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Supplementary Material Available: Summaries of AM1 calculations of transition states for reactions of cyclohexadiene with acetylene and ethylene; and AM1 calculated cartesian coordinates and eigenvalues/eigenvectors for the HOMOs and LUMOs of **2a**, **2b**, and **2c** (20 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of the Antisecretory Prostaglandin Enisoprost

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An efficient 11-step synthesis of the antisecretory prostaglandin enisoprost starting with (*Z*,*Z*)-1,5-cyclooctadiene has been developed. The key steps in the synthesis are a selective ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene, a zinc chloride catalyzed rearrangement of a furanylcarbinol, and a coupling reaction of a suitably substituted cyclopentenone with a dilithiocyanocuprate reagent derived from 4-methyl-1-octyn-4-ol.

Introduction

A 13-step synthesis of the antisecretory prostaglandin enisoprost was previously reported by Collins et al.[1] in 1983. The reported synthesis involved coupling of enone **6** with a cuprate reagent[2] derived from a suitably substituted vinylstannane and cuprous pentyne to give enisoprost **10** in 60% yield after removal of protecting groups and chromatographic purification.

Further development work on the synthesis of enisoprost has resulted in an improved method for preparing the key enone precursor **6** as outlined in Scheme I. Use of the *trans*-vinyl iodide **9** in place of the corresponding vinylstannane derivative and use of dilithiocyanocuprate[3] coupling technology resulted in an 85% isolated yield of enisoprost **10** as outlined in Scheme II.

Direct conversion of the terminal acetylene **8b** into protected enisoprost via a one-pot process has also been accomplished as outlined in Scheme II. This latter modification greatly simplified the process and resulted in a 71% isolated yield of enisoprost **10**.

Results and Discussion

Among the disadvantages of the reported synthesis of enisoprost were the 5% overall yield for the nine-step route used to prepare the hydroxycyclopentenone **5** and the need to chromatograph three of the intermediates in the sequence. The reported synthesis also utilized a Lindlar reduction of an acetylenic intermediate to generate a *cis*-olefin. Upon attempted scale-up, we found that the Lindlar reduction was always accompanied by the formation of 2–4% of the corresponding *trans*-olefin.[4] This impurity in turn was carried through the remaining steps of the synthesis to give 2–4% of the corresponding $\Delta^{4,5}$-trans analogue of enisoprost in the final product. In order to overcome these problems, we developed an improved synthesis of intermediate **5**.

Previous work by Piancatelli[5a–d] and Floyd[6a,b] suggested that rearrangement of a suitably substituted furanylcarbinol derivative might be a much more efficient method for preparing intermediate **5**. Tolstikov et al.[7] reported that selective ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene produced the half aldehyde–half acid **2a**, which could be converted into the half aldehyde–half ester **2b** via a two-step reaction sequence. Schreiber[8] subsequently reported a modified ozonolysis procedure for preparing half aldehyde–half esters directly via a one-pot ozonolysis of cyclic olefins. We felt that it should be possible to prepare the half aldehyde–half ester **2b** directly by ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene. Subsequent reaction of **2b** with 2-furanylmagnesium chloride would give the substituted furanylcarbinol **3** required for further elaboration into enisoprost.

Optimum yields of **2b** were obtained by carrying out the ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene to ~65–70% conversion. In this manner, **2b** could be obtained in isolated yields of 40–50% along with approximately 2–5% of the corresponding dialdehyde. Reaction of crude **2b** with 2-furanylmagnesium chloride[9] produced the furanylcarbinol **3** in good yield. Crude **3** was refluxed in aqueous dioxane in the presence of 3 equiv of zinc chloride for 18–24 h to produce a mixture of **4a** and **4b**.[10] The crude product

