a yellowish white solid (2.3 g). This was recrystallized from ethanol to yield white crystals (2.0 g): mp 174 °C.

Compounds **21-24** were prepared as given for **20**. During the preparation of compound **24**, the reaction mixture was stirred for 2 h at room temperature.

4-Phenyl-8-[[(β-chloroethoxy)carbonyl]amino]-2-methyl-1,2,3,4-tetrahydroisoquinoline (25). Method A. 8-Amino-4-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (3.5 g, 0.015 mol) was dissolved in anhydrous benzene (100 mL) and mixed with anhydrous pyridine (1.28 g, 0.016 mol), and then a solution of β-chloroethyl chloroformate (2.14 g, 0.015 mol) in anhydrous benzene (10 mL) was added dropwise at room temperature, with stirring and cooling. The reaction mixture was stirred at room temperature for 1 h. It was then poured into ice-water (50 mL), and the organic phase was separated and the aqueous phase extracted with benzene (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 then evaporated to dryness in vacuum to obtain a yellowish white substance (4.5 g). Two recrystallizations from ethanol gave white crystals (2.7 g, 52%): mp 154 °C.

8-[[(Ethylamino)acetyl]amino]-4-phenyl-1,2,3,4-tetrahydroisoquinoline Maleate (26). A mixture of 4-phenyl-8-[(chloroacetyl)amino]-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (11) (5.3 g, 0.015 mol) and ethylamine (15 mL, 10.4 g, 0.23 mol) in ethanol (50 mL) was heated in a bomb tube at 60 °C for 5 h. The reaction mixture was evaporated to dryness, and the residual yellow oil (7.1 g) was rubbed with water (50 mL), made alkaline with 30% NaOH solution (30 mL) with stirring and cooling, then extracted with ether (10 × 100 mL). The ethereal solution was dried over anhydrous Na_2SO_4 and evaporated to dryness, and the remaining oil was rubbed with petroleum ether. The product was a yellowish white powder (4.3 g, 0.0133 mol). This crude base was dissolved in ethanol (30 mL); a solution of maleic acid (1.6 g, 0.0138 mol) in alcohol (15 mL) was added, and the separated substance was collected after cooling to obtain a yellowish white powder (5.2 g): mp 169 °C. Recrystallization from ethanol (50 mL) gave a white powderlike substance (4.7 g, 71.2%): mp 170 °C.

Compounds **27-38** were prepared similarly, starting from the corresponding chloroacyl derivatives and using the appropriate amine. In cases involving reagents other than ethylamine, the reaction mixture was refluxed. In the case of compounds **32-34**, the crude base was purified via the dimaleate salt.

Acknowledgment. We gratefully acknowledge the financial support of this work by the EGIS Pharmaceutical Factory, Budapest. Thanks are due to Zsófia M. Koltay for her participation in the pharmacological investigations, to Mária Horváth, Erzsébet Tóth, Éva Meskó, and Mariann Bán for technical assistance, and to Gizella Kalász for the microanalyses.

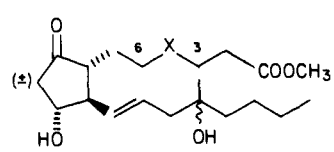
Synthesis and Gastric Antisecretory Properties of α Chain Diene Derivatives of Misoprostol[1]

Paul W. Collins,* Alan F. Gasiecki, Peter H. Jones, Raymond F. Bauer, Gary W. Gullikson, Emmett M. Woods, and Robert G. Bianchi

Departments of Medicinal Chemistry and Biological Research, G. D. Searle & Company, Skokie, Illinois 60077.
Received August 19, 1985

The synthesis and gastric antisecretory activity in dogs of seven α chain diene derivatives of misoprostol are described. The key intermediates in the preparation of these compounds were C-9 *tert*-butyldimethylsilyl enol ethers that were obtained by in situ silylation of cuprate enolates derived from α chain unsaturated cyclopentenones. Selenylation chemistry on these intermediates provided the C_2–C_3 trans dienes that, where possible, were also deconjugated to produce the corresponding C_3–C_4 dienes. The most interesting structure in this series is the C_5–C_6 cis, C_3–C_4 cis/trans (1:1) diene that could not be readily separated chromatographically into its individual geometric isomers. The gastric antisecretory activity of the mixture of isomers was approximately 3 times greater than that of misoprostol by intragastric administration. The separation of undesired diarrheogenic effects from antisecretory activity was significantly improved relative to misoprostol.

Insertion of a cis double bond between carbons 4 and 5 of misoprostol (**1a**; 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 methyl ester)[2] imparts favorable changes in the pharmacological profile of the resulting compound **1b**.[3] This unsaturated derivative was more potent as a gastric antisecretory agent, longer acting, and more selective with respect to diarrheogenic activity than the parent compound **1a**.



1a, X = CH_2CH_2
b, X = CH=CH (cis)

On the basis of these findings, we decided to examine the effects that two double bonds in the α chain might have on the intensity and duration of the gastric antisecretory activity of **1a**. Of particular interest was the $\Delta^{3,5}$ conjugated diene system because these olefinic bonds flank carbons 4 and 5 and thus mimic the electronic environment at this position in **1b**. In addition, a conjugated diene moiety at this position has been reported to dramatically improve antinidatory effects in a series of $PGF_{2\alpha}$ compounds.[4]

