Diastereoselective Synthesis of an Isoprostane: (±)-8-*epi*-$PGF_{2\alpha}$ Ethyl Ester

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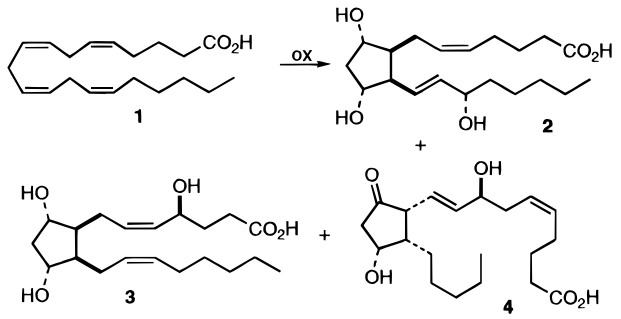
A total synthesis of the isoprostane (±)-8-*epi*-$PGF_{2\alpha}$ ethyl ester (**5**) is described, based on the diastereoselective cyclization of α-diazo ketone **7**. This ketone is assembled by aldol condensation between α-diazo ketone **8** and aldehyde **9**. The sequential α-diazo ketone aldol/insertion described here offers a powerful new approach to cycloalkane construction.

In 1990, L. Jackson Roberts and co-workers reported[1] that under conditions of oxidative stress, phospholipid-bound[2] arachidonic acid (**1**) is converted by free-radical oxidation to a family of epimeric prostanoids collectively known as the isoprostanes, exemplified by isomers **2**−**4**. While a detailed physiological investigation of these compounds has only just begun,[3] it has already been shown that the kidney failure and death associated with severe liver disease is a consequence of the production and release of the isoprostanes.[4] It has also been demonstrated that the effects of 8-*epi*-$PGF_{2\alpha}$ (**2**) on the renal vasculature result from specific receptor binding.



To investigate the physiological role of the ninety-six isoprostanes, it will be necessary to prepare each of these by total synthesis.[7] In 1992, we reported a new route to *cis*-2,3-dialkyl prostanoids based on a rhodium(II)-catalyzed cyclization of an α-diazo ketone **7** to produce bicyclic ketone **6** stereoselectively. The relative configuration of the alkyl side chains on the ring was then established by kinetic opening of the activated cyclopropane with thiophenol and $BF_3{\cdot}OEt_2$.[8] We now report a more easily scaled-up route to **7**, based on aldol condensation of the α-diazo ketone **8** with decadienal (**9**) (Scheme 1). Furthermore, we describe improved procedures for the elaboration of **6** that allow routine preparation of multi-milligram quantities of (±)-8-*epi*-$PGF_{2\alpha}$ ethyl ester (**5**).

Our new route to **7** is outlined in Scheme 2. Alkylation of THP-protected propargyl alcohol (**10**) with 1,3-dibromopropane, followed by displacement with sodium cyanide, produced the internal acetylene **12**. This was deprotected and hydrogenated[9] to produce the allylic alcohol **14**. Base hydrolysis followed by Lewis acid-catalyzed esterification and exposure to CBr_4/Ph_3P then efficiently produced the bromide **17**. α-Alkylation[10] of benzoylacetone (**18**) with **17** yielded the diketone **19**, which underwent selective fragmentation and diazo transfer under our recently described conditions[10] to provide the α-diazo ketone **8**.

While aldol condensation of an α-diazo ketone had not previously been reported, our earlier studies suggested that this would be a feasible process.[11] Indeed, enolization of ketone **8** with KHMDS, followed by addition of the LiBr-coordinated (*E*,*E*)-decadienal (**9**) provided an intermediate *β*-hydroxy adduct that was not isolated, but was immediately silylated to provide the cyclization precursor **7**.[12] Cyclization of **7** with rhodium(II) octanoate proceeded with 83:17 diastereoselectivity, to provide bicyclic ketone **6**.

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(11) Bhamidipati, R., unpublished results, University of Delaware.

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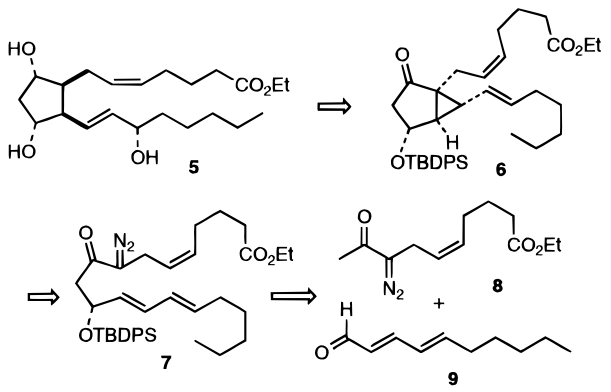
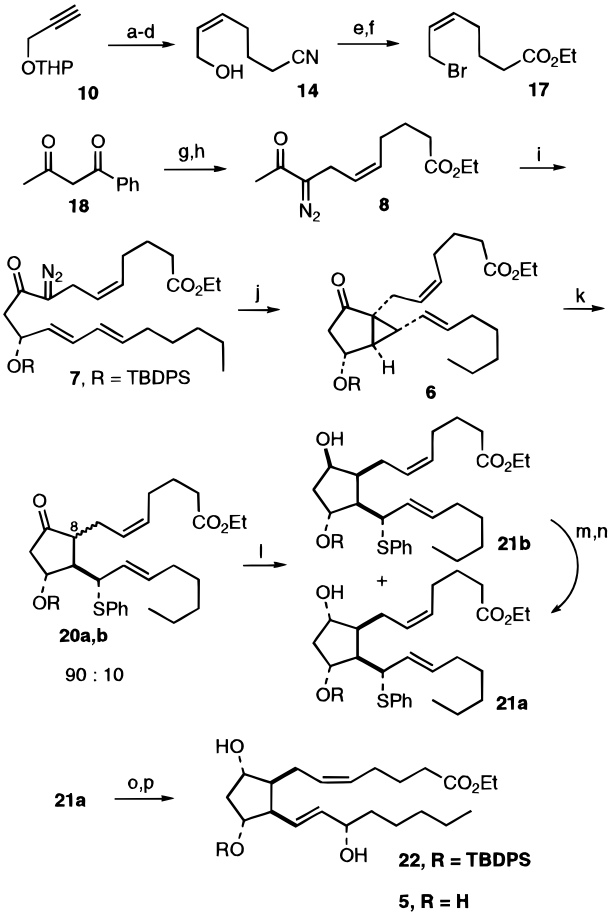
Scheme 1