(1) Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786–790.
(2) Collins, P. W.; Jung, C. J.; Gasiecki, A. F.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187–3190.
(3) The use of dilithiocyanocuprates in the synthesis of prostaglandin analogues has previously been reported: Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641–2643.
(4) Dygos, J. H.; Scaros, M., G. D. Searle and Co., unpublished results.
(5) (a) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, 3555–3558. (b) Piancatelli, G.; Scettri, A. *Ibid.* **1977**, 1131–1134. (c) Piancatelli, G.; Scettri, A.; David, G.; D'Auria, M. *Tetrahedron* **1978**, *34*, 2775–2778. (d) Scettri, A.; Piancatelli, G.; D'Auria, M.; David, G. *Ibid.* **1979**, *35*, 135–138.
(6) (a) Floyd, M. B. *J. Org. Chem.* **1978**, *43*, 1641–1643. (b) Floyd, M. B. US 4,076,732. A variation of the Floyd procedure for the rearrangement of furanylcarbinols has also been reported: Lee, T. *Tetrahedron Lett.* **1979**, 2297–2300.
(7) Tolstikov, G. A.; Odinokov, V. N.; Miftakhov, M. S.; Galeeva, R. I.; Valeev, F. A.; Sidorov, N. N.; Mukhametzyanova, R. S.; Ishmuratov, G. Y. *Zh. Org. Khim.* **1982**, *18*, 721–727.
(8) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1986**, *64*, 150–156.
(9) Furanylmagnesium chloride was prepared in situ by adding *n*-BuLi to a solution of furan in THF at −10 °C. The mixture was stirred at 0 °C for 30 min followed by the addition of anhydrous $MgCl_2$. The mixture was warmed to room temperature to effect transmetallation of the initially formed furanyllithium intermediate.
(10) Varying amounts of intermediate **5** and its corresponding acid were also present in the crude reaction mixture.

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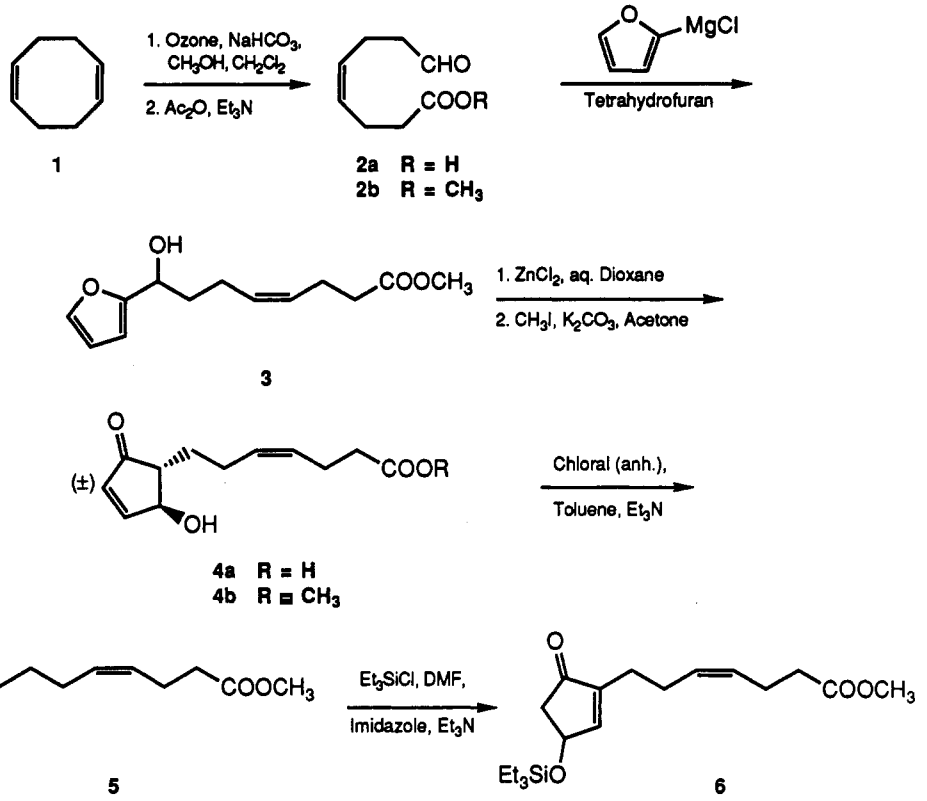
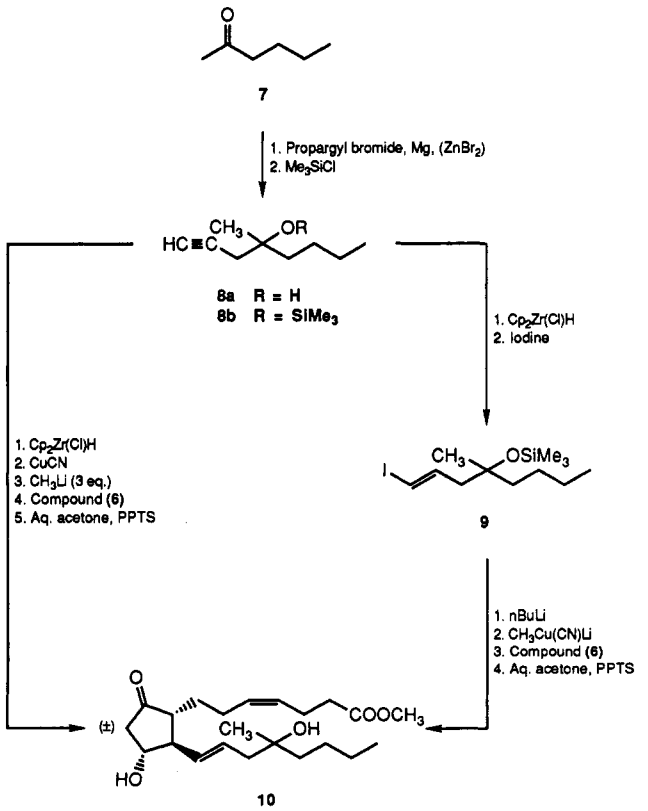
Scheme I