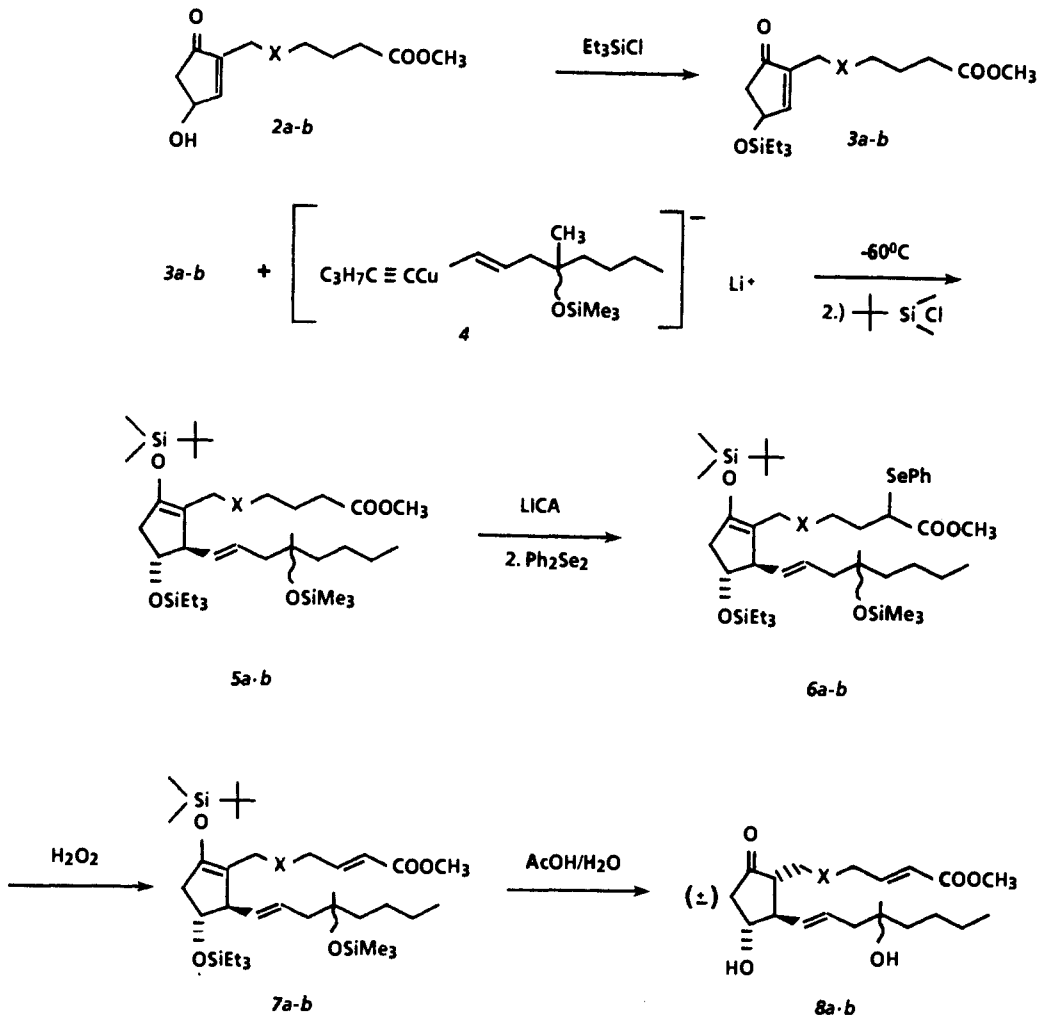
Chemistry

The synthesis of the C_2–C_3 trans,C_5–C_6 dienes is outlined in Scheme I. The C_5–C_6 cis hydroxy cyclopentenone **2a**[2] was protected as its triethylsilyl ether **3a** by treatment with triethylchlorosilane in dimethylformamide and imidazole at room temperature[5] and then subjected to the well-documented[3] conjugate addition reaction with the cuprate species **4**[3] at −60 °C. Instead of the usual acidic quenching, the enolate was converted in situ to the silyl enol ether **5a** by treatment of the reaction mixture with excess *tert*-bu-

(1) This work was presented at the 19th National Medicinal Chemistry Symposium, June 17-21, 1984, Tucson, AZ.
(2) Collins, P. W.; Dajani, E.Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152.
(3) Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786.
(4) Hayashi, M.; Arai, Y.; Wakatsuka, H.; Kawamura, M.; Konishi, Y.; Tsuda, T.; Matsumoto, K. *J. Med. Chem.* **1980**, *23*, 525.
(5) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

0022-2623/86/1829-1195$01.50/0

Scheme I



tyldimethylchlorosilane and hexamethylphosphoric triamide (HMPT) at −20 °C for about 1 h. Enol ether formation did not occur at temperatures below −20 °C or in the absence of HMPT. The enol ether so formed was sufficiently stable to allow an acidic workup and chromatographic purification of **5a** on silica gel. The C_2–C_3 trans double bond was introduced by standard selenium chemistry.[6] Thus, **5a** was treated at −60 °C with lithium isopropylcyclohexylamide (LICA), and the resulting carbanion was quenched with diphenyl diselenide to give **6a**. Interestingly, the use of less bulky silyl enol ethers of **5a** such as trimethyl- or triethylsilyl gave rise to several side products and poor yields of **6a** in this reaction, presumably because of nonselective anion formation. Oxidative elimination of the phenyl selenide was carried out with hydrogen peroxide in a water–methylene chloride mixture in the presence of pyridine to provide the C_2–C_3 trans compound **7a**. Hydrolysis of the protecting groups of **7a** in a 3:1:1 mixture of acetic acid, tetrahydrofuran, and water[5] yielded the C_2–C_3 trans–C_5–C_6 cis diene **8a**. The stability of the *tert*-butyldimethylsilyl enol ether was further demonstrated in the hydrolytic procedure. Although the silyl groups at C-11 and C-16 were cleaved in about 30 min at room temperature, complete removal of the silyl enol was observed only after overnight exposure.

(6) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 1637.

