hydrofuran-3-carboxaldehyde, 50634-05-4; 1-*n*-propylpyrrole-3-carboxaldehyde, 128600-69-1; 1-(1-*n*-propylpyrrol-3-yl)-2-nitropropene, 128600-70-4; *n*-amylamine, 110-58-7; 1-*n*-amylpyrrole-3-carboxaldehyde, 35250-63-6; 1-(1-*n*-amylpyrrol-3-yl)-2-nitropropene, 128600-71-5; 1-*n*-propylindole, 16885-94-2; 1-*n*-propylindole-3-carboxaldehyde, 119491-08-6; nitroethane, 79-24-3; indole, 120-72-9; 1-bromopentane, 110-53-2; 1-amylindole, 59529-21-4; 1-amylindole-3-carboxaldehyde, 128600-72-6; chloroacetonitrile, 107-14-2; phthalic anhydride, 85-44-9; 1-(5-methoxyindol-3-yl)-2-aminopropane, 85181-23-3.

Chemistry and Structure–Activity Relationships of C-17 Unsaturated 18-Cycloalkyl and Cycloalkenyl Analogues of Enisoprost. Identification of a Promising New Antiulcer Prostaglandin

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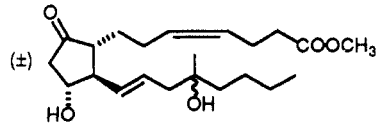
A series of Δ^{17} unsaturated cycloalkyl and cycloalkenyl analogues of enisoprost was synthesized to investigate the effects of ω chain unsaturation on gastric antisecretory activity and diarrheogenic side effects. Of these, the 17*E*, 18-cyclopentenyl analogue **5d** displayed potent gastric antisecretory activity in dogs but very weak diarrheogenic properties in rats and is the most selective prostaglandin compound discovered in these laboratories. Structurally, **5d** contains both a conjugated diene and tertiary allylic alcohol in the ω chain, and these chemical features impart some interesting oxidative and acid-catalyzed epimerization and allylic rearrangement reactivities, respectively.

Introduction

In an earlier paper[1] we reported that incorporation of cycloalkyl groups at C-18 of enisoprost (**1**)[2] led to compounds **2a–e** with reduced gastric antisecretory activity in dogs, but with greater selectivity with respect to diarrheogenic side effects in rats. There was also an indication of increased duration of antisecretory activity with the 18-cyclobutyl analogue **2b**.



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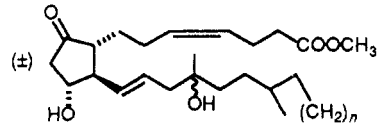

2a–e; n = 1–5

In the quest for more selective and longer acting analogues, we continued our investigation of this series and established several interrelated structure–activity relationships. As previously reported,[1] gastric antisecretory activity drops dramatically once a particular ring size is exceeded (cyclopentyl ≫ cyclohexyl). We next examined the effect of chain length between C-16 and the cycloalkyl moiety. Interestingly, there was an inverse relationship between ring size and chain length. Thus, as chain length increased, the maximally allowed ring size to maintain good gastric antisecretory activity decreased. Similarly, when an angular methyl group was placed on the ring juncture carbon, gastric antisecretory activity decreased more sharply as ring size increased. These findings prompted the establishment of a useful empirical rule that, for optimal gastric antisecretory activity, the total number of carbon atoms composing the ring and the chain linking the ring to C-16 should not exceed seven. Diarrheogenic activity in this expanded series of compounds generally paralleled the finding in the original work; that is, diarrheogenic activity was more sensitive than antisecretory activity to total ω chain size, again suggesting that the parietal cell receptor is more accommodative of larger chains than are the receptors responsible for the diarrheogenic response. Although none of the aforementioned compounds was superior to the initial cycloalkyl compounds, **2a–c**, we decided to continue this line of investigation by studying the effects of unsaturation both at C-17 and, where synthetically feasible, within the rings of **2a–d**. This report details the synthesis and structure–activity relationships of a series of Δ^{17} unsaturated cycloalkyl and cycloalkenyl analogues of enisoprost. The strategy of adding unsaturation eventually led to the discovery of a very promising compound, **5d** (Table I), which possesses the greatest separation of gastric antisecretory and diarrheogenic activities thus far observed in our research. The presence of a tertiary allylic alcohol and a conjugated diene in **5d** imparts some interesting chemical reactivities which also are described.

Chemistry

Synthesis. Compounds **5a–g** of Table I were prepared by standard cuprate addition of the respective racemic cuprate reagents (**4a–g**) to the racemic cyclopentenone **3**[3] followed by mild acid hydrolysis of protecting groups and chromatographic purification (Figure 1). In previous work, an aqueous acetic acid medium was employed to deprotect prostaglandin products, but in the present series a milder reagent, pyridinium *p*-toluenesulfonate (PPTS)[4] in aqueous acetone, was used to minimize formation of various

(1) Collins, P. W.; Gasiecki, A. F.; Perkins, W. E.; Gullikson, G. W.; Jones, P. H.; Bauer, R. F. *J. Med. Chem.* **1989**, *32*, 1004.
(2) Thomson, A. B. R.; McCullough, H. N.; Kirdeikis, P.; Zuk, L.; Simpson, I.; Cook, D. J.; Wildeman, R. A. *Aliment. Pharmacol. Therap.* **1988**, *2*, 325.
(3) Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *36*, 786.
(4) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

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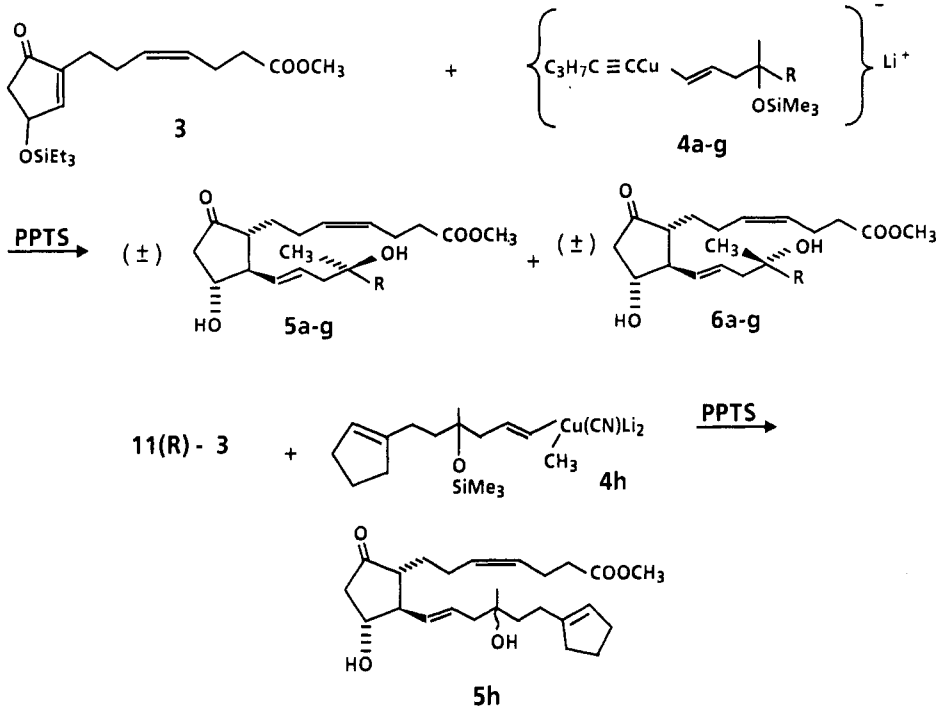


Figure 1.

acid-generated side products due to allylic rearrangement or elimination of the C-16 hydroxyl group. Compound **5h** was prepared in a similar manner except resolved 11-(*R*)-cyclopentenone[5] and higher order cuprate methodology[6] were employed (Figure 1). Interestingly, the presence of unsaturation at C-17 allows the chromatographic separation of the two diastereomeric racemates **5a–g** and **6a–g** produced in the coupling reaction, a separation not practically achievable with misoprostol,[7] enisoprost or the C-17 saturated analogue **5h**. Configurational assignments of **5a–g** were based on chromatographic elution sequence and biological activity. Thus gastric antisecretory activity was observed only with the slower eluting diastereomers **5a–g** which were assigned the same relative stereochemistry as the bioactive isomers of misoprostol and enisoprost.[7,8]

The cuprate reagents **4a–g** were prepared by one of three routes (Figure 2). For **4a–f**, the respective aldehydes **7a–f**, which were either commercially available or easily accessible from the corresponding acids or alcohols, were each condensed with 1-(triphenylphosphoranylidene)-2-propanone to provide the methyl ketones **8a–f**. However, in the case of **8d**, reduction of the commercially available 1-cyclopentene-1-carboxylic acid to **7d** by either LAH or the Rosenmund procedure was complicated by considerable overreduction to the saturated aldehyde. This problem was avoided by use of palladium-catalyzed tri-*n*-butyltin hydride reduction of the corresponding acid chloride.[9] Separate reactions of **8a–f** with the Grignard reagent derived from propargyl bromide followed by treatment with trimethylchlorosilane and imidazole in

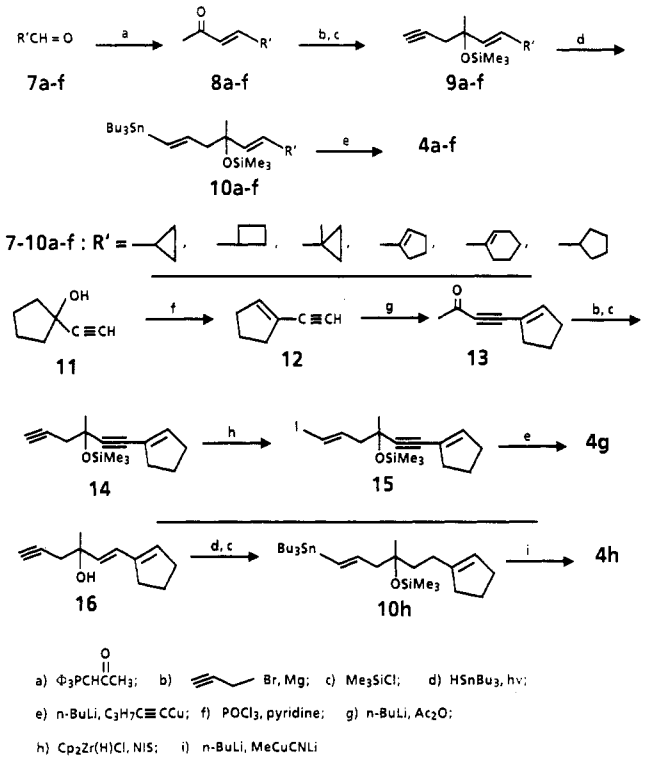
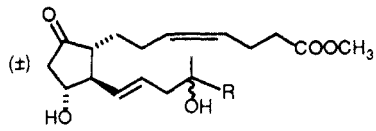


Figure 2.

