(3-pyridinyl)hexyl]-1*H*-isoindole-1,3-dione, 88940-37-8; 3-(6-hydroxyhexyn-1-yl)pyridine, 88940-60-7; *N*-[7-(3-pyridinyl)-heptyl]acetamide, 88940-86-7; 3-(4-hydroxypentyn-1-yl)pyridine, 104877-15-8; 4-(5-pyrimidinyl)butyl chloride, 88940-78-7; 1*H*-imidazole-1-butanenitrile, 72338-63-7; 2-methyl-1*H*-imidazole-1-butyronitrile, 88940-53-8; 6-(3-pyridinyl)-5-hexynenitrile, 88940-62-9; phthalic anhydride, 85-44-9; 3-pyridine heptanenitrile, 88940-85-6; 5-bromopyridine, 4595-59-9; potassium phthalimide, 1074-82-4; 3-(chloromethyl)pyridine hydrochloride, 6959-48-4; thromboxane synthase, 61276-89-9.

# Synthesis and Gastrointestinal Pharmacology of a 3*E*,5*Z* Diene Analogue of Misoprostol

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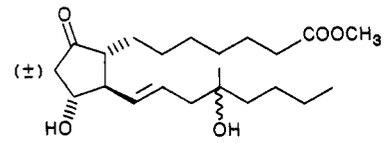
A stereospecific synthesis and the gastric antisecretory and diarrheal activity of a 3*E*,5*Z* diene analogue of misoprostol are described. The key intermediate in the synthesis was an $\alpha$ chain truncated acetylene that was obtained by a cuprate/enolate capture procedure on the corresponding cyclopentenone. Palladium-catalyzed coupling of the acetylene with methyl 4-iodo-3(*E*)-butenoate provided the conjugated enyne. Although selective hydrogenation of the enyne with Lindlar catalyst failed, the desired 3*E*,5*Z* diene was obtained with P-2 nickel as catalyst. The diene was about 3 times more potent than misoprostol in inhibiting gastric acid secretion in dogs and also in producing diarrhea in rats.

Misoprostol (1),[1] a 15-deoxy-16-hydroxy-16-methyl analogue of $PGE_1$, is an effective agent for the treatment of peptic ulcer disease.[2] Recent research with $\alpha$ chain diene analogues of misoprostol resulted in the identification of a 1:1 mixture of 3*E*,5*Z* (**2a**) and 3*Z*,5*Z* (**2b**) isomers

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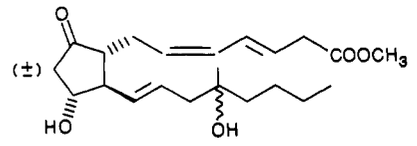


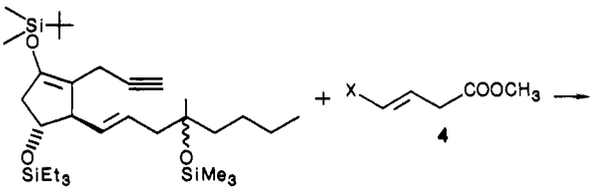

**2a**

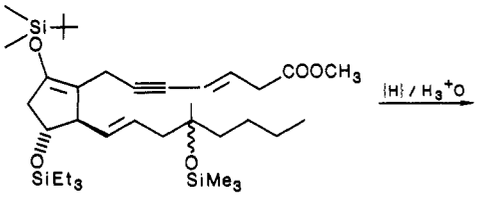
with potent gastric antisecretory activity in dogs.[3,4] Although chromatographic separation of the mixture was very difficult, a few milligrams of each isomer was obtained by HPLC, and preliminary antisecretory studies indicated that most of the activity resided in the 3*E*,5*Z* isomer **2a**.[3] This paper describes a stereospecific synthesis and the pharmacological activity of the active isomer **2a**.

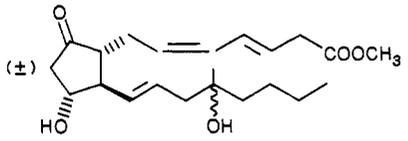
## Chemistry

The key intermediate in the preparation of **2a** was the $\alpha$ chain truncated compound **3** (Scheme I). There are several methods available for coupling acetylenes or acetylenic derivatives with vinyl halides, alkenylcopper compounds, or alkenylboranes to provide conjugated enynes.[5-7]

**Scheme I.** Synthetic Strategy




**2a**

Thus our synthetic strategy centered upon the coupling of **3** with a suitable four-carbon ester **4** in which the *E* stereochemistry of the double bond has been established and "X" is either halogen, copper, or boron. The conjugated enyne **5** could then be converted to **2a** by selective catalytic hydrogenation of the 5-yne and removal of protecting groups.