Scheme 2[a]



[a] Reaction conditions. (a) nBuLi, THF, −78 °C to 0 °C; 1,3-dibromopropane , 0 °C to 55 °C 24 h, 80%; (b) NaCN, DMSO, 45 °C, 20 h, 99%; (c) Dowex resin, MeOH, rt, 11 h, 78%; (d) $Ni(OAc)_2$/$NaBH_4$, MeOH/EDA, H_2, rt 24 h, 87%; (e) NaOH, MeOH/H_2O, reflux, 24 h; BF_3·OEt_2, EtOH, 60 °C, 3 h, 84%; (f) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to rt, 1 h, 76%; (g) K_2CO_3, nBu_4NBr, $PhCH_3$, 100 °C, 3 h; **17**, 40 °C, 18 h, 82%; (h) pNBSA, DBU, CH_2Cl_2, 0 °C, 1 h, 83%; (i) KHMDS, THF, −78 °C, 40 min; **9**, LiBr, −78 °C, 1 h; TBDPSCl, DMAP, imidazole, CH_2Cl_2, rt 24 h, 38%; (j) $Rh_2(oct)_4$, CH_2Cl_2, rt, 15 min, 70%; (k) thiophenol, BF_2·OEt_2, CH_2Cl_2 −78 °C, 2.5 h, 90%; (l) $NaBH_4$, EtOH, 1 h, 76%, (1:1); (m) *p*-nitrobenzoic acid, Ph_3P, DEAD, PhH, rt, 19 h, 74%; (n) K_2CO_3, EtOH, 2 h, 87%; (o) mCPBA, CH_2Cl_2, −78 °C, 1.5 h; $(MeO)_3P$/EtOH −78 °C to rt, 85%; (p) nBu_4NF, THF, 3 h, rt 81%.

Our earlier synthesis of PGE_2 was based on the boron trifluoride etherate-mediated addition of thiophenol to the bicyclic ketone **6**, resulting in a 77:23 selectivity for the *cis*-2,3 relative configuration.[8] With careful control of reaction conditions and a neutral, *low temperature* workup, we have now significantly improved this diastereoselectivity, to give a 90:10 ratio of **20a** to **20b**.

Reduction of the **20a,b** ketone mixture produced a 1:1 mixture of epimeric alcohols **21a** and **21b**, accompanied by a minor amount of the reduction product from **20b**, all of which are easily separable. The undesired **21b** was converted into **21a** using Mitsunobu coupling.[13] Oxidation and Mislow rearrangement[14] of **21a** cleanly produced the allylic alcohol **22**. Desilylation of **22** then yielded the 8-*epi*-$PGF_{2\alpha}$ ethyl ester (**5**), identical (TLC, ^1H and ^{13}C NMR) to the ethyl ester we had prepared from the authentic isoprostane.

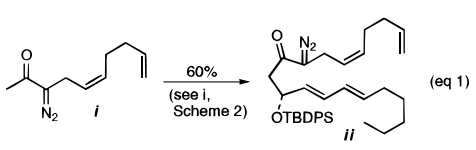
We believe that the sequential α-diazo ketone aldol/insertion described here offers a powerful new approach to cycloalkane construction. The kinetic conjugate opening of fused cyclopropyl ketones with thiophenol may also prove to be generally useful for the construction of *cis*-2,3-dialkyl cyclic ketones.

Experimental Procedures[15]

***O*-Tetrahydropyranyl-6-bromo-2-hexyn-1-ol (11).** To a solution of 40.0 g (285 mmol) of THP-protected propargyl alcohol (**10**) in 250 mL of dry THF at −78 °C was added 134 mL (314 mmol) of *n*-butyllithium (2.34 M solution in hexanes) over 30 min. The mixture was warmed to rt, and 34.8 mL (342 mmol) of 1,3-dibromopropane was added over 10 min. The mixture was heated at 55 °C for 24 h. The cooled mixture was then partitioned between ethyl acetate and, sequentially, ice−water, water, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was purified by bulb-to-bulb distillation (bath = 110 °C/0.5 mmHg) to provide bromide **11** as a colorless oil (62.4 g, 80% from **10**). R_f (10% ethyl acetate/petroleum ether) = 0.48; IR (film) 2942, 1440, 1347, 1117, 1024 cm^{-1}; ^1H NMR δ 4.79 (dd, 1H, J = 3.3, 3.1 Hz), 4.24 (ddt, 2H), 3.85 (m, 1H), 3.53 (m, 1H), 3.51 (t, 2H, J = 6.5 Hz), 2.42 (m, 2H), 2.04 (m, 2H), 1.90−1.30 (m, 6H); ^{13}C NMR δ up: 83.8, 77.5, 61.5, 54.0, 31.9, 31.0, 29.9, 25.0, 18.7, 17.1; down: 96.2; EI MS m/z (rel intensity) 261 (M^+, 1), 161 (44), 159 (44), 101 (28), 85 (99), 79 (100), 77 (58); HRMS (calcd for $C_{11}H_{17}O_2Br$) 261.0333, found 261.0313. Anal. Calcd for $C_{11}H_{17}O_2Br$: C, 50.57%; H, 6.56%. Found: C, 50.91%; H, 6.84%.