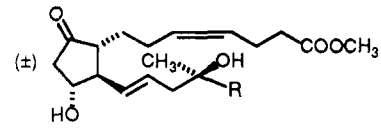
DMF gave the protected acetylenic side chains **9a–f**. Irradiation with a sunlamp[7,10] of individual mixtures of the acetylenes **9a–f** and tri-*n*-butyltin hydride produced the corresponding (*E*)-vinylstannanes **10a–f**. Treatment of the stannanes with *n*-butyllithium at −50 °C followed by addition of an ethereal solution of copper 1-pentyne solubilized with hexamethylphosphorus triamide gave the cuprate reagents **4a–f**. While the hydrostannation reaction worked reasonably well for the monounsaturated ω chains, **9a–c** and **9f**, it was very sluggish with the conjugated di-

(5) Pappo, R.; Collins, P.; Jung, C. *Tetrahedron Lett.* **1973**, 943.
(6) Lipshutz, B. H.; Wilhelm, R. S.; Koslowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938.
(7) Pappo, R.; Collins, P. W.; Bruhn, M. S.; Gasiecki, A. F.; Jung, C. J.; Sause, H. W.; Schulz, J. A. *Chemistry, Biochemistry and Pharmacological Activity of Prostanoids*; Roberts, S. M., Scheinmann, F., Eds.; Pergamon Press: New York, 1979; p 17.
(8) The pharmacologically active (11*R*,16*S*) stereoisomer of misoprostol[7] is slower eluting under a variety of chromatographic conditions relative to its pharmacologically inert (11*R*,16*R*) diastereoisomer.
(9) Four, P.; Guibe, F. *J. Org. Chem.* **1981**, *46*, 4439.
(10) Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187.

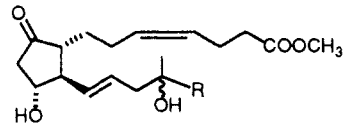
Table I. Comparative Oral Gastric Antisecretory and Diarrheal Activities of Enisoprost Analogues



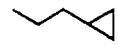
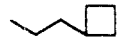
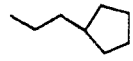
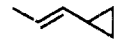
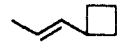
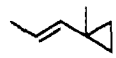
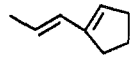
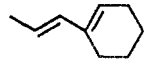
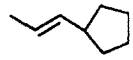
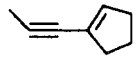
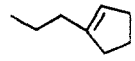
1, 2a–c



5a–g



5h

compd	R	ED_{50}, μg/kg, and 95% confidence limits[d]	
		gastric antisecretory activity in dogs[a]	diarrheal effects in rats[b]
enisoprost (1)		0.023 (0.017–0.032)	49 (37–77)
2a		0.09 (0.083–0.094)	273 (106–698)
2b		0.09 (0.069–0.096)	316 (141–1134)
2c		0.09 (0.06–0.12)	1310 (947–1848)
5a		0.1[c]	402 (105–1532)
5b		0.05 (0.005–0.10)	530 (173–1619)
5c		0.02 (0.004–0.37)	1337 (208–8626)
5d		0.02 (0.005–0.38)	>3160
5e		0.3 (0.18–0.76)	>3160
5f		0.3 (0.05–66.1)	1950 (1016–3743)
5g		2.8 (0.60–11.89)	>3160
5h		0.1[c]	1180 (629–2206)

[a] Determined in food-stimulated Pavlov dogs by intrapouch administration. ED_{50} values for new compounds were generated with 2–7 dogs/dose and 2–5 doses/compound. [b] Determined in adult male rats by intragastric administration. [c] Confidence limits could not be estimated because of the shallow slope of the dose–response curve. [d] Data for enisoprost and **2a–c** are from ref 1.

enes **9d** and **9e**. Prolonged reaction times, elevated temperatures, added free radical initiator (AIBN), and additional tin hydride were required to drive the addition to completion and ensure a reasonably high conversion of the initially formed (*Z*)-vinylstannane to the desired *E* isomer.[7,10] Under these forcing conditions, considerable side reactions occurred resulting in complex mixtures which yielded either very meager amounts of the (*E*)-vinylstannanes after chromatographic purification or very poor yields of prostaglandin products if the vinyl stannane was utilized directly in the cuprate reaction. Two alternative procedures have been found. First, we discovered that the hydrostannation reaction and the subsequent *Z*/*E* isomerization were much cleaner and more facile if carried out with **16**, the free alcohol of **9d**. The resulting hydroxy (*E*)-vinylstannane was purified by chromatography and trimethylsilylated in the usual fashion to give **10d** in acceptable purity and yield (45%). A superior method to hydrostannation, however, is sequential hydrozirconation/iodination to produce the corresponding (*E*)-vinyl iodides which can be converted to the respective cuprate reagents by successive treatment with *n*-butyllithium and copper 1-pentyne. This approach, as a modification of the original Schwartz procedure,[11] has been used quite successfully with **9d** and related conjugated diene compounds[12] as well as for the conversion of the enyne **14** to **15** (Figure 2). Compound **14** was obtained by dehydration of the acetylenic alcohol **11** with phosphorus oxychloride, followed by condensation of the *n*-butyllithium-generated acetylide of **12** with acetic anhydride[13] to give **13**, propargyl Grignard addition to **13**, and silylation of the resulting acetylenic alcohol. The protected acetylene **14** was treated with zirconocene chloride hydride in benzene followed by *N*-iodosuccinimide (NIS) in THF to provide the (*E*)-vinyl iodide **15**. The vinyl stannane precursor **10h** required for preparation of **5h** actually arose unexpectedly from a large scale preparation of **10d**. When **16** was treated with an excess (2 equiv) of tri-*n*-butyltin hydride in the presence of AIBN and sunlamp irradiation for 12 h, a small amount (15%) of the 17,18 saturated

(11) Hart D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.
(12) Kalish, V. J.; Shone, R. L.; Kramer, S. W.; Collins, P. W.; Babiak, K. A.; McLaughlin, K. T.; Ng, J. S. *Syn. Comm.*, in press.
(13) Brandsma, L. *Preparative Acetylenic Chemistry*, Elsevier Publishing Co.: New York, NY, 1971; p 137.

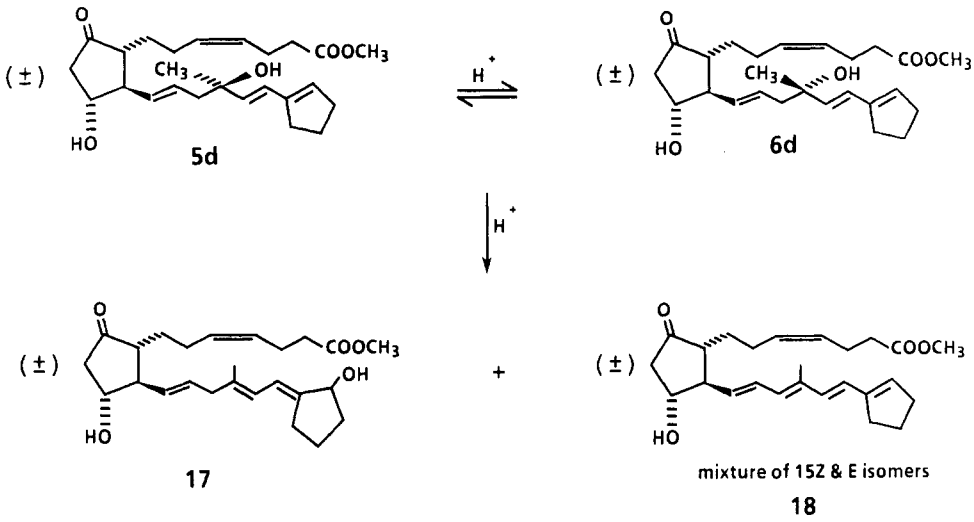


Figure 3.

(*E*)-vinyl stannane was obtained after chromatographic separation from the major product, the alcohol of **10d**. Silylation of the hydroxy stannane provided **10h** which was then converted to the cuprate reagent **4h** by successive treatment with *n*-butyllithium and lithium methyl cyanocuprate.[6]

Acid-Catalyzed Reactions of 5d. The key compound (**5d**) of this series was studied for its behavior in various acid media since the tertiary allylic alcohol at C-16 would be expected to undergo epimerization and allylic rearrangement reactions under acidic conditions.[14] Indeed, when a solution of **5d** in a 3:1:1 mixture of acetic acid/water/THF was allowed to stand at room temperature, epimerization at C-16 occurred readily. After 1 h the ratio of **5d** to **6d** (Figure 3) was about 3:1 and after 2 h the ratio was approximately 1:1. At 1 h small amounts (~5%) of both the allylic rearrangement product **17** and the dehydration product **18** (Figure 3) were observed, and the amounts of these compounds increased over time. Interestingly, the corresponding 18-hydroxy allylic rearrangement product was not detected under these or any other conditions. The weaker acid PPTS, under the conditions used to hydrolyze protecting groups in the synthesis of **5d**, caused only minimal epimerization of **5d** and virtually no conversion to **17** and **18** after several hours of exposure. However, when a higher concentration of PPTS was employed and the reaction allowed to proceed for 24 h, increasing amounts of epimerization and formation of **17** and **18** were observed. In contrast, complete epimerization of **5d** to form a 1:1 mixture of **5d** and **6d** occurred rapidly upon dissolution in a 0.1 N HCl medium at room temperature. Substantial amounts of **17** and **18** were also formed under these conditions. Reversion of **17** to a 1:1 mixture of **5d** and **6d** was also demonstrated by treating **17** with aqueous acetic acid at room temperature for 1–2 h.