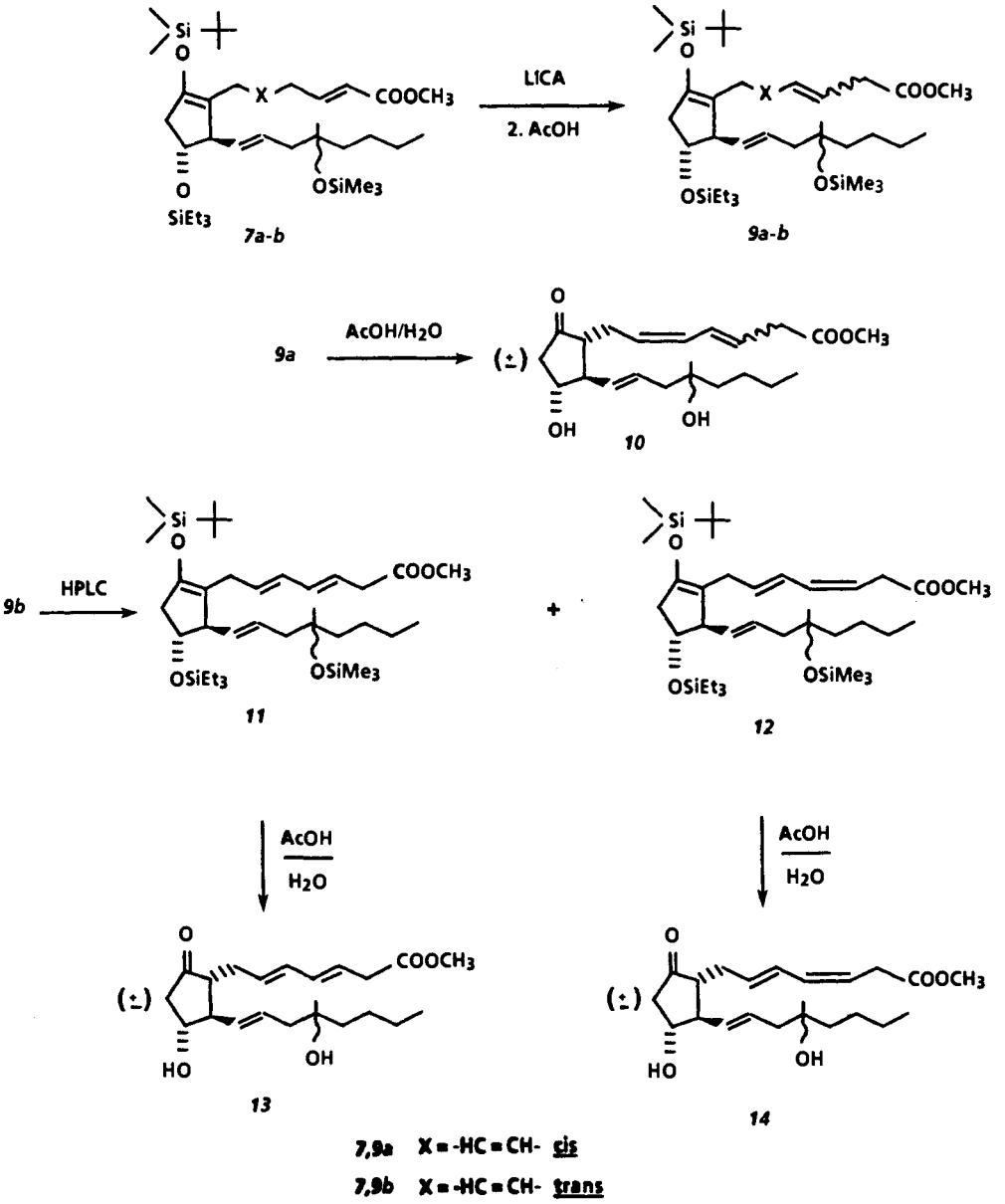
Another point of interest is that hydrolysis of the enol produced very little (less than 10%) of the corresponding 8-epimer. This epimer was separable from the main product by chromatography. The C_2–C_3 trans–C_5–C_6 trans diene, **8b**, was obtained by analogous chemistry starting with the C_5–C_6 trans cyclopentenone **2b**.

The synthesis of the C_3–C_4,C_5–C_6 dienes is shown in Scheme II. These conjugated dienes were obtained by deconjugation of the C_2–C_3 trans double bond of **7a,b** with LICA at −60 °C followed by a proton quench with acetic acid. In the case of **7a** this procedure produced an approximate 1:1 mixture of C_3–C_4 cis–C_5–C_6 cis and C_3–C_4 trans–C_5–C_6 cis isomers of **9a**. Hydrolysis of protecting groups and chromatographic purification yielded **10**. Efforts to chromatographically separate the diene isomers at either the protected stage (**9a**) or deprotected stage (**10**) were not successful. Thus, pharmacological studies were conducted on the mixture **10**.

Deconjugation of **7b** again yielded a mixture of cis and trans isomers at C_3–C_4. In this case the protected intermediates **11** and **12** were successfully separated by HPLC. Hydrolysis of protecting groups and chromatographic purification provided the individual isomeric dienes **13** and **14**.

The assignments of double-bond geometry in the four C_3–C_4,C_5–C_6 dienes were based on ^{13}C NMR analysis. In disubstituted olefins such as $CH{=}CHCH_2$, the ^{13}C NMR chemical shift of the allylic carbon of the cis isomer gen-

Scheme II



erally is about 5 ppm upfield from the corresponding signal of the trans isomer.[7] Thus, the relative chemical shifts of the C-2 carbons were used to assign the 3-ene geometry, and the chemical shifts of the C-7 carbons, to assign the 5-ene geometry. The ratio of isomers in **9a** and **10** was estimated from relative heights of signals due to carbon-2 in the ^{13}C NMR spectra and carbon-2 proton signals (partially overlapping doublets) in the ^{1}H NMR spectra.

The preparation of the C_5–C_6 *trans* cyclopentenone **2b** is outlined in Scheme III. Reduction of the acetylene **15**[8] with lithium metal in liquid ammonia followed by acid hydrolysis of protecting groups provided the trans keto alcohol **16**. Jones oxidation at 0 °C gave the acid **17**, which was purified by an acid–base extractive procedure. Condensation of **17** with dimethyl oxalate in the presence of excess potassium *tert*-butoxide in refluxing *tert*-butyl alcohol followed by treatment with refluxing 1 N HCl afforded the triketone **18**. The keto ester **19** was obtained by esterification of **18** in methanol, acetone dimethyl acetal, and concentrated HCl followed by treatment with water that selectively hydrolyzed the methyl enols. Reduction of **19** with sodium borohydride in ethanol and water at 0 °C cleanly yielded the hydroxy dione **20**. Treatment of **20** with 2,4,6-triisopropylbenzenesulfonyl chloride (TIBS-Cl) provided exclusively the desired enol ether **21**.[9] In previous work[2,3] we had esterified related hydroxy diones with methanol that gave a mixture of isomeric enol ethers. The present procedure is a distinct improvement over the older process in terms of yield and ease of operation. Reduction of **21** with sodium borohydride followed by acid-catalyzed dehydration of the resulting intermediate produced **2b** in good yield.

