Treatment commenced 1 day after cell inoculation. 1a solubilized in 1:1 PBS-propylene glycol, was administered ip for 9 consecutive days, and the evaluation was done after 60 days by the percent ratio of mean survival time of treated and untreated animals.

Experimentally Induced Melanoma Metastases. B16F10.9 cells (2×10^4) were injected to the lateral veins in the tail of C57BL/6 mice (groups of 8), 8–9 weeks old (20 g). The animals, were treated ip every other day with 1a (solubilized in 1:1:8 ethanol-DMSO-propylene glycol) or with a single 50 mg/kg injection of cytoxan (cyclophosphamide) as positive control, given on day 1. After 3 weeks the animals were sacrificed, lungs were weighed, and lesions were counted after fixation in Bouin's fixative using a Zeiss stereomicroscope.

Antitumor Effect of 1a on Spontaneous Metastases of 3LL. Mice (groups of 19) were given sc to the left hind footpad 6×10^5 log phase 3LL cells. When the tumor reached a diameter of approximately 1 cm, the primary foot pad tumor and the regional lymph nodes were removed, and treatment commenced

1 day after surgery.

Registry No. 1a, 122110-53-6; 1b, 138460-00-1; 1c, 108761-29-1; 1d, 122110-52-5; 1e, 138460-01-2; 1f, 137373-55-8; 2a, 55696-44-1; 2b, 25572-25-2; 2c, 117802-47-8; 2d, 138460-02-3; 3, 60-01-5; 4, 137373-52-5; 5a, 137373-53-6; 5b, 55696-45-2; 6, 137373-54-7; 7a, 138460-03-4; 7b, 138460-04-5; 8a, 138460-05-6; 8b, 138460-06-7; Me(CH₂)₂CO₂H, 107-92-6; [Me(CH₂)₂CO]₂O, 106-31-0; MeCH2CO2H, 79-09-4; Me2CHCO2H, 79-31-2; Me(CH2)2CO2H, 109-52-4; BocNH(CH₂)₃CO₂H, 57294-38-9; ClCH₂OOCCMe₃, 18997-19-8; ClCH2OOC(CH2)6Me, 61413-70-5; ClCHMeOOCOEt, 50893-36-2; ClCH₂OOCCHMe₂, 61644-18-6; CH₂=O, 50-00-0; MeCH=O, 75-07-0; Me(CH₂)₂CH=O, 123-72-8; Me₃CCH=O, 630-19-3; ClCH₂OOC(CH₂)₂Me, 33657-49-7; octanoic acid, 124-07-2; chloromethyl chlorosulfate, 49715-04-0; iodomethyl octanoate, 111013-41-3; 3-chlorophthalide, 6295-21-2; 4-(bromomethyl)-5-methyl-2-oxo-1,3-dioxolane, 80715-22-6; glycerol, 56-81-5.

Synthesis and Structure-Activity Relationships of Acyclic ω Chain Conjugated Diene Analogues of Enisoprost

P. W. Collins,* R. L. Shone, W. E. Perkins, A. F. Gasiecki, V. J. Kalish,¹ S. W. Kramer, and R. G. Bianchi

Gastrointestinal Diseases Research, G.D. Searle & Co., Skokie, Illinois 60077. Received August 12, 1991

A series of acyclic ω chain conjugated diene analogues of enisoprost were synthesized and evaluated for gastric antisecretory and diarrheagenic activities in comparison to enisoprost and a previously identified cyclic dienyl analogue. Several novel approaches to the cuprate reagents involved in the synthesis of the series are described. From this SAR study, it appears that both the conjugated diene and the overall space filling characteristics of the ω chain are important components to the pharmacological profiles and selectivity of these compounds and that a cyclic structure is not required.

Introduction

In a previous paper² we reported that incorporation of Δ^{17} unsaturated cycloalkyl and cycloalkenyl functionality into the ω chain of enisoprost 1 produced compounds with increased separation of gastric antisecretory activity from diarrheagenic side effects. In particular the 17(*E*)-18cyclopentenyl compound 2 displayed antisecretory activity



comparable to enisoprost but, unlike enisoprost, was virtually devoid of diarrheagenic activity. In an effort to determine the relative contributory roles of the conjugated diene system and the terminal cyclic structure to the selectivity of 2, we decided to examine a series of acyclic conjugated dienes in which the diene system was either unsubstituted (5f) or methylated at C-19,20 (5a-e,g,h) to serve as test mimics of the cyclopentene structure of 2. In addition the 17- and 18-methyl analogues (5i,j) were also prepared to complete the methyl substitution pattern along the diene system (Table I).

Chemistry

Compounds 5a-j of Table I were prepared by conjugate addition of the respective racemic cuprate reagents 4a-j to the racemic cyclopentenone 3^3 followed by mild acid hydrolysis of protecting groups with pyridinium ptoluenesulfonate (PPTS) in aqueous acetone (Figure 1). As in previous work,² use of PPTS was required to avoid acid-catalyzed allylic rearrangement and elimination of the 16-hydroxyl group caused by stronger acidic conditions. Chromatographic purification on silica gel provided the desired compounds 5a-j and their corresponding diastereomers 6a-j. Configurational assignments of 5 and 6 were based on chromatographic elution sequence and biological activity.² Thus gastric antisecretory activity was observed only with the slower eluting compounds 5a-j which were assigned the same relative stereochemistry as the bioactive isomers of misoprostol and enisoprost.

The cuprate reagents 4a-j were accessed by four distinct routes (Figures 2-6). These routes represent an evolu-

Present address: Agouron Pharmaceuticals, Inc. La Jolla, CA 92037.

⁽²⁾ Collins, P. W.; Gasiecki, A. F.; Perkins, W. E.; Gullikson, G. W.; Bianchi, R. G.; Kramer, S. W.; Ng, J. S.; Yonan, E. E.; Swenton, L.; Jones, P. H.; Bauer, R. F. Chemistry and Structure-Activity Relationships of C-17 Unsaturated 18-Cycloalkyl and Cycloalkenyl Analogues of Enisoprost. Identification of a Promising New Antiulcer Prostaglandin. J. Med. Chem. 1990, 33, 2784-2793.

⁽³⁾ Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. Synthesis and Gastric Antisecretory Properties of 4,5-Unsaturated Derivatives of 15-Deoxy-16hydroxy-16-methylprostaglandin E₁. J. Med. Chem. 1983, 36, 786-790.



Figure 3.

Figure 2.

Figure 1.

Collins et al.







		ED_{50} , $\mu g/kg$ and 95% confidence limits ^a		
compd	R	gastric antisecretory activity in dogs ^b	diarrheal effects in rats ^c	selectivity ratio ^d
1	\sim	0.023	49	2
2		0.02	>3160	>158
5f		0.007^{a}	243 (68.2-863.1)	35
5j	Y	I at 3.0	>3160	
51		0.71 (0.439–1.94)	1033 (424. 9– 2511.1)	1.4
5e	\checkmark	0.002 (0.0003-0.0053)	420 (188.8–933.9)	210
5a	\checkmark	0.03 (0.02-0.058)	250 (157.6-396.5)	8
5g		0.009 (0.0001-0.034)	306 (151.8-616.1)	34
5c		0.003 (0.001-0.006)	185 (86.3-396.7)	62
5 h		0.016 (0.0012–0.033)	1226 (581.8-2583.1)	76
5b	\checkmark	0.06 (0.01-0.11)	>3160	>53
5 d		0.06 (0.015-0.153)	>3160	>53

^a Data for 1 and 2 are from ref 2. Confidence limits for 5f could not be determined. ^b Determined in food-stimulated Pavlov dogs by intrapouch administration. ED_{50} values for new compounds were generated with 2–7 dogs/dose and 2–5 doses/compound. ^c Determined in adult male rats by intragastric administration. ^d Quotient of diarrheal ED_{50} value divided by antisecretory $ED_{50} \times 10^{-3}$. As computed, the higher the number, the greater the selectivity.

tionary approach to solving the incompatibility of the side chain conjugated diene system with the hydrostannation technique traditionally used in these laboratories. For 4a-d the corresponding aldehydes 7a-d were condensed with 1-(triphenylphosphoranylidene)-2-propanone to give the methyl ketones 8a-d (Figure 2). The ketones 8a,b were reacted with propargyl magnesium bromide and then with trimethylchlorosilane to give the protected dienynes 9a,b $(\mathbf{R}'' = \mathbf{SiMe}_3)$. Irradiation of individual mixtures of 9a,b,tri-n-butyltin hydride and a catalytic amount of AIBN with a sunlamp produced an approximate 80:20 E/Z mixture of vinylstannanes $10a, b^2$ For 9c, d (R["] = H) the trimethylsilylation-hydrostannation sequence was reversed. The acetylenic alcohols 9c,d were first reacted with tri-nbutyltin hydride, purified by chromatography and then protected with trimethylchlorosilane to give 10c,d. This sequence was based on a previous finding² that hydrostannation of dienyne alcohols is cleaner and more facile than hydrostannation of the trimethylsilyl protected dienynes. Treatment of the vinylstannanes 10a-d with *n*-butyllithium at -70 °C followed by addition of an ether solution of copper 1-pentyne solubilized with hexamethylphosphorous triamide (HMPT) gave the cuprates 4a-d.

The cuprate reagents 4e - g were prepared via the (E)vinyl bromide 13 (Figure 3). This route was the first pathway developed as an alternative to vinylstannanes to avoid the persistent problems associated with their synthesis. The synthetic difficulties include: (a) a generalized sluggishness of the hydrostannation reaction with the dienynes even when the unprotected acetylenic alcohols are employed; (b) the nonstereoselectivity of the hydrostannation reaction and the slow Z to E isomerization rate;⁴ (c) a lack of chemoselectivity of the dienyne hydrostannation that can produce a number of undesired products;^{5,6} (d) an inability to efficiently purify the vinylstannanes because of their sensitivity to silica gel resulting in substantial material losses during chromatog-

- (5) Light-catalyzed hydrostannation of 4,7-dimethyl-5(E)-octadien-1-yn-4-ol (the initially selected precursor to 4e) with 1.5 equiv of tri-*n*-butyltin hydride gave 6% of the desired (E)vinylstannane diene, 3% of the (Z)-vinylstannane diene, 20% of two diastereomeric (E)-vinylstannane cyclopentanols that were presumably formed by intramolecular vinylstannane radical cyclization and 35% of two bisvinylstannanes of undetermined structure.
- (6) For previous reports of facile acetylene-olefin intramolecular cyclizations to methylene cyclopentanes via intermediate vinylstannane radicals, see: (a) Stork, G.; Mook, R., Jr. Vinyl Radical Cyclizations Mediated by the Addition of Stannyl Radicals to Triple Bonds. J. Am. Chem. Soc. 1987, 109, 2829-2831. (b) Nozaki, K.; Oshima, K.; Utimoto, K. J. Et₃B-Induced Radical Addition of R₃SnH to Acetylenes and its Application to Cyclization Reactions. J. Am. Chem. Soc. 1987, 109, 2547-2549. (c) Lee, E.; Ko, S. B.; Jung, K. W. Intramolecular Cyclization of Allylic Propiolates Mediated by the Addition of Stannyl Radicals: A New Synthetic Route to α-Methylene-γ-butyrolactones. Tetrahedron Lett. 1989, 30, 827-828.