Scheme II



was treated with methyl iodide and potassium carbonate in acetone to convert **4a** into **4b**. Rearrangement of **4b** to **5** was effected by treatment of a toluene solution of **4b** with a catalytic amount of anhydrous chloral[11] in the presence of triethylamine. Use of stoichiometric quantities of anhydrous chloral for similar transformations has previously been reported by Stork et al.[12] and by Novák et al.[13] Partial purification of **5** was effected by complexation with anhydrous lithium bromide[14] with use of a solvent combination of toluene and heptane. Silylation of partially purified **5** with chlorotriethylsilane followed by chromatographic purification afforded pure **6**.

The ω side chain **8b** required for enisoprost was prepared by a modification[15] of the procedure reported by Chen and Grudzinskas.[16] Reaction of **8b** with zirconocene chloride hydride in tetrahydrofuran followed by quenching with iodine gave the *trans*-vinyl iodide **9**.[16,17]

Coupling of intermediates **6** and **9** using dilithiocyanocuprate technology afforded protected enisoprost.[18] The protecting groups were removed by treatment with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone to give enisoprost **10** in 85% yield based upon intermediate **6** after chromatographic purification.

Alternatively, hydrozirconation of **8b** followed by in situ conversion to a dilithiocyanocuprate[19a,b] and coupling with

(11) Varying amounts of anhydrous chloral (0.05–1.0 equiv) were used with no appreciable differences in the yield or quality of product.

(12) Stork, G.; Kowalski, C.; Gracia, G. *J. Am Chem. Soc.* **1975**, *97*, 3258–3256.

(13) Novák, L.; Rohály, J.; Kajtár, M.; Szántay, Cs. *Acta Chim. Acad. Sci. Hung.* **1979**, *102*, 91–100.

(14) The use of anhydrous lithium bromide for the purification of alcohols has previously been reported: Hill, J. B.; Erickson, R. A. US 4,452,994; US 4,529,811.

(15) Zinc bromide (2 mol %) was used to catalyze the Grignard reaction of propargyl bromide with 2-hexanone. The use of zinc halides for activating magnesium metal has previously been reported: Gilman, H.; Peterson, J. M.; Schulze, F. *Recl. Trav. Chim. Pays-Bas* **1928**, *47*, 19–27.

(16) Chen, S-M. L.; Grudzinskas, C. V. *Prostaglandins* **1979**, *17*(5), 707–717.

