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THREE-COMPONENT COUPLING SYNTHESIS OF PROSTAGLANDINS. A SIMPLIFIED, GENERAL PROCEDURE†

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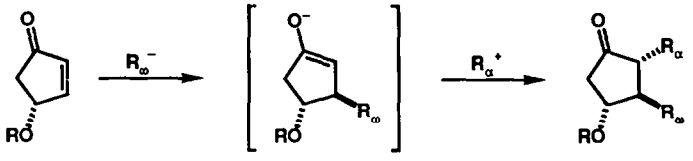
Abstract: In the presence of dimethylzinc, (*R*)-*tert*-butyldimethylsiloxy-2-cyclopentenone can be linked with (*S*,*E*)-1-lithio-3-*tert*-butyldimethylsiloxy-1-octene and methyl 7-iodo-5-heptynoate, giving a protected 5,6-didehydroprostaglandin E_2. Use of an ω side-chain aldehyde or nitroalkene in place of the propargylic iodide affords the C-7 and C-6 functionalized prostaglandins, respectively. This new protocol constitutes the simplest three-component method for the synthesis of various natural and unnatural prostaglandins.

Prostaglandins (PGs) are physiologically important compounds which are involved in vital defense processes such as inflammation, tissue repair, and the immune response.[2]

Since the PG skeleton contains three structural components, a cyclopentane ring and seven- and eight-carbon side chains named α and ω, respectively, the consecutive linking of the two side chain units to a 2-cyclopentenone block is an ideal way to create the PG framework because of its directness and synthetic flexibility.[3b] The organometallic conjugate addition of an ω side-chain unit to a protected 4-



† Dedicated to Professor David Ollis on the occasion of his 65th birthday and retirement from Sheffield following a successful career.

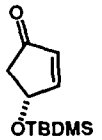
hydroxy-2-cyclopentenone derivative would occur from the direction opposite the oxygen functionality thereby avoiding nonbonded interaction. Similarly, the electrophilic trapping of the enolate intermediate generates the trans relationship of the two side chains in the product. Thus, using just enantiomerically pure cyclopentenone and ω side-chains, all of the absolute stereochemistries required for the E series of PGs may be secured via asymmetric inductions in the three-component coupling process. The tandem carbacondensation needs an efficient conjugate addition method and a reliable procedure that allows alkylation of the regio-defined enolate intermediate, where metallic species manipulate the delicate balance of the reactivity and selectivity of the metallo-organic reactions. Unfortunately, the lack of organometallic tools which are compatible with the two carbon–carbon bond forming steps has long hampered the realization of this attractive route.[3] Reaction of lithium enolates and alkyl halides is widely used for α-alkylation of ketones, although highly selective monoalkylation with strict exclusion of undesired proton exchange has remained difficult.[4] Pure vinyllithium reagents, however, are unable to undergo conjugate addition to α,β-unsaturated ketones. We have succeeded in the three-component synthesis of natural PGs along this line by combined use of a phosphine-complexed organocuprate and organotin chloride,[5] but development of the simpler method has been desired. We here disclose that, with the aid of dimethylzinc, a siloxy-2-cyclopentenone can be combined with an ω side-chain vinyllithium and various α side-chain electrophiles to directly create a whole PG skeleton.[6]

Results

The optically active siloxy cyclopentenone **1** (TBDMS = $Si(CH_3)_2$-*t*-C_4H_9) and ω side-chain components, **2a** or **2b**, required for this concise synthesis are available in various ways.[7] The chiral vinylstannane **2c** in 98% ee, like the vinyl iodide **2d**, is easily prepared by enantioselective reduction of the enone **3**[8] with the binaphthol-modified lithium aluminum hydride (BINAL-H) reagent, **4**.[10]

Conjugate addition of ω side-chain organometallics. The three-component synthesis starts with conjugate addition of ω side-chain units to the enone **1**. Thus a salt-free solution of (*E*)-vinylic lithium **2e** in THF was obtained by transmetalation of vinylstannane **2b** with 1 equiv of *n*-butyllithium at −78 °C. When this solution was mixed with 1 equiv of dimethylzinc and then treated with an equimolar amount of optically pure **1** at −78 °C, the 1,4-addition product **5** was obtained in 85% yield. The 3,4-trans stereochemistry was confirmed by ^{13}C NMR measurement showing a single set of signals assignable to 25 carbons in this structure. Treatment of the vinylic iodide **2a** with 2 equiv of *tert*-butyllithium in ether or THF generates a solution of **2e** containing 1 equiv of lithium iodide. Such a THF solution was also used for the dimethylzinc aided conjugate addition giving **5** in 94% yield.

Short synthesis of natural prostaglandins. Treatment of the enolate intermediate, generated from **1** and the salt-free vinyllithium **2e**, with 10 equiv of hexamethylphosphoric triamide (HMPA) and then with 5 equiv of propargylic iodide **6** gave the desired 5,6-didehydro-PGE_2 product **7** in 71% yield, which was a single stereoisomer as judged by ^{13}C NMR analysis. No cyclopentenones corresponding to the β-siloxy ketone **5** or **7** were formed. The yield of **7** was slightly lowered by the use of the vinylic lithium derived from **2a**.