The structures of **17** and **18** were determined on the basis of proton and carbon-13 NMR data. In the proton NMR spectrum of **17**, the C-16–CH_3 signal was at δ 1.78, indicating a methyl group on a double bond. A 2-proton doublet signal at δ 2.86 was assigned to the doubly allylic C-15–H's. A one-proton broad triplet signal at δ 4.49 indicated the presence of another methine carbon bearing oxygen, and was assigned to the C-20–H. The coupling between the C-17–H and C-18–H was 11 Hz, consistent with the vicinal coupling of two olefinic protons on conjugated double bonds. The carbon-13 spectrum indicated that the sample was a mixture of two isomers. There were only small differences, <0.2 ppm, between the signals of the isomers, indicating that the isomerization was not due to different geometries of the double bonds, but rather to the presence of C-20 *R* and *S* stereoisomers. The stereochemistry of the 16-ene was assigned as *E* on the basis of the carbon-13 shift of the C-16 methyl (δ 16.7). The stereochemistry of the 18-ene was tentatively assigned as *E* on the basis of the carbon-13 shifts of C-20 and C-23. The proton and carbon-13 signals of the remainder of the molecule were similar to the starting material. The dehydration product **18** was a mixture of two isomers, differing in geometry about the 15-ene. The geometries of the 13-ene and the 17-ene were *E* based on the magnitude of the olefinic coupling constants. The difference in the carbon-13 chemical shifts of the two C-16–CH_3 carbon signals also indicated both 15*E* and 15*Z* isomers were present.

Oxidation Reactions of 5d. During the work with **5d** we observed that the compound decomposed when exposed to air for prolonged periods. The TLC of a typical sample showed multiple spots more polar than **5d** as well as material at the origin. Two products seemed to predominate, however, and we decided to attempt to isolate and identify them. Although several procedures were tried, the best method of obtaining reasonable quantities of the two compounds was to spread a neat film of **5d** over the surface of a glass round-bottomed flask and warm the flask to 50–55 °C in a water bath for 6–7 h while open to the atmosphere. The two compounds were obtained in low yield by chromatographic purification and were identified as the epoxide **20** and the corresponding ketone **21** (Figure 4). The epoxide **20** was quite elusive because of its facile conversion to the ketone **21** under both the reaction and chromatographic conditions. In fact, **20** was obtained only after numerous attempts with both **5d** and **6d** even though it was clearly present by TLC in each experiment prior to chromatographic purification. Successful isolation of **20** was achieved by careful monitoring of the reaction and chromatography on Chromegasphere Si 60 silica gel. The proton and carbon-13 NMR data for **20** showed that there were two diastereomeric epoxides present. The C-20 olefinic signal was missing in both the proton and carbon-13 spectra. The proton spectrum had singlet signals at δ 3.40 and 3.43, due to the epoxide methine of the two diastereomers (the epoxide protons on cyclopentane rings have very small couplings with vicinal protons.) The carbon-13

(14) Robert, A.; Yankee, E. W. *Proc. Soc. Exp. Biol. Med.* **1975**, *148*, 1155.

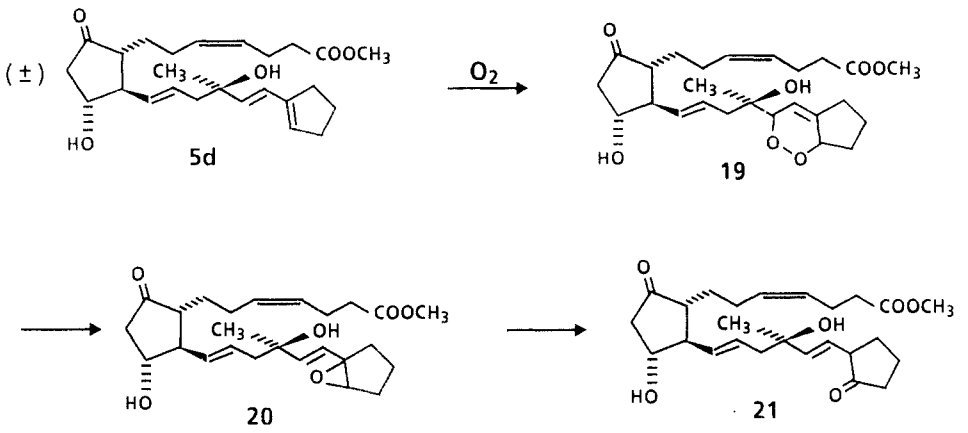


Figure 4.

spectrum had two methine signals at δ 65.4 and 65.6 and two quarternary carbon signals at δ 66.3 and 66.5, which were assigned to the epoxide carbons C-20 and C-19, respectively. The ketone **21** was a mixture of diastereomers as indicated by the presence of two sets of carbon-13 signals. The stereochemistry of the 17-ene was still *E*, as indicated by the olefinic proton coupling constant of 16 Hz. However, the multiplicity of the C-18–H signal, dd, J = 16, 6 Hz, indicated that there was a proton on C-19 (δ 2.80, br d, J = 6 Hz). The carbon-13 spectrum showed the presence of two ketones, C-9 and C-20, as well as the C-19 methine. In Figure 4, the intermediacy of the cyclic peroxide **19** is proposed to explain the formation of **20** and **21** but **19** was never isolated and identified. However, similar intermediates have been isolated and characterized.[15,16] The formation of these products involved light independent 1,4 addition of triplet molecular oxygen across cisoid diene systems. Like these reactions, the oxidation of **5d** was also independent of illumination.

Results and Discussion

The compounds **5a–h** were evaluated for gastric antisecretory activity in Pavlov pouch dogs by intrapouch administration and for diarrheogenic side effects in rats by intragastric administration. The results and comparison with enisoprost and the corresponding C-17 saturated cycloalkyl analogues **2a–c** are presented in Table I. Unlike enisoprost and **2a–c**, which are mixtures of two racemates, compounds **5a–g** are single racemates. In addition compound **5h** is a mixture of two diastereomers by virtue of its preparation from resolved 11(*R*)-cyclopentenone and racemic side chain **10h** (Figures 1 and 2) and its failure to chromatographically separate into the two C-16 diastereomers. Since it is very likely that only one stereoisomer of all these prostaglandin analogues is biologically active,[7,17] the data in Table I should be adjusted to reflect the differences in isomeric content when comparing compounds **5a–h** with enisoprost or **2a–c**.

The first two members of this series, **5a** and **5b**, were prepared to determine the effect of a 17*E* double bond on biological activity in the original cycloalkyl series. Relative to their respective saturated counterparts **2a** and **2b**, **5a** and **5b** showed comparable gastric antisecretory activity, a finding in variance with earlier work in which incorporation of a 17*E* double bond into misoprostol reduced activity by 5-fold.[7,17] On the other hand, diarrheogenic properties of **5a** and **5b** were diminished relative to **2a** and **2b**, especially if differences in isomer content are considered. For example, **5b** has a diarrheogenic ED_{50} value of 530 relative to 316 for **2b**. However, the active isomer of **5b** is diluted one-half by its biologically inactive enantiomer while the active isomer of **2b** represents only one-fourth of the total amount of **2b**. Thus, to compare the active isomers of **5b** and **2b**, the ED_{50}'s of **5b** and **2b** should be divided by 2 and 4, respectively, giving ED_{50} values of 265 and 79 for the respective active isomers of **5b** and **2b**. On this basis, the insertion of a 17*E* double bond into **2b** has increased the separation of gastric antisecretory activity from diarrheogenic side effects. This type of comparison is, of course, based on the assumption 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.[17]

The next compound in this series, **5c**, possessed an even wider separation of activities, and its favorable profile prompted us to examine the effects that a conjugated diene system might have. Since the cyclobutenyl analogue of **5b** represents a significant synthetic challenge, we selected the more accessible cyclopentenyl analogue as the test structure. The resulting compound, **5d**, displayed potent gastric antisecretory activity, comparable to enisoprost but about twice that of the corresponding saturated analogue **2c** when based on isomeric content. Furthermore, **5d** was virtually devoid of diarrheogenic side effects in rats with only a few animals showing diarrhea at the highest dose tested, 3160 μg/kg.[18] The remaining compounds in Table I were prepared to investigate SAR surrounding **5d**. Increasing the ring size to cyclohexenyl (**5e**) maintained the desirable weak diarrheogenic activity but caused a reduction in gastric antisecretory activity, again illustrating that the parietal cell receptor has a finite capacity for the ω chains of prostaglandins. However, compound **5e** is a much more potent gastric antisecretory agent than its fully saturated analogue (**2d**, ED_{50} = 70 μg/kg),[1] suggesting that the reduced rotational freedom and flattening of the ring caused by the conjugated diene permits a better receptor fit of the ω chain terminus. The necessity for the presence of both double bonds in **5d** is demonstrated in compounds **5f** and **5h**, both of which have reduced gastric antisecretory

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(16) Bowes, C. M.; Monticalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, 3181.
(17) Collins, P. W. Misoprostol: Discovery, Development and Clinical Applications. *Med. Res. Rev.* **1990**, *10*, 149, and unpublished data.
(18) In rhesus monkeys **5d** caused diarrhea in 3 of 7 animals, at 300 μg/kg, ig. This approximate ED_{50} value compares to ED_{50} values and 95% confidence limits of 26 (13–50), 54 (26–110), and 137 (75–248) μg/kg, for 16,16-dimethyl-PGE_2, enisoprost, and misoprostol. Animals were fasted for approximately 18 h prior to dosing, and observations for diarrhea (defined as liquid feces) were made for up to 24 h after dosing.

activity and enhanced diarrheogenic properties. Finally, the substitution of an acetylene unit for the C-17 double bond to give **5g** dramatically reduced gastric antisecretory activity. Compound **5d** is the most potent and selective prostaglandin analogue ever found in our laboratories and was elected for more detailed pharmacological evaluation. However, we decided to prepare and study the biologically active 11*R*,16*R* enantiomer[19,20] of **5d** rather than **5d** itself. The extensive pharmacological studies of this isomer, SC-46275, will be reported separately.

