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; $Me(CH_2)_2CO_2H$, 107-92-6; $[Me(CH_2)_2CO]_2O$, 106-31-0; $MeCH_2CO_2H$, 79-09-4; Me_2CHCO_2H, 79-31-2; $Me(CH_2)_3CO_2H$, 109-52-4; $BocNH(CH_2)_3CO_2H$, 57294-38-9; $ClCH_2OOCCMe_3$, 18997-19-8; $ClCH_2OOC(CH_2)_6Me$, 61413-70-5; $ClCHMeOOCOEt$, 50893-36-2; $ClCH_2OOCCHMe_2$, 61644-18-6; $CH_2{=}O$, 50-00-0; $MeCH{=}O$, 75-07-0; $Me(CH_2)_2CH{=}O$, 123-72-8; $Me_3CCH{=}O$, 630-19-3; $ClCH_2OOC(CH_2)_2Me$, 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

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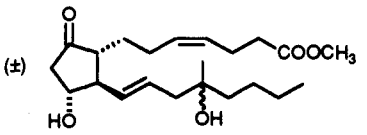
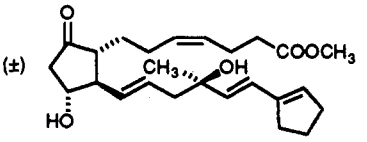
A series of acyclic ω chain conjugated diene analogues of enisoprost were synthesized and evaluated for gastric antisecretory and diarrheagenic activities in comparison to enisoprost and a previously identified cyclic dienyl analogue. Several novel approaches to the cuprate reagents involved in the synthesis 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 paper[2] 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*)-18-cyclopentenyl compound 2 displayed antisecretory activity



1



2

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 *p*-toluenesulfonate (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-

(1) 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-16-hydroxy-16-methylprostaglandin E_1. *J. Med. Chem.* **1983**, *36*, 786–790.

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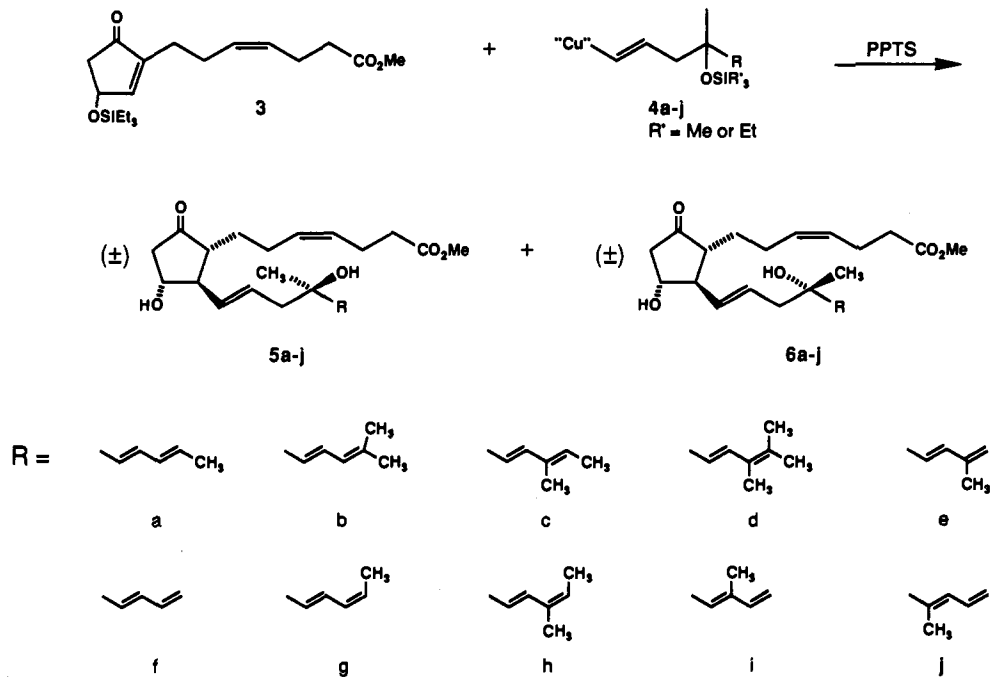


Figure 1.