⁽⁴⁾ Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. Synthesis of Antisecretory Prostaglandins Using Vinyl Tin Precursors. *Tetrahedron Lett.* 1978, 3187–3190.

raphy. The key (*E*)-vinyl bromide 13 was obtained from 11 by chemo- and stereoselective hydrozirconation using bis(cyclopentadienyl)zirconium chloride hydride (Schwartz's reagent)^{7,8} followed by in situ NBS bromination of the intermediate vinyl zirconate to give the bromo ester 12. Reduction of 12 with diisobutylaluminum hydride (DIBAL) at -78 °C in toluene provided 13.

The synthesis of the vinyl bromide dienes 16, 19, and 20 was carried out using a sequence (Figure 4) that allowed variation of substituents and their location on the C-18-20 portion of the ω chain. Compound 16 was synthesized by reaction of 13 with 1-(triphenylphosphoranylidene)-2propanone to give the methyl ketone 15 and subsequent methylenation of the ketone with bis[(bromozincio)methylene]zinc⁹ and TiCl₄. Vinyl bromide dienes 19 and 20 were prepared by reacting 13 with (carbethoxymethylene)triphenylphosphorane to give the ester 17. The latter was converted to the unsaturated aldehyde 18 by DIBAL reduction to an intermediate allylic alcohol that was immediately¹⁰ oxidized with oxalyl chloride, DMSO, and triethylamine (Swern conditions). The aldehyde 18 was then transformed to the vinyl bromide dienes 19 and 20 by reaction with methylenetriphenylphosphorane and ethylidenetriphenylphosphorane, respectively. The latter reaction was carried out under conditions¹¹ that favor formation of the Z isomer. Lithiation of 16, 19, and 20 with tert-butyllithium at -78 or -100 °C in ether and addition of a solution of HMPT solubilized copper 1-pentyne provided the cuprates 4e-g.

The cuprate reagents 4h,i (Figure 5) were obtained from vinyl bromide diene 23 and vinyl iodide diene 27, respectively. In contrast to 16, 19, and 20 these vinyl halides were prepared by introducing the halogen in the last step prior to cuprate formation. The success of late introduction of the vinyl halide group depends on the chemoselective hydrozirconation of dienynes 22 and 26. In our hands these dienynes underwent virturally complete hydrozirconation at the terminal alkyne.¹² Subsequent bromination (NBS) or iodination (NIS) produced only 1-3% of the acetylenic homoallylic halide resulting from attack of Schwartz's reagent at the unhindered diene terminus (C-20). This result is consistent with the diene behaving as an isolated double bond since terminal acetylenes react with Schwartz's reagent 70-100 times faster than terminal acyclic olefins.^{7b} Chemoselective hydrozirconation of the alkyne function in 1-en-3-ynes has also

- (7) (a) Schwartz, J.; Labinger, J. A. Hydrozirconation: A New Transition Metal Reagent for Organic Synthesis. Angew. Chem., Int. Ed. Engl. 1976, 15, 333-340. (b) Hart, D. W.; Blackburn, T. F.; Schwartz, J. Hydrozirconation. III. Stereospecific and Regioselective Functionalization of Alkylacetylenes via Vinylzirconium (IV) Intermediates. J. Am. Chem. Soc. 1975, 97, 679-680.
- (8) Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. Macrolide Antibiotics. 1. Total Synthesis of the Prelog-Djerassi Lactone and Methynolide. J. Am. Chem. Soc. 1979, 101, 4749–4752.
- (9) Prepared by refluxing 195 g of zinc powder, 50 mL of 6 N HCl/dioxane, 15 mL of 1.6 M aluminum isopropoxide/THF, and 280 g of dibromomethane in 350 mL of THF overnight with vigorous stirring.
- (10) When isolated and stored, the allylic alcohol underwent silyl group migration to produce a mixture of four compounds.
- Reitz, A. B.; Nortey, S. O.; Jordan, A. D.; Mutter, M. S.; Maryanoff, B. E. Dramatic Concentration Dependence of Stereochemistry in the Wittig Reaction. Examination of the Lithium Salt Effect. J. Org. Chem. 1986, 51, 3302-3308.
 Kalish, V. J.; Shone, R. L.; Kramer, S. W.; Collins, P. W.;
- (12) Kalish, V. J.; Shone, R. L.; Kramer, S. W.; Collins, P. W.; Babiak, K. A.; McLaughlin, K. T.; Ng, J. S. An Improved Procedure for the Synthesis of Prostaglandin Analogues. Syn. Commun. 1990, 20 (11), 1641-1645.

been reported.¹³ Late introduction of the vinyl halide group permitted the use of vinyl iodides as cuprate precursors which are more reactive than vinyl bromides toward metallation with alkyllithium reagents.

Dienyne 22 (Figure 5) was prepared by reacting aldehyde 3) Figure with 14 (from 1-(triphenylphosphoranylidene)-2-propanone to obtain the methyl ketone 21 and subsequent reaction with ethylidenetriphenylphosphorane. Dienyne 26 was obtained by reaction of 14 with (carbethoxyethylidene)triphenylphosphorane to furnish the ester 24, sequential DIBAL reduction/PCC oxidation to give the unsaturated aldehyde 25, and finally methylenation with methylenetriphenylphosphorane. Both 23 and 27 were lithiated with tert-butyllithium. The vinyllithium intermediate of 23 was converted to a copper 1-pentynyl cuprate 4h while that of 27 was treated with cuprous cyanide and methyllithium to produce the higher order vinyl cuprate 4i.

The remaining vinyl cuprate 4j was prepared by converting the vinyl zirconate 32 directly to 4j without the intermediacy of a vinyl halide or a vinylstannane (Figure 6). Reaction of the γ -keto ester 28 with propargylmagnesium bromide and treatment of the resulting alcohol with triethylchlorosilane gave the ester 29. Reduction of 29 with DIBAL and Swern oxidation of the intermediate allylic alcohol produced the unsaturated aldehyde 30. Methylenation of 30 with methylenetriphenylphosphorane furnished the dienyne 31 which was then subjected to hydrozirconation to give 32. Treatment of 32 with n-butyllithium, cuprous cyanide, and methyllithium according to a recent protocol^{14,15} achieved in situ generation of the higher order cyanocuprate and permitted a one-pot synthesis of the protected prostaglandin. The new procedure significantly shortened and simplified the preparation of 5j, and is currently our preferred method of synthesis for ω chain diene prostaglandins.

Results and Discussion

The compounds 5a-j were evaluated for gastric antisecretory activity in Pavlov pouch dogs by intrapouch administration and for diarrheagenic side effects in rats by intragastric administration. The results and comparison with enisoprost (1) and its 17(E)-18-cyclopentenyl analogue (2) are presented in Table I. With the exception of enisoprost, all of these compounds are single racemates. Enisoprost is a mixture of two racemates of four stereoisomers, only one of which is biologically active while the bioactive isomers of 2 and 5a-j are diluted by only their respective enantiomers.² Thus the data in Table I for enisoprost should be divided by two when comparing enisoprost with 2 and 5a-j. This type of comparison assumes that the inactive isomers do not interfere with the activity of the bioactive isomer. The assumption appears to be valid, however, because the inactive isomers of misoprostol do not affect the biological activity of its active isomer.¹⁶

(15) Lipschutz, B. H.; Ellsworth, E. L. Hydrozirconation-Transmetallation. A Mild, Direct Route to Higher Order Vinylic Cuprates from Monosubstituted Acetylenes. J. Am. Chem. Soc. 1990, 112, 7440-7441.

⁽¹³⁾ Fryzuk, M. D.; Bates, G. S.; Stone, C. Transition Metal Dienyls in Organic Synthesis: A Convenient Preparation of σ -Bonded Tin and Zirconium Dienyls. Tetrahedron Lett. 1986, 27, 1537–1540.

⁽¹⁴⁾ Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. One-Pot Synthesis of Protected Prostaglandins from Alkynes and Cyclopentenones. In Situ Generation of Higher Order Cyanocuprates Derived from Alkenylzirconium Intermediates. J. Am. Chem. Soc. 1990, 112, 7441-7442.

The selectivity ratios in Table I were computed by dividing the diarrheal ED_{50} 's by gastric antisecretory ED_{50} 's and then by 1000 to reduce the size of the quotient. The higher the ratio value, the greater is the separation of desired gastric antisecretory effects from undesired diarrheagenic side effects.

The simplest compound of this series, 5f, is the unsubstituted diene analogue of enisoprost. When isomeric content is considered, the antisecretory potency of 5f is comparable to enisoprost's, whereas its diarrheagenic activity is reduced approximately 10-fold. Thus, it appears that the conjugated diene system plays a significant contributory role to the reduced diarrhea potency observed in the present series and in compound 2. This conclusion is supported by the fact that removal of either of the double bonds of 2 increases diarrheagenic activity.² The reason for this effect is uncertain but may involve conformational preferences of the diene versus the saturated system. Placement of a methyl group at either C-17 or C-18 significantly reduces both pharmacological activities, probably due to direct interference with proper receptor binding of the C-16 hydroxy group by the C-17 methyl group of 5j and, to a lesser extent, by the C-18 methyl group of 5i. In contrast, when the methyl group is placed at C-19 in 5e, both activities are modestly influenced in favorable directions resulting in the greatest degree of selectivity in this series (with the possible exception of 5b and 5d). Compounds 5a and 5g represent the two possible C-20 methyl geometric isomers. Interestingly, their respective diarrheagenic activities are approximately the same while 5g is about three times more potent as an antisecretory agent. Relative to the parent unsubstituted compound 5f, the introduction of a cis methyl group in 5g does not affect gastric antisecretory activity while a trans-methyl group in 5a reduces that activity about 4-fold, suggesting that the parietal cell receptor has directional spacial limitations for accommodating the ω chain of these prostaglandin analogues. In contrast, interactions at the receptors responsible for diarrhea production appear unaffected with both geometric isomers even though previous work² suggests that the diarrheagenic receptors are less accommodative to ω -chain size than are parietal cell receptors. A possible explanation for this result is that the ω chains of 5a and 5g can adopt a cisoid conformation and avoid adverse interactions within the cavities of the diarrheagenic receptors.¹⁷ The next three compounds in Table I represent the various combinations of placing two methyl groups at C-19 and -20. Compound 5c is a hydride of 5e and 5a while 5h is the hybrid of 5e and 5g. It is puzzling that the effects of C-20 cis- and trans-methyl group substitution on the gastric antisecretory activity of the 19-methyl analogue 5e are reversed from those with the unsubstituted diene 5f. Thus addition of a C-20 cismethyl group to 5f to give 5g does not alter antisecretory activity while the same substitution to 5e to give 5h reduces activity 8-fold. Yet introduction of a C-20 transmethyl group to 5f to give 5a reduces antisecretory activity 4-fold while its presence in 5c does not change its potency relative to 5e. Equally perplexing is the divergence in diarrheagenic potency between 5h and 5c relative to 5e since neither the cis or trans methyl group substitution had

an appreciable effect on the diarrheagenic potency of 5f. The reduction in antisecretory and diarrheagenic activities of 5h relative to 5e may be due to its inability to adopt a cisoid conformation and thus its activities are a truer reflection of relative receptor fit than are the activities of analogues capable of assuming a cisoid conformation. Thus, adoption of a cisoid conformation by 5c would explain the maintenance of high activity in both assays relative to 5e. Comparison of the calculated energy requirements for the cisoid conformations of 5h and 5c support this explanation. (Respective energies required to adopt a cisoid formation are 5.38 and 1.03 K cal/mol for 5h and 5c using macromodel V 2.5 for MM2 calculations.) These potency differences again illustrate the sensitivities of the parietal cell and diarrheagenic receptors to ω -chain bulk and the particular location of that bulk within the receptors. The 20,20-dimethyl analogue 5b and the trimethylated compound 5d displayed reduced gastric antisecretory potency relative to the unsubstituted diene 5f. but were very weakly diarrheagenic with ED₅₀'s exceeding the highest dose tested. Thus, as with the cyclopentenyl analogue 2, diarrheal side effects can be virtually eliminated while maintaining a reasonable level of gastric antisecretory activity by proper placement of bulk on the ω chain. From this and previous work,² it would appear that both the conjugated diene and the overall steric or space filling characteristics of the ω chain are important components to the pharmacological profiles and selectivity of these compounds and that cyclic structures per se are not required.