The various acid-catalyzed and oxidative side products from **5d** also were assessed for biological activity. The allylic rearranged product, **17**, did not inhibit acid secretion in dogs at an intrapouch dose of 0.3 μg/kg under the normal protocol, but when a 0.1 N HCl solution was used in place of the saline solution to flush the dose into the pouch, this same dose inhibited total acid output by 87%. These results suggest that, similar to the in vitro findings, **17** will revert to the 16-hydroxy species in the presence of acid in vivo. A similar experiment was done with **6d**, the biologically inactive diastereomer of **5d**. Again, the weak acid inhibitory activity[21] of **6d** was markedly enhanced when an acid flush was employed, suggesting that its epimerization to **5d** was accelerated. The other degradation products, **18**, **20**, and **21**, showed a wide range of acid inhibition activities. The tetraene **18** was inactive at the highest dose tested (3.0 μg/kg), while the epoxide **20** had an ED_{50} of 0.3 μg/kg, an unexpectedly high level of activity. In contrast, the ketone **21** was weakly active with an ED_{50} of 8.7 μg/kg.

Experimental Section

The NMR spectra were obtained on either a Varian FT-80A, a Varian XL-200, a GE-QE 300, a Varian VXR-400, or a Varian VXR-500 spectrometer in $CDCl_3$ or in CD_3CN for **5d** and **6d** 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.

4-Cyclopropyl-3(*E*)-buten-2-one (8a). A mixture of 6.2 g (89 mmol) of cyclopropylcarboxaldehyde (**7a**) and 36.6 g (115 mmol) of 1-(triphenylphosphoranylidene)-2-propanone in 250 mL of benzene was refluxed for 3.5 h. The reaction mixture was allowed to stand at room temperature overnight and filtered, and the filtrate was carefully concentrated on a rotary evaporator at 5 °C to a small volume. The residue was treated with 500 mL of hexane and chilled in an ice bath. The precipitated triphenylphosphine oxide was removed by filtration, and the filtrate carefully concentrated on a rotary evaporator at 5 °C. The residue was distilled at atmospheric pressure to give 2.6 g (29%) of a light yellow liquid: bp 100 °C; ^1H NMR δ 0.50–1.00 (complex band, 4 H), 1.55 (m, 1 H), 2.20 (s, 3 H), 6.25 (complex band, 2 H). Anal. ($C_7H_{10}O$) C, H.

4-Cyclobutyl-3(*E*)-buten-2-one (8b). In a similar manner, **8b** was prepared from **7b** in 70% yield: ^1H NMR δ 1.70–2.40 (complex band, 6 H), 2.20 (s, 3 H), 3.05 (br m, 1 H), 5.95 (dd, *J* = 16, 1 Hz, 1 H), 6.85 (dd, *J* = 16, 7 Hz, 1 H). Anal. ($C_8H_{12}O$) C, H.

4-(1-Methylcyclopropyl)-3(*E*)-buten-2-one (8c). In a similar manner, **8c** was prepared from **7c** in 48% yield: ^1H NMR δ 0.84 (s, 4 H), 1.22 (s, 3 H), 2.21 (s, 3 H), 6.00 (d, *J* = 16 Hz, 1 H), 6.35 (d, *J* = 16 Hz, 1 H). Anal. ($C_8H_{12}O$) C, H.

4-(1-Cyclopenten-1-yl)-3(*E*)-buten-2-one (8d). 1-Cyclopentene-1-carboxylic acid (38.0 g, 338.9 mmol) and 50.8 g (400.2 mmol) of oxalyl chloride were mixed in a flame dried flask at room temperature under N_2. After a vigorous evolution of gas subsided, the reaction mixture was refluxed for 1 h and cooled, and the excess oxalyl chloride was removed on a rotary evaporator. The residue was distilled at reduced pressure to produce 42.0 g (95%) of the acid chloride (stench): bp 70–72 °C (15 mm); ^1H NMR δ 2.04 (p, *J* = 7 Hz, 2 H), 2.65 (t, *J* = 7 Hz, 4 H), 7.18 (m, 1 H). A 17.5 g (134 mmol) portion of the acid chloride was added to 100 mL of anhydrous benzene containing a suspension of 1.0 g (0.87 mmol) of tetrakis(triphenylphosphine)palladium. Over a period of 15 min 43.7 g (150 mmol) of tri-*n*-butyltin hydride was added as a neat liquid during which time the reaction mixture reached a temperature of 58 °C. The reaction mixture was stirred for an additional 15 min, and then the apparatus was set up for distillation at reduced pressure. The pressure was gradually reduced to ~110 mmHg at which point the distillate began to collect in a receiver chilled in a dry ice–*i*-PrOH bath. The pressure was gradually reduced to about 5–10 mmHg, and the boiling point allowed to rise to about 60 °C at which point no more material distilled. Due to the volatile nature of the product, the benzene solution was used directly in the next step without further purification. A mixture of the benzene solution and 119 g (375 mmol) of 1-(triphenylphosphoranylidene)-2-propanone in 600 mL of benzene was refluxed for 18 h. The reaction mixture was cooled, filtered, and concentrated on a rotary evaporator at 5 °C to a small volume. The residue was treated with 1 L of hexane and chilled in an ice bath to precipitate triphenylphosphine oxide. The solid was removed by filtration and the filtrate carefully concentrated on a rotary evaporator at 5 °C. The residue was purified via flash chromatography on silica gel (20% EtOAc and 80% hexane) to afford 23.8 g of **8d** (47% yield from the acid chloride) as a light yellow liquid which solidified to a white solid upon standing at 0 °C: ^1H NMR δ 1.99 (p, *J* = 7 Hz, 2 H), 2.28 (s, 3 H), 2.40–2.60 (complex band, 4 H), 6.01 (d, *J* = 16 Hz, 1 H), 6.25 (m, 1 H), 7.35 (d, *J* = 16 Hz, 1 H). Anal. ($C_9H_{12}O$) C, H.

4-(1-Cyclohexen-1-yl)-3(*E*)-buten-2-one (8e). The title compound was prepared from **7e** (obtained by oxidation of 1-cyclohexenylmethanol) in a similar manner as **8a** in 44% yield: ^1H NMR δ 1.50–1.90 (complex band, 4 H), 1.90–2.25 (complex band, 4 H), 2.28 (s, 3 H), 6.02 (d, *J* = 16 Hz, 1 H), 6.18 (m, 1 H), 7.09 (d, *J* = 16 Hz, 1 H). Anal. ($C_{10}H_{14}O$) C, H.

4-Cyclopentyl-3(*E*)-buten-2-one (8f). In a similar manner **8f** was prepared from **7f** in 62% yield. Anal. ($C_9H_{14}O$) C, H.

1-Ethynyl-1-cyclopentene (12). 1-Ethynyl-1-cyclopentanol (**11**) (25.0 g, 226.9 mmol) was placed in a 500-mL flask fitted with a thermometer and containing 45 mL of pyridine. The reaction mixture was heated on the steam bath to 92 °C and a mixture of 17 mL of $POCl_3$ and 20 mL of pyridine was added in several portions over a period of 25 min while the flask was continually swirled. After each addition, the temperature rose to about 110 °C. After the final addition, the reaction was maintained at 100–105 °C for 10 min and then allowed to cool to 75 °C. The reaction mixture was poured onto 200 mL of ice water and the reaction flask rinsed with 100 mL of cold water and then 200 mL of a 1:1 mixture of ether and hexane. The combined layers were separated and the aqueous portion was extracted with 1:1 ether/hexane (4 × 100 mL). The organic extracts were combined and washed with 3 N HCl (3 × 100 mL) and water (4 × 100 mL), dried (Na_2SO_4), and concentrated. The residue was distilled at reduced pressure to afford 9.7 g (46%) of a slightly tinted liquid: bp 70–71 °C (120 mm); ^1H NMR δ 1.90 (p, *J* = 7 Hz, 2 H), 2.25–2.75 (complex band, 4 H), 2.97 (s, 1 H), 6.12 (m, 1 H). Anal. (C_7H_8) C, H.

4-(1-Cyclopenten-1-yl)-3-butyn-2-one (13). A solution of 9.7 g (105 mmol) of **12** in 40 mL of dry THF was chilled under N_2 to −30 °C. A 1.6 M solution of *n*-BuLi (72 mL, 115 mmol) in hexane was added dropwise over 20 min, and the reaction mixture

(19) The two enantiomers of **5d** have been prepared and only one of these is biologically active. The bioactive isomer was prepared from 11(*R*)-**3** and the racemic cuprate reagent **4d** followed by chromatographic separation of the two diastereomers. The slower-eluting bioactive isomer was assigned the same absolute configuration as the active isomers of misoprostol and enisoprost.

(20) The presence of the C-17,18 double bond reverses the *RS* nomenclature assignments for C-16; thus the absolute stereochemistry for the bioactive isomers of **5a–g** is 11(*R*),16(*R*).

(21) Any gastric antisecretory activity associated with **6d** is likely due to partial epimerization to **5d** in gastric fluid.

was stirred for 15 min at −30 °C. In another flask fitted with a thermometer, addition funnel, and a mechanical stirrer was dissolved 21.4 g (210 mmol) of acetic anhydride in 35 mL of dry THF under N_2. The lithium acetylide was placed in the addition funnel and the reaction flask was chilled to −60 °C. The acetylide was added at a rate which avoided elevation of the reaction mixture temperature above −37 °C. After the addition was completed, the reaction mixture was allowed to warm to −10 °C and was added in small portions to a solution of 25 g of $NaHCO_3$ in 100 mL of water. The mixture was vigorously stirred until the evolution of CO_2 ceased. The layers were separated, the aqueous portion was extracted with ether (5 × 50 mL), and the combined organic extracts were washed with water (2 × 50 mL) and then saturated NaCl solution (1 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (4% EtOAc and 96% hexane) to give 7.2 g (51%) of a yellow liquid: ^{1}H NMR δ 1.92 (p, J = 7 Hz, 2 H), 2.35 (s, 3 H), 2.35–2.65 (complex band, 4 H), 6.37 (m, 1 H); IR 2200, 1665, 1600 cm^{-1}. Anal. ($C_9H_{10}O$) C, H.