The preparation of the C_2–C_3,C_4–C_5 dienes is presented in Scheme IV. Starting with the C_4–C_5 cis cyclopentenone **22**[3] and carrying it through the usual sequence produced the protected diene intermediate **23**. Hydrolysis of **23** yielded the C_2–C_3 trans–C_4–C_5 cis isomer **24**. Alternatively, irradiation of **23** with a sunlamp for several hours com-

(7) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: 1972; p 80.
(8) Sih, C. J.; Heather, J. B.; Sood, R.; Price, P.; Peruzzotti, G.; Hsu Lee, L. F.; Lee, S. S. *J. Am. Chem. Soc.* **1975**, *97*, 865.
(9) Paul Reynolds and colleagues at the Searle Research Center in High Wycombe, England, discovered the selectivity of this reagent and worked out the experimental details for the general sequence.

Scheme III

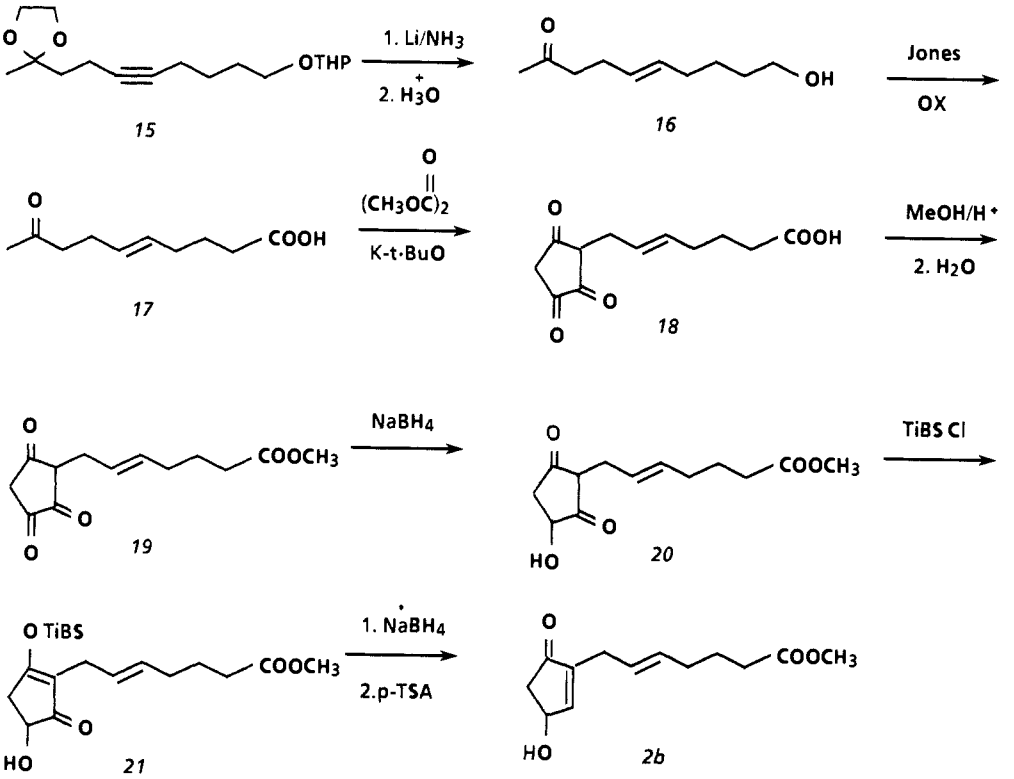
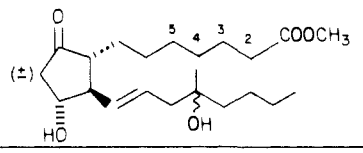


Table I. Gastric Antisecretory Activity of α Chain Dienes in Dogs



compd	struct	% inhibn of TAO at 1 μg/kg iv[a]
1a	satd	79
1b	C_4–C_5 cis	92*
8a	C_2–C_3 trans–C_5–C_6 cis	0*
8b	C_2–C_3 trans–C_5–C_6 trans	68
10	C_3–C_4 cis/trans–C_5–C_6 cis	83
13	C_3–C_4 trans–C_5–C_6 trans	21*
14	C_3–C_4 cis–C_5–C_6 trans	96
24	C_2–C_3 trans–C_4–C_5 cis	41
25	C_2–C_3 trans–C_4–C_5 trans	53

[a] Determined in histamine-stimulated Heidenhain pouch dogs. $n = 2$ for each compound except for those indicated by an asterisk (*), for which $n = 1$. Values expressed for 1 μg/kg doses are part of dose-response curves generated from three to five points for each compound. In all cases the percentage inhibition shown reflects typical sigmoidal log dose-response relationships. TAO = total acid output.

pletely isomerized the C_4–C_5 cis double bond to the trans configuration, a reaction that can be followed by thin-layer chromatography. Hydrolysis of protecting groups and chromatographic purification gave the trans–trans isomer **25**.

Results and Discussion

The intravenous gastric antisecretory activities of these compounds were determined in histamine-stimulated Heidenhain Pouch (HP) dogs at a test dose of 1.0 μg/kg (Table I). Comparative data are given for misoprostol (**1a**) and the C_4–C_5 cis analogue (**1b**). In the current work the most interesting structure is the conjugated diene **10**, which is approximately a 1:1 mixture of the cis and trans isomers

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

	ED_{50}, μg/kg, ig			act. ratio: ED_{50}(diarrhea)/ ED_{50} (antisec)
compd	gastric antisec effects in dogs[a]	rel antisec pot. and 95% CL	diarrheal effects in rats[c]	
1b	0.05[b]	1.0	62	1240
10	0.08	0.31–1.27	570	7125
1a	0.28[b]	0.08–0.33	366	1307

[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 twelve dogs were used at each dose. ED_{50} values for **1b** and **10** are significantly different from **1a** ($p < 0.05$) but not from each other. [b] These values differ from those reported in ref 3 because of changes in assay protocol. [c] 95% confidence limits (CL) for diarrheal ED_{50}'s are 43–90 (**1b**), 429–960 (**10**), and 264–588 **1a**.