The synthesis of **3** (Scheme II) was based on chemistry developed by Piancatelli[8] for the conversion of 2-furylcarbinols to hydroxycyclopentenones. Reaction of furfuraldehyde with propargylmagnesium bromide cleanly generated the carbinol **6**. Unlike the facile conversion and high yields observed by Piancatelli with acid-catalyzed

(1) Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152.
(2) Brooks, F. P.; Watkinson, G.; Davies, H. C., Ed. *Prostaglandins in Gastroenterology, Focus on Misoprostol*, Proceedings of an International Symposium; Algarve, Portugal, Sept 13-14, 1984; *Dig. Dis. Sci.* **1985**, *60* (Suppl 11).
(3) Collins, P. W.; Gasiecki, A. F.; Jones, P. H.; Bauer, R. F.; Gullikson, G. W.; Woods, E. M.; Bianchi, R. G. *J. Med. Chem.* **1986**, *29*, 1195.
(4) Misoprostol, **2a**, and **2b** are each a mixture of two racemates or four stereoisomers. The mixture of geometric isomers (**2a** + **2b**) thus consists of eight stereoisomers.
(5) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683.
(6) Normant, J. F.; Commercon, A.; Villieras, J. *Tetrahedron Lett.* **1975**, 1465.
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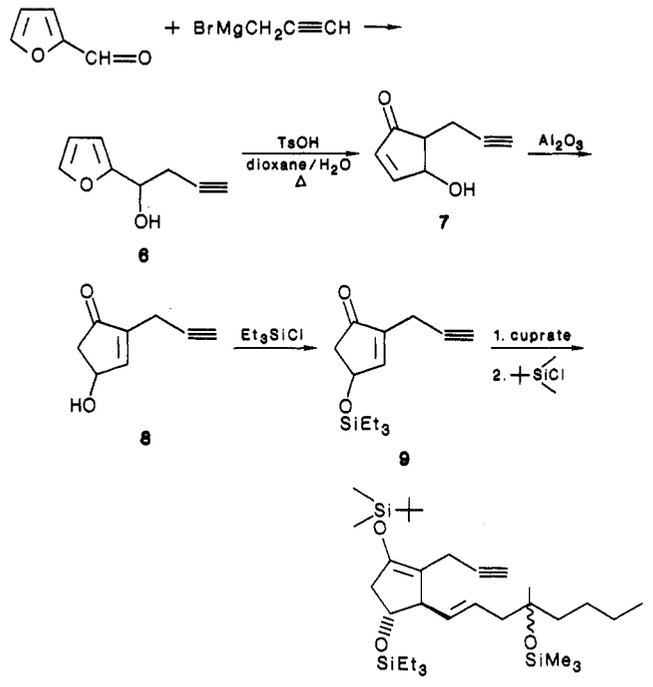
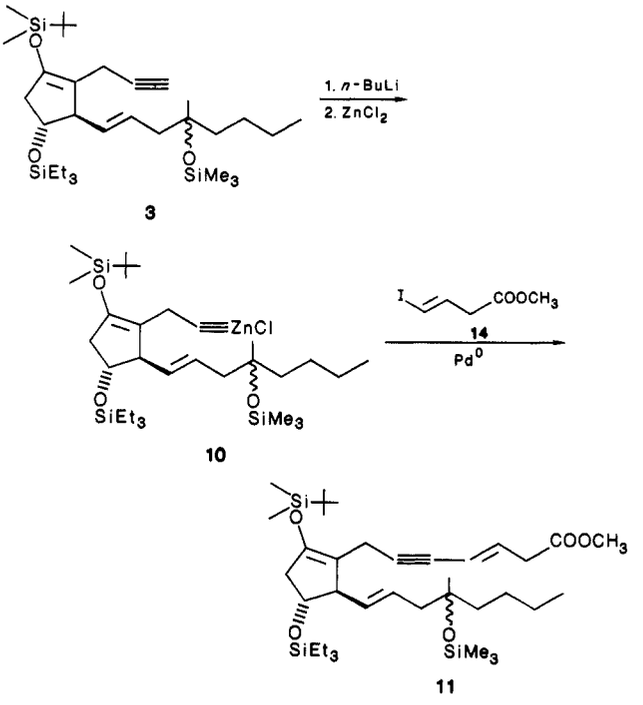
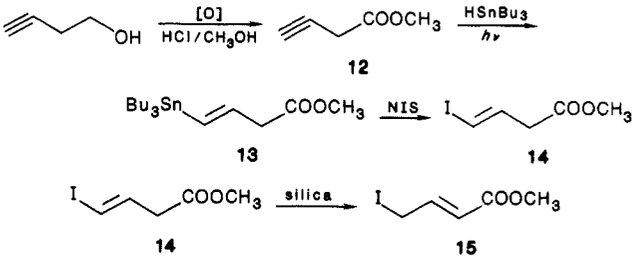
**Scheme II**