Experimental Section

The NMR spectra were obtained on either a Varian XL-200, a GE-QE 300, a Varian VXR-400, or a Varian VXR-500 spectrometer in CDCl₃ with Me₄Si as internal standard. The ¹³C NMR spectra were determined with use of the APT pulse technique. Infrared spectra were recorded on a Perkin-Elmer 685 spectrophotometer in CHCl₃. Elemental analyses were within $\pm 0.4\%$ of the theoretical values. Solvents were removed under reduced pressure on a rotary evaporator. TL chromatograms were run on Polygram Sil G/UV plastic sheets (Macherey-Nagel Co.), or on Analtech TL plates precoated with Woelm silica gel GF (250 μ m) with PMA as visualization agent.

Trimethyl[[1-methyl-1-(2-propynyl)-2(E),4(E)-hexadie**nyl]oxy]silane** (9a). In a flame-dried flask under N_2 were suspended 316 mg (13 mmol) of magnesium turnings and a catalytic amount of HgCl₂ in 50 mL of dry THF. To this suspension was added 10 mL of a solution containing 1.55 g (13 mmol) of propargyl bromide and 1.4 g (12.7 mmol) of (3E,5E)-heptadien-2-one¹⁸ in 50 mL of THF. After the reaction began, the remainder of the solution was added at a rate sufficient to maintain gentle reflux. After the addition was completed, the reaction was stirred for 1 h and then poured into a mixture of ether and 1 N HCl and shaken well. The layers were separated, the aqueous portion was extracted with ether twice, and the combined organic solutions were washed with water, then saturated NaCl solution, dried (Na2SO4), and evaporated to afford 1.85 g (97%) of amber colored oil. To a solution of the crude alcohol in 15 mL of dry DMF under N2 at room temperature was added 1.90 g (28 mmol) of imidazole and 1.62 g (15 mmol) of trimethylchlorosilane. The reaction mixture was stirred for 0.5 h and then poured onto a mixture of ether and water and shaken well. The layers were separated and the aqueous portion was extracted with a 1:1 mixture of ether and hexane. The organic

⁽¹⁶⁾ Collins, P. W. Misoprostol: Discovery, Development and Clinical Applications. Med. Res. Rev. 1990, 10, 149–172 and unpublished data.

⁽¹⁷⁾ To better address this and related SAR questions, a computer-generated receptor model has been developed by Searle's Drug Design Department. Results and conclusions from this work will be reported separately.

^{(18) (}a) Huang, Y.; Chen, C.; Shen, Y. Studies on the Application of Group 15 and 16 Organometallic Compounds in Organic Synthesis. 63. Alpha-enones by the Reaction of Aldehydes and Alpha-bromo Ketones with Tri-n-butylstibine. Syn. Commun. 1989, 19, 501-509. (b) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Grande, M. E.; Ganem, B.; Carpenter, B. K. The Mechanism of Rearrangement of Chorismic Acid and Related Compounds. J. Am. Chem. Soc. 1987, 109, 1170-1186.

extracts were combined and washed with water three times and saturated NaCl solution once, dried (Na₂SO₄), and evaporated. The residue was vacuum distilled to give 2.12 g (75%) of **9a**: bp 47-48 °C (0.1 mm); ¹H NMR δ 0.12 (s, 9 H), 1.43 (s, 3 H), 1.75 (d, J = 8 Hz, 3 H), 1.96 (t, J = 3 Hz, 1 H), 2.39 (d, J = 3 Hz, 2 H), 5.00-6.75 (complex band, 4 H). Anal. (C₁₃H₂₂OSi) C, H.

Trimethyl[[1-methyl-1-[3-(tributylstannyl)-2(E)propenyl]-2(E),4(E)-hexadienyl]oxy]silane (10a). A mixture of 1.0 g (4.5 mmol) of 9a, 1.3 g (4.5 mmol) of freshly distilled tri-*n*-butyltin hydride, and a catalytic amount of AIBN (α,α' azoisobutyronitrile) contained in a Pyrex flask was irradiated under argon with a GE sunlamp for 8 h at approximately 55-60 °C (heat generated by the lamp placed at a distance of about 8 in. from the reaction vessel). The resulting product was used directly without purification in the cuprate reaction: ¹H NMR δ 0.11 (s, 9 H), 0.70-1.05 (complex band, 15 H), 1.30 (s, 3 H), 1.05-1.60 (complex band, 12 H), 1.73 (d, J = 7 Hz, 3 H), 2.33 (m, 2 H), 5.00-6.50 (complex band, 6 H).

(±)-Methyl 7-[3α -Hydroxy- 2β -(4(R)-hydroxy-4-methyl-1-(E),5(E),7(E)-nonatrienyl)-5-oxo-1 α -cyclopentyl]-4(Z)heptenoate (5a). A solution of 2.2 g (4.28 mmol) of 10a in 20 mL of dry THF was cooled to -50 °C under argon and treated with 2.7 mL of a 1.6 M solution (4.32 mmol) of n-BuLi in hexane. The solution was stirred for 45 min at -50 °C, cooled to -60 °C, and treated with a solution of 562 mg (4.3 mmol) of copper 1-pentyne and 1.41 g (8.6 mmol) of hexamethylphosphorous triamide in 10 mL of ether. The reaction mixture was stirred for 30 min at -60 °C and then a solution of 1.23 g (3.5 mmol) of 3³ in 10 mL of ether was added in one portion. The solution was stirred for 30 min and then poured into a mixture of ether and 1 N HCl and shaken well. The extracts were separated and the aqueous portion was extracted with ether and then EtOAc. The combined organic extracts were washed with water three times and saturated NaCl solution once, dried (Na2SO4), and evaporated. The residue was chromatographed on silica gel (5% EtOAchexane) to afford 884 mg (44%) of a viscous oil. The oil was dissolved in a mixture of 15 mL of acetone and 1.5 mL of water and 50 mg of pyridinium p-toluenesulfonate (PPTS) was added. The reaction mixture was stirred at room temperature under argon for 1 h and then partitioned between ether and 5% aqueous NaHCO₃ solution. The aqueous portion was extracted with ether and then EtOAc. The combined organic extracts were washed with water and then saturated NaCl solution, dried (Na_2SO_4) , and evaporated. The residue was chromatographed on silica gel (65% EtOAc-hexane) to afford 96 mg of 6a, 46 mg of the more polar racemate 5a, and 175 mg of an overlap fraction of the two racemates, all as colorless viscous oils (23.2% of total prostaglandin from 3). 5a: ¹H NMR δ 1.32 (s, 3 H, 16-CH₃), 1.55 (m, 1 H, 7-H), 1.67 (m, 1 H, 7-H), 1.75 (dd, J = 6.8, 1.4 Hz, 3 H, 20-CH₃), 2.00 (dtd, J = 12.0, 6.0, 1.0 Hz, 1 H, 8-H), 2.13 (m, 2 H, 6-H's), 2.23 $(dd, J = 18.4, 9.8 Hz, 1 H, 10\alpha - H), 2.31 (ddd, J = 14.0, 8.0, 1.0)$ Hz, 1 H, 15-H), 2.32-2.37 (complex band, 5 H, 15-H, 2-H's, 3-H's), 2.37 (dt, J = 12.0, 8.8 Hz, 1 H, 12-H), 2.73 (ddd, J = 18.4, 7.4 Hz,1.0 Hz, 1 H, 10β -H), 3.66 (s, 3 H, OCH₃), 4.03 (ddd, J = 9.8, 8.8,7.4 Hz, 1 H, 11-H), 5.33 (m, 2 H, 4-H, 5-H), 5.42 (ddt, J = 15.2, 8.8, 1.0 Hz, 1 H, 13-H), 5.63 (dd, J = 15.2, 0.4 Hz, 1 H, 17-H), 5.66 (ddd, J = 15.2, 8.0, 6.8 Hz, 1 H, 14-H), 5.69 (dq, J = 15.0, 6.8 Hz, 1 H, 20-H), 6.03 (ddqd, J = 15.0, 10.4, 1.4, 0.4 Hz, 1 H, 19-H), 6.17 (dd, J = 15.2, 10.4 Hz, 1 H, 18-H). Anal. (C₂₃H₃₄O₅) C, H.

6-Methyl-3(*E*),5-heptadien-2-one (8b). A mixture of 11.1 g (132 mmol) of 3-methyl-2-butenal and 47.6 g (150 mmol) of 1-(triphenylphosphoranylidene)-2-propanone in 275 mL of benzene was refluxed for 16 h. The reaction mixture was allowed to cool to room temperature and was filtered, and the filtrate was evaporated to a volume of about 50 mL. The residue was treated with 500 mL of hexane and chilled in an ice bath. The precipitated triphenylphosphine oxide was removed by filtration, the filtrate concentrated in vacuo and distilled to afford 9.4 g (57%) of a liquid: bp 40-41 °C (0.3 mm); ¹H NMR, δ 1.79 (s, 6 H), 2.25 (s, 3 H), 5.98 (br d, J = 12 Hz, 1 H), 6.02 (d, J = 16 Hz, 1 H), 7.38 (dd, J = 16, 12 Hz, 1 H). Anal. (C₈H₁₂O) C, H.