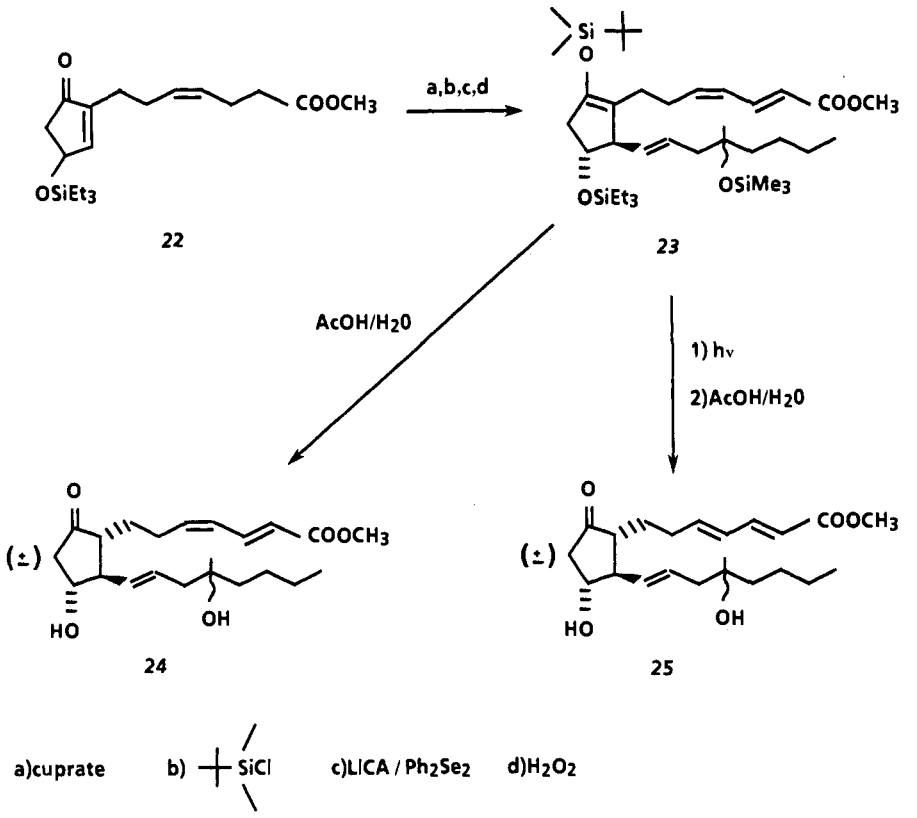
at C_3–C_4. Compound **10** and the two standard compounds **1a** and **1b** have comparable activity at the test dose in this assay. Compound **14**, the C_3–C_4 cis–C_5–C_6 trans conjugated derivative, also displayed good activity at the screening dose, but its activity diminished appreciably at doses below 1 μg/kg.[10] A conjugated trans–trans system at C_3–C_6 (compound **13**) reduced activity significantly.

Insertion of a C_2–C_3 trans double bond appears, in general, to reduce gastric antisecretory activity as observed in compounds **8a** and **24**. The C_5–C_6 cis analogue of **1a** is as active as **1a**,[2] but its C_2–C_3 trans analogue, **8a**, was considerably less active on the basis of the available data. Likewise **24**, which is the C_2–C_3 trans analogue of **1b**, was less active than **1b**. In contrast was the reasonably good activity seen with compounds **8b** and **25**.

Because of the high intravenous potency of **10**, additional studies were performed to compare its intragastric

(10) The percent inhibition of total acid output by compound 14 at a dose of 0.3 μg/kg was 46% ($n = 2$). No inhibition was seen at a dose of 0.1 μg/kg ($n = 2$).

Scheme IV



antisecretory activity with that of the standard compounds **1a** and **1b** in gastric fistula dogs (GF) (Table II). The intragastric antisecretory potency of **10** was found to be approximately equal to that of the 4,5 cis compound (**1b**) and about 3 times that of misoprostol (**1a**). This high level of oral activity suggests that, similar to a 4,5 cis double bond,[11] the conjugated diene system at carbons 3–6 may be protecting the α chain from metabolic degradation. Metabolic and duration studies are needed to confirm this possibility.

Diarrhea is a major side effect of natural and synthetic prostaglandins in animals[12] and man.[13-15] Previous studies in rats have established that the 16-hydroxy compounds **1a** and **1b** have a much greater separation of gastric antisecretory activity from diarrheogenic activity than standard 15-hydroxyprostaglandins.[3] To assess the separation of these activities in **10** relative to that of **1a** and **1b**, diarrheogenic activity in rats was determined (Table II).

The diarrheogenic activity of **10** was quite low, being somewhat less than in **1a** and about 9 times less than in **1b**. Calculation of activity ratios of diarrheal to antisecretory ED_{50} values clearly demonstrates that **10** is considerably more selective than either **1a** or **1b**.

This very desirable pharmacological profile of **10** prompted us to investigate more thoroughly the chromatographic separation of its geometric isomers. Although numerous systems and parameters were investigated, an efficient and practical method was not found. However, one HPLC system (silver nitrate treated Partisil SCX) did provide small amounts (3–4 mg) of the individual geometric isomers. Preliminary intravenous antisecretory studies in HP dogs indicated that the C_3–C_4 trans–C_5–C_6 cis isomer is responsible for most of the activity of **10**. In order to confirm this finding and to obtain more complete pharmacological data for both isomers, efforts have been undertaken to stereospecifically synthesize each isomer using novel aproaches not involving selenium chemistry.

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.

(±)-Methyl 7-[3-[(Triethylsilyl)oxy]-5-oxo-1-cyclopenten-1-yl]-5(*Z*)-heptenoate (3a). A solution of 238 mg (1 mmol) of **2a**[2] in 3 mL of DMF was treated successively with 100 mg of imidazole and 180 mg (1.2 mmol) of triethylchlorosilane. The solution was stirred for 1 h at room temperature, diluted with ether, washed with H_2O four times, dried (Na_2SO_4), and evaporated to give **3a** as an oil, which was purified by chromatography (silica gel, 10% EtOAc in hexane).