[[1-(2-Cyclopropyl-(*E*)-ethenyl)-1-methyl-3-butynyl]oxy]trimethylsilane (9a). In a flame-dried flask under N_2 were suspended 580 mg (23.9 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 2.6 g (24 mmol) of **8a** and 2.7 g (23 mmol) of propargyl bromide in 50 mL of dry 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 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 three times and once with saturated NaCl solution, dried (Na_2SO_4), and evaporated to a small volume. To a solution of the crude alcohol in 50 mL of DMF under N_2 at room temperature were added 3.3 g (49 mmol) of imidazole and 3.0 g (28 mmol) of trimethylchlorosilane. The reaction mixture was stirred for 30 min and then poured into a mixture of ether and water and shaken well. The layers were separated, and the aqueous portion was extracted three times with a 1:1 mixture of ether and hexane. The organic extracts were combined and washed with water three times and saturated NaCl solution once, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on silica gel (2% EtOAc and 98% hexane) to give 1.6 g (30%) of a clear liquid: ^{1}H NMR δ 0.10 (s, 9 H), 0.20–1.00 (complex band, 5 H), 1.40 (s, 3 H), 1.97 (t, J = 3 Hz, 1 H), 2.37 (d, J = 3 Hz, 2 H), 5.12 (dd, J = 16, 8 Hz, 1 H), 5.66 (d, J = 16 Hz, 1 H). Anal. ($C_{13}H_{22}OSi$) C, H.

[[1-(2-Cyclobutyl-(*E*)-ethenyl)-1-methyl-3-butynyl]oxy]trimethylsilane (9b). In a similar manner **9b** was prepared from **8b** in 25% yield: ^{1}H NMR δ 0.12 (s, 9 H), 1.41 (s, 3 H), 1.65–2.20 (complex band, 6 H), 1.96 (t, J = 3 Hz, 1 H), 2.37 (d, J = 3 Hz, 2 H), 2.90 (br m, 1 H), 5.47 (d, J = 15 Hz, 1 H), 5.74 (dd, J = 15, 6 Hz, 1 H). Anal. ($C_{14}H_{24}OSi$) C, H.

[[1-(2-(1-Methylcyclopropyl)-(*E*)-ethenyl)-1-methyl-3-butynyl]oxy]trimethylsilane (9c). In a similar manner **9c** was prepared from **8c** in 62% yield: ^{1}H NMR δ 0.12 (s, 9 H), 0.57 (s, 4 H), 1.17 (s, 3 H), 1.41 (s, 3 H), 1.97 (t, J = 3 Hz, 1 H), 2.38 (d, J = 3 Hz, 2 H), 5.17 (d, J = 16 Hz, 1 H), 5.55 (d, J = 16 Hz, 1 H). Anal. ($C_{14}O_{24}OSi$) C, H.

1-(1-Cyclopenten-1-yl)-3-methyl-1(*E*)-hexen-5-yn-3-ol (16). In a similar manner, **16** was prepared from **8d** in 88% yield after chromatographic purification on silica gel (10% EtOAc and 90% hexane): bp 85–86 °C (0.25 mm); ^{1}H NMR δ 1.41 (s, 3 H), 1.92 (p, J = 7 Hz, 2 H), 2.10 (t, J = 3 Hz, 1 H), 2.12 (s, 1 H), 2.41 (t, J = 7 Hz, 4 H), 2.48 (d, J = 3 Hz, 2 H), 5.67 (d, J = 16 Hz, 1 H), 5.74 (m, 1 H), 6.53 (d, J = 16 Hz, 1 H). IR 3580, 2120, 1720, 1670 cm^{-1}. Anal. ($C_{12}H_{16}O$) C, H.

[[1-[2-(1-Cyclohexen-1-yl)-(*E*)-ethenyl]-1-methyl-3-butynyl]oxy]trimethylsilane (9e). In a similar manner **9e** was prepared from **8e** in 44% yield: bp 76–79 °C (0.1 mm). Anal. ($C_{16}H_{26}OSi$) C, H.

[[1-(2-Cyclopentyl-(*E*)-ethenyl)-1-methyl-3-butynyl]oxy]trimethylsilane (9f). In a similar manner **9f** was prepared from **8f** in 52% yield: ^{1}H NMR δ 0.12 (s, 9 H), 1.41 (s, 3 H), 1.90–2.25 (complex band, 9 H), 1.95 (t, J = 3 Hz, 1 H), 2.37 (d, J = 3 Hz, 2 H), 5.55 (complex band, 2 H). Anal. ($C_{15}H_{26}OSi$) C, H.

[[1-[(1-Cyclopenten-1-yl)ethynyl]-1-methyl-3-butynyl]oxy]trimethylsilane (14). In a similar manner **14** was prepared from **13** in 38% yield: ^{1}H NMR δ 0.21 (s, 9 H), 1.57 (s, 3 H), 1.90 (p, J = 7 Hz, 2 H), 2.02 (t, J = 3 Hz, 1 H), 2.56 (d, J = 3 Hz, 2 H), 2.75–2.95 (complex band, 4 H), 6.00 (m, 1 H). Anal. ($C_{15}H_{22}OSi$) C, H.

[[1-(2-Cyclopropyl-(*E*)-ethenyl)-1-methyl-4-(tributylstannyl)-3(*E*)-butenyl]oxy]trimethylsilane (10a). A mixture of 1.5 g (6.7 mmol) of **9a**, 2.0 g (6.9 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.

Compounds **10b**, **10c**, and **10f** were prepared in a similar manner from **9b**, **9c**, and **9f**, respectively, and each was used directly in the cuprate reactions.

[[1-[2-(1-Cyclopenten-1-yl)-(*E*)-ethenyl]-1-methyl-4-(tributylstannyl)-3(*E*)-butenyl]oxy]trimethylsilane (10d). A mixture of 5.0 g (28 mmol) of **16**, 8.7 g (30 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 ca. 3 in. from the reaction vessel. After 2 h the reaction was about 25% complete by TLC analysis. Another 3.0 g (10.3 mmol) of tin hydride was added and the irradiation continued. The reaction and isomerization of the initially formed *Z* isomer to the *E* isomer proceeded smoothly over the next 2 h. Irradiation was continued for a total of 8 h, after which time the starting material was mostly consumed and the *E* isomer dominated approximately 4:1. The reaction mixture was purified on silica gel by eluting with 1% EtOAc, 99% hexane until the excess tin hydride was removed, and then with 5% EtOAc and 95% hexane to afford 6.4 g (48%) of the vinyl stannyl alcohol as a 4:1 mixture of *E*:*Z* isomers: ^{1}H NMR δ 0.89 (t, J = 7 Hz, 15 H), 1.32 (s, 3 H), 1.20–1.70 (complex band, 12 H), 1.92 (p, J = 7 Hz, 2 H), 2.25–2.50 (complex band, 6 H), 5.62 (d, J = 16 Hz, 1 H), 5.70 (m, 1 H), 5.91 (dt, J = 19, 7 Hz, 1 H), 6.06 (d, J = 19 Hz, 1 H), 6.44 (d, J = 16 Hz, 1 H). To a solution of 6.3 g (13.5 mmol) of the alcohol in DMF under N_2 at room temperature was added 1.4 g (20.6 mmol) of imidazole and 1.5 g (14.0 mmol) of trimethylchlorosilane. The reaction mixture was stirred for 30 min and then poured into a mixture of ether and water and shaken well. The layers were separated and the aqueous portion was extracted three times 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 6.8 g (94%) of a clear oil which was used directly in the cuprate reaction: ^{1}H NMR δ 0.11 (s, 9 H), 0.89 (t, J = 7 Hz, 15 H), 1.32 (s, 3 H), 1.20–1.70 (complex band, 12 H), 1.92 (d, J = 7 Hz, 2 H), 2.25–2.50 (complex band, 6 H), 5.61 (d, J = 16 Hz, 1 H), 5.68 (m, 1 H), 5.87 (d, J = 19 Hz, 1 H), 5.98 (dt, J = 19, 7 Hz, 1 H), 6.33 (d, J = 16 Hz, 1 H).

[[1-[2-(1-Cyclohexen-1-yl)-(*E*)-ethenyl]-1-methyl-4-(tributylstannyl)-3(*E*)-butenyl]oxy]trimethylsilane (10e). In a manner similar to the preparation of **10a** from **9a**, the title compound was obtained from **9e**. The reaction was conducted for 7 h at a temperature > 100 °C induced by wrapping the reaction flask and sunlamp with aluminum foil. The resulting product was not as pure as **10a** but was nevertheless used directly in the cuprate reaction.

[[1-[(1-Cyclopenten-1-yl)ethynyl]-4-iodo-1-methyl-3(*E*)-butenyl]oxy]trimethylsilane (15). Compound **14** (5.05 g, 20.5 mmol) was dissolved in 150 mL of anhydrous benzene, and 5.28 g (20.5 mmol) of zirconocene chloride hydride was added as a solid in one portion under N_2 at 5 °C. The suspension was stirred and allowed to gradually warm to room temperature during which time the solid dissolved to give a light yellow solution. The solution was concentrated to a golden oil and then dissolved in 75 mL of dry THF at 5 °C under N_2. A solution of 4.6 g (20.5 mmol) of *N*-iodosuccinimide in 25 mL of dry THF was added, and the stirring was continued for 30 min. The reaction mixture was diluted with 50 mL of ether and 50 mL of hexane and washed successively with a 10% aqueous solution of Na_4EDTA (4 × 50 mL), 5% Na_2SO_3 solution (2 × 50 mL), H_2O (1 × 50 mL), and saturated NaCl solution (1 × 50 mL), dried ($MgSO_4$), and con-

centrated. The residue was chromatographed on silica gel (0.5% EtOAc and 99.5% hexane) to afford 3.1 g (40%) of a straw colored liquid: ^{1}H NMR δ 0.19 (s, 9 H), 1.43 (s, 3 H), 1.88 (p, J = 7 Hz, 2 H), 2.25–2.55 (complex band, 6 H), 5.96 (m, 1 H), 6.05 (d, J = 14 Hz, 1 H), 6.59 (dt, J = 14, 7 Hz, 1 H). Anal. ($C_{15}H_{23}OSiI$) C, H.