6-[(Tetrahydropyranyl)oxy]-4-hexynenitrile (12). To a solution of 8.60 g (31.3 mmol) of bromide **11** in 50 mL of dry DMSO under N_2 was added 1.69 g (34.5 mmol) of sodium cyanide. The mixture was then heated at 45 °C for 20 h. The cooled mixture was partitioned between 10% ethyl acetate/petroleum ether and, sequentially, ice−water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated to provide the nitrile **12** as a yellow oil suitable for use without further purification (6.41 g, 99% from **11**). *Rf* (20% ethyl acetate/petroleum ether) = 0.31; IR (film) 2943, 2247, 1441, 1345, 1117, 1023 cm^{-1}; ^1H NMR δ 4.78 (dd, 1H, J = 3.2, 3.1 Hz), 4.24 (ddt, 2H), 3.84 (m, 1H), 3.53 (m, 1H), 2.50 (t, 2H, J

(12) This low yield was due to complications involving the acidic protons α to the ester functionality. When precursor **i** was used, the two-step process yields diazo ketone **ii** in 60% yield (eq 1).



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= 7.2 Hz), 2.47−2.37 (m, 2H), 2.00−1.50 (m, 8H); ^{13}C NMR δ up: 118.4, 82.8, 77.2, 61.1, 53.5, 29.6, 24.7, 23.8, 18.4, 17.1, 15.3; down: 95.9; EI MS *m/z* (rel intensity) 201 (M^+, 1), 95 (11), 85 (100), 79 (62), 77 (36), 55 (69); HRMS (calcd for $C_{12}H_{17}NO_2$) 207.1345, found 207.1259. Anal. Calcd for $C_{12}H_{17}O_2N$: C, 69.54%; H, 8.27%; N, 6.76%. Found: C, 69.43%; H, 8.27%; N, 5.40%.

6-Hydroxy-4-hexynenitrile (13). To a solution of 27.7 g (134 mmol) of THP-protected hydroxy nitrile **12** in 300 mL of methanol at rt was added 45 g (1.5 wt equiv) of Dowex 50W-X8 acidic cation exchange resin (prewashed with 200 mL of 6 N aqueous HCl, water, and methanol, respectively), and the mixture was stirred for 11 h. The resin was filtered off and was washed with 100 mL of methanol. The combined organic extract was then dried (Na_2SO_4) and concentrated. The residue was purified by bulb-to-bulb distillation (bath = 80 °C/0.5 mmHg) to provide hydroxy nitrile **13** as a colorless oil (12.75 g, 78% from **12**). R_f (20% ethyl acetate/petroleum ether) = 0.10; IR (film) 3414, 2933, 2249, 1021, 734 cm^{-1}; ^{1}H NMR δ 4.26 (m, 2H), 2.51 (t, 2H, J = 7.1 Hz), 2.48−2.37 (m, 2H), 1.88 (m, 2H), 1.69 (m, 1H); ^{13}C NMR δ up: 119.0, 82.3, 80.0, 50.0, 23.8, 17.3, 15.5; EI MS *m/z* (rel intensity) 121 ($M^+ - 1$, 4), 95 (18), 94 (46), 69 (19), 67 (100), 66 (21), 65 (36), 55 (58); HRMS (calcd for C_7H_9NO) 123.0675, found 123.0684.

(*Z*)-6-Hydroxy-4-hexenenitrile (14). To a solution of 1.6 g (6.5 mmol) of nickel (II) acetate tetrahydrate in 60 mL of methanol at rt was added portionwise 0.25 g (6.5 mmol) of sodium borohydride. The flask was purged with hydrogen and 0.87 mL (13.0 mmol) of ethylenediamine and 8.00 g (65.0 mmol) of the hexynenitrile **13** was added. The mixture was stirred until the uptake of hydrogen had ceased (24 h), after which the mixture was filtered through 50 g of coarse silica gel with 200 mL of methanol. The solvent was removed *in vacuo* and the residue was partitioned between 50% ethyl acetate/petroleum ether and, sequentially, water and brine. The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was futher purified by bulb-to-bulb distillation (bath = 100 °C/0.5 mmHg), to provide (*Z*)-hexenenitrile **14** as a colorless oil (7.07 g, 87% from **13**). R_f (50% ethyl acetate/petroleum ether) = 0.30; IR (film) 3414, 3017, 2938, 2247, 1033 cm^{-1}; ^{1}H NMR δ 5.72 (m, 1H), 5.46 (m, 1H), 4.23 (t, 2H, J = 5.8 Hz), 2.37 (t, 2H, J = 7.0 Hz), 2.27 (m, 2H), 1.76 (m, 2H), 1.46 (s, 1H); ^{13}C NMR δ up: 119.3, 57.3, 25.5, 24.5, 15.8; down: 130.5; 128.6; EI MS *m/z* (rel intensity) 125 (M^+, 1), 97 (11), 96 (58), 82 (18), 69 (45), 67 (45), 57 (100), 55 (41); HRMS (calcd for $C_7H_{11}NO$) 125.0857, found 125.0841.