(17) The product from this reaction was almost exclusively the trans isomer **9**. This is a significant improvement over the reaction of **8b** with *n*-Bu_3SnH, which produces an 85/15 equilibrium mixture of the trans/cis vinylstannanes, respectively.

(18) Kalish, V. J.; Shone, R. L.; Kramer, S. W.; Collins, P. W.; Babiak, K. A.; McLaughlin, K. T.; Ng, J. S. *Synth. Commun.* **1990**, *20*(11), 1641–1645.

6 afforded protected enisoprost. Deprotection with PPTS in aqueous acetone afforded enisoprost 10 in 71% yield based upon intermediate 6 after chromatographic purification.

Summary

An improved synthesis of the antisecretory prostaglandin enisoprost 10 has been developed. Significant improvements included the development of an efficient, cost-effective synthesis of the key enone precursor 6 and the development of improved methodology for attaching the ω side chain.

Experimental Section

General Procedures. Infrared (IR) spectra were obtained on neat samples. Nuclear magnetic resonance (NMR) spectra were recorded on 200- or 300-MHz spectometers with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Chromatographic separations were performed by medium-pressure chromatography with glass columns packed with Merck SiO_2 60. Gas chromatographic (GC) analyses were performed by use of a methyl silicone column (10 m × 0.53 mm × 2.65 μm film thickness). (*Z,Z*)-1,5-Cyclooctadiene, furan, 2-hexanone, and propargyl bromide were purchased from the Aldrich Chemical Co. Zirconocene chloride hydride was purchased from Aldrich and Boulder Scientific Co. Methyllithium in cumene was purchased from FMC Corp., Lithium Division. Anhydrous chloral was obtained from Fluka AG, Chemische Fabrik.

All reactions were carried out under an inert atmosphere.

Methyl 8-Oxo-4(*Z*)-octenoate (2b). *Caution! This ozonolysis reaction produces peroxidic intermediates that can present a potential explosion hazard. Accordingly, it is recommended that the following experiment be carried out in a hood and behind a safety shield.* A slurry of 1 (108 g, 1.00 mol), $NaHCO_3$ (211 g, 2.51 mol), CH_3OH (185 mL), and CH_2Cl_2 (1.20 L) was ozonated at −40 °C for 8 h. The progress of the reaction was monitored by quenching aliquots with Et_3N and Ac_2O and analyzing toluene extracts of the quenched aliquots by GC. The reaction was allowed to proceed to ~65% completion. The reaction mixture was purged with N_2 for 30 min, and Et_3N (202 g, 2.00 mol) was added over a 30-min period while the temperature was maintained below −20 °C. After Et_3N addition was complete, Ac_2O (206 g, 2.02 mol) was slowly added over a 2-h period while the temperature was maintained below −20 °C. The mixture was allowed to warm to 25 °C and stirred overnight under N_2. The mixture was filtered, and the inorganic salts were washed with toluene (3.30 L). The organic phase was treated with a solution of $FeSO_4 \cdot 7H_2O$ (50 g, 180 mmol) and 12 N HCl (5 mL) in water (1 L) until the absence of peroxides was indicated by a negative starch–iodide test. The phases were separated, and the organic phase was washed twice with water (1 L total) and filtered through a mixture of silica gel (100 g) and diatomaceous earth (50 g). The filtrate was concentrated in vacuo to give 89.2 g (524 mmol, 52%) of crude methyl 8-oxo-4(*Z*)-octenoate (**2b**). The crude material was approximately 80% pure (uncorrected for solvent) by GC analysis and was used without further purification.

An analytical sample of **2b** was prepared via chromatography on silica gel with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.25; 15/85 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give a pale yellow oil. This sample was identical by IR and NMR analysis with material prepared by the procedure of Tolstikov et al.[7]

Methyl 8-(2-Furanyl)-8-hydroxy-4(*Z*)-octenoate (3). A solution of furan (50 g, 734 mmol) in THF (500 mL) was cooled to −10 °C, and a solution of 2.5 M *n*-butyllithium in hexane (185 mL, 463 mmol) was added dropwise while the reaction temperature was maintained below 0 °C. The solution was stirred at 0 °C for 30 min, and anhydrous $MgCl_2$ (42.2 g, 440 mmol) was added in one portion. The mixture was warmed to room temperature for 1.5 h and cooled to −25 °C. A solution of crude **2b** (80 g, 470 mmol, uncorrected for purity) in THF (200 mL) was added, and the mixture was stirred at −25 °C for 15 min. The mixture was quenched by the dropwise addition of saturated aqueous NH_4Cl solution (250 mL) and diluted with EtOAc (300 mL). The layers were separated, and the aqueous layer was extracted three times with EtOAc (450 mL total). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 126 g of crude hydroxy ester **3**, which was used without further purification.