**Scheme III**




**Scheme IV**




rearrangements of simple alkyl- and arylfurylcarbinols,[9] great difficulty was encountered in converting **6** to **7**. None of the conditions described in that work provided any useful amounts of **7** but instead resulted in either no reaction or formation of a multitude of products. Zinc chloride catalysis[10] was also ineffective for transforming **6** to **7**. After extensive research, modest yields (20–30%) of **7** were obtained by heating a solution of **6** and *p*-toluenesulfonic acid (0.5%) in an 8:1 mixture of dioxane and water at 83–85 °C for 36 h. Slight deviations from these conditions caused significant reductions in the yield of **7**. Conversion of **7** to **8** was effected by adsorption of **7** on an alumina chromatography column for 16 h[11] or by stirring **7** in an ether slurry of alumina for the same period. The yield of **8** from **7** was also low and varied between 30% and 50%, depending upon the purity of **7**. Although the overall yield of **8** from **6** was quite poor, the ready accessibility of **6**, and the short reaction sequence make this route an attractive one relative to other procedures for cyclopentenone formation.[1,12] Silylation of **8** with triethylchlorosilane in dimethylformamide and imidazole gave **9** which, after chromatography, was a stable, colorless oil. In contrast, both **7** and **8** were brownish-black oils after chromatographic purification and were prone to decomposition. The intermediate **3** was formed by treating **9** with the cuprate reagent derived from (*E*)-(tri-*n*-butylstannyl)-4-methyl-4-[(trimethylsilyl)oxy]-1-octene[13] followed by enolate capture with *tert*-butyldimethylchlorosilane.[3] Concerns that the acidic acetylenic proton of **9** might interfere with the cuprate reaction or quench the resulting enolate were unfounded. The isolated yield of **3** from **9** was excellent (76%), and there was no evidence of the corresponding 9-keto derivative of **3**. The stability of **3** was similar to that of related silyl enol ethers.[3] It was stable to acidic work-up conditions and silica gel chromatography and could be stored indefinitely at 0 °C without significant decomposition. At low temperatures (−50 to −20 °C), **3** readily reacted with *n*-butyllithium to form the acetylide anion, but did not decompose in the presence of excess *n*-butyllithium even at room temperature. The acetylide anion of **3** reacted smoothly at low temperatures with a variety of electrophiles such as aldehydes, iodine, and dimethylformamide. In addition to its utility in the present work, **3** has been a very useful intermediate for the preparation of numerous other $\alpha$ chain prostaglandin analogues.

The crucial step in this sequence was the coupling of the acetylene intermediate **3** with the (*E*)-vinyl iodide **14** (Scheme III). The selection of this coupling approach was based on the work of Negishi,[5,14] who reported that simple alkynylzinc chlorides could be coupled under mild conditions with vinyl halides in the presence of a palladium(0) catalyst to give conjugated enynes. Furthermore, this reaction was compatible with esters, and only small amounts of undesired side products such as dienes and diynes were produced. Treatment of **3** in THF with *n*-butyllithium at −20 °C followed by addition of 1 equiv of solid anhydrous zinc chloride generated the alkynylzinc

(9) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, 3555.
(10) Piancatelli, G.; Scettri, A.; David, G.; D'Auria, M. *Tetrahedron* **1978**, *34*, 2775.
(11) Scettri, A.; Piancatelli, G.; D'Auria, M.; David, G. *Tetrahedron* **1979**, *35*, 135.
(12) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic: New York, 1977; p 121.
(13) Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786.
(14) We thank Professor Negishi for helpful comments on the use of this reaction.

**Table I.** Comparative Oral Gastric Antisecretory and Diarrheal Effects of 16-Hydroxyprostaglandin Analogues

| compd | $ED_{50}$, g/kg ig: gastric antisecretory effects in dogs[a] | rel antisecretory potencies and 95% CL | diarrheal effects in rats[c] | act. ratio $ED_{50}$ diarrhea/$ED_{50}$ antisecretory |
|---|---|---|---|---|
| **2a** | 0.08 | 1 | 131 | 1638 |
| **2a + 2b** | 0.08 | 0.95 (0.53–1.76) | 642[b] | 8025 |
| **1** | 0.28 | 0.26 (0.13–0.48) | 382[b] | 1364 |