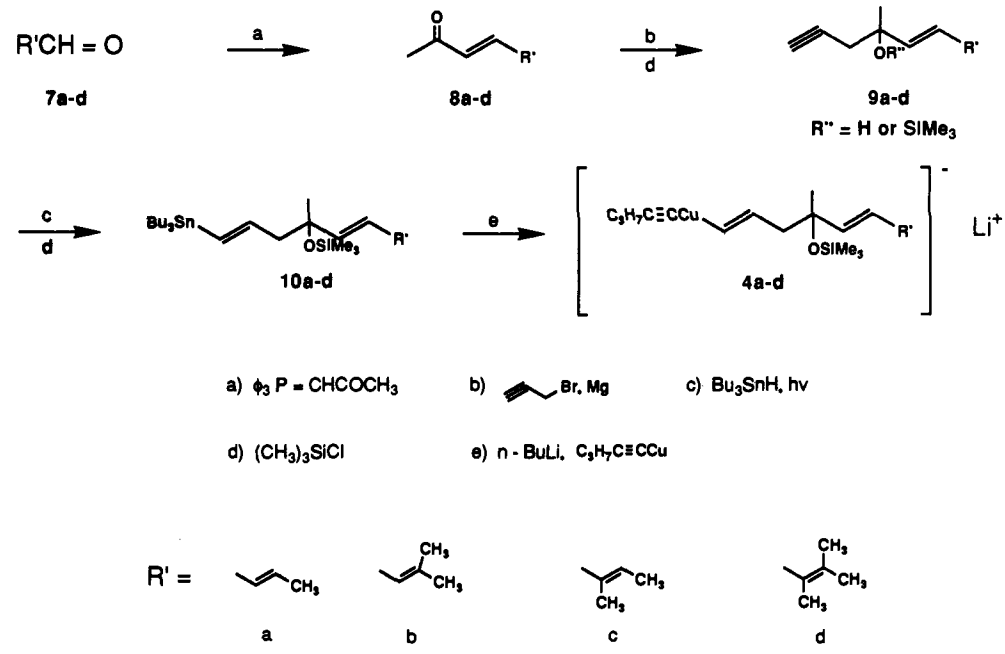


Figure 2.

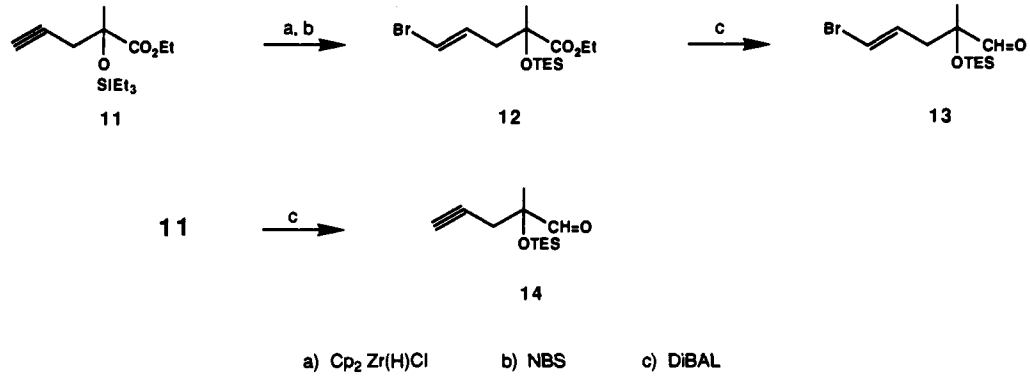


Figure 3.