Ethyl (*Z*)-7-Hydroxy-5-heptenoate (16). A mixture of 50.0 g (1.25 mol) of sodium hydroxide and 7.80 g (62.3 mmol) of hydroxy nitrile **14** in 300 mL of methanol/water (1:1) was heated at reflux for 24 h. The mixture was cooled to 0 °C and partitioned between ethyl acetate and, sequentially, 6 N aqueous HCl saturated with NaCl, and brine. The combined organic extract was dried ($MgSO_4$) and concentrated to provide hydroxy acid **15** as a colorless oil of suitable purity for further use. R_f (1% acetic acid in 40% ethyl acetate/petroleum ether) = 0.10; IR (film) 3332, 3017, 2937, 1709, 1412, 1243 cm^{-1}; ^{1}H NMR δ 5.68 (m, 1H), 5.52 (m, 1H), 4.90 (s, 2H), 4.18 (d, 2H, J = 7.0 Hz), 2.37 (t, 2H, J = 7.2 Hz), 2.17 (m, 2H), 1.73 (m, 2H); ^{13}C NMR δ up: 177.5 (s), 130.9 (d), 129.1 (d), 57.6 (t), 33.0 (t), 26.2 (t), 24.2 (t); EI MS *m/z* (rel intensity) 126 ($M^+ - H_2O$, 31), 84 (49), 81 (98), 70 (48), 67 (67), 60 (52), 57 (100), 55 (83); HRMS (calcd for $C_7H_{12}O_3$) 144.0751, found 144.0786.

The crude acid **15** was diluted with 250 mL of dry ethanol, to which 1.53 mL (12.5 mmol) of $BF_3{\cdot}OEt_2$ was added. The mixture was then heated at 60 °C for 3 h. The cooled mixture was partitioned between ethyl acetate and, sequentially, saturated aqueous $NaHCO_3$, water, and brine. The combined organic extract was then dried ($MgSO_4$) and concentrated. The residue was purified by bulb-to-bulb distillation (bath = 100 °C/0.5 mmHg), to produce ethyl ester **16** as a colorless oil (9.02 g, 84% from **14**). R_f (50% ethyl acetate/petroleum ether) = 0.53; IR (film) 3405, 2938, 1732, 1375, 1032 cm^{-1}; ^{1}H NMR δ 5.68 (m, 1H), 5.52 (m, 1H), 4.16 (d, 2H, J = 7.9 Hz), 4.13 (q, 2H, J = 7.0 Hz), 2.31 (t, 2H, J = 7.2 Hz), 2.20−2.10 (m, 2H), 1.80−1.65 (m, 3H), 1.23 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ up: 173.3, 59.8, 57.4, 33.0, 26.1, 24.2; down: 130.1, 129.6, 13.7; EI MS *m/z* (rel intensity) 154 ($M^+ - H_2O$, 12), 109 (21), 81 (100), 80 (79), 79 (42), 67 (42), 55 (56); HRMS (calcd for $C_9H_{14}O_2$, $M - H_2O$) 154.0991, found 154.0994. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77%; H, 9.36%. Found: C, 62.77%; H, 9.52%.

Ethyl (*Z*)-7-Bromohex-5-enoate (17). To a solution of 2.28 g (13.2 mmol) of alcohol **16** in 40 mL of dry CH_2Cl_2 at 0 °C was added 4.84 g (14.6 mmol) of carbon tetrabromide. This was followed by the addition of 3.83 g (14.6 mmol) of triphenylphospine in 10 mL of dry CH_2Cl_2 over 10 min. The mixture was warmed to rt and stirred for 1 h, after which 5 mL of methanol was added. The solvents were removed *in vacuo*, and the residue was filtered through 50 g of coarse silica gel with 300 mL of 50% ethyl acetate/petroleum ether. The solvents were removed *in vacuo* to produce bromide **17** as a colorless oil suitable for use without further purification (2.344 g, 76% from **16**). R_f (10% ethyl acetate/petroleum ether) = 0.28; IR (film) 3020, 2980, 1732, 1374, 1206, 1033 cm^{-1}; ^{1}H NMR δ 5.77 (m, 1H), 5.48 (m, 1H), 4.13 (q, 2H, J = 7.1 Hz), 3.99 (d, 2H, J = 8.3 Hz), 2.33 (t, 2H, J = 7.4 Hz), 2.20 (m, 2H), 1.74 (m, 2H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ up: 172.6, 59.7, 33.0, 26.4, 25.7, 23.8; down: 134.0, 126.0, 13.8; EI MS *m/z* (rel intensity) 191 ($M^+ + 2$ OEt, 5), 189 ($M^+ -$ OEt, 5), 155 (34), 109 (63), 85 (22), 81 (100), 67 (57).