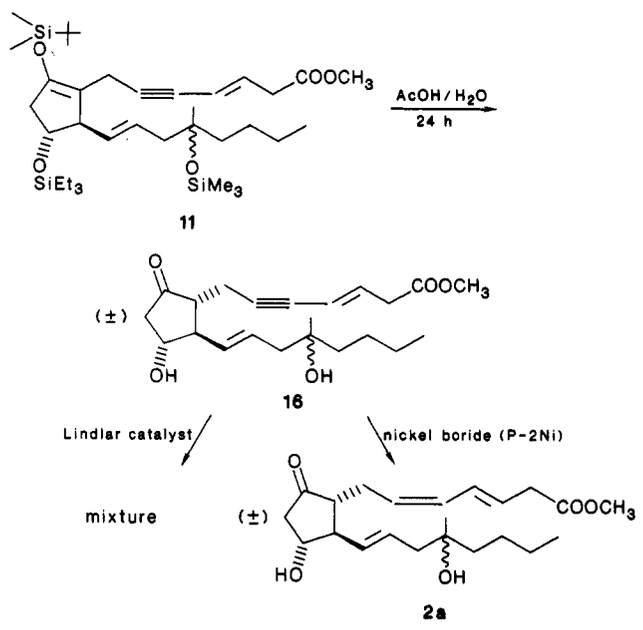
[a] Determined in histamine-stimulated gastric fistula dogs. $ED_{50}$ values were estimated from dose–response curves of percent inhibition of total acid output at three doses. Four to 12 dogs were used at each dose. $ED_{50}$ values for **2a** and **2a + 2b** are significantly different from 1 ($p < 0.05$) but not from each other. [b] These values differ from those reported in ref 3 because of differences in the method of computation. [c] 95% confidence limits for diarrheal $ED_{50}$'s are as follows: **2a** (101–169), **2a + 2b** (429–960), and 1 (255–572).

chloride **10**. To this solution at 0 °C were added several equivalents of **14** and a catalytic amount of tetrakis(triphenylphosphine)palladium, and the mixture was stirred at room temperature for about 2 h. The desired product **11** was obtained in low yield (30% from **3**) along with a substantial amount of unreacted **3**. Longer reaction times did not improve the yield. However, substitution of another palladium catalyst, bis(dibenzylideneacetone)palladium[15-17] in the reaction boosted the yield of **11** to about 70%. Also, with this catalyst, the coupling occurred readily at 0 °C and side products were less pronounced.

The synthesis of the vinyl iodide **14** is outlined in Scheme IV. Jones oxidation of 3-butyn-1-ol followed by esterification in acidic methanol gave the acetylenic ester **12**. Irradiation of a mixture of **12** and tri-*n*-butyltin hydride with a sunlamp under argon provided the (*E*)-vinylstannane **13**. Treatment of **13** with a solution of *N*-iodosuccinimide in THF yielded **14**. Varying but minor amounts (0–10%) of the corresponding *Z* isomers of **13** and **14** were present due to incomplete isomerization during the hydrostannation reaction.[18] However, the subsequent stereospecific preparation of **2a** was not imperiled because, unlike the corresponding dienes, the *Z* enyne derivative of **11** was easily separated from **11** by chromatography. Interestingly, **14** was converted to the allylic iodide **15** when purified by chromatography on fresh silica gel. Subsequent studies established that **14** could be purified without isomerization by either chromatography on deactivated silica gel or by vacuum distillation.

The final step in the synthesis of **2a** was the selective catalytic hydrogenation of the enyne to the diene. No difficulty with this step was anticipated because the literature is replete with successful examples using Lindlar catalyst.[19,20] Hydrogenation of **11** (Scheme V) with either Lindlar catalyst or more active catalysts failed, perhaps due to steric hindrance of the C-9 silyl group. Therefore, reduction studies were performed on the deprotected compound **16**, which was obtained by treatment of **11** with a 3:1:1 mixture of acetic acid, tetrahydrofuran, and water at room temperature for 24 h.[3] Surprisingly, hydrogenation of **16** with Lindlar catalyst and quinoline in a 1:1 mixture of THF and cyclohexane at 0 °C yielded a complex mixture of several dienes and monoenes of which the desired product was only a minor constituent. Thorough investigation of various reaction conditions provided little improvement in the initial results. A different catalyst, nickel boride or P-2 nickel,[21] which was reported to catalyze hydrogenation of isolated acetylenes to *Z* olefins in good yield, was then tried. Reduction of **16** with this catalyst generated two products in a 4:1 ratio: the desired diene **2a** and the $\Delta^5$-*Z* monoolefin, which was separated from **2a** by HPLC.