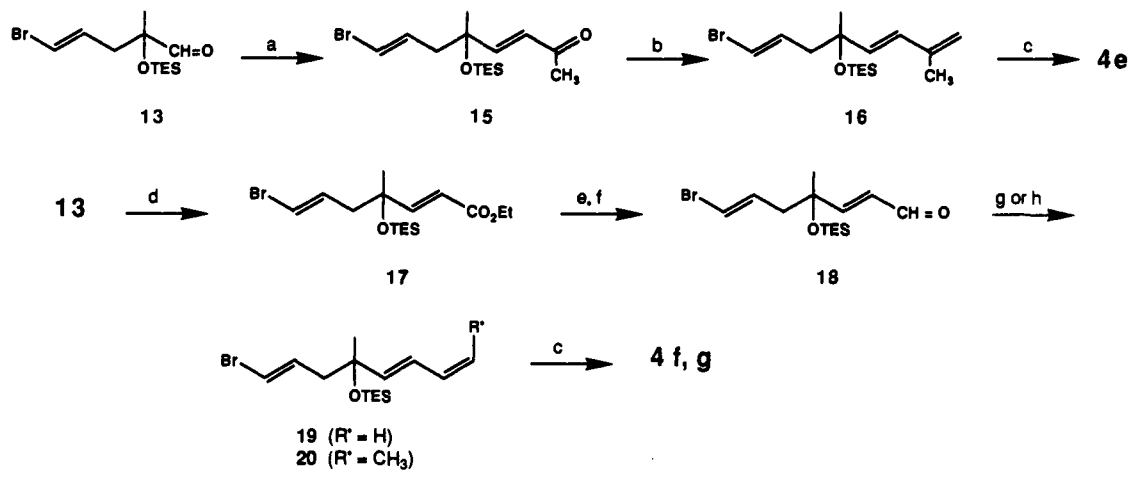


Figure 4.

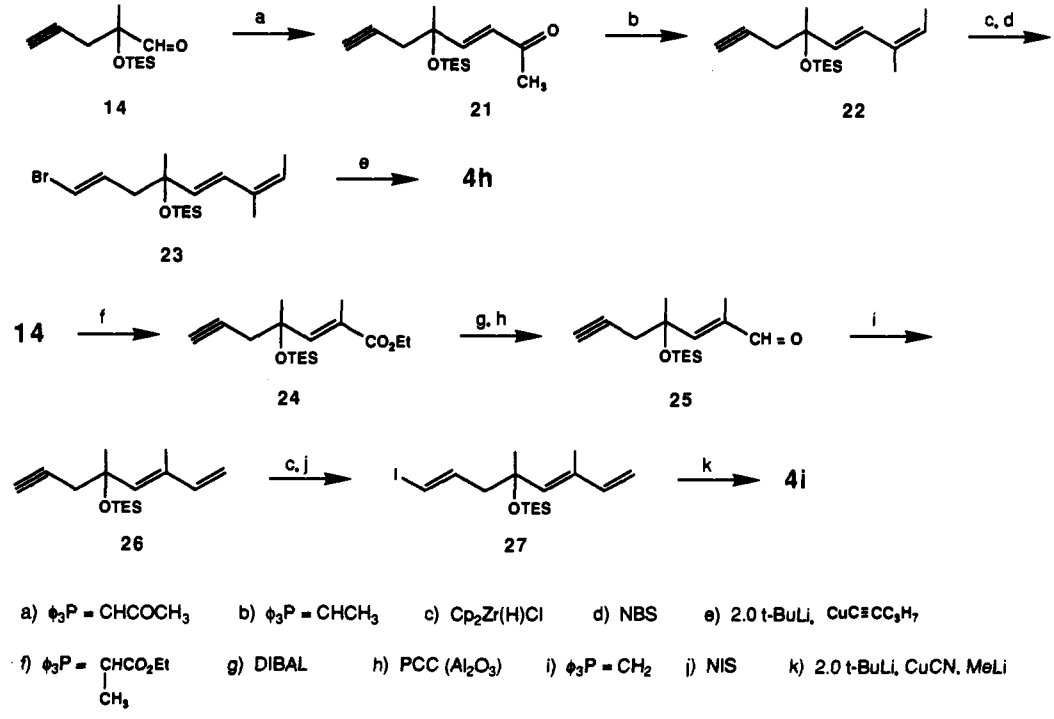


Figure 5.