[[1,5-Dimethyl-1-(2-propynyl)-2(E),4-hexadienyl]oxy]trimethylsilane (9b). The title compound was prepared from 8b in a similar manner as 9a in 37% yield: ¹H NMR δ 0.15 (s, 9 H), 1.47 (s, 3 H), 1.77 (s, 3 H), 1.79 (s, 3 H), 1.99 (t, J = 3 Hz, 1 H), 2.43 (d, J = 3 Hz, 2 H), 5.65 (d, J = 15 Hz, 1 H), 5.81 (d, heptet, J = 15, 1.5 Hz, 1 H), 6.43 (dd, J = 15, 11 Hz, 1 H). Anal. (C₁₄H₂₄OSi) C, H.

Trimethyl[[1-methyl-1-[3-(tributylstannyl)-2(E)propenyl]-2(E),4(E)-hexadienyl]oxy]silane (10b). In a manner similar to the preparation of 10a, the title compound was obtained from 9b. The reaction was conducted for 4 h at a temperature > 100 °C induced by wrapping the reaction flask and sunlamp with aluminum foil. The resulting vinylstannane was not as pure as 10a but was nevertheless used directly in the cuprate reaction: ¹H NMR δ 0.11 (s, 9 H), 0.70–1.05 (complex band, 15 H), 1.31 (s, 3 H), 1.05–1.65 (complex band, 12 H), 1.75 (s, 6 H), 2.34 (m, 2 H), 5.25–6.50 (complex band, 5 H).

(±)-Methyl 7-[3α -Hydroxy-2 β -(4(R)-hydroxy-4,8-dimethyl-1(E),5(E),7-nonatrienyl)-5-oxo-1 α -cyclopentyl]-4-(Z)-heptenoate (5b). In a manner similar to the preparation of 5a, the more polar diastereomer 5b was obtained from 10b in 11% yield: ¹H NMR δ 1.34 (s, 3 H), 1.78 (s, 6 H), 2.01 (dd, J = 12, 6 Hz, 1 H), 2.22 (dd, J = 18, 10 Hz, 1 H), 2.40 (ddd, J = 12, 8, 8 Hz, 1 H), 2.73 (dd, J = 18, 7 Hz, 1 H), 3.68 (s, 3 H), 4.04 (q, J = 8 Hz, 1 H), 5.43 (dd, J = 15, 8 Hz, 1 H), 5.63 (d, J = 15 Hz, 1 H), 5.69 (dt, J = 15, 7 Hz, 1 H), 5.81 (d, J = 11 Hz, 1 H), 6.43 (dd, J = 15, 11 Hz, 1 H). Anal. (C₂₄H₃₆O₅) C, H.

5-Methyl-3(*E***)**,**5(***E***)**-heptadien-2-one (8c). In a similar manner to the preparation of 8b, the title compound was prepared from tiglic aldehyde in 39% yield: ¹H NMR δ 1.79 (p, *J* = 1 Hz, 3 H), 1.81 (d, *J* = 7.5 Hz, 3 H), 2.30 (s, 3 H), 6.04 (qq, *J* = 7.5, 1 Hz, 1 H), 6.08 (d, *J* = 16 Hz, 1 H), 7.17 (d, *J* = 16 Hz, 1 H). Anal. (C₈H₁₂O) C, H.

4,7-Dimethyl-5(E),7(E)-nonadien-1-yn-4-ol (9c). In a manner similar to the preparation of the alcohol precursor of 9a, the title compound was obtained from 8c in 60% yield after purification on silica gel (10% EtOAc-hexane): ¹H NMR δ 1.42 (s, 3 H), 1.65–1.85 (complex band, 6 H), 2.08 (t, J = 2 Hz, 1 H), 2.46 (d, J = 3 Hz, 2 H), 5.64 (qq, J = 7.5, 1 Hz, 1 H), 5.68 (d, J = 16 Hz, 1 H), 6.31 (d, J = 16 Hz, 1 H). Anal. (C₁₁H₁₆O) C, H.

[[1,4-Dimethyl-1-[3-(tributylstannyl)-2(E)-propenyl]-2-(E),4(E)-hexadienyl]oxy]trimethylsilane (10c). A mixture of 2.46 g (15 mmol) of 9c, 4.51 g (15.5 mmol) of freshly distilled tri-*n*-butyltin hydride and a catalytic amount of AIBN contained in a Pyrex flask was irradiated under argon with a GE sunlamp placed approximately 3 in. from the reaction vessel. After 2 h another 1.46 g (5 mmol) of tri-*n*-butyltin hydride was added and irradiation continued for 4 h. The reaction mixture was purified on silica gel by elution first with 1% EtOAc-hexane and then 5% EtOAc-hexane to afford 2.11 g (31%) of the hydroxyvinylstannane as a 4:1 mixture of E/Z isomers.

To a solution of 2.0 g (4.39 mmol) of the hydroxy vinylstannane in 15 mL of DMF under N₂ at room temperature was added 680 mg (10 mmol) of imidazole and 540 mg (5 mmol) of trimethylchlorosilane. The mixture was stirred for 30 min, then poured into a mixture of ether and water, and shaken well. The layers were separated, and the aqueous portion was extracted with a 1:1 mixture of ether and hexane. The organic extracts were combined, washed with water three times and saturated NaCl solution once, dried (Na₂SO₄), and evaporated to yield 2.09 g (90%) of a clear oil that was used directly in the cuprate reaction: ¹H NMR δ 0.10 (s, 9 H), 0.70–1.05 (complex band, 15 H), 1.32 (s, 3 H), 1.15–1.85 (complex band, 18 H), 2.37 (m, 2 H), 5.20–6.65 (complex band, 5 H).

(±)-Methyl 7-[3α -Hydroxy- 2β -(4(R)-hydroxy-4,7-dimethyl-1(E),5(E),7(E)-nonatrienyl)-5-oxo-1 α -cyclopentyl]-4(Z)-heptenoate (5c). The title compound was prepared from 10c in 21% yield in a manner similar to the preparation of 5a: ¹H NMR δ 1.34 (s, 3 H), 1.73 (complex band, 3 H), 1.74 (complex band, 3 H), 2.73 (dd, J = 18, 7 Hz, 1 H), 3.67 (s, 3 H), 4.03 (q, J = 8 Hz, 1 H), 5.43 (dd, J = 15, 8 Hz, 1 H), 5.57 (complex band, 1 H), 5.62 (d, J = 15 Hz, 1 H), 5.68 (dt, J = 15, 7 Hz, 1 H), 3.8 (C-2), 22.5 (C-3), 128.1, 130.4 (C-4,5), 24.3 (C-6), 27.3 (C-7), 53.7 (C-8), 215.1 (C-9), 45.9 (C-10), 71.6 (C-11), 54.8 (C-12), 133.6 (C-13), 129.2 (C-14), 45.7 (C-15), 72.4 (C-16), 27.3 (16-CH₃), 132.8 (C-17), 131.9 (C-18), 133.4 (C-19), 13.7 (19-CH₃), 126.8 (C-20), 11.9 (C-21). Anal. (C₂₄H₃₆O₅) C, H.

5,6-Dimethyl-3(E),5-heptadien-2-one (8d). In a similar manner to the preparation of 8b, the title compound was prepared

from 2,3-dimethyl-1-butenal¹⁹ in 59% yield after purification on silica gel (10% EtOAc-hexane): ¹H NMR δ 1.81 (s, 3 H), 1.91 (s, 3 H), 1.99 (s, 3 H), 2.30 (s, 3 H), 6.12 (d, J = 16 Hz, 1 H), 7.75 (d, J = 16 Hz, 1 H). Anal. (C₉H₁₄O) C, H.

4,7,8-Trimethyl-5(E),7-nonadien-1-yn-4-ol (9d). The title compound was prepared in a manner similar to the alcohol precursor of 9a in 67% yield after purification on silica gel (10% EtOAc-hexane): ¹H NMR δ 1.43 (s, 3 H), 1.76 (s, 3 H), 1.80 (s, 3 H), 1.86 (s, 3 H), 2.09 (t, J = 4 Hz, 1 H), 2.20 (s, 1 H), 2.46-2.50 (complex band, 2 H), 5.70 (d, J = 16 Hz, 1 H), 6.81 (d, J = 16Hz, 1 H). Anal. (C₁₂H₁₈O) C, H.

Trimethyl[[1,4,5-trimethyl-1-[3-(tributylstannyl)-2(E)propenyl]-2(E),4-hexadienyl]oxy]silane (10d). In a manner similar to the preparation of 10c, the title compound was obtained from 9d and was used directly in the cuprate reaction: ¹H NMR δ 0.11 (s, 9 H), 0.65–1.05 (complex band, 15 H), 1.34 (s, 3 H), 1.75 (s, 3 H), 1.79 (s, 3 H), 1.82 (s, 3 H), 2.39 (m, 2 H), 5.63 (d, J =16 Hz, 1 H), 5.89–5.99 (complex band, 2 H), 6.61 (d, J = 16 Hz, 1 H).

(±)-Methyl 7-[3α -Hydroxy- 2β -(4(R)-hydroxy-4,7,8-trimethyl-1(E),5(E),7-nonatrienyl)-5-oxo- 1α -cyclopentyl]-4-(Z)-heptenoate (5d). In a manner similar to the preparation of 5a from 10a, the title compound was obtained from 10d in 13% yield: ¹H NMR δ 1.35 (s, 3 H), 1.75 (s, 3 H), 1.79 (s, 3 H), 1.83 (s, 3 H), 2.23 (dd, J = 18, 10 Hz, 1 H), 2.73 (dd, J = 18, 7 Hz, 1 H), 3.66 (s, 3 H), 4.03 (q, J = 8 Hz, 1 H), 5.33 (complex band, 2 H), 5.44 (dd, J = 15, 7 Hz, 1 H), 5.65 (d, J = 16 Hz, 1 H), 5.70 (dt, J = 15, 7 Hz, 1 H), 6.71 (J = 16 Hz, 1 H). Anal. (C₂₅H₃₈O₅) C, H.

Ethyl 2-Methyl-2-[(triethylsilyl)oxy]-4-pentynoate (11). A 500-mL flask was charged with 16.6 g (0.106 mol) of ethyl 2-hydroxy-2-methyl-4-pentynoate,²⁰ 15.9 g (0.234 mol) of imidazole, 20.6 g (0.136 mol) of triethylchlorosilane, and 300 mL of dry DMF. The mixture was stirred 1 h at room temperature and then kept at 5 °C overnight. The reaction contents were poured into a stirred mixture of 1 L of water and 1 L of 1:1 ether-hexane. The aqueous layer was extracted twice with a 1:1 mixture of ether-hexane. The combined extracts were washed three times with water, once with saturated NaCl solution and dried (MgSO₄). Solvent evaporation gave 30.8 g of crude yellow oil that was purified on silica gel (0.75%)EtOAc-hexane) to furnish 25.3 g (88%) of 11 as a colorless oil: ¹H NMR δ 0.62 (q, J = 8 Hz, 6 H), 0.96 (t, J = 8 Hz, 9 H), 1.30 (t, J = 7 Hz, 3 H), 1.53 (s, 3 H), 2.0 (t, J = 2.5 Hz, 1 H), 2.57 (dd, J = 2.5 Hz, 1J = 17, 2.5 Hz, 1 H), 2.65 (dd, J = 17, 2.5 Hz, 1 H), 4.18 (q, J =7 Hz, 2 H). Anal. $(C_{14}H_{26}O_3Si)$ C, H.

