cyclopentenone (±)-**1** has previously been prepared by a lengthy route from 2-cyclopentenone.[8]

Scheme I



Scheme II



Dugger[9] has reported on attempts to prepare optically active **1** from ribose, but the key transformations were unsatisfactory.

† Dedicated to Prof. E. J. Corey on the occasion of his 60th birthday.

(1) For a review, see: Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

(2) For indirect variations of this approach, see: (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1384. (b) Tanaka, T.; Toru, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Ibid.* **1983**, *24*, 4103. (c) Suzuki, M.; Kawagishi, T.; Noyori, R. *Ibid.* **1982**, *23*, 5563. (d) Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Ibid.* **1982**, *23*, 4057. (e) Donaldson, R. E.; Saddler, J. C.; Byrn, S.; McKenzie, A. T.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167. (f) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

(3) (a) Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755. (b) Patterson, J. W.; Fried, J. H. *Ibid.* **1974**, *39*, 2506.

0002-7863/88/1510-4726$01.50/0