**Scheme V**




## Results and Discussion

The gastric antisecretory activity of **2a** was determined by intragastric administration in gastric fistula (GF) dogs. The results were compared to that of misoprostol (**1**) and the 1:1 mixture of 3*Z* and 3*E* isomers (**2a + 2b**) previously reported[3] (Table I). The antisecretory potency of **2a** was approximately equal to that of the 1:1 mixture of isomers and about 3 times that of misoprostol. These data support the results of preliminary intravenous studies in Heidenhain pouch dogs, which indicated that the 3*Z*,5*Z* isomer **2b** was only weakly active and that the 3*E*,5*Z* isomer **2a** possessed most of the antisecretory activity of the geometric mixture.[3]

To assess the separation of undesired diarrheogenic effects from gastric antisecretory activity in **2a** relative to misoprostol and the geometric mixture **2a + 2b**, diarrheogenic activity in rats was determined and activity ratios were calculated (Table I). As previously reported,[3] the mixture (**2a + 2b**) was less diarrheogenic than misoprostol (**1**). The activity ratio of the mixture was 5–6 times larger than that of misoprostol, indicating a greater sep-

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(16) Available from Spex Industries, Metuchen, NJ.
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(18) Collins, P. W.; Jung, C. J.; Gasiecki, A. F.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187.
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(20) Nicolaou, K. C.; Petasis, N. A.; Seitz, S. P. *J. Chem. Soc., Chem. Commun.* **1981**, 1195.
(21) Brown, C. H.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553.

aration of diarrheal and antisecretory effects. In contrast, **2a** was approximately 3 times more diarrheogenic than misoprostol and showed an equivalent separation of diarrheal and antisecretory activities as misoprostol because of its greater gastric antisecretory potency. The data suggest that, when the two geometric isomers are given as a 1:1 mixture, the 3*Z*,5*Z* isomer **2b** moderates the ability of **2a** to induce diarrhea in rats, but does not significantly affect the antisecretory activity of **2a** in dogs.

The intermediate enyne **16** was also evaluated for gastric antisecretory activity in histamine-stimulated Heidenhain pouch dogs.[3] Interestingly, **16** was inactive at a test dose of 1 μg/kg iv.

## Experimental Section

The NMR spectra were obtained on either a Varian FT-80-A or XL-100 spectrometer in $CDCl_3$ with $Me_4Si$ as internal standard. $^{13}C$ spectra were obtained at 25.2 MHz. Where elemental analyses are given, results were within ±0.4% of the theoretical values. Solvents were removed under reduced pressure on a rotary evaporator. Where $R_f$ values are given, a single spot was seen on development by phosphomolybdic acid/heat. The chromatograms were run on Woelm silica gel plates (1 × 3 in.) and with the same solvent systems used for the column purification except where indicated.

**α-2-Propynyl-2-furanmethanol (6).** A solution of propargyl bromide (145.5 g of 80% by weight solution in toluene, 0.976 mol) in 150 mL of ether was added dropwise to a mixture of 26 g (1.07 mol) of magnesium, which had been activated with 100 mg of $I_2$ and 340 mg of $HgCl_2$, in 450 mL of ether. The reaction mixture was stirred at room temperature for an additional 1 h and cooled to 0 °C. A solution of 45 g (0.78 mol) of freshly distilled furfuraldehyde in 400 mL of THF was added dropwise. After stirring at room temperature for 15 min, the reaction mixture was poured onto a cold, saturated $NH_4Cl$ solution with vigorous stirring. The layers were separated, and the aqueous phase was extracted with ether. The organic phases were combined, washed with saturated $NH_4Cl$ solution and saturated NaCl solution, dried ($Na_2SO_4$), filtered, and evaporated. Chromatography of the crude material on silica gel (15% EtOAc, 85% hexane) gave 101 g (95%) of **6** as a colorless oil. $^1H$ NMR: δ 2.03 (t, *J* = 2.5 Hz, C≡CH), 2.73 (dd, *J* = 6, 2.5 Hz, $CH_2$), 4.86 (td, *J* = 6, 5 Hz, CHOH), 6.33 (2 H, d, *J* = 1.5 Hz, =CH), 7.38 (1 H, t, *J* = 1.5 Hz, =CH).

Anal. ($C_8H_8O_2$) C, H.

**4-Hydroxy-5-(2-propynyl)-2-cyclopenten-1-one (7).** To a solution of 40.2 g (0.295 mol) of **6** in 800 mL of a 8:1 dioxane/water mixture was added 4 g (0.021 mol) of *p*-toluenesulfonic acid. The reaction mixture was heated at 83–85 °C for 36 h under argon, cooled, and diluted with 500 mL of EtOAc. The organic phase was washed once with $H_2O$ and twice each with 5% $NaHCO_3$ solution and saturated NaCl solution. The aqueous washes were combined and extracted with EtOAc. The combined organic phases were dried ($Na_2SO_4$), filtered, and evaporated. Chromatography of the crude residue on silica gel (25% EtOAc, 75% hexane) yielded 12.45 g (31%) of **7** as a brown oil ($R_f$ = 0.24 in 1:1 EtOAc/hexane). $^1H$ NMR: δ 2.00 (t, *J* = 2.5 Hz, C≡CH), 6.28 (dd, *J* = 6, 1 Hz, C-2), 7.63 (dd, *J* = 6, 2 Hz, C-3).