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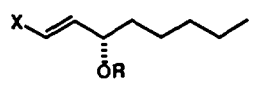
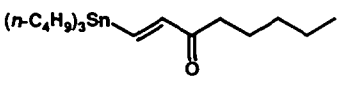


2a, X = I; R = TBDMS
b, X = Sn(*n*-C_4H_9)$_3$; R = TBDMS
c, X = Sn(*n*-C_4H_9)$_3$; R = H
d, X = I; R = H
e, X = LI; R = TBDMS
f, X = I; R = $CONHC_6H_3$-3,5-$(NO_2)_2$



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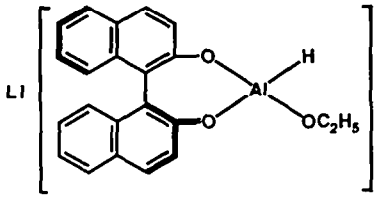

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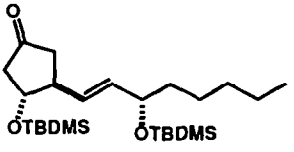

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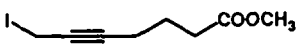

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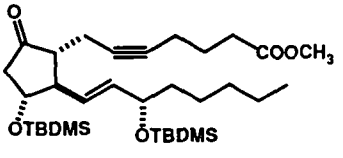

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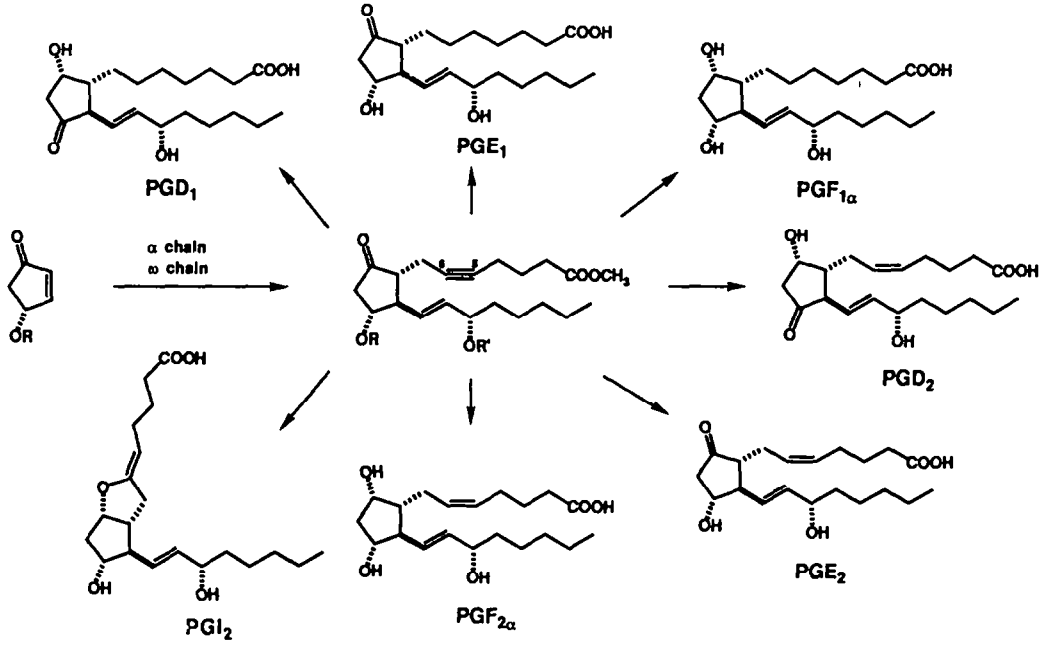
The acetylenic intermediates of type **7** serve as key intermediates for the general synthesis of PGs as outlined in Scheme 1.[3b,5b] They are converted to a wide variety of naturally occurring E and F series of PGs by controlled hydrogenation of the 5,6-triple bond and, when necessary, stereoselective reduction of the 9-keto function. Appropriate selection of protective groups at the C-9 and C-15 hydroxyl functions allows reversal of the oxidation state at the C-9 and C-11 positions, leading to the D

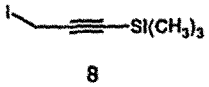
series of PGs. Prostacyclin (PGI_2), having a 5*Z*-alkylidenetetrahydrofuran structure, is also made from **7** by α-selective reduction of the 9-keto function in a stereo-defined manner and the subsequent intramolecular alkoxypalladation/depalladation procedure.[5b]



Scheme 1. General Synthesis of Prostaglandins

Synthesis of functionalized prostaglandins. The above described alkylation procedure can be applied to the construction of structures having shorter α chains. For example, reaction of the enolate intermediate with 3-iodo-1-trimethylsilylpropyne (**8**) produced **9**, in 67% yield, which is used for the synthesis of isocarbacyclin (**10**)[11], a most promising stable PGI_2 analogue for cardiovascular and circulatory diseases.[12]