(±)-Methyl 9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-16-methyl-11α-[(triethylsilyl)oxy]-16-[(trimethylsilyl)oxy]-prosta-5(*Z*),8,13(*E*)-trien-1-oate (5a). A solution of 1 g (2 mmol) of (*E*)-1-(tri-*n*-butylstannyl)-4-methyl-4[(trimethylsilyl)oxy]-1-octene[3] in 4 mL of dry THF was cooled to −50 °C under argon and treated with 0.87 mL of a 2.3 M solution of *n*-BuLi in hexane. The solution was stirred for 1 h at −50 °C, cooled to −60 °C, and treated with an ether solution (4 mL) of 260 mg of copper 1-pentyne and 640 mg of hexamethylphosphorus triamide. The reaction mixture was stirred for 10 min at −60 °C, and then an ether solution (2 mL) of 350 mg (1 mmol) of **3a** was added dropwise. The reaction mixture was stirred at −60 °C for 1 h and then treated successively with 4 mL of hexamethylphosphoric triamide and 300 mg (2 mmol) of *tert*-butyldimethylchlorosilane dissolved in 2 mL of ether. The temperature of the reaction mixture was allowed to rise to −20 °C and was maintained there

(11) Green, K.; Samuelsson, B.; Magerlein, B. J. *Eur. J. Biochem.* **1976**, *62*, 527.
(12) Dajani, E. Z.; Roge E. A. W.; Bertermann, R. E. *Eur. J. Pharmacol.* **1975**, *34*, 105.
(13) Horton, E. W.; Main, I. H. M.; Thompson, C. J.; Wright, P. M. *Gut* **1968**, *9*, 655.
(14) Misiewicz, J. J.; Waller, S. L.; Kiley, N.; Horton, E. W. *Lancet* **1968**, *1*, 648.
(15) Karim, S. M. M.; Amy, J. J. *Prostaglandins* **1974**, *7*, 293.

for 1 h. The reaction mixture was poured in a mixture of 0.5 N HCl and ether. After this mixture was shaken well, the organic layer was separated, washed with H_2O twice, and filtered, and the filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (2% EtOAc, 98% hexane) to give 410 mg (60%) of **5a** as a colorless viscous oil. ^1H NMR: δ 0.1 (s, Me_3Si), 0.13 (s, Me_2-*t*-BuSi), 0.93 (s, Me_2 *t*-*Bu*Si), 1.14 (s, C-16), 3.64 (s, *Me* ester), 3.95 (m, C-11).

(±)-Methyl 9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-16-methyl-2-(phenylseleno)-11α-[(triethylsilyl)oxy]-16-[(trimethylsilyl)oxy]prosta-5(*Z*),8,13(*E*)-trien-1-oate (6a). A solution of 156 mg (1.1 mmol) of *N*-isopropylcyclohexylamine in 3 mL of dry THF was cooled to −20 °C under argon and treated with 0.59 mL of a 1.7 M solution of *n*-BuLi. After stirring for about 1 h at −20 °C, the solution was cooled to −60 °C and treated dropwise with a solution of 340 mg (0.5 mmol) of **5a** in 5 mL of THF. After the addition was complete, a solution of 175 mg of diphenyl diselenide in 3 mL of THF was added dropwise. The reaction mixture was diluted with ether, washed twice with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (2% EtOAc, 98% hexane) to give 375 mg (90%) of **6a** as a viscous oil. ^1H NMR: δ 3.59 (s, Me ester), 3.95 (m, C-11), 5.27 (m, C-5,6), 7.25 and 7.52 (m, PhSe).

(±)-Methyl 9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-16-methyl-11α-[(triethylsilyl)oxy]-16-[(trimethylsilyl)oxy]prosta-2(*E*),5(*Z*),8,13(*E*)-tetraen-1-oate (7a). A solution of 200 mg (0.24 mmol) of **6a** in 10 mL of methylene chloride containing 100 mg of pyridine was treated with a solution of 1 g of 30% H_2O_2 in 1 mL of H_2O, and this two-phased system was stirred vigorously for about 4 h at room temperature. The mixture was diluted with ether, and the organic layer was separated, washed with 1 N HCl, twice with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (2% EtOAc, 98% hexane) to provide 65 mg (40%) of **7a** as a viscous oil.

(±)-15-Deoxy-16-methyl-16-hydroxy-2(*E*)-didehydroprostaglandin E_2 Methyl Ester (8a). Approximately 65 mg of **7a** was dissolved with stirring in about 2 mL of a 3:1:1 mixture of AcOH–THF–H_2O and allowed to stand at room temperature for 24 h. The solution was diluted with ether, washed four times with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (80% EtOAc, 20% hexane) to give 22 mg (60%) of **8a** as a viscous oil. ^1H NMR: δ 1.18 (s, 16-CH_3), 3.73 (s, OCH_3), 4.07 (q, C-11), 5.5 (m, C-5,6), 5.81 (d, C-2, $J_{2,3}$ = 16 Hz). Anal. ($C_{22}H_{34}O_5$) C, H.

(±)-15-Deoxy-16-methyl-16-hydroxy-3(*E*/*Z*)-didehydroprostaglandin E_2 Methyl Ester (10). A solution of 25 mg (0.18 mmol) of *N*-isopropylcyclohexylamine in 1 mL of dry THF was cooled to −20 °C under argon and treated with 0.1 mL of a 1.7 M solution of *n*-BuLi. After stirring for about 1 h at −20 °C, the solution was cooled to −60 °C and treated with 25 mg of hexamethylphosphoric triamide. A solution of 55 mg (0.08 mmol) of **7a** in 1 mL of dry THF was added dropwise. Approximately 30 min after the addition was complete, the reaction mixture was quenched by addition of acetic acid (20 mg) in THF. The reaction mixture was diluted with ether, washed once with 1 N HCl and twice with H_2O, dried (Na_2SO_4), and evaporated to give **9a**. The residue was dissolved with stirring in about 2 mL of a 3:1:1 mixture of AcOH–THF–H_2O and allowed to stand at room temperature for 24 h. The solution was diluted with ether, washed four times with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (80% EtOAc, 20% hexane) to give 17 mg (55%) of **10** as a viscous oil. ^{13}C NMR (25.2 MHz): (3*E* isomer) δ 38.2 (C-2), 126.0, 127.8, 129.3, and 129.9 ($C_{3\text{-}6}$), 130.4 (C_{14}), 133.5 (C_{13}); (3*Z* isomer) δ 33.0 (C-2), 123.1, 125.1, 126.4, and 130.2 ($C_{3\text{-}6}$), 130.4 (C_{14}), 133.5 (C_{13}). ^1H NMR: δ 3.16, 3.24 (partially overlapping d, C-2). Anal. ($C_{22}H_{34}O_5$) C, H.