**4-Hydroxy-2-(2-propynyl)-2-cyclopenten-1-one (8).** A solution of 14.5 g (0.11 mol) of **7** in 50 mL of ether was added to a column packed with 282 g of grade III alumina (6% water by weight). The column was closed and allowed to stand at room temperature for 16 h. Elution of the column with ether and then EtOAc provided 7.3 g (50%) of **8** as a brown oil ($R_f$ 0.24 in 1:1 EtOAc/hexane). $^1H$ NMR: δ 2.15 (t, *J* = 3 Hz, C≡CH), 3.08 (dt, *J* = 3, 2 Hz, $CH_2$C≡CH), 4.97 (dt, *J* = 6, 2 Hz, C-4), 7.47 (q, *J* = 2 Hz, C-3).

**2-(2-Propynyl)-4-[(triethylsilyl)oxy]-2-cyclopenten-1-one (9).** A solution of 2.5 g (18.4 mmol) of **8** in 40 mL of DMF was treated successively with 2 g (30 mmol) of imidazole and 3 g (20 mmol) of triethylchlorosilane. After stirring for 30 min at room temperature, the reaction mixture was diluted with ether, washed with $H_2O$ four times, dried ($Na_2SO_4$), and evaporated, and the residue was chromatographed on silica gel (10% EtOAc, 90% hexane) to give 3.7 g (80%) of **9** as a colorless oil. $^1H$ NMR: δ 2.14 (t, C≡CH), 2.30 (1 H, dd, *J* = 19, 2 Hz, C-5), 2.82 (1 H, dd, *J* = 19, 5 Hz, C-5), 3.07 (dt, *J* = 3, 2 Hz, $CH_2$C≡CH), 4.92 (m, C-4), 7.34 (q, *J* = 2 Hz, C-3). Anal. ($C_{14}H_{22}O_2Si$) C, H.

**(1,1-Dimethylethyl)dimethyl[[3β-[4-methyl-4-[(trimethylsilyl)oxy]-1(*E*)-octenyl]-2-(2-propynyl)-4α-[(triethylsilyl)oxy]-1-cyclopenten-1-yl]oxy]silane (3).** A solution of 10 g (0.02 mol) of (*E*)-1-(tri-*n*-butylstannyl)-4-methyl-4-[(trimethylsilyl)oxy]-1-octene[13] in 25 mL of dry THF was cooled to −50 °C under argon and treated with 11.8 mL of a 1.7 M solution of *n*-BuLi in hexane (0.02 mol). The solution was stirred for 1 h at −50 °C, cooled to −60 °C, and treated with a solution of 2.62 g (0.02 mol) of copper 1-pentyne and 6.4 g (0.04 mol) of hexamethylphosphorous triamide in 75 mL of ether. After 10 min, a solution of 2.50 g (0.01 mol) of **9** in 20 mL of ether was added. The reaction mixture was stirred at −60 °C for 45 min and then treated successively with 25 mL of hexamethylphosphoric triamide and a solution of 3 g (0.02 mol) of *tert*-butyldimethylchlorosilane in 15 mL of ether. The temperature of the reaction mixture was allowed to rise to −20 °C and was maintained there for 1 h. The reaction mixture was poured into 0.5 N HCl and ether. After this mixture was shaken well, the organic layer was separated, washed with $H_2O$ twice, filtered, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on silica gel (1% EtOAc, 99% hexane) to give 4.4 g (76%) of **3** as a colorless, viscous oil. $^1H$ NMR: δ 0.1 (s, $Me_3Si$), 0.13 (s, $Me_2$-*t*-BuSi), 0.94 (s, $Me_2$-*t*-*Bu*Si), 1.16 (s, $CH_3$), 1.82 (t, *J* = 3 Hz, C≡CH), 3.07 (dd, *J* = 16, 3 Hz, $CH_2$C≡CH), 4.00 (dt, *J* = 7, 4 Hz, CHOSi), 5.15 (dd, *J* = 16, 8 Hz, olefinic H), 5.55 (dt, *J* = 16, 7 Hz, olefinic H).

Anal. ($C_{32}H_{62}O_3Si_3$) C, H.