Enolate trapping is accomplished with an array of electrophiles in addition to alkyl iodides, allowing the preparation of C-6 or C-7 functionalized PG analogues that possess significant physiological properties. Thus the reaction of equimolar amounts of **1**, **2e** (generated from **2a**), and dimethylzinc followed by addition of a small excess of methyl 6-formylhexanoate (**11a**) gave the aldol **12** in 82–92% yield with the stereochemistry of 7*S*/7*R* = 10:1.[13a] The aldol product is readily converted to antineoplastic and antiviral Δ^7-PGE_1 and -PGA_1 methyl esters[13b,c] (**13** and **14**, respectively) by simple dehydration procedures. The aldol reaction with a conjugated acetylenic aldehyde, **11b**, required the addition of 1 equiv of boron trifluoride



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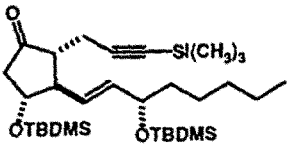

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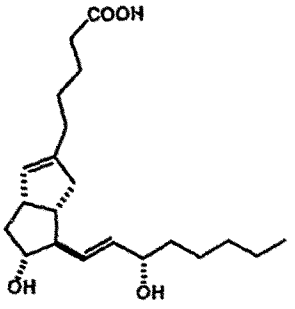

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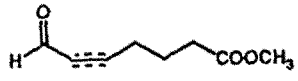
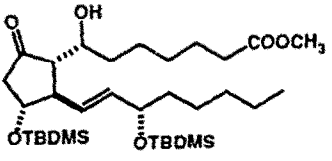


11a, 5,6-single bond
b, 5,6-triple bond



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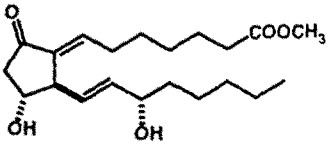

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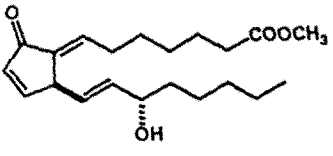

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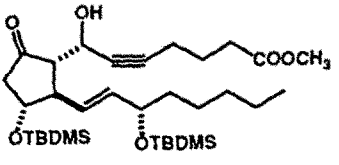

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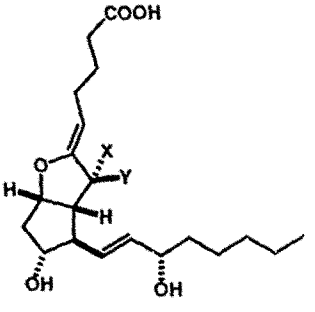
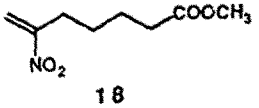


16; X = F, Y = H
17; X = H, Y = F



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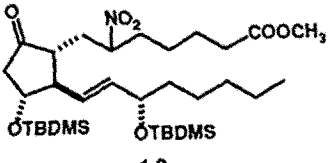

19

etherate,[3b,14a] to avoid side reactions, to give the adduct **15**[14a] in 80% yield with 7*S*/7*R* = 1:1.4.[14b] The C-7 stereochemistries were determined by the exciton chirality method after conversion of **15** to the benzoates of 7-hydroxy-PGE_2 derivatives by controlled hydrogenation of the 5,6-triple bond followed by benzoylation.[13a,14b] The acetylenic aldol products can be transformed to 7*R*- and 7*S*-fluoro-PGI_2 (**16**[15a,b] and **17**[15c,d,e]), which are more stable than natural PGI_2. The dimethylzinc aided reaction of salt-free **2e** and **1** followed by Michael trapping of the enolate with methyl 6-nitro-6-heptenoate (**18**) at −78 °C afforded the adduct **19**[16] in 63% yield with 6*R*/6*S* = 1:1. Subsequent desilylation of **19**[16a] gives the 6-nitro-PGE_1 methyl esters which possess antiulcer activity.[16b]

Conclusion

The presence of dimethylzinc effects consecutive linking of a protected 4-hydroxy-2-cyclopentenone with an ω side-chain vinyllithium and various α side-chain electrophiles. The reaction of dimethylzinc and vinylic lithium **2e** may form a lithium methyl/vinyl mixed zincate as the reactive species but only the sp^2 carbon undergoes the conjugate addition to the enone. Notably, although the lithium enolate intermediate tends to cause dehydration via double-bond migration,[3a] added dimethylzinc effectively suppresses this side reaction, resulting in direct alkylation with propargylic iodides in satisfactory yields. The enolate reacts with other α side-chain electrophiles facilely. The yields of this new protocol are comparable with those of our original organocopper route.[3b,5,14a,16a,b,c] However, the organolithium/zinc chemistry eliminates the need for tertiary phosphine/copper(I) iodide complex or triphenyltin chloride and results in considerable simplification; particularly the product isolation is much easier. Now a number of natural and unnatural PGs can be prepared by this three-component synthesis in a highly reproducible manner.