10-Hydroxy-5(*E*)-decen-2-one (16). Lithium metal (3.15 g, 0.454 mol) was dissolved in 500 mL of anhydrous ammonia in a flask fitted with a dry ice condenser. To this stirred solution was added dropwise a mixture of 45 g (0.15 mol) of 15[8] and 15 mL of *t*-BuOH. The reaction mixture was stirred for 2 h at refluxing temperature and then carefully quenched by the portionwise addition of solid ammonium chloride. The condenser was removed, and 200 mL of ether was added dropwise, followed by 100 mL of water. This mixture was diluted with more ether, washed twice with 1 N HCl and then twice with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in 125 mL of 1 N HCl, 3 mL of THF, and 50 mL of MeOH. This solution was allowed to stand at room temperature for about 24 h. The reaction mixture was neutralized by portionwise addition of solid potassium carbonate, evaporated to about half its volume, diluted with water, and extracted with ether twice and then twice with EtOAc. The extracts were combined, dried (Na_2SO_4), and evaporated to give 29 g of crude **16**, which was used without characterization or purification in the next step.

9-Oxo-5(*E*)-decenoic Acid (17). A solution of 29 g of crude **16** in 300 mL of acetone was cooled to 0 °C and treated dropwise with stirring with 135 mL of 2.67 M Jones reagent (chromic acid in aqueous sulfuric acid). After the addition was complete, the acetone solution was decanted from the solid chromium salts, which were washed with additional acetone. The acetone solutions were combined, evaporated to about half of their volume, and poured into a mixture of ether and water. The organic layer was separated, washed once with water, and extracted three times with 5% K_2CO_3 solution. The alkaline extracts were combined, extracted once with ether, acidified with 2 N HCl, and extracted twice with ether and twice with EtOAc. The extracts were combined, dried (Na_2SO_4), and evaporated to give 19.8 g (75%) (from **15**) of **17** as a viscous oil. ^{13}C NMR: δ 31.8 and 26.8 (carbons 4 and 7, respectively). Trans stereochemistry was assigned on the basis of the chemical shifts of the allylic carbons.[7] ^1H NMR: δ 2.17 (s, C_{10}). Anal. ($C_{10}H_{16}O_3$) C, H.

7-(2,3,5-Trioxocyclopentyl)-5(*E*)-heptanoic Acid (18). To a gently refluxing solution of 70.7 g (0.63 mol) of potassium *tert*-butoxide in 500 mL of dry *tert*-butyl alcohol was added dropwise a solution of dimethyl oxalate (37.2 g, 0.315 mol) and 19.3 g (0.11 mol) of **17**. The reaction mixture was refluxed for 2 h after the addition was complete, cooled to room temperature, and filtered. The filter cake was added to 700 mL of 1 N HCl, and the resulting solution was refluxed for 3 h, cooled, and extracted with EtOAc three times. The extracts were combined, washed twice with saturated NaCl solution, dried (Na_2SO_4), and evaporated. The dark oily residue (35 g) was used without characterization in the next step.

Methyl 7-(2,3,5-Trioxocyclopentyl)-5(*E*)-heptanoate (19). The residue (35 g) from the previous step was dissolved in 380 mL of methanol, 90 mL of acetone dimethyl acetal, and 1.5 mL of concentrated HCl and the resultant mixture allowed to stand at room temperature for 48 h. Water (400 mL) was added, and the reaction mixture was allowed to stand at room temperature for 2 h. The solution was evaporated to one-third of its volume under reduced pressure, diluted with EtOAc, and extracted several times with 5% K_2CO_3 solution. The basic extracts were combined, acidified carefully with 1 N HCl, and extracted three to four times with EtOAc. The extracts were combined and evaporated to give 20 g of dark red oil that was chromatographed on acidic silica gel (Biosil, 50% EtOAc, 50% hexane) to give 19.3 g (70% from **17**) of **19** as a yellow oil. ^1H NMR: δ 3.67 (s, OCH_3), 5.5 (m, olefinic protons). Anal. ($C_{13}H_{16}O_5$) C, H.

(±)-Methyl 7-(3-Hydroxy-2,5-dioxocyclopentyl)-5(*E*)-heptenoate (20). To a solution of 8.6 g (34.1 mmol) of **19** in a mixture of 135 mL of EtOH and 135 mL of H_2O at 0 °C was added dropwise a solution of 1.29 g of $NaBH_4$ in 35 mL of H_2O. After the addition was complete, the reaction mixture was evaporated under reduced pressure to about one-third of its volume, diluted with EtOAc, and acidified with 1 N HCl. The aqueous layer was separated and extracted twice with EtOAc. These extracts were combined with the original organic layer, washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under reduced pressure to give 7.1 g (83%) of viscous oil, which was used directly in the next step.

(±)-Methyl 7-[4-Hydroxy-2-[(2,4,6-triisopropylphenyl)sulfonyloxy]-5-oxo-1-cyclopent-1-yl]-5(*E*)-heptenoate (21). A stirred solution of 7.1 g (2.8 mmol) of **20** and 9.4 g of Et_3N in 40 mL of THF was cooled to −20 °C and treated dropwise with a solution of 9.36 g (31 mmol) of triisopropylbenzenesulfonyl chloride (TiBSCl) in 35 mL THF. The reaction mixture was allowed to warm to room temperature, after which it was filtered and evaporated under reduced pressure to give 18 g of **21**, which was used in the next step without purification.

(±)-Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)-5(*E*)-heptenoate (2b). A solution of 18 g of **21** in 125 mL of

MeOH was treated portionwise with 1.2 g of $NaBH_4$ over a 30-min period. The reaction mixture was poured into a mixture of EtOAc and 1 N HCl, and the organic layer separated. The aqueous layer was extracted twice with EtOAc, and the extracts were combined with the original organic layer. After it was washed with saturated NaCl solution, the organic solution was dried (Na_2SO_4), treated with an ether solution of 50 mg of *p*-toluenesulfonic acid, evaporated to near dryness, and allowed to stand 2–3 h at room temperature. The material was dissolved in EtOAc, washed with 5% K_2CO_3 solution, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on silica gel (40% EtOAc, 60% hexane) to give 3.3 g (50%) of **2b** as a viscous oil. ^1H NMR: δ 3.65 (s, OCH_3), 4.82 (m, C-3), 5.46 (m, olefinic protons at carbons 5 and 6), 7.15 (d, C-2). Anal. ($C_{13}H_{18}O_4$) C, H.