(±)-[[1-[2-(1-Cyclopenten-1-yl)ethyl]-1-methyl-4-(tributylstannyl)-3(*E*)-butenyl]oxy]trimethylsilane (10h). A mixture of 17.5 g (99.3 mmol) of **16**, 120 mg of AIBN, and 61 g (209.6 mmol) of freshly distilled tri-*n*-butyltin hydride contained in a Pyrex flask was irradiated under argon with a GE sunlamp for 12 h at approximately 55–65 °C (heat generated by lamp placed at a distance of about 5 in. from the reaction vessel). The crude product was chromatographed on silica gel (10% EtOAc and 90% hexane to afford the alcohols of **10d** (11.1 g, 24% yield) and **10h** (2.06 g, 4% yield), respectively. To a solution of 1.6 g (3.41 mmol) of the alcohol of **10h** in 10 mL DMF under N_2 at room temperature was added 353 mg (5.19 mmol) of imidazole followed by dropwise addition of 379 mg (3.49 mmol) of trimethylchlorosilane. The reaction mixture was stirred at room temperature for 2.5 h, and then poured into a mixture of ice–water and ether, and shaken well. The layers were separated, and the aqueous portion was extracted three times with 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 give 1.85 g (100%) of **10h**: ^{1}H NMR δ 0.11 (s, 9 H), 0.89 (t, J = 7 Hz, 9 H), 0.87 (t, J = 7 Hz, 6 H), 1.19 (s, 3 H), 1.23–1.61 (complex band, 14 H), 1.84 (p, J = 7.5 Hz, 2 H), 2.03–2.34 (complex band, 4 H), 5.30 (br s, 1 H), 5.92 (d, J = 19 Hz, 1 H), 5.99 (dt, J = 19, 6 Hz, 1 H).

(±)-Methyl 7-[2β-(6-Cyclopropyl-4(*R*)-hydroxy-4-methyl-1(*E*),5(*E*)-hexadienyl)-3α-hydroxy-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (5a).[19] A solution of 3.0 g (5.84 mmol) of **10a** in 20 mL of dry THF was cooled to −50 °C under argon and treated with 3.77 mL of a 1.55 M solution (5.84 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 763 mg (5.84 mmol) of copper 1-pentyne and 1.91 g (11.68 mmol) of hexamethylphosphorus triamide in 20 mL of ether. The reaction mixture was stirred for 30 min at −60 °C and then a solution of 1.50 g (4.26 mmol) of **3** in 12 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 layers were separated, and the aqueous portion was extracted with ether and then EtOAc. The organic extracts were combined and washed with water three times and saturated NaCl once, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (5% EtOAc, 95% hexane) to afford 1.10 g (45%) of a viscous oil. The oil was dissolved in a solution of 20 mL of acetone and 2 mL of water, and 100 mg of pyridinium *p*-toluenesulfonate (PPTS)[4] 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 and 35% hexane) to afford 106 mg of the less polar racemate (**6a**), 118 mg of the more polar racemate (**5a**), and 175 mg of an overlap fraction of the two racemates (53% total prostaglandin yield from **3**; 16% yield for pure **5a** (excluding overlap), all as colorless viscous oils. ^{1}H NMR for **5a**: δ 0.20–0.40 (complex band, 4 H), 1.27 (s, 3 H), 2.73 (dd, J = 19, 7 Hz, 1 H), 3.65 (s, 3 H), 4.01 (q, J = 8 Hz, 1 H), 5.11 (dd, J = 16, 8 Hz, 1 H), 5.32 (complex band, 2 H), 5.39 (dd, J = 15, 9 Hz, 1 H), 5.61 (d, J = 16 Hz, 1 H), 5.67 (dt, J = 15, 7 Hz, 1 H). Anal. ($C_{23}H_{34}O_5$) C, H.

(±)-Methyl 7-[2β-(6-Cyclobutyl-4(*R*)-hydroxy-4-methyl-1(*E*),5(*E*)-hexadienyl)-3α-hydroxy-5-oxo-1α-cyclopentyl]-4-(*Z*)-heptenoate (5b).[19] In a similar manner **5b** was prepared from **10b** in 16% yield (excluding overlap) from **3**: ^{1}H NMR δ 1.28 (s, 3 H), 2.72 (dd, J = 19, 7 Hz, 1 H), 2.85 (m, 1 H), 3.66 (s, 3 H), 4.02 (q, $J \simeq$ 8 Hz, 1 H), 5.32 (complex band, 2 H), 5.40 (dd, J = 15, 9 Hz, 1 H), 5.41 (d, J = 15 Hz, 1 H), 5.68 (dt, J = 15, 7 Hz, 1 H), 5.74 (dd, J = 15, 6 Hz, 1 H). Anal. ($C_{24}H_{36}O_5$) C, H.

(±)-Methyl 7-[3α-Hydroxy-2β-[4(*R*)-hydroxy-4-methyl-6-(1-methylcyclopropyl)-1(*E*),5(*E*)-hexadienyl]-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (5c).[19] In a similar manner **5c** was prepared from **10c** in 15% yield (excluding overlap) from **3**: ^{1}H NMR δ 0.56 (s, 4 H), 1.15 (s, 3 H), 1.28 (s, 3 H), 2.72 (dd, J = 18, 7 Hz, 1 H), 3.66 (s, 3 H), 4.00 (q, $J \simeq$ 8 Hz, 1 H), 5.19 (d, J = 16 Hz, 1 H), 5.33 (complex band, 2 H), 5.37 (dd, J = 15, 9 Hz, 1 H), 5.49 (d, J = 16 Hz, 1 H), 5.68 (dt, J = 15, 7 Hz, 1 H). Anal. ($C_{24}H_{36}O_5$) C, H.

(±)-Methyl 7-[2β-[6-(1-Cyclopenten-1-yl)-4(*R*)-hydroxy-4-methyl-1(*E*),5(*E*)-hexadienyl]-3α-hydroxy-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (5d)[19] **and (±)-Methyl 7-[2β-[6-(1-Cyclopenten-1-yl)-4(*S*)-hydroxy-4-methyl-1(*E*),5-(*E*)-hexadienyl]-3α-hydroxy-5-oxo-1α-cyclopentyl)-4(*Z*)-heptenoate (6d).** In a similar manner **5d** and **6d** were prepared from **10d** in 50% combined yield from **3**. **5d**: ^{1}H NMR (CD_3CN) δ 1.22 (s, C-16–CH_3), 1.48 (dddd, J = 13.8, 9.6, 6.4, 5.6 Hz, C-7 H), 1.55 (ddt, J = 13.8, 9.3, 6.2 Hz, C-7 H), 1.88 (p, J = 7.5 Hz, C-22 H), 1.93 (m, CD_2HCN), 1.98 (dddd, J = 11.8, 6.2, 5.6, 1.3 Hz, C-8 H), 2.06 (dd, J = 18.3, 9.2 Hz, C-10α-H), 2.03–2.13 (m, C-6 H), 2.23–2.33 (complex band, 7 H, C-2, 3, 12, and 15 H), 2.34–2.40 (complex band, C-21 and 23 H), 2.57 (ddd, J = 18.2, 7.4, 1.3 Hz, C-10β-H), 2.72 (s, C-16-OH), 3.22 (br s, C-11-OH), 3.60 (s, C-1-OCH_3), 3.96 (br q, $J \simeq$ 8.3 Hz, C-11-H), 5.32 (m, C-4 and C-5 H), 5.41 (ddt, J = 15.3, 8.5, 1.2 Hz, C-13 H), 5.57 (dtd, J = 15.3, 7.3, 0.7 Hz, C-14 H), 5.63 (dd, J = 16.2, 0.8 Hz, C-17 H), 5.68 (m, C-20 H), 6.40 (d, J = 16.2 Hz, C-18 H); ^{13}C NMR (CD_3CN) δ 23.5 (C-3), 23.8 (C-22), 25.3 (C-6), 28.4 (C-16-CH_3), 28.4 (C-7), 32.1 (C-21), 33.4 (C-23), 34.6 (C-2), 47.0 (C-15), 47.1 (C-10), 52.0 (C-1-OCH_3), 54.3 (C-8), 55.4 (C-12), 72.5 (C-11), 73.0 (C-16), 124.7 (C-18), 129.3, 131.5 (C-4,5), 129.9 (C-14), 130.8 (C-20), 134.6 (C-13), 138.3 (C-17), 143.2 (C-19), 174.3 (C-1), 216.3 (C-9). Anal. ($C_{25}H_{36}O_5$) C, H. **6d**: ^{1}H NMR (CD_3CN) δ 1.22 (s, 3 H), 1.49 (dddd, 1 H), 1.57 (ddt, 1 H), 1.89, (p, 2 H), 1.99 (dddd, 1 H), 2.06 (dd, 1 H), 2.03–2.14 (m, 2 H), 2.25–2.33 (complex band, 7 H), 2.34–2.41 (complex band, 4 H), 2.57 (ddd, 1 H), 2.67 (s, 1 H), 3.13 (d, J = 4.4 Hz, 1 H), 3.60 (s, 3 H), 3.96 (dddd, 1 H), 5.33 (m, 2 H), 5.42 (ddt, 1 H), 5.59 (dddd, 1 H), 5.64 (dd, 1 H), 5.68 (m, 1 H), 6.41 (d, 1 H); ^{13}C NMR (CD_3CN) δ 23.5, 23.8, 25.2, 27.7, 28.4, 32.0, 33.4, 34.6, 46.9, 47.1, 52.1, 54.3, 55.3, 72.3, 72.8, 124.6, 129.2, 129.7, 130.9, 131.5, 134.7, 138.4, 143.2, 174.5, 216.7. Anal. ($C_{25}H_{36}O_5$) C, H.