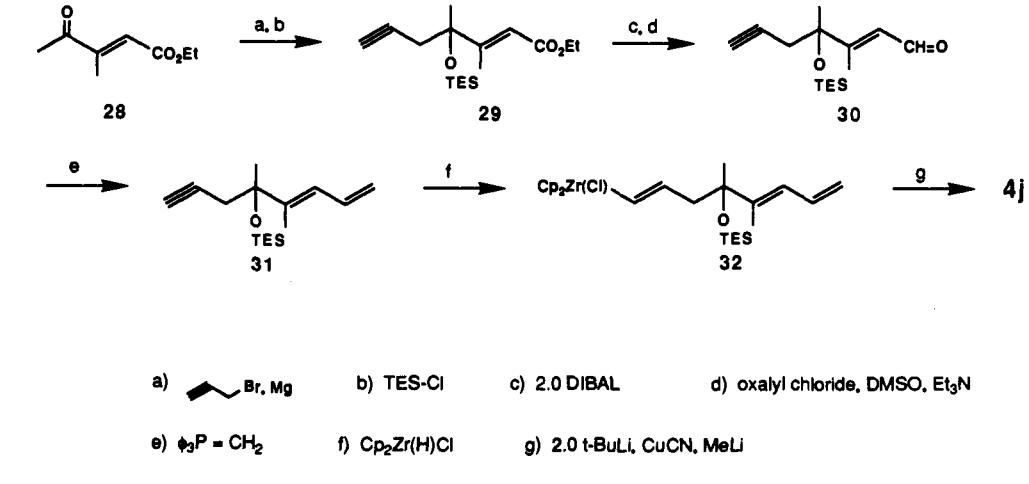
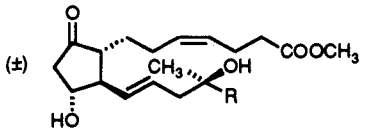
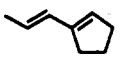
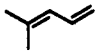
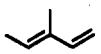
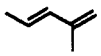
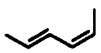
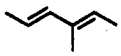
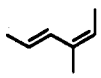
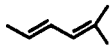
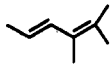


Figure 6.

Table I



compd	R	ED$_{50}$, μg/kg and 95% confidence limits[a] gastric antisecretory activity in dogs[b]	diarrheal effects in rats[c]	selectivity ratio[d]
1		0.023	49	2
2		0.02	>3160	>158
5f		0.007[a]	243 (68.2–863.1)	35
5j		*I* at 3.0	>3160	
5i		0.71 (0.439–1.94)	1033 (424.9–2511.1)	1.4
5e		0.002 (0.0003–0.0053)	420 (188.8–933.9)	210
5a		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
5h		0.016 (0.0012–0.033)	1226 (581.8–2583.1)	76
5b		0.06 (0.01–0.11)	>3160	>53
5d		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$_{50}$ valves 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$_{50}$ × 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** (R″ = $SiMe_3$). 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-*n*-butyltin hydride, purified by chromatography and then protected with trimethylchlorosilane to give **10c,d**. This sequence was based on a previous finding[2] 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-

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

(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. Et_3B-Induced Radical Addition of R_3SnH 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.

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)-2-propanone to give the methyl ketone **15** and subsequent methylenation of the ketone with bis[(bromozincio)-methylene]zinc[9] and $TiCl_4$. 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 immediately[10] 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 conditions[11] 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 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 **14** (from Figure 3) with 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]

(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.

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(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.

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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 work[2] 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 *cis*-methyl 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 *trans*-methyl 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 ED_{50}'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 $CDCl_3$ with Me_4Si as internal standard. The ^{13}C NMR spectra were determined with use of the APT pulse technique. Infrared spectra were recorded on a Perkin-Elmer 685 spectrophotometer in $CHCl_3$. Elemental analyses were within ±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 μm) with PMA as visualization agent.