(±)-15-Deoxy-16-methyl-16-hydroxy-2(*E*),5(*E*)-tetradehydroprostaglandin E_1 Methyl Ester (8b). Compound **8b** was prepared from **2b** by the same procedure described for **8a** above. ^{13}C NMR: δ 121.5 (C_2), 147.6 (C_3), 35.0 (C-4), 128.4 and 129.6 (C_5 and C_6), 133.3 (C_{13}), 130.0 (C_{14}). Anal. ($C_{22}H_{34}O_5$) C, H.

(±)-15-Deoxy-16-methyl-16-hydroxy-3(*E*),5(*E*)-tetradehydroprostaglandin E_1 Methyl Ester (13) and (±)-15-Deoxy-16-methyl-16-hydroxy-3(*Z*),5(*E*)-tetradehydroprostaglandin E_1 Methyl Ester (14). Employment of the deconjugation reaction described above for **9a** produced from **9b** a mixture (approximately 1:1) of 11 and 12, which were separated by HPLC (Whatman Partisil 10; mobile phase 0.6% THF–99.4% 2,2,4-trimethylpentane). Hydrolysis and purification as described for **10** were carried out on 11 and 12 to give 13 and 14.

13: ^{13}C NMR δ 37.8 (C_2), 133.7, 132.5, 130.2, 123.8, (C_{3-6}), 30.3 (C_7), 133.3 (C_{13}), 130.2 (C_{14}). Anal. ($C_{22}H_{34}O_5$) C, H.

14: ^{13}C NMR δ 33.2 (C_2) 132.5, 131.3, 127.6, 120.9 (C_{3-6}), 30.5 (C_7). Anal. ($C_{22}H_{34}O_5$) C, H.

(±)-Methyl 9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-16-methyl-11α-[(triethylsilyl)oxy]-16-[(trimethylsilyl)oxy]-prosta-2(*E*),4(*Z*),8,13(*E*)-tetraen-1-oate (23). Substitution of **22**[3] into the reaction sequence described for the preparation of **7a** from **3a** above produced **23** as a viscous oil in 40% overall yield.

(±)-15-Deoxy-16-methyl-16-hydroxy-2(*E*),4(*Z*)-tetradehydroprostaglandin E_1 Methyl Ester (24). Hydrolysis of **23** in a 3:1:1 mixture of AcOH–THF–H_2O for 24 h at room temperature provided, after workup and chromatogrpahic purification (silica gel 60% EtOAc in hexane), **24** as a viscous oil in 60% yield. ^{13}C NMR: δ 121.3 (C_2) 140.8 (C_3), 127.3 (C_4), 139.8 (C_5; could be reversed with C_3), 25.8 (C_6). ^1H NMR: δ 1.20 (s, 16-CH_3), 3.80 (s, OCH_3), 4.11 (q, C_{11}), 5.90 (d, J = 15.5 Hz, C_2). Anal. ($C_{22}H_{34}O_5$) C, H.

(±)-15-Deoxy-16-methyl-16-hydroxy-2(*E*),4(*E*)-tetradehydroprostaglandin E_1 Methyl Ester (25). A solution of 200 mg of **23** in 5 mL of ether was placed in a Pyrex round-bottomed flask and irradiated under argon with a G.E. sunlamp for 3 h at room temperature. A thin-layer chromatogram was taken (silica gel, 10% EtOAc in hexane) to ensure complete isomerization. The solution was evaporated to dryness, and the residue was hydrolyzed (3:1:1 AcOH–H_2O–THF, 24 h at room temperature) and purified by chromatography (silica gel, 60% EtOAc in hexane) to give 30 mg (30%) of **25** as a viscous oil. ^{13}C NMR: δ 119.4 (C_2), 145.1 (C_3), 129.2 (C_4), 143.5 (C_5; could be reversed with C_3), 30.3 (C_6). Anal. ($C_{22}H_{34}O_5$) C, H.

Gastric Antisecretory Studies. Adult female mongrel dogs (15–18 kg) surgically prepared with Heidenhain pouches (HP) and adult female Beagles (6–12 kg) prepared with simple gastric fistulas (GF) were used in these experiments. 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.

All 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 isoosmotic phosphate buffer (pH 7.4) so that the final ethanol concentration did not exceed 20%.

Gastric antisecretory activity of 1.0 μg/kg (iv) doses of the prostaglandins in Table I were determined in HP dogs. Experiments were initiated by fasting the dogs for 18 h. On the morning of an experiment, the dogs were placed in Pavlov stands and infused intravenously with 0.15 M NaCl solution. Gastric secretion was collected at 15-min intervals, and the volume was measured to the nearest 0.1 mL. After a 15–30-min basal secretion period, the dogs were infused with a histamine solution at the submaximal stimulatory dose of 1.0 mg/h. Approximately 1 h after the start of histamine infusion, a steady state of gastric secretion was obtained. At this time, the prostaglandin was administered by a single iv bolus injection using a total volume not exceeding 3.0 mL.

The GF dogs were used to determine the antisecretory ED_{50} values after intragastric administration. These values were used for calculation of activity ratios in Table II. 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 per h 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 in HP dogs was calculated from the degree of maximum inhibition of total acid output. Percent inhibition in GF dogs was calculated as a mean reduction for 4 h. ED_{50} values in GF dogs (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 for GF studies using the bioassay program Parlin-7.[16]

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.[17] ED_{50} values at 8 h were used to calculate the activity ratios in Table II.

Acknowledgment. We thank E. L. Phillips and J. Casler for technical assistance in the antisecretory and diarrheal studies, the group of E. Hajdu, especially W. Syverson, for spectral data, L. Swenton for assistance in interpretation of spectral data, the group of E. Zielinski for microanalyses, D. Honda for HPLC support, D. Calhoun for statistical assistance, and S. Christian and L. Tepper for typing the manuscript.

(16) Finney, D. J. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 487.
(17) Fisher, R. A. *Statistical Methods for Research Workers*, 14th ed.; Hafner: New York, 1970; Chapter 9.