Experimental

General. Chemical shifts of ^1H NMR spectra are reported relative to tetramethylsilane (δ 0) or chloroform (δ 7.26). Chemical shifts of ^{13}C NMR spectra are reported relative to tetramethylsilane (δ 0) or chloroform-*d* (δ 77.1). The abbreviations s, d, t, m, and br signify singlet, doublet, triplet, multiplet, and broad, respectively.

Rf values on TLC were recorded on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. The plates were sprayed with a solution of 2% *p*-anisaldehyde in 5% ethanolic sulfuric acid and then heated until the spots became clearly visible. Deactivated silica gel (E. Merck) was prepared by mixing with water (5−10%). Medium-pressure silica gel chromatography was conducted with an equipment of a Kiriyama ILC-PB column system (a glass column and a pump). The high-performance liquid chromatography (HPLC) for analysis of optical purity was carried out on

Shimadzu LC-6A with Shimadzu SPD-6A UV detector using a column of Sumipax Sumichiral OA-4100 of Sumitomo Chemical Co.: solvent, 100:10:1 hexane/1,2-dichloroethane/ethanol; flow rate, 1.2 mL/min; pressure, 140 kg/cm^2; detection, UV (254 nm). Recycling preparative HPLC was conducted using a Japan Analytical Industry Model LC-908 chromatograph (column, Japan Analytical Industry, JAIGEL AJ2H x 2, 20 mmø x 60 cm; solvent, $CHCl_3$; pressure, 20–30 kg/cm^2; flow rate, 3.5 mL/min; detection, UV (254 nm) and RI two-pen system).

Ether, tetrahydrofuran (THF), and toluene were distilled over Na-benzophenone ketyl under argon atmosphere. Hexamethylphosphoric triamide (HMPA) was distilled over CaH_2.

Commercial *n*-butyllithium hexane solution (Mitsuwa) and *tert*-butyllithium pentane solution (Aldrich) were used directly from the bottles after titration.[17] A stock solution of dimethylzinc was prepared in a Schlenk tube by mixing toluene and 99% dimethylzinc (Toyo Stauffer Chemical Co.).

Optically pure (*R*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopentenone (**1**) ($[\alpha]^{22}_D$ +67.4° (*c* 0.4, CH_3OH)), (*S,E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene (**2a**) ($[\alpha]^{23}_D$ –37.5° (*c* 0.97, CH_3OH)), 3-iodo-1-trimethylsilylpropyne (**8**), and methyl 6-nitro-6-heptenoate (**18**) were donated from Teijin Co. Methyl 7-iodo-5-heptynoate (**6**), methyl 6-formylhexanoate (**11a**), and methyl 6-formylhexynoate (**11b**) were prepared from methyl 7-hydroxy-5-heptynoate.[5b,14a]

Reactions with organometallic reagents were conducted under argon atmosphere. Prior to such reactions, the apparatus (ampule and flask) were evacuated by heating with a heat gun under high vacuum and then filled with argon. Unless otherwise stated, an ampule with a spiral tube[5b] was used in the three-component coupling process.

(S,E)-1-Tributylstannyl-1-octen-3-ol (2c). A solution of 1-tributylstannyl-1-octen-3-one (**3**)[8] (207.1 mg, 0.50 mmol) in THF (1.5 mL) was treated at –100 to –80 °C for 3 h with a solution of (S)-BINAL-H (**4**) in THF prepared by mixing $LiAlH_4$ (1.0 M THF solution, 1.5 mL, 1.50 mmol), ethanol (5.0 M THF solution, 0.3 mL, 1.5 mmol), and (S)-(–)-binaphthol (428.8 mg, 1.50 mmol, $[\alpha]^{24}_D$ –35.0° (*c* 2.22, THF), 100% ee) in THF (3 mL).[10] The excess reducing agent was decomposed by addition of methanol (0.5 mL) at –78 °C and the mixture was warmed to room temperature. Water (1 mL) and then ether (10 mL) were added and the mixture was stirred for 30 min. The mixture was treated with $MgSO_4$ and filtered. The filtrate was evaporated and diluted with hexane, precipitating binaphthol (418.1 mg, 98%) as crystals. After filtration, the resulting hexane solution was evaporated to yield the oily material which was chromatographed on a column of Florisil® (3 g) using a 100:1 mixture of hexane and ethyl acetate afforded **2c** (187.8 mg, 90%) as a colorless oil. TLC *Rf* 0.39 (10:1 hexane/ethyl acetate); $[\alpha]^{25}_D$ +1.9° (*c* 1.28, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.7–