Ethyl (*Z*)-8-Benzoyl-9-oxodec-5-en-1-oate (19). A mixture of 4.28 g (26.4 mmol) of benzoylacetone (**18**), 14.6 g (106 mmol) of anhydrous K_2CO_3, and 0.085 g (0.26 mmol) of tetrabutylammonium bromide in 150 mL of dry toluene was heated at 100 °C for 3 h. The mixture was cooled to 40 °C for the addition of 6.20 g (26.4 mmol) of bromide **17**. The mixture was then stirred at 40 °C for 14 h. The mixture was further cooled to rt and partitioned between 50% ethyl acetate/petroleum ether and, sequentially, water and brine. The combined organic extract was concentrated *in vacuo*, and the residue was filtered through 30 g of coarse silica gel with 300 mL of CH_2Cl_2. The solvent was removed *in vacuo*, and the residue was chromatographed to produce the diketone **19** as a yellow oil (6.89 g, 82% from **17**). R_f (20% ethyl acetate/petroleum ether) = 0.31; IR (film) 3062, 2979, 1731, 1678, 1448, 1030 cm^{-1}; ^{1}H NMR δ 7.95 (d, 2H, J = 7.4 Hz), 7.65−7.30 (m, 3H), 5.45−5.20 (m, 2H), 4.46 (t, 1H, J = 7.2 Hz), 4.09 (q, 2H, J = 7.2 Hz), 2.70 (t, 2H, J = 6.8 Hz), 2.25 (t, 2H, J = 7.5 Hz), 2.20−2.00 (m, 2H), 2.12 (s, 3H), 1.70−1.50 (m, 2H), 1.21 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ up: 203.4, 195.9, 173.3, 136.3, 62.6, 28.1, 14.0; down: 133.5, 131.4, 128.7 (× 2), 128.5 (× 2), 125.9, 60.0, 33.5, 26.7, 26.4, 24.5; EI MS *m/z* (rel intensity) 316 (M^+, 1), 161 (12), 154 (37), 105 (100), 81 (19), 77 (51), 55 (12); HRMS (calcd for $C_{19}H_{24}O_4$) 316.1675, found 316.1693.

Ethyl (*Z*)-8-Diazo-9-oxo-dec-5-en-1-oate (8). To a solution of 0.661 (2.1 mmol) of diketone **19** in 6 mL of dry CH_2Cl_2 at 0 °C was added 0.63 mL (4.2 mmol) of DBU. The mixture was stirred for 5 min, after which 0.954 g (4.2 mmol) of *p*-nitrobenzenesulfonyl azide (*p*NBSA) in 3 mL of dry CH_2Cl_2 was added over 5 min. The solution was stirred for 1 h and then partitioned between CH_2Cl_2 and, sequentially, 10% aqueous NaOH, water, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was then immediately chromatographed to produce α-diazo ketone **8** as a yellow oil (0.568 g, 83% from **19**). R_f (20% ethyl acetate/petroleum ether) = 0.32; IR (film) 2938, 2072, 1732, 1640, 1330, 1032 cm^{-1}; ^{1}H NMR δ 5.65−5.50 (m, 1H), 5.50−5.35 (m, 1H), 4.13 (q, 2H, J = 7.2 Hz), 3.08 (d, 2H, J = 7.4 Hz), 2.30 (t, 2H, J = 7.4 Hz), 2.24 (s, 3H), 2.15−2.05 (m, 2H), 1.75−1.60 (m, 2H), 1.26 (t, 3H, J = 7.4 Hz); ^{13}C NMR δ up: 190.2, 173.0, 66.7, 60.0, 33.3, 26.2, 24.5, 19.8; down: 132.7, 123.4, 25.1, 14.0; EI MS *m/z* (rel intensity) 210 ($M^+ - N_2$, 2), 164 (10), 122 (45), 95 (100), 79 (49), 55 (25); HRMS (calcd. for $C_{12}H_{18}O_3$) 210.1265, found 210.1256.

***tert*-Butyldiphenylsilyl-Protected *β*-Hydroxy α-Diazo Ketone 7.** To a solution of 2.2 mL (1.1 mmol, 0.50 M solution in toluene) of potassium hexamethyldisilyl azide in 10.0 mL of dry THF at −78 °C was added a solution of 0.238 g (1.0 mmol) of α-diazo ketone **8** in 5 mL of dry THF over 10 min. The mixture was stirred for 40 min at −78 °C, after which a solution of 0.110 g (1.3 mmol) of anhydrous LiBr and 0.137 g

(0.9 mmol) of (*E*,*E*)-2,4-decadienal (**9**) in 5 mL of dry THF was added over 5 min. This mixture was stirred for 60 min at −78 °C, after which 10 mL of saturated NH_4Cl solution was added and the mixture was warmed to rt. The mixture was then partitioned between ethyl acetate and sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated to provide the crude β-hydroxy α-diazo ketone which was immediately diluted with 20 mL of dry CH_2Cl_2 and stirred at rt. To this solution were added 0.160 g (2.4 mmol) of imidazole and 0.025 g (0.20 mmol) of DMAP. To the resulting mixture was then added 0.43 mL (1.7 mmol) of *tert*-butylchlorodiphenylsilane and stirring was maintained for 24 h. The mixture was partitioned between CH_2Cl_2 and sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography to provide the silylated β-hydroxy α-diazo ketone **7** as a yellow oil (0.2360 g, 38% from **8**). R_f (10% ethyl acetate/petroleum ether) = 0.51; IR (film) 3454, 3071, 2930, 2857, 2077, 1732, 1634, 1471, 1428, 1361, 1112 cm^{-1}; ^1H NMR δ 7.75−7.55 (m, 4H), 7.45−7.30 (m, 6H), 5.85−5.25 (m, 6H), 4.68 (m, 1H), 4.12 (q, 2H, J = 7.2 Hz), 3.01 (m, 2H), 2.79 (dd, 1H, J = 13.5, 7.5 Hz), 2.49 (dd, 1H, J = 13.5, 5.7 Hz), 2.28 (t, 2H, J = 7.4 Hz), 2.15−1.95 (m, 4H), 1.68 (m, 2H), 1.40−1.20 (m, 6H), 1.25 (t, 3H, J = 7.0 Hz), 1.03 (s, 9H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ up: 194.0, 152.9, 135.3 (× 2), 60.3, 46.6, 33.6, 32.5, 31.3, 28.8, 26.4, 24.7, 22.5, 19.2, 19.0; down: 135.9, 135.8, 134.8 (× 2), 129.5 (× 2), 129.4, 129.1, 127.6 (× 4), 127.5, 127.3, 72.3, 26.5 (× 3), 14.2, 14.0; FAB MS m/z (rel intensity) 628 (M^+, 0.1), 599 (1), 543 (1), 523 (1), 391 (48), 199 (38), 197 (45), 135 (100).