**(±)-Methyl 9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-16-methyl-11α-[(triethylsilyl)oxy]-16-[(trimethylsilyl)oxy]-prosta-3(*E*),8,13(*E*)-trien-5-yn-1-oate (11).** To a solution of 1.15 g (2 mmol) of **3** in 16 mL of dry THF at −30 °C under argon was added 1.8 mL of a 1.66 M solution of *n*-BuLi in hexane (3 mmol). The solution was stirred at −20 to −30 °C for 1 h and treated with 272 mg (2 mmol) of solid, anhydrous $ZnCl_2$ (Alfa Products, ultrapure, dried over $P_2O_5$ at 60 °C in vacuo for 1 h just prior to use). The reaction mixture was stirred at 0 °C for 30 min, recooled to −10 °C, and treated successively with 750 mg (3.3 mmol) of **14** dissolved in 4 mL of THF and 100 mg of bis(dibenzylideneacetone)palladium.[16] The reaction mixture was stirred at −10 °C for 1 h and 0 °C for 1 h and poured into a mixture of ether and 0.5 N HCl. The organic layer was separated, washed twice with $H_2O$, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on silica gel (2% EtOAc, 98% hexane) to give 925 mg (70%) of **11** as a viscous oil ($R_f$ = 0.3). $^1H$ NMR: δ 3.08 (d, *J* = 7 Hz, C-2), 3.68 (s, $OCH_3$), 5.48 (d, *J* = 16 Hz, C-4), 6.03 (dt, *J* = 16, 7 Hz, C-3).

**Methyl 3-Butynoate (12).**[22] A solution of 21 g (0.3 mol) of 3-butyn-1-ol in 300 mL of acetone was added dropwise to a mechanically stirred solution of 60 g of chromium trioxide in 750 mL of 10 N $H_2SO_4$ at 0 °C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 1.5 h. The liquid was decanted into a mixture of EtOAc and $H_2O$. The aqueous layer was extracted five times with EtOAc. The extracts were combined, washed twice with saturated NaCl solution, dried ($Na_2SO_4$), and evaporated. The residue (22 g) was dissolved in 150 mL of MeOH, 20 mL of 2,2-dimethoxypropane, and 5 drops of concentrated HCl and the mixture allowed to stand at room temperature overnight. The solution was evaporated to near dryness, diluted with EtOAc, washed with 5% $NaHCO_3$ solution, dried ($Na_2SO_4$), and evaporated. The residue was distilled to give 16.5 g (56%) of **12** as a clear, colorless liquid, bp 30–32 °C (10–15 mm). $^1H$ NMR: δ 2.20 (t, C≡CH), 3.28 (d, C-2), 3.75 (s, $OCH_3$).

**Methyl 4-(Tri-*n*-butylstannyl)-3(*E*)-butenoate (13).** A mixture of 980 mg of **12** and 2.91 g of tri-*n*-butyltin hydride contained in a Pyrex round-bottomed flask was irradiated under argon with a General Electric sunlamp for 2 h at room temperature (a circulating water bath was required to control the temperature) and then at about 55 °C (heat generated by lamp) for 4 h. The resulting product was purified by chromatography (5% EtOAc, 95% hexane) on silica gel to give 1.5 g (39%) of **13** ($R_f$ = 0.4). $^1H$ NMR: δ 3.15 (m, C-2), 3.67 (s, $OCH_3$), 6.05 (m, CH=CH).

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**Methyl 4-Iodo-3(*E*)-butenoate (14).** A solution of 1.4 g (3.6 mmol) of **13** in 6 mL THF was cooled to −20 °C and treated dropwise with a solution of 810 mg of *N*-iodosuccinimide (NIS) dissolved in 6 mL of THF. The reaction mixture was allowed to warm to room temperature, diluted with ether/hexane (1:1), washed with a dilute solution of sodium sulfite and twice with $H_2O$, filtered, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on a low-pressure silica gel column, which had been deactivated by prolonged washing with 100% EtOAc and then equilibrated to the solvent system employed (5% EtOAc, 95% hexane). There was obtained 600 mg (74%) of pure **14** ($R_f$ = 0.25). $^1$H NMR: δ 3.16 (dd, $J$ = 7, 1 Hz, C-2), 3.70 (s, $OCH_3$), 6.20 (dt, $J$ = 15, 1 Hz, C-4), 6.60 (dt, $J$ = 15, 7 Hz, C-3).

Chromatography of **14** on fresh silica gel or silica gel incompletely deactivated with EtOAc produced, respectively, the allylic iodide **15**[23] ($R_f$ = 0.25) ($^1$H NMR: δ 3.74 (s, $OCH_3$), 3.92 (dd, $J$ = 8, 1 Hz, C-4), 5.91 (dt, $J$ = 16, 1 Hz, C-2), 7.02 (dt, $J$ = 16, 8 Hz, C-3)) or a mixture of **14** and **15**.