An analytical sample of **3** was prepared via chromatography on silica gel with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.15; 20/80 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give a pale yellow oil: IR (neat 3450, 1740, 1440, 1010, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80–2.00 (m, 2 H), 2.05–2.45 (m, 7 H), 3.66 (s, 3 H), 4.66 (t, J = 6.7 Hz, 1 H), 5.25–5.55 (m, 2 H), 6.22 (b dd, J = 3.2 Hz, J = 0.9 Hz, 1 H), 6.32 (dd, J = 3.2 Hz, J = 1.9 Hz, 1 H), 7.38 (dd, J = 1.9 Hz, J = 0.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.7, 23.2, 33.9, 35.2, 51.6, 66.8, 105.6, 110.0, 128.3, 130.1, 141.7, 156.6, 173.6; HRMS calcd for $C_{13}H_{18}O_4$ 238.1205 ($M^{\cdot+}$), found 238.1206.

(±)-Methyl *trans*-7-(2-Hydroxy-5-oxo-3-cyclopenten-1-yl)-4(*Z*)-heptenoate (4b). A solution of **3** (125 g, 470 mmol, theoretical amount based on **2b**) and $ZnCl_2$ (250 g, 1.83 mol) in dioxane (1.5 L) and water (1 L) was refluxed for 22 h at which time TLC analysis indicated the complete disappearance of starting material. The mixture was cooled to room temperature, acidified to pH 1 with 12 N HCl, and extracted with EtOAc (900 mL). The extract was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 132 g of a product mixture that contained **4a** as the major component. The crude mixture was dissolved in acetone (2 L) and treated with K_2CO_3 (218 g, 1.58 mol) and iodomethane (223 g, 1.58 mol). The mixture was refluxed for 9 h at which time TLC indicated the complete conversion of **4a** to **4b**. The mixture was filtered, and the filtrate was concentrated in vacuo to give 120 g of crude cyclopentenone **4b**, which was used without further purification.

An analytical sample of **4b** was prepared via chromatography on silica gel with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.16; 50/50 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give a pale yellow oil: IR (neat) 3440, 1735, 1710, 1440, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (m, 1 H), 1.95 (m, 1 H), 2.16–2.58 (m, 7 H), 3.13 (d, J = 6.7 Hz, 1 H), 3.66 (s, 3 H), 4.71 (m, 1 H), 5.25–5.55 (m, 2 H), 6.20 (dd, J = 5.8 Hz, J = 1.4 Hz, 1 H), 7.52 (dd, J = 5.8 Hz, J = 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.5, 24.8, 28.4, 33.7, 51.5, 54.5, 76.3, 128.3, 130.1, 133.5, 162.4, 173.8, 208.2; HRMS calcd for $C_{13}H_{18}O_4$ 238.1205 ($M^{\cdot+}$), found 238.1208.

Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate (5). A solution of **4b** (120 g, 470 mmol, theoretical amount based on **2b**), Et_3N (43 g, 310 mmol), anhydrous chloral (4.0 g, 27.0 mmol), and toluene (1.6 L) was heated to 65 °C for 6 h, at which time TLC analysis indicated the complete conversion of **4b** to **5**. The mixture was added to a slurry of anhydrous LiBr (1.15 kg) in heptane (1.3 L) and toluene (2.0 L). The resulting mixture was stirred for 2 h. The LiBr complex was collected by filtration and washed with a mixture of toluene (1.2 L) and heptane (400 mL). The isolated LiBr complex was added portionwise to a mixture of water (4.6 L) and toluene (2.3 L) and stirred for 30 min. The layers were separated, and the aqueous layer was extracted three times with toluene (2.25 L total). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 69 g (289 mmol, 62%) of crude **5**, which was used without further purification.