Trimethyl[[1-methyl-1-(2-propynyl)-2(*E*),4(*E*)-hexadienyl]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 $HgCl_2$ 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 (3*E*,5*E*)-heptadien-2-one[18] 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 (Na_2SO_4), 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 N_2 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

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(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.

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extracts were combined and washed with water three times and saturated NaCl solution once, dried (Na_2SO_4), 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. ($C_{13}H_{22}OSi$) 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-1α-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 **3**[3] 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 (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (5% EtOAc–hexane) 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 $NaHCO_3$ 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-CH_3), 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-CH_3), 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, 10α-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, OCH_3), 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. ($C_{23}H_{34}O_5$) 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. ($C_8H_{12}O$) 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. ($C_{14}H_{24}OSi$) 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-2β-(4(*R*)-hydroxy-4,8-dimethyl-1(*E*),5(*E*),7-nonatrienyl)-5-oxo-1α-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. ($C_{24}H_{36}O_5$) 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. ($C_8H_{12}O$) 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. ($C_{11}H_{16}O$) 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 N_2 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 (Na_2SO_4), 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-1α-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), 6.23 (d, J = 15 Hz, 1 H); ^{13}C NMR δ 51.4 (OCH_3), 173.5 (C-1), 33.8 (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-CH_3), 132.8 (C-17), 131.9 (C-18), 133.4 (C-19), 13.7 (19-CH_3), 126.8 (C-20), 11.9 (C-21). Anal. ($C_{24}H_{36}O_5$) 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-butenal[19] in 59% yield after purification on silica gel (10% EtOAc–hexane): ^{1}H 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. ($C_9H_{14}O$) 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): ^{1}H 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 = 16 Hz, 1 H). Anal. ($C_{12}H_{18}O$) 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: ^{1}H 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: ^{1}H 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. ($C_{25}H_{38}O_5$) 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 ($MgSO_4$). 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: ^{1}H 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 = 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 Na_2SO_4 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 $NaHCO_3$ solution, water, and saturated NaCl solution, and dried ($MgSO_4$). Solvent evaporation gave 8.6 g (95%) of **14** as a colorless oil. An analytical sample was purified on deactivated silica gel: ^{1}H 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 = 2.5 Hz, 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. ($C_{12}H_{22}O_2Si$) 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: ^{1}H 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: ^{1}H 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), 6.70 (d, J = 16 Hz, 1 H); IR 3005, 2995, 2940, 2860, 2895, 1665, 1620 cm^{-1}. Anal. ($C_{15}H_{27}O_2SiBr$) 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]zinc[9] in THF. The solution was cooled to −10 °C, and 10.2 mL of 1.0 M titanium tetrachloride (10.2 mmol) in CH_2Cl_2 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 $NaHCO_3$ solution, water, saturated NaCl solution, and dried ($MgSO_4$). Solvent evaporation and purification on silica gel (hexane) gave 756 mg (54%) of **16** as a colorless oil: ^{1}H 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 $NaHCO_3$ 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/CH_3CN,[21] stirred for 2 h, and poured into 150 mL of ether. The ether was

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washed with saturated $NaHCO_3$ solution and water and dried (Na_2SO_4). 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), 6.32 (d, J = 16 Hz, 1 H). Anal. ($C_{23}H_{34}O_5$) 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% EtOAc–hexane). 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. ($C_{16}H_{29}O_3SiBr$) 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 CH_2Cl_2 was cooled to −78 °C, and 11.8 mL of 1.0 M DIBAL (diisobutylaluminum hydride) in CH_2Cl_2 (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 = 7.5 Hz, 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 immediately[10] subjected to Swern oxidation as follows: A solution of 698 mg (5.5 mmol) of oxalyl chloride in 40 mL of CH_2Cl_2 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 CH_2Cl_2 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 $NaHCO_3$ solution, water, and saturated NaCl solution, dried ($MgSO_4$), 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 = 8 Hz, 9 H), 1.42 (s, 3 H), 2.33 (d, J = 7 Hz, 2 H), 6.09 (d, J = 14 Hz, 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 $NaHCO_3$ solution, saturated NaCl solution and dried ($MgSO_4$). 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. ($C_{15}H_{27}OSiBr$) C, H.