2-Methyl-2-[(triethylsilyl)oxy]-4-pentynal (14). A solution of 10.8 g (40 mmol) of 11 in 125 mL of toluene was cooled to -78 °C and 80 mL of 1.0 M diisobutylaluminum hydride in toluene (80 mmol) was added dropwise. The reaction was stirred for 1 h and was then quenched by slow addition of 7 g (0.16 mmol) of acetaldehyde in 50 mL of toluene. After stirring for 1 additional hour, saturated Na₂SO₄ solution (50 mL) and ether (150 mL) were added, the reaction was warmed to room temperature and poured into a vigorously stirred mixture of 3 N HCl (250 mL) and ether (250 mL). After 15 min of stirring the organic layer was separated, washed successively with dilute NaHCO₃ solution, water, and saturated NaCl solution, and dried (MgSO₄). Solvent evaporation gave 8.6 g (95%) of 14 as a colorless oil. An analytical sample was purified on deactivated silica gel: ¹H NMR δ 0.65 (q, J =8 Hz, 6 H), 0.98 (t, J = 8 Hz, 9 H), 1.39 (s, 3 H), 2.04 (t, J = 2.5Hz, 1 H), 2.47, 2.52 (dd, J = 16.5, 2.5 Hz, 2 H), 9.60 (s, 1 H); IR 3300, 3015, 2955, 2905, 2870, 2115, 1732 cm⁻¹. Anal. (C₁₂H₂₂O₂Si) C, H.

Ethyl 5-Bromo-2-methyl-2-[(triethylsilyl)oxy]-4(E)-pentenoate (12). To a solution of 27 g (0.1 mol) of 11 in 500 mL of dry benzene was added 27.1 g (0.105 mol) of zirconocene chloride hydride, and the solution was stirred for 3 h. Tetrahydrofuran (400 mL) and 18.7 g (0.105 mol) of N-bromosuccinimide were added, and the mixture was stirred for 1 h. The reaction was poured into 2 L of 4:1 ether-water and stirred for 15 min. The organic layer was washed twice with water and once with saturated NaCl solution and dried $(MgSO_4)$. Evaporation to a volume of 500 mL produced solids that were removed by filtration. Evaporation to a cloudy oil and elution through a pad of silica gel with 10% EtOAc-hexane gave 31.2 g (90%) of a clear yellow oil: 1 H NMR δ 0.62 (q, J = 8 Hz, 6 H), 0.95 (t, J = 8 Hz, 9 H), 1.28 (t, J = 7 Hz, 3 H), 1.42 (s, 3 H), 2.35 (dd, J = 14, 7 Hz, 1 H), 2.46 (dd, J = 14, 7 Hz, 1 H), 4.17 (q, J = 7 Hz, 2 H), 6.07 (d, J = 13)Hz, 1 H), 6.20 (dt, J = 13, 7 Hz, 1 H).

5-Bromo-2-methyl-2-[(triethylsilyl)oxy]-4(*E*)-pentenal (13). The title compound was prepared from 31.2 g (90.4 mmol) of 12 in a manner similar to that of 14 to give 24 g (95%) of 13 as a yellow oil: ¹H NMR δ 0.63 (q, *J* = 8 Hz, 6 H), 0.97 (t, *J* = 8 Hz, 9 H), 1.28 (s, 3 H), 2.23 (dd, *J* = 14, 7 Hz, 1 H), 2.36 (dd, *J* = 14, 7 Hz, 1 H), 6.09 (d, *J* = 13 Hz, 1 H), 6.18 (dt, *J* = 13, 7 Hz, 1 H), 9.57 (s, 1 H).

8-Bromo-5-methyl-5-[(triethylsilyl)oxy]-3(E),7(E)-octadien-2-one (15). A solution of 2.24 g (7.3 mmol) of 13 and 4.18 g (13.1 mmol) of 1-(triphenylphosphoranylidene)-2-propanone in 100 mL of toluene was refluxed for 18 h. The toluene was evaporated and the resulting residue triturated with hexane. Filtration, evaporation of solvent, and purification of the residue on silica gel (7% EtOAc-hexane) gave 1.42 g (56%) of 15 as a clear oil: ¹H NMR δ 0.61 (q, J = 8 Hz, 6 H), 0.97 (t, J = 8 Hz, 9 H), 1.38 (s, 3 H), 2.27 (s, 3 H), 2.29 (d, J = 7 Hz, 2 H), 6.06 (d, J = 13.5 Hz, 1 H), 6.15 (dt, J = 13.5, 7 Hz, 1 H), 6.18 (d, J = 16 Hz, 1 H); IR 3005, 2995, 2940, 2860, 2895, 1665, 1620 cm⁻¹. Anal. (C₁₅H₂₇O₂SiBr) C, H, Br.

[[1-(3-Bromo-2(E)-propenyl)-1,4-dimethyl-2(E),4-pentadienyl]oxy]triethylsilane (16). A solution of 1.42 g (4.1 mmol) of 15 in 70 mL of dry THF was treated with 13.5 mL of 1.5 M (20.5 mmol) bis[(bromozincio)methylene]zinc⁹ in THF. The solution was cooled to -10 °C, and 10.2 mL of 1.0 M titanium tetrachloride (10.2 mmol) in CH₂Cl₂ was added. The mixture was warmed to room temperature, stirred for 1 h, and poured into a mixture of 300 mL of ether and 100 mL of 1 N HCl. The organic layer was washed successively with NaHCO3 solution, water, saturated NaCl solution, and dried (MgSO₄). Solvent evaporation and purification on silica gel (hexane) gave 756 mg (54%) of 16 as a colorless oil: ¹H NMR δ 0.57 (q, J = 8 Hz, 6 H), 0.95 (t, J = 8 Hz, 9 H), 1.44 (s, 3 H), 1.85 (br s, 3 H), 2.22 (ddd, J = 13, 7.5, 1 Hz, 1 H), 2.27 (ddd, J = 13, 7.5, 1 Hz, 1 H), 4.98 (br s, 2 H), 5.67 (d, J = 16 Hz, 1 H), 6.02 (dt, J = 13, 1 Hz, 1 H), 6.20 (dt, J = 13, 7.5 Hz, 1 H), 6.22 (d, J = 16 Hz, 1 H).

(±)-Methyl 11α , 16(R)-Dihydroxy-16, 19-dimethyl-9-oxoprosta-4(Z), 13(E), 17(E), 19-tetraen-1-oate (5e). A solution of 396 mg (1.15 mmol) of 16 in 4 mL of dry ether under argon was cooled to -78 °C and treated with 1.35 mL of 1.7 M t-BuLi (2.29 mmol) in pentane. The mixture was stirred for 20 min at -78°C. A solution of 150 mg (1.15 mmol) of copper 1-pentyne and 374 mg (2.29 mmol) of hexamethylphosphorous triamide in 4 mL of ether was added, and the solution was stirred for 20 min. A solution of 224 mg (0.64 mmol) of 3 in 2 mL ether was then added. After 20 min the reaction mixture was poured into a stirred mixture of 75 mL of 1 N HCl and 75 mL of ether. The organic layer was separated, washed successively with dilute NaHCO3 solution, water, and saturated NaCl solution, and dried (Na_2SO_4) . Solvent evaporation gave 544 mg of crude oil that was purified on silica gel (7% EtOAc-hexane) to give 135 mg (34%) of protected prostaglandin as a colorless oil. The oil was dissolved in 25 mL of a 1:2:4 mixture of pyridine/70% HF-pyridine/CH₃CN,²¹ stirred for 2 h, and poured into 150 mL of ether. The ether was

^{(19) (}a) Blanco, L.; Amice, P.; Conia, J-M. Reaction of Chloromethylcarbene with Trimethylsilyl Enol Ethers; Preparation of Alpha-methylene Ketones and Aldehydes. Synthesis 1981, 291-293. (b) Satsumabayashi, S.; Nakajo, K.; Soneda, R.; Motoki, S. Preparation of Some Alpha, Beta-unsaturated Aldehydes. Bull. Chem. Soc. Jpn. 1970, 43, 1586-1588. (c) Ono, N.; Miyake, H.; Tanakaga, R.; Kaji, A. A new Synthesis of Alpha, Beta-unsaturated Aldehydes from Nitroparaffins. J. Org. Chem. 1982, 47, 5017-5019.

⁽²⁰⁾ Mayrargue, J.; Avril, J-L.; Miocque, M. Cyclisations Pyrazolique et Pyridazinique d'Hydrazides β et γ Acetyleniques. Bull. Chem. Soc. Fr. 1984, II, 129–132.

⁽²¹⁾ Tanaka, T.; Hazato, A.; Bannui, K.; Okamura, N.; Sugiura, S.; Manabe, K.; Toru, T.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. Nitro-olefin Trapping Reaction of Enolates In Situ Generated by Conjugate Addition Reactions: Short Syntheses of PGE₁, 6-Oxo-PGF_{1α} and PGI₂. Tetrahedron 1987, 43, 813-816.

washed with saturated NaHCO₃ solution and water and dried (Na₂SO₄). Purification on silica gel (60% EtOAc-hexane) gave 16.9 mg of 6e, 16.1 mg of 5e, and 11.1 mg of a mixture of 5e and 6e. Total yield of prostaglandin was 42%. 5e: ¹H NMR δ 1.35 (s, 3 H), 1.57 (m, 1 H), 1.67 (s, 3 H), 2.02 (dtd, J = 12, 6, 1 Hz, 1 H), 2.13 (br q, J = 7 Hz, 2 H), 2.30–2.35 (complex band, 7 H), 2.73 (ddd, J = 18, 7.5, 1 Hz, 1 H), 3.67 (s, 3 H), 4.03 (br q, J = 8.5 Hz, 1 H), 4.99 (br s, 2 H), 5.33 (complex band, 2 H), 5.44 (dd, J = 15, 9 Hz, 1 H), 5.70 (dt, J = 15, 7 Hz, 1 H), 5.73 (d, J = 16 Hz, 1 H). Anal. (C₂₃H₃₄O₅) C, H.

Ethyl 7-Bromo-4-methyl-4-[(triethylsilyl)oxy]-2(E),6-(E)-heptadienoate (17). A solution of 4.98 g (16.2 mmol) of 13 and 9.58 g (27.5 mmol) of (carbethoxymethylene)triphenylphosphorane in 70 mL of benzene was refluxed for 3 h. After the reaction mixture cooled, the solvent was evaporated and the residue was passed through a pad of silica gel (10% EtOAchexane). Evaporation of the filtrate gave 5.42 g of crude yellow oil that was purified on silica gel (1% EtOAc-hexane) to give 4.02 g (66%) of 17 as a clear oil: ¹H NMR δ 0.60 (q, J = 8 Hz, 6 H), 0.96 (t, J = 8 Hz, 9 H), 1.32 (t, J = 7 Hz, 3 H), 1.37 (s, 3 H), 2.28 (d, J = 7 Hz, 2 H), 4.21 (q, J = 7 Hz, 2 H), 5.93 (d, J = 16 Hz, 1 H), 6.05 (d, J = 13 Hz, 1 H), 6.14 (dt, J = 13, 7 Hz, 1 H), 6.88 (d, J = 16 Hz, 1 H); IR 3020, 3010, 2955, 2905, 2870, 1710, 1655, 1620 cm⁻¹. Anal. (C₁₆H₂₉O₃SiBr) C, H, Br.