Bicyclic Ketones 6 and 6a. To a solution of 60.0 mg (0.10 mmol) of diazo ketone **7** in 1.9 mL of dry CH_2Cl_2 at rt was added 0.8 mg (1 mol %) of rhodium(II) octanoate dimer. The mixture was stirred for 15 min after which the mixture was filtered through 20 g of coarse silica gel with 20% ethyl acetate/petroleum ether. The solvent was removed *in vacuo*, and the residue was immediately chromatographed to produce the minor diastereomer **6a** as a yellow oil (0.0076 g, 13% from **7**). R_f (20% ethyl acetate/petroleum ether) = 0.72. This was followed by the major diastereomer **6** as a yellow oil (0.0403 g, 70% from **7**). R_f (20% ethyl acetate/petroleum ether) = 0.62; IR (film) 3444, 2930, 1734, 1590, 1472, 1428, 1157, 1113, 909 cm^{-1}; ^1H NMR δ 7.64 (dd, 4H, J = 7.3, 16.9 Hz), 7.41 (m, 6H), 5.42 (m, 3H), 5.00 (dd, 1H, H = 7.8, 15.3 Hz), 4.45 (d, 1H, J = 4.8 Hz), 4.14 (d, 2H, J = 7.2 Hz), 2.69 (dd, 1H, J = 5.4, 15.4 Hz), 2.32 (t, 2H, J = 7.4 Hz), 2.20 (d, 1H, J = 4.9 Hz), 2.10 (m, 5H), 1.97 (d, 1H, J = 3.1 Hz), 1.72 (t, 2H, J = 7.4 Hz), 1.60 (m, 1H), 1.26 (t, 3H, J = 7.2 Hz), 1.28 (m, 6H), 1.06 (s, 9H), 0.86 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ up: 212.2, 173.6, 133.9, 133.6, 60.2, 43.8, 42.7, 33.8, 32.5, 31.3, 29.0, 26.8, 24.9, 22.5, 21.3, 19.1; down: 135.8 (× 2), 135.7 (× 2), 134.8, 129.8 (× 2), 129.6, 127.8, 127.7 (× 4), 124.5, 69.3, 39.9, 31.7, 27.0, 26.8 (× 3), 14.3, 14.0; FAB MS m/z (rel intensity) 601 (M^+, 70), 543 (100), 523 (20), 391 (16), 345 (33), 318 (16), 199 (89), 197 (81), 135 (88); FAB HRMS (calcd for $C_{38}H_{53}O_4Si$) 601.3714, found 601.3713.

Ethyl (*Z*,*E*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-9-oxo-13-(phenylthio)prosta-5,14-dienoates 20a and 20b. To a solution of 0.078 g (0.13 mmol) of bicylic ketone **6** and 0.020 mL (0.17 mmol) of thiophenol in 3.0 mL of dry CH_2Cl_2 at −78 °C was added 0.16 mL of a boron trifluoride etherate solution (0.18 mmol, 1.0 M in CH_2Cl_2). The mixture was stirred for 2.5 h at −78 °C and diluted with 1.0 mL of cold saturated aqueous $NaHCO_3$. The mixture was warmed to rt and partitioned between CH_2Cl_2 and sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography to produce an inseparable 10:1 mixture of ketone epimers **20a** and **20b** as a yellow oil (0.0830 g, 90% from **6**). **20a:** R_f (10% ethyl acetate/petroleum ether) = 0.42; IR (film) 3072, 2926, 2859, 2361, 2339, 1733, 1717, 1652, 1558, 1456 cm^{-1}; ^1H NMR δ 7.63 (m, 4H), 7.40 (m, 6H), 7.18 (bs, 5H), 5.41 (m, 2H), 5.15 (m, 2H), 4.59 (d, 1H, J = 5.8 Hz), 4.11 (q, 2H, J = 7.2 Hz), 3.36 (q, 1H, J = 3.4 Hz), 2.85 (m, 2H), 2.65 (m, 1H), 2.51 (d, 1H, J = 6.1 Hz), 2.25 (m, 3H), 2.19 (t, 2H, J = 8.0 Hz), 1.93 (m, 2H), 1.79 (m, 2H), 1.61 (t, 2H, J = 7.4 Hz), 1.24 (t, 2H, J = 7.2 Hz), 1.26 (m, 2H), 1.06 (m, 4H), 1.04 (s, 9H), 0.84 (t, 2H, J = 7.3 Hz); ^{13}C NMR δ up: 216.9, 173.4, 136.5, 134.8 (× 2), 60.2, 47.2, 33.7, 32.1, 31.3, 28.8, 26.8, 24.7, 22.8, 22.4, 19.0; down: 135.8 (× 2), 135.7 (× 2), 134.8, 133.4, 132.3, 130.3, 129.9, 129.8, 128.6, 128.5, 128.1, 127.8 (× 2), 127.7 (× 2), 127.3, 70.1, 52.4, 51.4, 50.3, 26.9 (× 3), 14.2, 14.0; FAB MS m/z (rel intensity) 711 (M^+, 1), 653 (1), 633 (1), 543 (5), 401 (5), 355 (9), 281 (27), 221 (38), 174 (100); FAB HRMS (calcd for $C_{44}H_{58}O_4SSi$) 711.3921, found 711.3903.