**(±)-Methyl 11α,16-Dihydroxy-16-methyl-9-oxoprosta-3(*E*),13(*E*)-dien-5-yn-1-oate (16).** A suspension of 925 mg of **11** in 15 mL of a 3:1:1 mixture of AcOH, THF, and $H_2O$ was stirred vigorously for about 1 h until homogeneous. The resulting solution was allowed to stand at room temperature for 24 h, diluted with ether, washed with $H_2O$ four times, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on silica gel (80% EtOAc, 20% hexane) to yield 370 mg (71%) of **16** as a viscous oil. $^1$H NMR: δ 3.09 (br d, $J$ = 7 Hz, C-2), 3.68 (s, $OCH_3$), 4.11 (q, $J$ = 9 Hz, C-11), 5.40 (dd, $J$ = 16, 7 Hz, C-13), 5.50 (br d, $J$ = 16 Hz, C-4), 5.77 (dt, $J$ = 15, 7 Hz, C-14), 6.07 (dt, $J$ = 16, 7 Hz, C-3).

$^{13}$C NMR: δ 132.8 (C-3), 113.7 (C-4), 86.7 and 80.4 (C-5,6), 71.9 (C-11), 134.4 (C-13), 130.4 (C-14).

Anal. ($C_{22}H_{32}O_5$) C, H.

**(±)-15-Deoxy-16-methyl-16-hydroxy-3(*E*),4-didehydroprostaglandin $E_2$ Methyl Ester (2a).** A solution of 20.7 mg of nickelous acetate in 15 mL of EtOH under $H_2$ was treated with 84.2 μL of a 1 M solution of $NaBH_4$ in EtOH, injected by syringe through a side-arm septum. The solution turned black. A solution of 126 mg (0.33 mmol) of **16** and 5.5 μL of ethylenediamine in 10 mL of EtOH was added, and the resulting solution was stirred under $H_2$ until theoretical amount of $H_2$ was consumed (40 min). The vessel was vented and the solution filtered and evaporated. The residue was dissolved in ether, washed with 0.5 N HCl and twice with $H_2O$, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on a Partisil ODS-3 reverse-phase column (65% MeOH, 35% $H_2O$) to give 56 mg (44%) of **2a** as a viscous oil. $^{13}$C NMR: δ 172.2 (C-1), 38.2 (C-2), 126.0, 127.8, 129.3, 129.9 (C-3-6), 25.5 (C-7), 54.1 (C-8), 214.5 (C-9), 46.3 (C-10), 72.1 (C-11), 54.8 (C-12), 133.5 (C-13), 130.4 (C-14), 45.0 (C-15), 72.6 (C-16), 26.3, 26.9 (C-16 methyl, 2 peaks due to mixture of diastereomers[4]), 42.4, 41.5 (C-17), 26.2 (C-18), 23.3 (C-19), 14.1 (C-20).

Anal. ($C_{22}H_{34}O_5$) C, H.

**Gastric Antisecretory Studies.** The prostaglandins were dissolved in absolute ethanol stock solution (1 mg/mL) and stored at −10 °C when not in use. Appropriate dilutions of the stock solution were carried out with an isosmotic phosphate buffer (pH 7.4) so that the final ethanol concentration did not exceed 20%.

Adult female beagles (6–12 kg) prepared with simple gastric fistulas (GF) were used to determine antisecretory $ED_{50}$ values after intragastric administration. The dogs were trained to stand quietly in Pavlov supports and were conscious during all studies. The animals were not used more than once per week. Experiments were initiated by fasting the dogs for 18 h. Following a 30-min basal secretion period, the PG's were administered directly into the stomach through a specially constructed dosing plug, and the cannula was closed for 30 min to allow sufficient contact with gastric mucosa. At the end of 30 min, gastric juice collections were resumed, and a 15 μg kg$^{-1}$ h$^{-1}$ infusion of histamine was begun. Collections were continued at 30-min intervals for 4 h.

All gastric samples were measured for total acidity by titration with 0.1 N sodium hydroxide solution to pH 7.0 (Radiometer, Copenhagen). Percent inhibition was calculated as a mean reduction for 4 h. $ED_{50}$ values (dose causing 50% inhibition of total acid output over 4 h) were calculated from percent inhibition of secretion curves. Relative antisecretory potencies and limits as well as statistical differences were calculated by using the bioassay program Parlin-7.[24] These values were used for calculation of activity ratios in Table I.

**Diarrheal Studies.** Adult Charles River male rats weighing 210–230 g were individually housed and fasted for 24 h prior to the test. The animals ($n$ = 6–12) were orally administered logarithmically graded doses of the prostaglandin. Immediately after administration, the animals were returned to their cages, and diarrhea, if any, was assessed on an all-or-none basis hourly up to 8 h after drug treatment. Hourly $ED_{50}$ values and approximately asymptotic 95% confidence limits were estimated from a logistic dose–response model, fitted by the method of maximum likelihood.[25] $ED_{50}$ values at 8 h were used to calculate the activity ratios in Table I.

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