7-Bromo-4-methyl-[(triethylsilyl)oxy]-2(E),6(E)-heptadienal (18). A solution of 17 (1.97 g, 5.2 mmol) in 150 mL of CH₂Cl₂ was cooled to -78 °C, and 11.8 mL of 1.0 M DIBAL (diisobutylaluminum hydride) in CH₂Cl₂ (11.8 mmol) was added dropwise. The reaction was warmed to room temperature, 50 mL of saturated sodium potassium tartrate solution was added, and the mixture was poured into a mixture of 300 mL of ether and 100 mL of sodium potassium tartrate solution and stirred for 30 min. The layers were separated, and the organic layer was dried $(MgSO_4)$ and evaporated to give 1.73 g (99%) of bromo alcohol as a light oil: ¹H NMR δ 0.57 (q, J = 8 Hz, 6 H), 0.96 (t, J = 8 Hz, 9 H), 1.30 (t, J = 4 Hz, 1 H), 1.32 (s, 3 H), 2.22 (d, J = 7.5Hz, 2 H), 4.17 (dd, J = 5, 4 Hz, 2 H), 5.72 (d, J = 16 Hz, 1 H), 5.77 (dt, J = 16, 5 Hz, 1 H), 6.02 (d, J = 14 Hz, 1 H), 6.19 (dt, J = 14, 7.5 Hz, 1 H). The bromo alcohol was immediately¹⁰ subjected to Swern oxidation as follows: A solution of 698 mg (5.5 mmol) of oxalyl chloride in 40 mL of CH₂Cl₂ was cooled to -78 °C, and 938 mg (852 uL, 12 mmol) of DMSO was added. The mixture was warmed to -35 °C and then recooled to -78 °C, and 1.7 g (5 mmol) of the bromo alcohol in 40 mL of CH₂Cl₂ was added. After the mixture was warmed to -35 °C for 5 min, 2.5 g (25 mmol) of triethylamine was added. The flask was warmed to room temperature, 15 mL of water was added, and the contents was poured into a stirred mixture of 100 mL of 9:1 ether-water. The organic layer was washed twice with 1 N HCl, then successively with dilute NaHCO3 solution, water, and saturated NaCl solution, dried (MgSO₄), and evaporated, and the residue was purified on silica gel (8% EtOAc-hexane) to give 1.05 g (63%) of 18 as a colorless oil: ¹H NMR δ 0.61 (q, J = 8 Hz, 6 H), 0.97 (t, J = 8Hz, 9 H), 1.42 (s, 3 H), 2.33 (d, J = 7 Hz, 2 H), 6.09 (d, J = 14Hz, 1 H), 6.15 (dt, J = 14, 7 Hz, 1 H), 6.23 (dd, J = 15, 8 Hz, 1 H), 6.73 (d, J = 15 Hz, 1 H), 9.58 (d, J = 8 Hz, 1 H); IR 3005, 2955, 2905, 2870, 1690, 1615 cm⁻¹.

[[1-(3-Bromo-2(E)-propenyl)-1-methyl-2(E),4(E)-pentadienyl]oxy]triethylsilane (19). A solution of 18, (315 mg, 0.93 mmol) in 15 mL of dry THF was cooled to -78 °C, and a solution of methylenetriphenylphosphorane prepared separately by treating 360 mg (1.0 mmol) of methyltriphenylphosphonium bromide with 0.63 mL of 1.6 M n-BuLi (1.0 mmol) in 8 mL of THF at -10 °C was added by cannulation. The mixture was warmed to room temperature and then poured into a stirred mixture of 100 mL of ether and 25 mL of 1 N HCl. The organic layer was washed with dilute NaHCO₃ solution, saturated NaCl solution and dried (MgSO₄). Solvent evaporation furnished a solid that was slurried in 10 mL of 0.25% EtOAc-hexane and filtered. Evaporation of the filtrate gave 266 mg of crude yellow oil that was purified on silica gel (0.25% EtOAc-hexane) to give 167 mg (55%) of 19 as a clear oil: ¹H NMR δ 0.57 (q, J = 8 Hz, 6 H), 0.95 (t, J = 8 Hz, 9 H), 1.32 (s, 3 H), 2.23 (d, J = 7 Hz, 2 H), 5.09(dd, J = 10, 2 Hz, 1 H), 5.21 (dd, J = 17, 2 Hz, 1 H), 5.72 (d, J)= 15 Hz, 1 H), 6.02 (dt, J = 13, 1 Hz, 1 H), 6.13 (dd, J = 15, 10 Hz, 1 H), 6.19 (dt, J = 13, 7 Hz, 1 H), 6.32 (dt, J = 17, 10 Hz, 1 H). Anal. (C₁₅H₂₇OSiBr) C, H.

 (\pm) -Methyl 11 α , 16(R)-Dihydroxy-16-methyl-9-oxoprosta-4(Z), 13(E), 17(E), 19-tetraen-1-oate (5f). In the same manner as for 5e, 342 mg (1.03 mmol) of 19 was converted to 114 mg (33%) of protected prostaglandin. The protecting groups were removed by treatment with 5 mL of 9:1 acetone-water containing 1 mg/mL of pyridinium p-toluenesulfonate (PPTS) for 24 h at room temperature. Silica gel purification (65% EtOAc-hexane) gave 17.4 mg (25%) of 5f and 17.9 mg (25%) of 6f as colorless viscous oils. 5f: ¹H NMR δ 1.33 (s, 3 H), 1.57 (m, 1 H), 1.69 (m, 1 H), 2.02 (dt, J = 12, 6 Hz, 1 H), 2.13 (br q, J = 7 Hz, 2 H), 2.23 (dd, J)= 18, 10 Hz, 1 H), 2.35 (complex band, 6 H), 2.39 (dt, J = 12, 9 Hz, 1 H), 2.74 (dd, J = 18, 7.5 Hz, 1 H), 3.67 (s, 3 H), 4.04 (br q, J = 8.5 Hz, 1 H), 5.09 (dd, J = 10, 2 Hz, 1 H), 5.22 (dd, J =17, 2 Hz, 1 H), 5.33 (complex band, 2 H), 5.44 (dd, J = 15, 9 Hz, 1 H), 5.69 (dt, J = 15, 7.5 Hz, 1 H), 5.78 (d, J = 15, 1 H), 6.23 (dd, J = 15, 10.5 Hz, 1 H), 6.33 (dt, J = 17, 10 Hz, 1 H). Anal. $(C_{22}H_{32}O_5)$ C, H.

9-Bromo-6-methyl-6-[(triethylsilyl)oxy]-2(Z),4(E),8(E)nonatriene (20). A solution of 1.49 g (4 mmol) of ethyltriphenylphosphonium bromide in 48 mL of 6:1 toluene-THF was treated with 3.8 mL of 1.0 M sodium bis(trimethylsilyl)amide (3.8 mmol) in THF at room temperature, stirred for 1 h and then cooled to -100 °C. A solution of 882 mg (2.65 mmol) of 18 in 5 mL of toluene was added, and the mixture was allowed to warm slowly to 0 °C and then poured into a stirred mixture of 150 mL of ether and 50 mL of saturated NH₄Cl solution. The organic layer was separated, washed with water and then saturated NaCl solution, dried (MgSO₄), and evaporated and the residue purified on silica gel (0.25% EtOAc-hexane) to give 479 mg (52%) of 20 as a colorless oil: ¹H NMR δ 0.58 (q, J = 8 Hz, 6 H), 0.96 (t, J= 8 Hz, 9 H), 1.33 (s, 3 H), 1.77 (dd, J = 7.5, 1.5 Hz, 3 H), 2.24 (d, J = 7.5 Hz, 2 H), 5.52 (dq, J = 11, 7.5 Hz, 1 H), 5.67 (d, J = 11, 7.5 Hz, 1 H), 5.67 (15 Hz, 1 H), 5.98 (tq, J = 11, 1.5 Hz, 1 H), 6.02 (d, J = 13.5 Hz, 1 H), 6.20 (dt, J = 13.5, 7.5 Hz, 1 H), 6.47 (dd, J = 15, 11 Hz, 1 H). Anal. $(C_{16}H_{29}OSiBr)$ C, H.

(±)-Methyl 7-[3α -Hydroxy- 2β -(4(R)-hydroxy-4-methyl-1-(E),5(E),7(Z)-nonatrienyl)-5-oxo-1 α -cyclopentyl]-4(Z)heptenoate (5g). In a manner similar to the preparation of 5e and 6e, 5g and 6g were obtained by cuprate-mediated addition of 479 mg (1.39 mmol) of 20 to 271 mg (0.77 mmol) of 3 to give 281 mg (59%) of protected prostaglandin. The lithiation of 20 was carried out in ether at -100 °C by treatment with t-BuLi. The silvl groups were hydrolyzed at room temperature in 25 mL of 9:1 acetone-water containing 1 mg of PPTS/mL. 5g: ¹H NMR δ 1.35 (s, 3 H), 1.50–1.75 (complex band, 3 H), 1.77 (dd, J = 7.5, 1.5 Hz, 3 H), 2.02 (dtd, J = 12, 6, 1 Hz, 1 H), 2.14 (q, J = 7 Hz, 1 H), 2.23 (dd, J = 18.5, 9.5 Hz, 1 H), 2.30-2.40 (complex band, 6 H), 2.39 (dt, J = 12, 9 Hz, 1 H), 2.74 (ddd, J = 18.5, 7.5, 1 Hz, 1 H), 3.67 (s, 3 H), 4.04 (q, J = 8.5 Hz, 1 H), 5.34 (m, 2 H), 5.45 (dd, J = 15, 9 Hz, 1 H), 5.52 (dq, J = 11, 7.5 Hz, 1 H), 5.70 (dt, J = 11, 7.5 Hz, 1 H), 5.7J = 15, 7.5 Hz, 1 H), 5.75 (d, J = 15 Hz, 1 H), 6.00 (tq, J = 11, 1.5 Hz, 1 H), 6.54 (dd, J = 15, 11 Hz, 1 H). Anal. (C₂₃H₃₄O₅) C, H.