1.0 (m, 18, 3 CH_2 and 4 CH_3), 1.2–1.7 (m, 20, 10 CH_2), 4.06 (dt, 1, J = 5.4, 10.8 Hz, CHO), 5.97 (dd, 1, J = 5.3, 19.1 Hz, J_{Sn-H} = 60.3, 64.0 Hz, C(2)H), 6.11 (d, 1, J = 19.8 Hz, J_{Sn-H} = 70.2 Hz, C(1)H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 9.5 (J_{Sn-C} = 343.8, 328.7 Hz), 13.7, 14.0, 22.6, 25.0, 27.3 (J_{Sn-C} = 54.8, 52.3 Hz), 29.1 (J_{Sn-C} = 21.0 Hz), 31.8, 37.0, 75.6 (J_{Sn-C} = 61.6 Hz), 127.5 (J_{Sn-C} = 374.6, 358.0 Hz), 151.3 (J_{Sn-C} = 4.0 Hz). The optical purity was determined after converting it to 3,5-dinitrophenylcarbamate of (*E*)-1-iodo-3-hydroxy-1-octene **2f** as described in the following.

To a solution of vinyltin **2c** (15.1 mg, 0.036 mmol) in ether (0.5 mL), iodine (15 mg, 0.059 mmol) was added at 0 °C.[18] The resulting mixture was stirred for 1 h at 0 °C followed by addition of 10% aqueous $Na_2S_2O_3$ solution and then extracted with ethyl acetate (1 mL x 2). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residual material was dissolved in toluene (0.7 mL) and to this 3,5-dinitrophenyl isocyanate (40 mg 0.19 mmol) and pyridine (60 mg, 0.8 mmol) were added successively at room temperature. After 5 h, the mixture was subjected to column chromatography on silica gel (4 g) using a 20:1 mixture of hexane and ethyl acetate as eluant, giving **2f** (6.1 mg, 37%) as colorless solid. TLC Rf 0.67 (2:1 hexane/ethyl acetate); Analysis of optical purity by HPLC (for conditions, see General): t_R 31.9 min ((*S*)-isomer), 34.7 min ((*R*)-isomer) with the intensity ratio of 99.0:1.0.

(3*R*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-4-[(*S*,*E*)-3-(*tert*-butyldimethylsiloxy)-1-octen-1-yl]cyclopentanone (5). Conjugate addition was conducted with a similar procedure as described in the synthesis of **7** using (*S*,*E*)-3-(*tert*-butyldimethylsiloxy)-1-(tributylstannyl)-1-octene (**2b**) (410.8 mg, 0.77 mmol) in THF (4 mL), $Zn(CH_3)_2$ (2.88 M toluene solution, 0.27 mL, 0.77 mmol), and **1** (151.9 mg, 0.72 mmol) in THF (9 mL). The crude reaction product obtained after extractive workup and solvent removal was subjected to silica gel column chromatography with 200:1 to 40:1 mixtures of hexane and ethyl acetate as eluant to give **5** (276.0 mg, 85%). TLC Rf 0.40 (10:1 hexane/ethyl acetate); IR ($CHCl_3$) 1745 cm^{-1}; $[\alpha]^{14}_D$ –32.9° (*c* 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.01, 0.04, 0.07, and 0.09 (s each, 12, 2 $Si(CH_3)_2$), 0.8–1.1 (m, 21, CH_3 and 2 Si-*t*-C_4H_9), 1.1–1.7 (m, 8, 4 CH_2), 1.9–3.0 (m, 5, 2 CH_2 and CH), 4.0–4.4 (m, 2, 2 CHO), 5.5–5.7 (m, 2, vinyl); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ –4.7 (2C), –4.2 (2C), 14.0, 18.0, 18.2, 22.6, 25.0, 25.7 (3C), 25.9 (3C), 31.8, 38.3, 42.0, 46.8, 47.5, 73.0, 74.7, 128.8, 135.3, 215.3. The product was proven homogeneous as judged by measuring ^{13}C NMR of a 1:1 mixture of **5** and the stereo-defined authentic material obtained by organocopper method.[5b]

The compound **5** was also prepared in 94% yield with a similar conjugate addition procedure using **2a** (2.03 g, 5.5 mmol), *tert*-butyllithium (1.55 M pentane solution, 7.1 mL, 11 mmol), $Zn(CH_3)_2$ (0.9 M toluene solution, 6.1 mL, 5.5 mmol), and **1** (1.06 g, 5.0 mmol).