(±)-Methyl 7-[2β-[6-(1-Cyclohexen-1-yl)-4(*R*)-hydroxy-4-methyl-1(*E*),5(*E*)-hexadienyl]-3α-hydroxy-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (5e).[19] In a similar manner **5e** was prepared from **10e** in 6% yield (excluding overlap) from **3**: ^{1}H NMR δ 1.33 (s, 3 H), 2.72 (dd, J = 18, 7 Hz, 1 H), 3.69 (s, 3 H), 4.03 (q, $J \simeq$ 8 Hz, 1 H), 5.33 (complex band, 2 H), 5.41 (dd, J = 15, 8 Hz, 1 H), 5.62 (d, J = 16 Hz, 1 H), 5.73 (dt, J = 15, 7 Hz, 1 H), 5.77 (m, 1 H), 6.22 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 51.6 (OCH_3), 173.7 (C-1), 33.9 (C-2), 22.7 (C-3), 128.2–130.5 (C 4,5), 24.5 (C-6), 27.4 (C-7), 53.8 (C-8), 215.1 (C-9), 46.0 (C-10), 71.8 (C-11), 54.9 (C-12), 133.5 (C-13), 129.7 (C-14), 46.0 (C-15), 72.5 (C-16), 28.5 (16-CH_3), 131.6 (C-17), 129.8 (C-18), 134.7 (C-19), 131.1 (C-20), 24.4 (C-21), 22.4 (C-22), 22.4 (C-23), 25.8 (C-24). Anal. ($C_{26}H_{38}O_5$) C, H.

(±)-Methyl 7-[2β-(6-Cyclopentyl-4(*R*)-hydroxy-4-methyl-1(*E*),5(*E*)-hexadienyl)-3α-hydroxy-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (5f).[19] In a similar manner **5f** was prepared from **10f** in 23% yield (excluding overlap) from **3**: ^{1}H NMR δ 1.28 (s, 3 H), 3.65 (s, 3 H), 4.00 (q, $J \simeq$ 8 Hz, 1 H), 5.32 (complex band, 2 H), 5.35 (dd, J = 15, 9 Hz, 1 H), 5.42 (d, J = 15 Hz, 1 H), 5.65 (dd, J = 15, 5 Hz, 1 H), 5.66 (dt, J = 15, 7 Hz, 1 H). Anal. ($C_{25}H_{38}O_5$) C, H.

(±)-Methyl 7-[2β-[6-(1-Cyclopenten-1-yl)-4(*R*)-hydroxy-4-methyl-1(*E*)-hexen-5-ynyl]-3α-hydroxy-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (5g).[19] To a solution of 800 mg (2.14 mmol) of iodide **15** in 10 mL of dry ether under argon and chilled to −50 °C was added 1.34 mL (2.14 mmol, 1.6 M in hexane) of *n*-BuLi in one portion. The solution was stirred for 45 min at −50 °C, cooled to −60 °C, and treated with a solution of 280 mg (2.14 mmol) of copper 1-pentyne and 702 mg (4.28 mmol) of hexamethylphosphorus triamide in 10 mL of ether. The reaction mixture was stirred for 30 min at −60 °C and then a solution of 525 mg (1.50 mmol) of **3** in 5 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 layers were separated, and the aqueous portion was extracted with ether and then EtOAc.

The organic extracts were combined and washed with water three times, once with saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (10% EtOAc and 90% hexane) to afford 465 mg of viscous oil. The oil was dissolved in a solution of 10 mL of acetone and 2 mL of water containing 50 mg of pyridinium *p*-toluenesulfonate (PPTS). The reaction mixture was stirred at room temperature 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 extracts were washed with water, then saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (60% EtOAc and 40% hexane) to give 186 mg of **5g** in 26% yield (excluding overlap) from 3: ^{1}H NMR δ 1.53 (s, 3 H), 1.90 (p, J = 7 Hz, 2 H), 2.02 (dt, J = 12, 6 Hz, 1 H) 2.26 (dd, J = 18, 10 Hz, 1 H), 2.74 (dd, J = 18, 7 Hz, 1 H), 3.68 (s, 3 H), 4.07 (q, $J \simeq$ 8 Hz, 1 H), 5.34 (complex band, 2 H), 5.49 (dd, J = 15, 9 Hz, 1 H), 5.85 (ddd, J = 15, 8, 7 Hz, 1 H), 6.02 (m, 1 H); ^{13}C NMR δ 82, 94 (-C≡C-). Anal. ($C_{25}H_{34}O_5$) C, H.

Methyl 7-[2β-[6-(1-Cyclopenten-1-yl)-4-hydroxy-4-methyl-1(*E*)-hexenyl]-3α-hydroxy-5-oxo-(1*R*)-1α-cyclopentyl]-4(*Z*)-heptenoate (5h). To a flame-dried apparatus which was degassed three times under argon were added 1.8 g (3.33 mmol) of **10h** and 6.2 mL of dry THF. The solution was cooled to -80 °C and treated with 2.2 mL (3.52 mmol) of *n*-BuLi. The temperature rose to -60 °C. The mixture was cooled to -80 °C and stirred for 45 min. In another degassed, flame-dried apparatus under argon was added 298 mg (3.32 mmol) of copper cyanide followed by 6 mL of dry THF. The mixture was cooled to -75 °C, 2.3 mL (3.32 mmol) of MeLi was added, and the mixture was allowed to warm to -45 °C to effect homogeneity and then immediately was cooled to -80 °C. The cold anion solution (-75 °C) previously prepared was cannulated into the lithium methyl cyanocuprate (MeCuCNLi) solution and the mixture was stirred at -75 °C for 1 h. A solution of 782 mg (2.22 mmol) of 11(*R*)-3 in 3 mL of dry THF was added, and the reaction mixture was stirred at -80 °C for 1.5 h and then poured into a 9:1 mixture (180 mL) of saturated NH_4Cl/NH_4OH solution and 90 mL of ether. The mixture was stirred for 45 min, the layers separated, and the aqueous portion extracted three times with 50 mL of ether. The organic extracts were combined, washed three times with water and once with saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (4% EtOAc and 96% hexane) to give 950 mg of a colorless, viscous oil. The oil was dissolved in 18 mL of acetone and 6.7 mL of water containing 6.7 mg of PPTS. The reaction mixture was stirred at room temperature for 3.5 h and then was quenched with a mixture of 50 mL aqueous $NaHCO_3$ and 100 mL ether. The layers were separated, and the aqueous portion was extracted two times with ether. The organic extracts were combined, washed with water three times and saturated NaCl solution once, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (100% EtOAc) to give 450 mg (51% from 11(*R*)-3) of **5h** as a colorless, viscous oil: ^{1}H NMR δ 1.20 (s, C-16 CH_3), 1.54-1.73 (complex band, 4 H, C-7 H, C-17 H), 1.86 (m, C-22 H), 2.02 (dt, J = 12, 6 Hz, C-8α H), 2.14 (m, C-6 H), 2.24 (dd, J = 18.5, 9.5 Hz, 10α H), 2.35 (complex band, 4 H, C-2 H, C-3 H), 2.40 (dt, J = 12, 9 Hz, C-12β H), 2.74 (dd, J = 18.5, 7.5 Hz, C-10β H), 3.67 (s, 1-OCH_3), 4.05, 4.06 (ddd, J = 9.5, 9, 7.5 Hz, C-11 H diastereomers), 5.34 (complex band, 3 H, C-4 H, C-5 H, C-20 H), 5.44, 5.43 (dd, J = 15, 9 Hz, C-13 H diastereomers), 5.78, 5.76 (dt, J = 15, 7.5 Hz, C-14 H diastereomers); ^{13}C NMR δ 51.6 (OCH3), 173.7 (C-1), 34.0 (C-2), 22.8 (C-3), 128.4, 130.5 (C-4, C-5), 24.5 (C-6), 27.6 (C-7), 53.9 (C-8), 214.6 (C-9), 46.1, 46.0 (C-10 diastereomers), 72.1 (C-11), 55.0, 54.9 (C-12 diastereomers), 133.3 (C-13), 130.1, 130.0 (C-14 diastereomers), 45.0 (C-15), 72.3 (C-16), 26.5, 26.9 (C-16 CH_3 diastereomers), 39.5, 40.0 (C-17 diastereomers), 25.5 (C-18), 144.6, 144.7 (C-19 diastereomers), 123.3 (C-20), 32.4 (C-21), 23.4 (C-22), 35.2 (C-23). Anal. ($C_{25}H_{38}O_5$) C, H.