(±)-Methyl 11α,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 NH_4Cl solution. The organic layer was separated, washed with water and then saturated NaCl solution, dried ($MgSO_4$), 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 = 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-1α-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 silyl 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 = 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. ($C_{23}H_{34}O_5$) 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), 6.87 (d, J = 16 Hz, 1 H); IR 3300, 1672, 1625 cm^{-1}. Anal. ($C_{15}H_{26}O_2Si$) 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. ($C_{17}H_{30}OSi$) 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: ^{1}H 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-1α-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–H_2O and purification on silica gel (62% EtOAc–hexane) gave 14.5 mg (26%) of **6h** and 21 mg (38%) of **5h**: ^{1}H NMR δ 1.37 (s, 3 H), 1.58 (m, 1 H), 1.70 (m, 1 H), 1.75 (d, J = 7 Hz, 3 H), 1.80 (s, 3 H), 2.02 (dt, J = 12, 6 Hz, 1 H), 2.13 (q, J = 7 Hz, 2 H), 2.23 (dd, J = 18, 10 Hz, 1 H), 2.30–2.55 (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, 10 Hz, 1 H), 5.46 (q, J = 7 Hz, 1 H), 5.70 (dt, J = 15, 7.5 Hz, 1 H), 5.73 (d, J = 16 Hz, 1 H), 6.67 (d, J = 16 Hz, 1 H). Anal. ($C_{24}H_{36}O_5$) C, H.

Ethyl 2,4-Dimethyl-4-[(triethylsilyl)oxy]-2(*E*)-hepten-6-ynoate (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}; ^{1}H 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. ($C_{17}H_{30}O_3Si$) 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}; ^{1}H 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 immediately[10] 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 CH_2Cl_2 for 15 min. A solution of 790 mg (2.94 mmol) of the allylic alcohol in 8 mL of CH_2Cl_2 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}; ^{1}H NMR δ 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 = 16.4, 2.6 Hz, 1 H), 2.62 (dd, J = 16.4, 2.6 Hz, 1 H), 6.50 (d, 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}; ^{1}H NMR δ 0.61 (q, J = 7.8 Hz, 6 H), 0.94 (t, J = 7.8 Hz, 9 H), 1.53 (s, 3 H), 1.96 (d, J = 1.1 Hz, 3 H), 1.97 (t, J = 2.6 Hz, 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. ($C_{16}H_{28}OSi$) C, H.

Triethyl[[1-(3-iodo-2(*E*)-propenyl)-1,3-dimethyl-2(*E*),4-pentadienyl]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% Na_2SO_3, water, and saturated NaCl solution. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give 646 mg (92%) of **27** as a light-sensitive yellow oil: ^{1}H 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).

(±)-Methyl 11α,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 NH_4Cl–NH_4OH 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 ($MgSO_4$), 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% $NaHCO_3$ 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**: ^{1}H 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-6-ynoate (29). The title compound was prepared from 2.74 g (17.5 mmol) of ethyl 3-methyl-4-oxo-2(*E*)-pentenoate[22] (**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: ^{1}H 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. ($C_{11}H_{16}O_3$) C, H.

A solution of 2.45 g (12.5 mmol) of the above alcohol was silylated 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: ^{1}H 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**

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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. ($C_{16}H_{28}OSi$) C, H.

(±)-Methyl 11α,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 sequence[14] 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 NH_4Cl solution–concentrated NH_4OH, 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% EtOAc–hexane) 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 = 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. ($C_{22}H_{34}O_5$) 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 ED_{50} values were estimated by using linear regression and 95% confidence limits were determined by using Fieller's method.[24]

Diarrheal Studies.[2,3] 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 ED_{50} and 95% confidence intervals were calculated by logistic regression.

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