5,6-Didehydro-11,15-O-bis(*tert*-butyldimethylsilyl)PGE$_2$ methyl ester (7). The vinylstannane **2b** (3965.1 mg, 7.46 mmol) was placed in a 150-mL ampule with a spiral tube and dissolved in THF (16 mL). After the solution was cooled to -78 °C, *n*-butyllithium (1.46 M hexane solution, 5.11 mL, 7.46 mmol) was added and the mixture was stirred at -78 °C for 40 min. To this was added $Zn(CH_3)_2$ (2.10 M toluene solution, 3.55 mL, 7.46 mmol) and then the mixture was warmed up to 0 °C. The mixture was stirred at 0 °C for 15 min and cooled again to -78 °C. To this a solution of **1** (1543.9 mg, 7.27 mmol) in THF (16 mL) was added at -78 °C over a period of 40 min by using a glass syringe under the drive with a syringe pump. The mixture was stirred at the same temperature for 15 min and HMPA (12.65 mL, 72.7 mmol) was added to the mixture. After the mixture was stirred at -78 °C for 5 min, **6** (9711.6 mg, 36.5 mmol) was added and rinsed with THF (3 mL). Cold bath (-78 °C) was quickly replaced by a CryoCool-controlled bath (-40 °C). After being stirred at -40 °C for 24 h, the mixture was poured into saturated aqueous NH_4Cl solution (150 mL). The organic layer was separated and aqueous layer was extracted with ether (30 mL x 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, giving an oil. Nonpolar tetrabutylstannane and highly polar HMPA were easily removed by short-path silica gel column chromatography with a 20:1 mixture of hexane and ethyl acetate as eluant. A mixture of **6** and **7** was subjected to medium-pressure silica gel column chromatography (300 g) using a 50:1 and then 20:1 mixture of hexane and ethyl acetate as eluants, giving pure **7** as a colorless oil (2612 mg). The fractions containing a mixture of **6** and **7** were further subjected to column chromatography under the same conditions. Total yield of **7** was 71% (3049 mg). Unreacted **6** was recovered in 80% yield (6220 mg). **7**: TLC R_f 0.43 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 1745 cm^{-1}; $[\alpha]^{18}_D$ -12.4° (*c* 0.62, CH_3OH); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.01, 0.05, 0.06, and 0.07 (s each, 12, 2 $Si(CH_3)_2$), 0.88 and 0.89 (s each, 18, 2 Si-*t*-C_4H_9), 0.85–0.92 (br, 3, CH_3), 1.20–1.85 (m, 10, 5 CH_2), 1.95–2.30 (m, 5, 2 CH_2 and CH), 2.40 (t, 2, J = 7.4 Hz, CH_2), 2.58–2.84 (m, 3, CH_2 and CH), 3.66 (s, 3, OCH_3), 4.05–4.15 (m, 2, 2 CHO), 5.51 (dd, 1, J = 7.6, 15.5 Hz, vinyl), 5.64 (dd, 1, J = 5.1, 15.5 Hz, vinyl); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ -4.7, -4.5 (2C), -4.2, 14.1 (2C), 16.8, 18.0, 18.2, 22.6, 24.2, 25.0, 25.8 (3C), 31.8, 32.7, 38.5, 47.7, 51.4, 51.9, 52.9, 72.7, 73.1, 77.3, 80.7, 128.2, 136.8, 173.4, 213.4. These spectral data and TLC behavior are identical with those of authentic sample.[5b] Isolation of the product **7** from a 4:1 mixture of **6** and **7** was conveniently conducted by recycling preparative HPLC giving pure **7** after 4 times recycling (for conditions, see General).

The compound **7** was also synthesized in 66% yield with a similar procedure using **2a** (388.3 mg, 1.05 mmol), *tert*-butyllithium (1.17 M pentane solution, 1.80 mL, 2.11 mmol), $Zn(CH_3)_2$ (3.67 M toluene solution, 0.29 mL, 1.05 mmol), **1** (211.1 mg, 0.99 mmol), HMPA (1.8 mL, 10.5 mmol), and **6** (1.391 g, 5.25 mmol).

4-(*tert*-Butyldimethyl)siloxy-3-((*E*)-3-*tert*-butyldimethylsiloxy-1-octenyl)-2-(3-trimethysilyl-2-propynyl)cyclopentanone (9). The conjugate addition was conducted with a similar procedure as described in the synthesis of **7** by using **2b** (301.2 mg, 0.57 mmol) in THF (2.5 mL), *n*-butyllithium (1.6 M hexane solution, 0.35 mL, 0.57 mmol), $Zn(CH_3)_2$ (2.1 M toluene solution, 0.27 mL, 0.57 mmol), and **1** (110.0 mg, 0.52 mmol) in THF (4 mL). To the resulting enolate solution were added HMPA (1.0 mL) at -78 °C and the mixture was warmed to -40 °C followed by addition of a solution of **8** (624.6 mg, 2.62 mmol) in THF (1 mL) at this temperature. The cold bath was replaced by a CryoCool-controlled bath (-30 °C). After being stirred at -30 °C for 17 h, the mixture was poured into saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residual oil was subjected to column chromatography on silica gel (20 g) using a 1:1 mixture of hexane and benzene, giving a semi-purified product (375 mg) as a pale yellow oil, which was further chromatographed on silica gel (10 g) using a 1.3:1 mixture of hexane and benzene to give pure **9** (240.0 mg, 67%) as a colorless oil. *Rf* 0.63 (benzene); IR ($CHCl_3$) 2200, 1760, 1720, 1460, 1360, 1250 cm^{-1}; $[\alpha]^{25}_D$ -18.9° (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.0–0.2 (m, 21, 7 $SiCH_3$), 0.7–1.0 (m, 21, 2 Si-*t*-C_4H_9 and CH_3), 1.0–1.5 (m, 8, 4 CH_2), 2.0–2.4 (m, 3, CH_2 and CH), 2.6–2.9 (m, 3, CH_2 and CH), 4.0–4.2 (m, 2, 2 CHO), 5.52 (dd, 1, *J* = 7.4, 16.0 Hz, vinyl), 5.64 (dd, 1, *J* = 5.1, 15.3 Hz, vinyl); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ -4.6, -4.5, -4.7, -4.1, 0.1, 14.1, 18.0, 18.5, 22.7, 25.1, 25.8, 25.9, 31.9, 38.5, 47.9, 51.8, 52.5, 72.8, 73.1, 86.9, 103.6, 128.2, 136.8, 213.8; MS (*m/z*) 564 (M^+), 507 ($M^+ - C_4H_9$).