(±)-Methyl 7-[3α-Hydroxy-2β-[6-(2-hydroxy-(*E*)-cyclopentylidene)-4-methyl-1(*E*),4(*E*)-hexadienyl]-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (17) and (±)-Methyl 7-[2β-[6-(1-Cyclopenten-1-yl)-4-methyl-1(*E*),3(*E*/*Z*),5(*E*)-hexatrienyl]-3α-hydroxy-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (18). A solution of 240 mg of **5d** in 5 mL of a 3:1:1 mixture of AcOH, THF, and water was allowed to stand at room temperature for about 2 h. TLC (70% EtOAc and 30% hexane) indicated the presence of an approximate 1:1 mixture of **5d** and **6d** and minor amounts of two less polar compounds **17** and **18**. The reaction mixture was diluted with water and extracted three times with ether. The extracts were combined, washed with water twice and dilute $NaHCO_3$ solution once, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (60% EtOAc and 40% hexane) to afford 40 mg of **5d**, 48 mg of **6d**, 70 mg of a mixture of **5d** and **6d**, 30 mg of **17**, and 35 mg of **18**, all as viscous oils. **17**: ^{1}H NMR δ 1.78 (s, C-16 CH_3), 2.03 (dtd, J = 12, 6, 1 Hz, C-8 H), 2.14 (br q, J = 7 Hz, C-6 H), 2.24 (dd, J = 18.5, 9.5 Hz, C-10α H), 2.40 (dt, J = 12, 9 Hz, C-12 H), 2.75 (ddd, J = 18.5, 7.5, 1.0 Hz, C-10β H), 2.86 (d, J = 7 H, C-15 H), 3.67 (s, 1-OCH_3), 4.07 (ddd, J = 9.5, 9.0, 7.5 Hz, C-11 H), 4.49 (br t, J = 4.5 Hz, C-20 H), 5.33 (complex band, C-4, 5 H), 5.41 (dd, J = 15, 9 Hz, C-13 H), 5.69 (dt, J = 15, 7 Hz, C-14 H), 5.91 (dq, J = 11, 1 Hz, C-18 H), 6.37 (dq, J = 11, 2 Hz, C-17 H); ^{13}C NMR δ 16.7 (C-16 Me), 22.0 (C-22), 22.7 (C-3), 24.5 (C-6), 27.5 (C-7), 27.5 (C-23), 34.0 (C-2), 35.7 (C-21), 43.1 (C-15), 46.1 (C-10), 51.6 (1-OMe), 53.9 (C-8), 54.7 (C-12), 72.1 (C-11), 75.9 (C-20), 119.2 (C-18), 122.7 (C-17), 128.4, 130.5 (C-4,5), 131.3 (C-14), 132.3, 132.2 (C-13), 136.6, 136.7 (C-16), 146.6 (C-19), 173.7 (C-1), 215.1, 215.2 (C-9). Anal. ($C_{25}H_{36}O_5$) C, H. **18**: δ 1H NMR (mixture of 15*Z* and 15*E* isomers; *Z* isomer listed first for duplicate signals): 1.94, 1.92 (s, C-16-Me), 2.07 (dt, J = 12, 6 Hz, C-8 H), 2.27 (dd, J = 19, 9 Hz, C-10α H), 2.77 (dd, J = 19, 7.5 Hz, C-10β H), 3.65 (s, 1-OMe), 4.09, 4.08 (q, $J \simeq$ 8 Hz, C-11 H), 5.33 (m, C-4,5 H), 5.54, 5.61 (dd, J = 15, 9 Hz, C-13 H), 5.83, 5.79 (m, C-20 H), 5.98, 6.12 (d, J = 11.5 Hz, C-15 H), 6.54, 6.16 (J = 16 Hz, C-17 H), 6.64, 6.53 (d, J = 16 Hz, C-18 H), 6.75, 6.62 (dd, J = 15, 11.5 Hz, C-14 H); ^{13}C NMR (100 MHz) δ 20.5, 12.7 (C-16 Me), 134.4, 135.7 (C-16), 142.9, 143 (C-19). Anal. ($C_{25}H_{34}O_4$) C, H.

(±)-Methyl 7-[3α-Hydroxy-2β-[4(*R*)-hydroxy-4-methyl-6-(6-oxabicyclo[3.1.0]hex-1-yl)-1(*E*),5(*E*)-hexadienyl]-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (20) and (±)-Methyl 7-[3α-Hydroxy-2β-[4(*R*)-hydroxy-4-methyl-6-(2-oxocyclopentyl)-1(*E*),5(*E*)-hexadienyl]-5-oxo-1α-cyclopentyl]-4(*Z*)-heptenoate (21). A solution of 160 mg of **5d** in about 30 mL of ether was placed in a 250-mL round-bottomed flask and evaporated to dryness under a stream of N_2 with swirling to form a thin film of compound on the glass surface. The flask was placed in a water bath and warmed to 50–55 °C for about 7 h while exposed to the atmosphere. The residue was chromatographed on silica gel (Chromegasphere Si 60, 10 μm particle size, 50% EtOAc and 50% hexane) to yield 14 mg of **20** and 20 mg of **21** in addition to recovered **5d**. **20**: ^{1}H NMR[22] δ 1.31, 1.32 (s, C-16 Me), 2.21, 2.22 (dd, J = 18.5, 9.5 Hz, C-10α H), 2.72 (dd, J = 18.5, 7.5 Hz, C-10β H), 3.40, 3.43 (s, C-20 H), 3.67 (s, 1-OMe), 4.04 (q, $J \simeq$ 8 Hz, C-11 H), 5.34 (m, C-4,5 H), 5.35, 5.41 (dd, J = 15, 9 Hz, C-13 H), 5.66, 5.70 (d, J = 16 Hz, C-17 H), 5.70, 5.71 (dt, J = 15, 7.5 Hz, C-14 H), 5.90, 5.92 (d, J = 16 Hz, C-18 H); ^{13}C NMR (125 MHz) δ 19.0, 19.1 (C-22), 27.3, 27.7 (C-16 Me), 27.6 (C-21), 28.0, 28.3 (C-23), 65.4, 65.6 (C-20), 66.3, 66.5 (C-19), 125.0, 125.1 (C-18), 140.1, 140.5 (C-17). **21**: ^{1}H NMR δ 1.33, 1.34 (s, C-16 Me), 2.02 (dt, J = 12, 6 Hz, C-8 H), 2.25 (dd, J = 18, 9 Hz, C-10α H), 2.75 (dd, J = 18, 7 Hz, C-10β H), 2.80 (d, J = 6 Hz, C-19 H), 3.67 (s, 1-OMe), 4.06, 4.08 (q, J = 8 Hz, C-11 H), 5.34 (m, C-4,5 H), 5.42, 5.43 (dd, J = 15, 9 Hz, C-13 H), 5.58, 5.59 (dd, J = 16, 6 Hz, C-18 H), 5.65, 5.67 (d, J = 16 Hz, C-17 H), 5.65, 5.68 (dt, J = 15, 7 Hz, C-14 H); ^{13}C NMR (100 MHz) δ 20.7 (C-22), 27.7, 28.0 (C-16 Me), 29.8, 29.9 (C-23), 37.7, 37.8 (C-21), 52.2, 52.3 (C-20), 72.3, 72.4 (C-16), 124.2, 124.4 (C-18), 139.3, 139.5 (C-17), 219.6 (C-20). Anal. ($C_{25}H_{36}O_6$) 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

(22) The NMR data presented for **20** is for the epoxide obtained from **6d**. This data was the best that could be obtained due to the instability and low purity of **20** and should vary only slightly from the NMR data of **20** derived from **5d**.

(23) Collins, P. W.; Kramer, S. W.; Gullikson, G. W. *J. Med. Chem.* **1987**, *30*, 1952.

inervated (Pavlov) gastric pouches, were food deprived with access to water 24 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 2–5 doses and 2–7 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]

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

Diarrheal Studies. Adult Charles River male rats weighing 210–230 g were individually housed and fasted with water available ad libitum for a 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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Pyrroloisoquinoline Antidepressants. 3. A Focus on Serotonin

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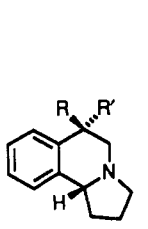
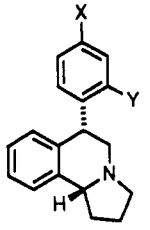
A collection of hexahydropyrroloisoquinoline derivatives (**1–22**), which represent a class of compounds that inhibit the neuronal uptake of dopamine (DA), norepinephrine (NE), and serotonin (5-HT), was investigated in vivo for serotonin-potentiating properties in the mouse head-twitch and rat serotonin syndrome assays. The *p*-methylthio compound **3b** (McN-5652-Z) was found to possess exceptional activity in these assays, and the activity was attributable almost exclusively to the (+)-6*S*,10b*R* enantiomer. Ten closely related analogues were synthesized, tested, and compared among themselves and with some previously prepared compounds, both in vivo and in vitro. Several trans diastereomers exhibited strong inhibition of 5-HT uptake and substantial potentiation of 5-HT, while the cis diastereomers (**3a**, **4a**, and **10a**) tested were virtually devoid of such activity. Although **3b** was only moderately selective in inhibiting the uptake of 5-HT vs NE, its 10-substituted analogues **4b**, **7b–9b** had improved 5-HT selectivity relative to NE, to the extent of 20–25 times (150–200 times relative to DA). Of these more selective compounds (in vitro), only **4b** and **7b** had substantial activity in vivo. Sulfoxide **11b** appeared to function as a prodrug of **3b** in vivo.

Drugs that potentiate the action of serotonin (5-HT) in the central nervous system (CNS) can be useful in a variety of therapeutic situations, including depression, obsessive–compulsive disorder, obesity, and alcohol abuse.[1] One approach to achieve this objective is the selective blockade of the uptake of serotonin into nerve cells. Over the years, such neuronal 5-HT uptake inhibitors have attracted considerable interest as antidepressants since they generally cause fewer side effects and are safer in overdosage than the more classical drugs, which generally function by potentiating central norepinephrine (NE) systems.[1b,2] Indeed, the recent favorable acceptance of fluoxetine, a selective 5-HT uptake inhibitor, serves to underscore the significance of this type of antidepressant.[3]

We have been investigating pyrroloisoquinoline derivatives for potential activity in the central nervous system.[4] This led to the discovery of a series of compounds, represented by prototype **1**, in which the trans diastereomers (**b** forms) are potent inhibitors of the uptake of biogenic amine neurotransmitters (Table I). Compound **2b** (McN-5707)[4a–c] was identified as a potential antidepressant from a drug-development perspective. During our extensive structure–activity study, we found that **3b** (McN-5652-Z) is an exceedingly potent inhibitor of the uptake of 5-HT into brain synaptosomes, although it is only



1a: R = Ph, R' = H
b: R = H, R' = Ph



2b: X = H, Y = Cl
3b: X = SMe, Y = H

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(2) Anon. *Scrip.* **1987**, October 14, No. 1248, 24.
(3) Anon. *Scrip* **1988**, August 19, No. 1336, 9.

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