5-Methyl-5-[(triethylsilyl)oxy]-3(*E*)-octen-7-yn-2-one (21). A solution of 3.4 g (15 mmol) of 14 and 9.55 g (30 mmol) of 1-(triphenylphosphoranylidene)-2-propanone in 100 mL of toluene was refluxed for 18 h. The toluene was evaporated to furnish a solid residue that was triturated with 300 mL of hexane. Filtration and evaporation of the hexane gave 3.62 g of crude red oil. The oil was purified on silica gel (5% EtOAc-hexane to yield 2.51 g (63%) of 21 as a clear oil: ¹H NMR δ 0.62 (q, J = 8 Hz, 6 H), 0.97 (t, J = 8 Hz, 9 H), 1.49 (s, 3 H), 2.05 (t, J = 2.5 Hz, 1 H), 2.30 (s, 3 H), 2.47 (d, J = 2.5 Hz, 2 H), 6.24 (d, J = 16 Hz, 1 H); IR 3300, 1672, 1625 cm⁻¹. Anal. (C₁₅H₂₆O₂Si) C, H.

[[1,4-Dimethyl-1-(2-propynyl)-2(E),4(Z)-hexadienyl]oxy]triethylsilane (22). The title compound was prepared from 666 mg (2.5 mmol) of 21 in a manner similar to the preparation of 20. The phosphorane was generated with 0.66 M potassium bis(trimethylsilyl)amide in toluene. The crude solid residue was slurried in 20 mL of 1% EtOAc-hexane and passed through a pad of silica gel. Filtrate concentration gave 698 mg of oil that was purified on silica gel (hexane) to furnish 341 mg (49%) of 22 as a colorless oil: ¹H NMR δ 0.61 (q, J = 8 Hz, 6 H), 0.97 (t, J = 8 Hz, 9 H), 1.48 (s, 3 H), 1.74 (d, J = 7 Hz, 3 H), 1.81 (s, 3 H), 1.99 (t, J = 2.5 Hz, 1 H), 2.45 (d, J = 2.5 Hz, 2 H), 5.46 (q, J = 7 Hz, 1 H), 5.83 (d, J = 16 Hz, 1 H), 6.70 (d, J = 16 Hz, 1 H). Anal. (C₁₇H₃₀OSi) C, H.

[[1-(3-Bromo-2(*E*)-propenyl)-1,4-dimethyl-2(*E*),4(*Z*)-hexadienyl]oxy]triethylsilane (23). The title compound was prepared from 483 mg (1.73 mmol) of 22 in a manner similar to the preparation of 12. Purification on silica gel (hexane) gave 220 mg (35%) of 23 as a colorless oil: ¹H NMR δ 0.58 (q, *J* = 8 Hz, 6 H), 0.96 (t, *J* = 8 Hz, 9 H), 1.34 (s, 3 H), 1.74 (d, *J* = 7 Hz, 3 H), 1.80 (s, 3 H), 2.26 (d, *J* = 7.5 Hz, 2 H), 5.45 (q, *J* = 7 Hz, 1 H)), 5.67 (d, *J* = 16 Hz, 1 H), 6.02 (d, *J* = 14 Hz, 1 H), 6.22 (dt, *J* = 14, 7.5 Hz, 1 H), 6.60 (d, *J* = 16 Hz, 1 H).

(±)-Methyl 7-[3α -Hydroxy- 2β -(4(R)-hydroxy-4,7-dimethyl-1(E),5(E),7(Z)-nonatrienyl)-5-oxo-1 α -cyclopentyl]-4(Z)-heptenoate (5h). The title compound was prepared from 220 mg (0.6 mmol) of 23 in a manner similar to the preparation of 5e using 120 mg (0.34 mmol) of 3. Deprotection with PPTS in 9:1 acetone-H₂O and purification on silica gel (62% EtOAc-hexane) gave 14.5 mg (26%) of 6h and 21 mg (38%) of 5h: ¹H NMR δ 1.37 (s, 3 H), 1.58 (m, 1 H), 1.70 (m, 1 H), 1.75 (d, J = 7 Hz, 2 H), 2.23 (dd, J = 18, 10 Hz, 1 H), 2.09-2.55 (complex band, 7 H), 2.74 (dd, J = 18, 7.5 Hz, 1 H), 3.67 (s, 3 H), 4.04 (q, J = 8.5 Hz, 1 H), 5.33 (m, 2 H), 5.45 (dd, J = 15, 7.5 Hz, 1 H), 5.73 (d, J = 16 Hz, 1 H), 6.67 (d, J = 16 Hz, 1 H). Anal. (C₂₄H₃₆O₅) C, H.

Ethyl 2,4-Dimethyl-4-[(triethylsilyl)oxy]-2(*E*)-hepten-6ynoate (24). A solution of 3.04 g (8.39 mmol) of (carboethoxyethylidene)triphenylphosphorane and 1.0 g (4.42 mmol) of 14 in 10 mL of toluene was refluxed for 14 h. The toluene was evaporated, and the residue was triturated with hexane. Filtration and evaporation gave a residue that was purified by flash chromatography (5% EtOAc-hexane) to give 1.13 g (82%) of a colorless oil: IR 3300, 2950, 1700 cm⁻¹; ¹H NMR δ 0.63 (q, J = 7.8 Hz, 6 H), 0.95 (t, J = 7.8 Hz, 9 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.55 (s, 3 H), 2.00 (t, J = 2.7 Hz, 1 H), 2.04 (d, J = 1.4 Hz, 3 H), 2.51 (dd, J = 16.4, 2.7 Hz, 1 H), 2.55 (dd, J = 16.4, 2.7 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 6.84 (d, J = 1.4 Hz, 1 H). Anal. (C₁₇H₃₀O₃Si) C, H.

2,4-Dimethyl-4-[(triethylsilyl)oxy]-2(E)-hepten-6-ynal (25). The title compound was prepared by DIBAL reduction of 1.0 g (3.22 mmol) of 24 in a manner similar to the preparation of 18 to give 815 mg (94%) of crude allylic alcohol as a colorless oil: IR 3600, 3300, 2950 cm⁻¹; ¹H NMR δ 0.61 (q, J = 7.8 Hz, 6 H), 0.95 (t, J = 7.8 Hz, 9 H), 1.32 (t, J = 4 Hz, 1 H), 1.51 (s, 3 H), 1.86 (d, J = 1.1 Hz, 3 H), 1.96 (t, J = 2.7 Hz, 1 H), 2.47 (dd, J = 16.4, 2.7 Hz, 1 H), 2.51 (dd, J = 16.4, 2.7 Hz, 1 H), 3.98 (d, J = 4 Hz, 2 H), 5.60 (d, J = 1.1 Hz, 1 H). The allylic alcohol was immediately¹⁰ subjected to oxidation.

A mixture of 1.0 g (4.41 mmol) of pyridinium chlorochromate (PCC) and 5.0 g of neutral alumina was vigorously stirred in 7 mL of CH₂Cl₂ for 15 min. A solution of 790 mg (2.94 mmol) of the allylic alcohol in 8 mL of CH₂Cl₂ was added dropwise to the orange suspension of PCC-alumina. The mixture was stirred for 3 h, diluted with ether, filtered through a short column of silica gel, and eluted with 10% EtOAc-hexane. Solvent evaporation gave 770 mg (89%) of 25 as an oil: IR 3300, 2950, 1685 cm⁻¹; ¹H NMR & 0.64 (q, J = 7.8 Hz, 6 H), 0.96 (t, J = 7.8 Hz, 9 H), 1.60 (s, 3 H), 1.95 (d, J = 1.1 Hz, 3 H), 2.02 (t, J = 2.6 Hz, 1 H), 2.55 (dd, J = 1.1 Hz, 1 H), 9.39 (s, 1 H).

[[1,3-Dimethyl-1-(2-propynyl)-2(*E*),4-pentadienyl]oxy]triethylsilane (26). The title compound was prepared from 750 mg (2.82 mmol) of 25 in a manner similar to the preparation of 19. The crude product was purified by flash chromatography (hexane) to afford 490 mg (66%) of 26 as a colorless oil: IR 3300, 2950 cm⁻¹; ¹H NMR δ 0.61 (q, J = 7.8 Hz, 6 H), 0.94 (t, J = 7.8Hz, 9 H), 1.53 (s, 3 H), 1.96 (d, J = 1.1 Hz, 3 H), 1.97 (t, J = 7.8Hz, 1 H), 2.50 (dd, J = 16.3, 2.7 Hz, 1 H), 2.55 (dd, J = 16.3, 2.7 Hz, 1 H), 5.00 (d, J = 10.7 Hz, 1 H), 5.20 (d, J = 17.4 Hz, 1 H), 5.64 (s, 1 H), 6.33 (dd, J = 10.7, 17.3 Hz, 1 H). Anal. (C₁₆H₂₈OSi) C, H.

Triethyl[[1-(3-iodo-2(E)-propenyl)-1,3-dimethyl-2(E),4pentadienyl]oxy]silane (27). Zirconocene chloride hydride (511 mg, 1.98 mmol) was added to a solution of 475 mg (1.80 mmol) of 26 in 5 mL of benzene, and the mixture was stirred for 3 h. The clear yellow solution was then treated with 410 mg (1.80 mmol) of solid N-iodosuccinimide and stirred for 30 min. The reaction was diluted with hexane and filtered to removed precipitated solids, and the filtrate was washed with 1% Na₂SO₃, water, and saturated NaCl solution. The organic layer was dried (MgSO₄) and the solvent evaporated to give 646 mg (92%) of 27 as a light-sensitive yellow oil: ¹H NMR δ 0.59 (q, J = 7.8 Hz, 6 H), 0.94 (t, J = 7.8 Hz, 9 H), 1.37 (s, 3 H), 1.93 (d, J = 1.1 Hz, 3 H), 2.30 (dd, J = 14, 7.5 Hz, 1 H), 2.38 (dd, J = 14, 7.5, 1 H), 5.00 (d, J = 10.6 Hz, 1 H), 5.18 (d, J = 17.4 Hz, 1 H), 5.47 (s, 3 H), 6.01 (d, J = 14.5 Hz, 1 H), 6.29 (dd, J = 17.3, 10.6 Hz, 1 H), 6.53 (dt, J = 14.5, 7.5 Hz, 1 H).

 (\pm) -Methyl 11 α ,16(R)-Dihydroxy-16,18-dimethyl-9-oxoprosta-4(Z), 13(E), 17(E), 19-tetraen-1-oate (5i). A three-necked flask was charged with 125 mg (1.40 mmol) of CuCN, heated under vacuum, and cooled to room temperature under argon. THF (5 mL) was added and the flask was cooled to -78 °C. A solution of 1.4 M MeLi in ether (1.0 mL) was added dropwise, and the flask was warmed until the solution became clear (-20 °C) and then recooled to -78 °C. In a separate flask a solution of 550 mg (1.40 mmol) of 27 in 5 mL of THF was cooled to -78 °C and treated with 1.7 mL of 1.7 M t-BuLi in pentane (2.89 mmol). The resulting vinyl lithium solution was cannulated into the cyanocuprate solution at -78 °C and stirred for 30 min. A solution of 363 mg (1.40 mmol) of 3 in 3 mL of THF was added and the reaction stirred for 1 h. The reaction was quenched by addition of 9:1 saturated NH₄Cl-NH₄OH solution and a 1:3 mixture of EtOAc-hexane and stirred until deep blue. The aqueous layer was separated and extracted with a 1:4 mixture of EtOAc-hexane. The combined organic layers were washed with water and saturated NaCl solution, dried (MgSO4), and evaporated. The residue was purified by flash chromatography (7% EtOAc-hexane) to afford 225 mg (50%) of protected prostaglandin as a colorless oil.