The compound **9** was also synthesized in 53% yield with a similar procedure using **2a** (2.03 g, 5.5 mmol), *tert*-butyllithium (1.55 M pentane solution, 7.1 mL, 11 mmol), $Zn(CH_3)_2$ (0.9 M toluene solution, 6.1 mL, 5.5 mmol), **1** (1.06 g, 5.0 mmol), HMPA (8.7 mL, 50 mmol), and **8** (1.79 g, 7.5 mmol).

11,15-*O*-Bis(*tert*-butyldimethylsilyl)-7-hydroxy-PGE$_1$ methyl ester (12). In a 500-mL three-necked round-bottomed flask equipped with a thermometer were placed *tert*-butyllithium (1.55 M pentane solution, 28.4 mL, 44 mmol) and THF (60 mL). At -90 °C, to this was added a solution of **2a** (8.83 g, 24 mmol) in THF (65 mL) via a stainless tube with maintaining the temperature of solution below -60 °C. After being stirred for 10 min, $Zn(CH_3)_2$ (0.9 M toluene solution, 24.4 mL, 22 mmol) was added and then the mixture was warmed up to 0 °C. The mixture was stirred at 0 °C for 15 min and cooled again to -90 °C. A solution of **1** (4.24 g, 20 mmol) in THF (65 mL) over 10 min at -90 °C by using a stainless tube. After the mixture was stirred at -70 to -80 °C for 60 min, a solution of **11a** (4.74 g, 30 mmol) in THF (65 mL) at -78 °C. This reaction mixture was stirred at this temperature for 30 min and at -30 to -40 °C for another 30 min and then poured into saturated aqueous NH_4Cl solution (400 mL).

The organic layer was separated, and the aqueous layer was extracted with hexane (200 mL). The combined organic extracts were washed with brine (400 mL x 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was subjected to silica gel column chromatography (300 g) with a 50:1 and then 9:1 mixture of hexane and ethyl acetate as eluants, yielding the aldol products **12** (11.29 g, 92%, a 10:1 mixture of 7*S* and 7*R* diastereomer) as a colorless oil. TLC R_f 0.32 (7*S* aldol product), 0.26 (7*R* aldol product), (4:1 hexane/ethyl acetate); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ –4.7 ($SiCH_3$), –4.6 ($SiCH_3$), –4.3 ($SiCH_3$), 14.0 (20), 18.0 ($SiC(CH_3)$), 18.2 ($SiC(CH_3)$), 24.9 (3), 25.0 (17), 25.4 (5), 25.7 ($SiC(CH_3)$), 25.9 ($SiC(CH_3)$), 29.0 (4), 31.8 (18), 34.2(2), 35.2 (6), 38.4 (16), 48.0 (10), 49.0 (12*R*), 51.4 (OCH_3), 51.9 (12*S*), 58.0 (8), 70.3 (7*R*), 71.8 (7*S*), 72.5 (11), 73.4 (15), 128.7 (13), 136.4 (14), 174.1 (1), 217.6 (9). These spectral data and TLC behavior are identical with those of the authentic materials.[13a]