Ethyl(*Z*,*E*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-9-hydroxy-13-(phenylthio)prosta-5,14-dienoates 21a and 21b. To 0.0615 g (0.087 mmol) of the inseparable ketone epimers **20a** and **20b** (7:1) in 2.0 mL of methanol at 0 °C was added 0.0330 g (0.87 mmol) of sodium borohydride over 5 min. The mixture was stirred for 60 min at 0 °C, after which 2 mL of 10% aqueous HCl was added over 5 min. The mixture was warmed to rt, saturated with NaCl, and partitioned between ethyl acetate and, sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to produce the β diastereomer **21b** as a colorless oil (0.024 g, 39% from mixture, 44% from **20a**). R_f (10% ethyl acetate/petroleum ether) = 0.33; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, 4H, J = 6.4, 12.2 Hz), 7.36 (m, 6H), 7.22 (s, 5H), 5.43 (m, 1H), 5.36 (m, 1H), 5.28 (dd, 1H, J = 5.8, 9.4 Hz), 4.92 (dt, 1H, J = 7.3, 15.1 Hz), 4.64 (m, 1H), 4.24 (m, 1H), 4.09 (q, 2H, J = 7.1 Hz), 3.52 (dd, 1H, J = 5.8, 9.4 Hz), 2.52 (m, 1H), 2.39 (d, 2H, J = 8.3 Hz), 2.35 (m, 1H), 2.23 (t, 2H, J = 7.7 Hz), 2.20 (m, 2H), 2.03 (m, 2H), 1.77 (m, 2H), 1.65 (dd, 2H, J = 7.5, 13.0 Hz), 1.23 (m, 2H), 1.22 (t, 3H, J = 7.2 Hz), 1.09 (m, 4H), 1.04 (s, 9H), 0.83 (t, 2H, J = 7.2 Hz); ^{13}C NMR (171 MHz, $CDCl_3$) δ up: 173.6, 134.6, 134.4, 134.0, 60.2, 44.9, 33.8, 32.0, 31.3, 28.9, 26.8, 24.8, 23.9, 22.5, 19.1; down: 135.9 (× 2), 135.8 (× 2), 133.3 (× 2), 131.5, 130.5, 129.8, 129.6 (× 2), 129.5, 128.6 (× 2), 127.6 (× 4), 127.3, 76.2, 73.3, 54.9, 53.0, 46.3, 27.0 (× 3), 14.2, 14.0; FAB MS m/z (rel intensity) 711 (M^+, 2), 603 (17), 585 (34), 545 (18), 291 (16), 219 (21), 197 (67), 135 (100); FAB HRMS (calcd for $C_{44}H_{60}O_4SSi$) 735.3927, found 735.3879. This was followed by the a diastereomer **21a** as a colorless oil (0.023 g, 37% from mixture, 43% from **20a**). R_f (10% ethyl acetate/petroleum ether) = 0.20; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.36 (m, 6H), 7.21 (s, 5H), 5.39 (m, 2H), 5.16 (m, 1H, J = 9.5 Hz), 4.88 (dt, 1H, J = 7.4, 14.9 Hz), 4.38 (m, 1H), 4.08 (q, 2H, J = 7.2 Hz), 3.99 (m, 1H), 3.45 (dd, 1H, J = 6.3, 9.4 Hz), 2.64 (m, 1H), 2.29 (m, 3H), 2.23 (t, 2H, J = 7.5 Hz), 2.07 (m, 2H), 2.01 (m, 2H), 1.84 (m, 1H), 1.72 (m, 1H), 1.63 (t, 2H, J = 7.4 Hz), 1.22 (m, 4H), 1.21 (t, 2H, J = 9.8 Hz), 1.05 (s, 9H), 0.90 (m, 2H), 0.81 (t, 2H, J = 7.3 Hz); ^{13}C NMR (171 MHz, $CDCl_3$) δ up: 173.6, 134.6, 134.4, 134.0, 60.2, 44.9, 33.8, 32.0, 31.3, 28.9, 26.8, 24.8, 23.9, 22.5, 19.1; down: 135.9 (× 2), 135.8 (× 2), 133.3 (× 2), 131.5, 131.4, 130.4, 130.3, 129.6 (× 2), 129.5, 128.6 (× 2), 127.6 (× 3), 127.3, 76.2, 73.3, 54.9, 53.0, 46.3, 27.0 (× 3), 14.2, 14.0 FAB MS m/z (rel intensity) 711 (M^+, 1), 695 (1), 457 (1), 329 (12), 290 (5), 219 (12), 146 (18), 135 (100); FAB HRMS (calcd for $C_{44}H_{60}O_4SSi$) 735.3854, found 735.3879.

Mitsunobu Conversion of 21b into 21a. To 0.0169 g (0.10 mmol) of *p*-nitrobenzoic acid and 0.0240 g (0.034 mmol) of β-epimer **21b** in 1.0 mL of dry benzene at rt was added 0.0353 g (0.13 mmol) of triphenylphosphine. The mixture was stirred for 5 min, after which 0.021 mL (0.13 mmol) of diethyl azodicarboxylate was added. The mixture was stirred for 19 h and concentrated *in vacuo*. The residue was immediately chromatographed to produce the acylated α-isomer **23** as a colorless oil (0.0215 g, 74% from **21b**). R_f (10% ethyl acetate/petroleum ether) = 0.43; IR (film) 3072, 2930, 2858, 2256, 1732, 1608, 1531, 1471, 1428, 1274, 1104 cm^{-1}; ^1H NMR δ 8.30 (d, 2H, J = 9.0 Hz), 8.19 (d, 2H, J = 9.0 Hz), 7.62 (dd, 4H, J = 1.4, 6.5 Hz), 7.31 (m, 6H), 7.22 (s, 5H), 5.37 (m, 2H), 5.21 (m, 2H), 5.01 (m, 1H), 4.50 (m, 1H), 4.07 (t, 2H, J = 7.2 Hz), 3.59 (dd, 1H, J = 6.4, 8.Hz), 2.69 (m, 2H), 2.34 (m, 4H), 2.21 (t, 2H, J = 7.6 Hz), 1.98 (m, 4H), 1.76 (m, 2H), 1.20 (t, 3H, J = 7.0 Hz), 1.10 (m, 4H), 1.05 (s, 9H), 0.82 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ up: 173.4, 164.1, 150.5, 135.0, 134.3, 133.6, 60.2, 40.8, 33.7, 32.0, 31.2, 28.8, 26.8, 25.8, 24.7, 22.4, 19.2; down: 136.0 (× 2), 135.8 (× 2), 133.2, 132.9, 130.7, 130.5, 130.2, 129.7, 129.6, 128.8, 128.5 (× 2), 128.3 (× 2), 127.6 (× 2), 127.5 (× 2),