An analytical sample of **5** was prepared via chromatography on silica gel with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.15; 50/50 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give a pale yellow oil. This sample was identical by IR, NMR, and HPLC analysis with material prepared by the procedure of Collins et al.[1]

Methyl 7-[5-Oxo-3-[(triethylsilyl)oxy]-1-cyclopenten-1-yl]-4(*Z*)-heptenoate (6). A solution of **5** (69 g, 289 mmol, uncorrected for purity), imidazole (22.5 g, 330 mmol), and Et_3N (33

(19) The direct conversion of acetylenic precursors to dilithiocyancuprates, followed by conjugate addition to give prostaglandins (including enisoprost and misoprostol) is the subject of two recent communications: (a) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440–7441. (b) Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. T.; Kramer, S. W.; Shone, R. L. *Ibid.* **1990**, *112*, 7441–7442.

g, 330 mmol) in dimethylformamide (DMF, 800 mL) was cooled to 10 °C, and chlorotriethylsilane (50 g, 332 mmol) was slowly added dropwise over a period of 20 min. The mixture was allowed to warm to room temperature over a period of 1.5 h and quenched by the addition of ice-cold water (2 L). The mixture was extracted five times with heptane (2.5 L total), and the combined extracts were washed twice with saturated aqueous NaCl solution (400 mL total), dried (Na_2SO_4), and filtered through a bed of diatomaceous earth. The filtrate was concentrated in vacuo to give 81 g of crude **6**, which was purified via chromatography on silica gel (2.24 kg) with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.52; 25/75 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give 49 g (139 mmol, 48%) of silyl ether **6** as a pale yellow oil. This sample was identical by IR, NMR, and HPLC analysis with material prepared by the procedure of Collins et al.[1]

[(1-Butyl-1-methyl-3-butynyl)oxy]trimethylsilane (8b). Compound **8b** was prepared by a modification[15] of the procedure reported by Chen and Grudzinskas.[16]

[[1-(3-Iodo-2(*E*)-propenyl)-1-methylpentyl]oxy]trimethylsilane (9). A solution of **8b** (1.90 g, 8.96 mmol) in THF (15 mL) was added to zirconocene hydride chloride (2.77 g, 10.7 mmol) under Ar, and the resulting mixture was stirred at 25 °C for 30 min. The mixture was cooled to 0 °C, and a solution of I_2 (2.28 g, 8.97 mmol) in THF (5 mL) was added. After being stirred for 10 min, the mixture was poured onto hexane (200 mL) and water (1.2 L). The layers were separated, and the aqueous layer was extracted with hexane (100 mL). The combined organic phases were washed twice with aqueous $Na_2S_2O_3$ solution (300 mL), once with water (200 mL), once with saturated NaCl solution (100 mL), and dried (Na_2SO_4). The organic phase was filtered through silica gel (40 g), and the silica gel was washed with hexane (150 mL). The filtrate was concentrated in vacuo to give 2.58 g (7.59 mmol; 85%) of vinyl iodide **9** as a yellow oil. The ^1H NMR resonances for this sample are in agreement with the reported values for **9** prepared from **8b** by an alternate procedure.[16]

(±)-Methyl 11α,16-Dihydroxy-16-methyl-9-oxoprosta-4(*Z*),13(*E*)-dien-1-oate (10) from Intermediate 9. A solution of **9** (6.00 g, 17.6 mmol) in Et_2O (20 mL) in a flame-dried flask was degassed with vacuum and placed under Ar by releasing the vacuum with Ar. The solution was cooled to −70 °C, and a solution of 1.6 M *n*-butyllithium in hexane (11.6 mL, 18.5 mmol) was added. The resulting solution was stirred at −70 °C for 2 h.