11,15-*O*-Bis(*tert*-butyldimethylsilyl)-5,6-didehydro-7-hydroxy-PGE$_2$ methyl ester (15). The vinyllithium **2e** was prepared by mixing **2a** (259.8 mg, 0.71 mmol) and *tert*-butyllithium (0.99 M pentane solution, 1.42 mL, 1.41 mmol) in ether (3 mL) at –78 °C for 3 h. The conjugate addition was conducted with a similar procedure as described in synthesis of **7** by using $Zn(CH_3)_2$ (2.10 M toluene solution, 0.34 mL, 0.71 mmol) and **1** (145.3 mg, 0.68 mmol) in THF (4 mL). To the resulting enolate was added $BF_3{\cdot}O(C_2H_5)_2$ (0.09 mL, 0.73 mmol) and the mixture was stirred for 3 h at –78 °C. To this was added a solution of **11b** (112.0 mg, 0.73 mmol) in THF (2.0 mL) at –78 °C. The mixture was stirred at this temperature for 30 min and poured into saturated aqueous NH_4Cl solution (6 mL). The organic layer was separated and the aqueous layer was extracted with ether (5 mL x 2). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual oil was subjected to two-layered column chromatography (Florisil® (2 g), upper layer and deactivated silica gel (7 g), lower layer) using a 10:1 mixture of hexane and ethyl acetate as eluant, yielding the aldol products **15** (333.0 mg, 80%, a 1:1.4 mixture of 7*S* and 7*R* diastereomer) as a pale yellow oil. TLC R_f 0.42 (7*S* aldol product), 0.39 (7*R* aldol product), (3:1 hexane/ethyl acetate); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ –4.78 ($SiCH_3$), –4.69 ($SiCH_3$), –4.34 ($SiCH_3$), –4.31 ($SiCH_3$), 13.98 (20), 17.91 ($SiC(CH_3)$), 17.96 ($SiC(CH_3)$), 18.11 (4), 22.53 (19), 23.66 (3*R*), 23.70 (3*S*), 24.93 (17), 25.68 ($SiC(CH_3)$), 25.83 ($SiC(CH_3)$), 31.77 (18), 32.63 (2), 38.28 (16*R*), 38.33 (16*S*), 47.76 (10*R*), 47.98 (10*S*), 50.80 (12*S*), 51.10 (12*R*), 51.44 (OCH_3), 58.47 (8*S*), 58.89 (8*R*), 61.80 (7*S*), 62.37 (7*R*), 72.47 (11), 73.02 (15*R*), 73.10 (15*S*), 79.53 (5), 85.55 (6*S*), 85.62 (6*R*), 127.43 (13*S*), 128.67 (13*R*), 136.56 (14*R*), 136.94 (14*S*), 173.38 (1), 214.34 (9*R*), 215.77 (9*S*). These spectral data and TLC behavior are identical with those of the authentic material.[14b]

11,15-*O*-Bis(*tert*-butyldimethylsilyl)-6-nitro-PGE$_1$ methyl ester (19). The conjugate addition was conducted with a similar procedure as described in the synthesis of **7** by using **2b** (855.5 mg, 1.61 mmol) in THF (6.0 mL), *n*-butyllithium (1.52 M hexane solution, 1.06 mL, 1.61 mmol), $Zn(CH_3)_2$ (2.1 M toluene solution, 0.77 mL, 1.61 mmol), and **1** (329.2 mg, 1.55 mmol) in THF (8.0 mL). To the resulting enolate, a solution of **18** (435.8 mg, 2.33 mmol) in THF (2 mL) was added. The cold bath (-78 °C) was replaced by a CryoCool-controlled bath (-40 °C). After being stirred at -40 °C for 3 h, the mixture was poured into saturated NH_4Cl (10 mL) aqueous solution and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual oil was subjected to silica gel column chromatography (25 g) with a 20:1 and then 10:1 mixture of hexane and ethyl acetate as eluants, yielding **19** (628.8 mg, 63%) and the 8-epi product (67.8 mg, 7%) as a colorless oil. **19**, a 1:1 mixture of 6*R* and 6*S* stereoisomers: TLC *Rf* 0.29 (5:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.0–0.1 (m, 12, 4 $SiCH_3$), 0.8–1.0 (m, 21, 2 Si-*t*-C_4H_9 and CH_3), 1.2–2.4 (m, 21, 10 CH_2 and CH), 2.6–2.8 (m, 1, CH), 3.64 (s, 3, OCH_3), 4.0–4.2 (m, 2, 2 CHO), 4.7–4.8 and 5.0–5.2 (br each, 1, $CHNO_2$), 5.3–5.7 (m, 2, vinyl); MS (*m/z*) 626 ($M^+ - CH_3$), 610 ($M^+ - OCH_3$), 584 ($M^+ - C_4H_9$). These spectral data and TLC behavior are identical with those of the authentic material.[16a] The 8-epi product, a 1:1 mixture of 6*R* and 6*S* stereoisomers: TLC *Rf* 0.39 (5:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.0–0.1 (m, 12, 4 $SiCH_3$), 0.8–1.0 (m, 21, 2 $SiC(CH_3)_3$ and CH_3), 1.2–2.1 (m, 16, 8 CH_2), 2.2–2.5 (m, 4, 2 CH_2), 2.6–2.9 (m, 2, 2 CH), 3.66 and 3.68 (s each, 3, OCH_3), 4.0–4.1 (m, 1, CHO), 4.1–4.3 (m, 1, CHO), 4.4–4.5 and 4.6–4.8 (br each, 1, $CHNO_2$), 4.9–5.1 (m, 1, vinyl), 5.6–5.8 (m, 1, vinyl); MS (*m/z*) 626 ($M^+ - CH_3$), 610 ($M^+ - OCH_3$), 584 ($M^+ - C_4H_9$). The use of **2a** as an ω side-chain unit gave **19** in 35% yield.

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