The oil (190 mg 0.34 mmol) was dissolved in 8.7 mL of 0.004 M PPTS in 9:1 acetone-water. After standing 20 h at room temperature the reaction mixture was evaporated and the residue dissolved in ether. The ether was washed with 5% NaHCO₃ solution and then saturated NaCl solution, dried $(MgSO_4)$, and evaporated, and the residue was purified by flash chromatography (65% EtOAc-hexane) to give 91 mg (67%) of a mixture of diastereomers as a colorless oil. A portion of the mixture was separated on silica gel (60% EtOAc-hexane) to give 14 mg of 5i: ¹H NMR δ 1.40 (s, 3 H), 1.58 (dq, J = 13, 7 Hz, 1 H), 1.67 (dq, J =13, 7 Hz, 1 H), 1.99 (s, 3 H), 2.01 (dt, J = 12, 6 Hz, 1 H), 2.12 (q, J = 7 Hz, 2 H), 2.23 (dd, J = 18, 10 Hz, 1 H), 2.34 (m, 4 H), 2.44 (m, 3 H), 2.74 (dd, J = 18, 8.5 Hz, 1 H), 3.67 (s, 3 H), 4.05 (q, J)= 8.5 Hz, 1 H), 5.00 (d, J = 10.6 Hz, 1 H), 5.19 (d, J = 17.4 Hz, 1 H), 5.33 (m, 2 H), 5.47 (dd, J = 15.2, 8.7 Hz, 1 H), 5.55 (s, 1 H), 5.73 (dt, J = 15.2, 7.3 Hz, 1 H), 6.31 (dd, J = 17.4, 10.6 Hz, 1 H). Anal. $(C_{23}H_{34}O_5)$ C, H.

Ethyl 3,4-Dimethyl-4-[(triethylsilyl)oxy]-2(E)-hepten-6ynoate (29). The title compound was prepared from 2.74 g (17.5 mmol) of ethyl 3-methyl-4-oxo-2(E)-pentenoate²² (28) in a manner similar to the preparation of 9a. The crude alcohol was purified on silica gel (20% EtOAc-hexane) to furnish 1.47 g (43%) of ethyl 3,4-dimethyl-4-hydroxy-2(E)-hepten-6-ynoate as a colorless oil: ¹H NMR δ 1.29 (t, 3 H), 1.42 (s, 3 H), 2.12 (t, 1 H), 2.18 (d, 3 H), 2.56 (s, 1 H), 2.57 (dq, 2 H), 4.16 (q, 2 H), 6.15 (d, 1 H); IR 3560, 3310, 3030, 3020, 2990, 1710, 1650 cm⁻¹. Anal. (C₁₁H₁₆O₃) C, H.

A solution of 2.45 g (12.5 mmol) of the above alcohol was silvlated with triethylchlorosilane in the usual fashion and purified on silica gel (3% EtOAc-hexane) to give 3.79 g (98%) of **29** as a colorless oil: ¹H NMR δ 0.63 (q, J = 8 Hz, 6 H), 0.97 (t, J = 8 Hz, 9 H), 1.29 (t, J = 7 Hz, 3 H), 1.50 (s, 3 H), 1.98 (t, J = 2.5 Hz, 1 H), 2.17 (d, J = 1 Hz, 3 H), 2.49 (d, J = 2.5 Hz, 2 H), 4.17 (q, J = 7 Hz, 2 H), 6.02 (q, J = 1 Hz, 1 H).

3,4-Dimethyl-4-[(triethylsilyl)oxy]-2(E)-hept-6-ynal (30). The title compound was prepared from 3.79 g (12.2 mmol) of 29

⁽²²⁾ Ley, S. V.; Somovilla, A. A.; Broughton, H. B.; Craig, D.; Slawin, A. M. Z.; Toogood, P. L.; Williams, D. J. Chemistry of Insect Antifeedants from Azadirachta Indica (Part 4); Synthesis Towards the Limonoid Azadirachtin; Preparation of a Functionalized Decalin Fragment. Tetrahedron 1989, 45, 2143-2164.

in a manner similar to the preparation of 18. The crude alcohol was not isolated but was immediately subjected to Swern oxidation to give 3.03 g (93%) of **30** as a colorless oil that was used without further purification: IR 3295, 2940, 2900, 2860, 1600 cm⁻¹; ¹H NMR δ 0.63 (q, J = 8 Hz, 6 H), 0.96 (t, J = 8 Hz, 9 H), 1.51 (s, 3 H), 1.98 (t, J = 2.5 Hz, 1 H), 2.20 (d, J = 1 Hz, 3 H), 2.52 (d, J = 2.5 Hz, 2 H), 6.17 (dq, J = 8, 1 Hz, 1 H), 10.08 (d, J = 8 Hz, 1 H).

[[1,2-Dimethyl-1-(2-propynyl)-2(*E*),4-pentadienyl]oxy]triethylsilane (31). The title compound was prepared from 1.13 g (4.24 mmol) of 30 in a manner similar to the preparation of 19. Purification on silica gel (1% EtOAc-hexane) gave 613 mg (60%, 3 steps) of 31 as a colorless oil: ¹H NMR δ 0.60 (q, *J* = 8 Hz, 6 H), 0.95 (t, *J* = 8 Hz, 9 H), 1.51 (s, 3 H), 1.70 (d, *J* = 1 Hz, 3 H), 1.95 (t, *J* = 2.5 Hz, 1 H), 2.45 (d, *J* = 2.5 Hz, 2 H), 5.12 (dd, *J* = 10, 2 Hz, 1 H), 5.22 (dd, *J* = 17, 2 Hz, 1 H), 6.16 (d, *J* = 11 Hz, 1 H), 6.59 (ddd, *J* = 17, 11, 10 Hz, 1 H). Anal. (C₁₆H₂₈OSi) C, H.

 (\pm) -Methyl 11 α , 16(R)-Dihydroxy-16, 17-dimethyl-9-oxoprosta-4(Z), 13(E), 17(E), 19-tetraen-1-oate (5j). A solution of 613 mg (2.32 mmol) of 31 in 7 mL of THF was treated with 629 mg (2.44 mmol) of zirconocene chloride hydride and the mixture stirred for 1 h. The reaction was cooled to -55 °C and an addition sequence¹⁴ that required 20 min of stirring for each addend was carried out with the following: 2.90 mL of a 1.6 M n-BuLi solution in hexane (4.64 mmol), 208 mg (2.32 mmol) of CuCN, 1.76 mL of a 1.39 M solution of MeLi in cumene (2.44 mmol), and 409 mg (1.16 mmol) of 3 in 4 mL of THF. The cold reaction mixture was poured into a mixture of 150 mL of ether and 40 mL of 9:1 saturated NH₄Cl solution-concentrated NH₄OH, and the mixture was stirred for 30 min. The organic layer was washed with water and saturated NaCl solution, dried $(MgSO_4)$, filtered, and evaporated and the residual oil purified on silica gel (3% EtOAchexane) to give 421 mg (60%) of protected prostaglandin as an oil. The purified mixture of diastereomers (407 mg, 0.67 mmol) was dissolved in 20 mL of 9:1 acetone-water containing 20 mg of PPTS. After 48 h, the solution was worked-up as described for 5i and purified on silica gel (70% EtOAc-hexane to give 88 mg (34%) of 6j and 83 mg (32%) of the more polar racemate 5j: ¹H NMR δ 1.35 (s, 3 H), 1.54 (dq, J = 13, 7 Hz, 1 H), 1.66 (dq, J = 13, 7 Hz, 1 H), 1.79 (s, 3 H), 1.99 (dt, J = 12, 6 Hz, 1 H), 2.12 (br q, J = 7 Hz, 2 H), 2.22 (dd, J = 18.5, 9.5 Hz, 1 H), 2.49 (dd, J)J = 15, 6 Hz, 2 H), 2.72 (dd, J = 18.5, 7.5 Hz, 1 H), 3.67 (s, 3 H), 5.12 (dd, J = 11, 2 Hz, 1 H), 5.21 (dd, J = 17, 2 Hz, 1 H), 5.33(m, 2 H), 5.43 (dd, J = 15, 9 Hz, 1 H), 5.56 (ddd, J = 15, 8, 6 Hz, 1 H), 6.18 (d, J = 11 Hz, 1 H), 6.58 (dt, J = 17, 11 Hz, 1 H). Anal. (C₂₂H₃₄O₅) C, H.

Gastric Antisecretory Studies. Prostaglandins were dissolved in absolute ethanol (1 mg/mL) and stored at -10 °C. Dosing solutions containing up to 20% ethanol were prepared by diluting stock solutions with pH 7.4 isoosmotic phosphate buffer. Antisecretory studies were done as previously described for enisoprost.²³ Briefly, adult female beagles (6-11 kg), with inervated (Pavlov) gastric pouches, were food deprived with access to water 14 h prior to experiments. Following a 30 min basal collection period, the prostaglandin in the buffer-ethanol vehicle was administered into the pouch through a Thomas cannula. Thirty minutes later the gastric pouch was emptied and gastric secretion was stimulated by feeding 10-12 oz. of canned dog food (Evanger's Dog and Cat Food Co., Inc., Wheeling, IL). Gastric juice samples were collected over a 4-h period at 30-min intervals. Total acid output (mequiv/30 min) was determined for each collection period by multiplying the volume of secretion (mL/30)min) and the acidity (mequiv/L). For new compounds, percent reduction of total acid output from control was calculated over each 4 h experiment for 3-6 doses and 2-4 dogs were used for each dose. Dose-response curves and ED₅₀ values were estimated by using linear regression and 95% confidence limits were determined by using Fieller's method.²⁴

Diarrheal Studies.²³ Adult Charles River male rats weighing 210–230 g were individually housed and fasted with water available ad libitum for 24 h prior to the test. The animals (N = 6-12) received logarithmically graded prostaglandin doses orally. Immediately after administration, the animals were returned to their cages, and diarrhea, if any, was assessed on an all or none basis for 8 h after drug treatment. The ED₅₀ and 95% confidence intervals were calculated by logistic regression.

Acknowledgment. We thank J. Casler and C. Ponte for technical assistance in the antisecretory and diarrheal studies, M. Carniello for statistical analysis of the data, K. Koehler for MM2 calculations of conformational energies for 5c and 5h, L. Swenton for spectral interpretation, the group of E. Hajdu for spectral data, the group of E. Zielinski for microanalyses, and D. Weiman for typing the manuscript.

⁽²³⁾ Collins, P. W.; Kramer, S. W.; Gullikson, G. W. Synthesis and Gastrointestinal Pharmacology of the 4-Fluoro Analogue of Enisoprost. J. Med. Chem. 1987, 30, 1952–1955.

⁽²⁴⁾ Draper, N. R.; Smith, H. Applied Regression Analysis, 2nd ed.; John Wiley & Son: New York, 1981; pp 30-31.