127.1, 123.5 (× 2), 80.4, 75.6, 54.4, 51.8, 47.0, 27.0 (× 3), 14.2, 14.0; FAB MS *m*/*z* (rel intensity) 861 (M^+, 1), 585 (5), 348 (9), 329 (15), 219 (13), 197 (37), 135 (100).

To 0.0250 g (0.029 mmol) of the acylated isomer **23** in 0.5 mL of ethanol at rt was then added 0.0200 g (0.14 mmol) of anhydrous K_2CO_3 The mixture was stirred for 2 h, and the solids were filtered off and washed with 10 mL of ethyl acetate. The combined organic extract was concentrated, and the residue was chromatographed to produce the α-epimer **21a** (spectra as above) as a colorless oil (0.018 g, 64% from **21b**).

Ethyl 11-*O*-(*tert*-Butyldiphenylsilyl)-8-*epi*-PGF$_{2\alpha}$ (22). To 0.0270 g (0.038 mmol) of thioether **21a** in 0.5 mL of dry CH_2Cl_2 at −78 °C was added 0.0098 g (0.057 mmol) of recrystallized mCPBA in 0.2 mL of dry CH_2Cl_2. The mixture was stirred for 90 min, after which 0.045 mL (0.38 mmol) of trimethyl phosphite in 1.0 mL of ethanol was added. The mixture was stirred at −78 °C for 5 min and then warmed to rt. The mixture was partitioned between ethyl acetate and, sequentially, saturated aqueous $NaHCO_3$, water, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography to produce diol **22** as a colorless oil (0.0200 g, 85% from **21a**). R_f (20% ethyl acetate/petroleum ether) = 0.14; IR (film) 3282, 2928, 2362, 1734, 1718, 1654, 1458, 1112, 700 cm^{-1}; ^{1}H NMR δ 7.62 (m, 4H), 7.38 (m, 6H), 5.23 (m, 2H), 5.14 (m, 2H), 4.07 (t, 2H, J = 7.1 Hz), 3.97 (m, 1H), 3.86 (m, 2H), 2.73 (m, 1H), 2.26 (t, 2H, J = 7.2 Hz), 2.09 (m, 3H), 2.06 (m, 6H), 1.64 (m, 4H), 1.23 (m, 4H), 1.22 (t, 3H, 7.1 Hz), 1.04 (s, 9H), 0.85 (t, 2H, J = 6.8 Hz); ^{13}C NMR δ up: 173.6, 134.0 (× 2), 60.3, 42.9, 37.0, 33.6, 31.7, 27.1, 26.7, 25.0, 24.7, 22.6; down: 135.8 (× 4), 129.7 (× 2), 129.6, 129.3, 128.4, 127.6 (× 5), 78.3, 77.1, 72.5, 53.9, 50.5, 26.9 (× 3), 14.2, 14.0; FAB MS *m*/*z* (rel intensity) 619 (M^+, 2), 603 (16), 585 (20), 545 (25), 347 (20), 329 (42), 238 (13), 199 (100), 197 (59), 135 (94); FAB HRMS (calcd for $C_{38}H_{56}O_5Si$) 621.3923, found 621.3975.

(±)-8-*epi*-PGF$_{2\alpha}$ Ethyl Ester (5). To a solution of 0.0110 g (0.018 mmol) of silyl ether **22** in 3.0 mL of dry THF at rt was added 0.050 mL (0.053 mmol, 1.0 M in THF) of tetrabutylammonium fluoride. The mixture was stirred for 3 h and then partitioned between ethyl acetate and saturated aqueous NH_4Cl. The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was purified by chromatography to provide the isoprostane ethyl ester **5** as a white solid (0.0055 g, 81% from **22**). R_f (30% acetone/CH_2Cl_2) = 0.18; ^{1}H NMR δ 5.53 (m, 2H), 5.42 (m, 2H), 4.01 (q, 2H, J = 7.1 Hz), 4.06 (m, 1H), 4.04 (m, 1H), 2.75 (m, 1H), 2.31 (m, 1H), 2.28 (m, 2H), 2.00 (m, 4H), 1.85 (m, 2H), 1.65 (m, 4H), 1.47 (m, 2H), 1.23 (m, 8H), 0.84 (m, 3H); ^{13}C NMR δ up: 173.8, 60.4, 42.4, 37.3, 33.6, 31.7, 30.3, 27.0, 26.7, 25.1, 24.7, 27.6; down: 136.2, 130.0, 129.1, 128.7, 76.5, 72.7, 53.7, 50.8, 14.2, 14.0, identical with authentic material.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be directly ordered from the ACS; see any current masthead page for ordering information.

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