CuCN (1.57 g, 17.6 mmol) was placed in a second flask and flame dried. Et_2O (50 mL) was added, and the mixture was cooled to −70 °C. A solution of 1.39 M methyllithium in cumene (13.0 mL, 17.9 mmol) was added, and the mixture was warmed to 0 °C for 45 min. The mixture was cooled to −70 °C, and the previous vinyllithium solution was added via cannula. The mixture was slowly warmed to −30 °C for 20 min and cooled to −70 °C. A solution of **6** (3.11 g, 8.80 mmol) in Et_2O (20 mL) was added. After 20 min, the reaction mixture was poured onto a mixture of 9/1 saturated aqueous NH_4Cl/NH_4OH solution (200 mL) layered with Et_2O (150 mL). The mixture was vigorously stirred for 30 min, and the layers were separated. The aqueous phase was extracted twice with Et_2O (200 mL total), and the combined organic phases were washed twice with a mixture of 9/1 saturated aqueous NH_4Cl/NH_4OH solution (50 mL total). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 15.7 g of a product mixture containing crude protected enisoprost.

The crude product was dissolved in a solution of acetone (100 mL) and water (20 mL). The solution was treated with PPTS (100 mg) and stirred at room temperature for 4 h. The solvent was removed in vacuo, and the residue was partitioned between EtOAc (125 mL) and saturated NaCl solution (25 mL). The layers were separated, and the aqueous phase was extracted twice with EtOAc (100 mL total). The combined organic phase was washed with saturated NaCl solution (20 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo to give 5.26 g of a product mixture containing crude **10**, which was purified by column chromatography on silica gel (69 g) with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.40; 100% EtOAc) were combined, and the solvent was removed in vacuo to give enisoprost (**10**; 2.86 g, 7.52 mmol, 85% based on **6**). This sample was identical by IR, NMR, and HPLC analysis with material prepared by the procedure of Collins et al.[1]

(±)-Methyl 11α,16-Dihydroxy-16-methyl-9-oxoprosta-4(*Z*),13(*E*)-dien-1-oate (10) from Intermediate 8b. Zirconocene chloride hydride (5.45 g, 21.0 mmol) was placed in a flask in a glove bag under Ar. THF (28 mL) was added followed by a solution of **8b** (4.23 g, 20.0 mmol) in THF (42 mL). The mixture was stirred at room temperature for 30 min to give a green solution. This solution was cooled to −50 °C, and solid CuCN (1.78 g, 20.0 mmol) was added under a positive argon atmosphere. A solution of 1.39 M methyllithium in cumene (43.9 mL, 61.0 mmol) was added via syringe while the temperature was maintained at −50 °C to give an amber solution. A solution of **6** (3.52 g, 9.94 mmol) in THF (28 mL) was added, and the resulting solution was stirred at −50 °C for 15 min and quenched by addition to a vigorously stirred mixture of 9/1 saturated aqueous NH_4Cl/NH_4OH solution (75 mL) and Et_2O (200 mL). The mixture was stirred for 30 min and filtered through a bed of diatomaceous earth. The filter cake was washed with a mixture of 9/1 saturated aqueous NH_4Cl/NH_4OH solution and Et_2O, and the layers were separated. The aqueous phase was extracted twice with Et_2O (200 mL total). The combined Et_2O phase was dried (Na_2SO_4) and filtered through a short column of silica gel (20 g). The column was washed with EtOAc, and the combined filtrate was concentrated in vacuo to give ~7 g of an oily residue.

The residue was dissolved in a solution of acetone (100 mL) and water (25 mL). The solution was treated with PPTS (350 mg) and stirred at room temperature for 3 h. Most of the acetone was removed in vacuo, and the aqueous residue was diluted with saturated NaCl solution (25 mL). The aqueous phase was extracted four times with EtOAc (200 mL total). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give crude enisoprost (5.14 g). The crude sample was purified by column chromatography on silica gel (134 g) with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.40; 100% EtOAc) were combined, and the solvent was removed in vacuo to give enisoprost (**10**; 2.69 g, 7.06 mmol, 71% based on **6**), which was identical by IR, NMR, and HPLC analysis with **10** produced by the route described previously.

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Supplementary Material Available: ^1H and ^{13}C spectra of compounds **3** and **4b** (4 pages). Ordering information is given on any current masthead page.