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Synthesis and Gastric Antisecretory Properties of 15-Deoxy-16-hydroxyprostaglandin E Analogues

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The preparation and gastric antisecretory activity of a series of 15-deoxy-16-hydroxyprostaglandin analogues are described. The compounds were tested intravenously in histamine-stimulated Heidenhain pouch dogs in relation to the reference standards PGE_1 and PGE_1 methyl ester (PGE_1ME). The parent compound of this series, (±)-15-deoxy-16α,β-hydroxyprostaglandin E_1 methyl ester (**3**), was found to be equipotent to the reference standard PGE_1ME. Methylation at C-16 of **3** produced **8** which was found to be some 40 times more potent than PGE_1. In sharp contrast, addition of two methyl groups to **3** at C_{15} or C_{17} markedly reduced the antisecretory action. The 16-ethyl analogue of **3** also showed reduced potency. Removal or epimerization of the C-11 hydroxy group of **8** reduced the activity. Likewise, hydrogenation or changing the stereochemistry of the 13,14 double bond from trans to cis decreased the activity. On the other hand, ω-homologation of **8** or the introduction of a cis-5,6 double bond did not affect the potency. From these studies, it appears that **8**, **16**, and **17** possess optimum gastric antisecretory effects in this series.

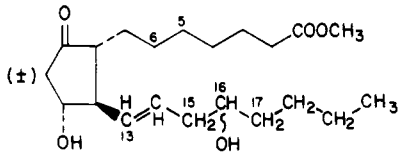
In preliminary communications[1-3] we described the influence on biological activity of transposing the 15-hydroxy group of PGE_1 and PGE_2 to carbon 16. For example, the transposition of the C-15 hydroxy group to the adjacent C-16 position significantly improved the gastric antisecretory and antiulcer actions of PGE_1. In fact, this modification confers oral activity, decreases the typical PGE_1 side effects, and prolongs biological action.[3]

We now wish to report the full experimental details of our work and define some structure–activity relationships (SAR) with respect to gastric antisecretory effects in the dog.

Chemistry. The synthesis of the parent compound of this series, (±)-15-deoxy-16α,β-hydroxyprostaglandin E_1 methyl ester (**3**), was accomplished by the stereospecific conjugate addition of the cuprate species **2** to the cyclopentenone **1b**,[4] followed by mild acid hydrolysis and purification by chromatography (Scheme I).

The cuprate reagent **2** was prepared (Scheme II) by reaction of the *tert*-butyldimethylsilyl ether of 1-octyn-4-ol (**4**) with catechol borane,[5] followed by hydrolysis to obtain the *trans*-boronic acid **5**. Treatment of **5** with sodium hydroxide in methanol followed by iodine gave the required *trans*-vinyl iodide **6**. The reaction of **6** with 1 equiv of *n*-butyllithium at −60 °C, followed by addition of an ethereal solution of 1-pentynylcopper solubilized with hexamethylphosphorous triamide,[6] yielded **2**. Although 2 equiv of *tert*-butyllithium is customarily employed to

Table I. Gastric Antisecretory Actions of 16-Hydroxyprostaglandin E Analogues Relative to PGE_1

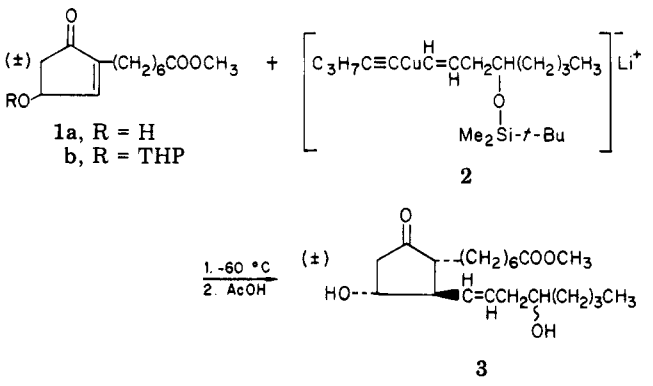


3

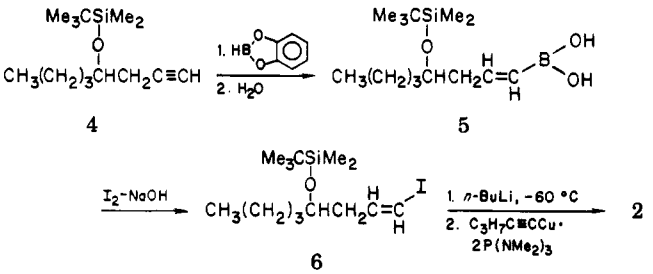
Compd	Structural difference from 3	Formula[d]	ID_{50} ± SE, μg/kg iv[a]	Potency ± SE rel to PGE_1
PGE_1			6.7 ± 0.9	1.0
PGE_1ME			3.8 ± 0.7	2.3 ± 0.5[b]
3	None	$C_{21}H_{36}O_5$	5.4 ± 2.9	0.7 ± 0.2
7	$\Delta^{5,6}$-Cis double bond	$C_{21}H_{34}O_5$	4.1 ± 1.2	1.9 ± 0.6
8	16-Methyl	$C_{22}H_{38}O_5$	0.16 ± 0.07	47.8 ± 12.2
9	15,15-Dimethyl	$C_{23}H_{40}O_5$	139.8 ± 93.3	0.05 ± 0.02[b]
10	17,17-Dimethyl	$C_{23}H_{40}O_5$	c	
11	16-Ethyl	$C_{23}H_{40}O_5$	27.8 ± 7.3	0.21 ± 0.07[b]
12	11-Deoxy-16-methyl free acid	$C_{21}H_{36}O_4$	4.3 ± 4.2	1.5 ± 0.9
13	11-Epi-16-methyl	$C_{22}H_{38}O_5$	16.9 ± 4.5	0.21 ± 0.15
14	13,14-Dihydro-16-methyl	$C_{22}H_{40}O_5$	5.9 ± 2.1	0.98 ± 0.56
15	13,14-*cis*-16-Methyl	$C_{22}H_{38}O_5$	39.8 ± 5.0	0.17 ± 0.03[b]
16	ω-Homo-16-methyl	$C_{23}H_{40}O_5$	0.31 ± 0.07	19.9 ± 5.4[b]
17	$\Delta^{5,6}$-*cis*-16-Methyl	$C_{22}H_{36}O_5$	0.30 ± 0.11	24.9 ± 6.4[b]

[a] Represents the dose needed to reduce maximal total output by 50%. [b] Significantly different from PGE_1 at $p \leq 0.05$. [c] The compound was inactive at 30 μg/kg in two dogs. Insufficient supply of the compound precluded testing at higher dosages. [d] All compounds were analyzed for C and H. The results were within ±0.4% of the calculated values except 7 (C: calcd, 68.82; found, 68.00) and 17 (C: calcd, 69.60; found, 68.85).

Scheme I



Scheme II

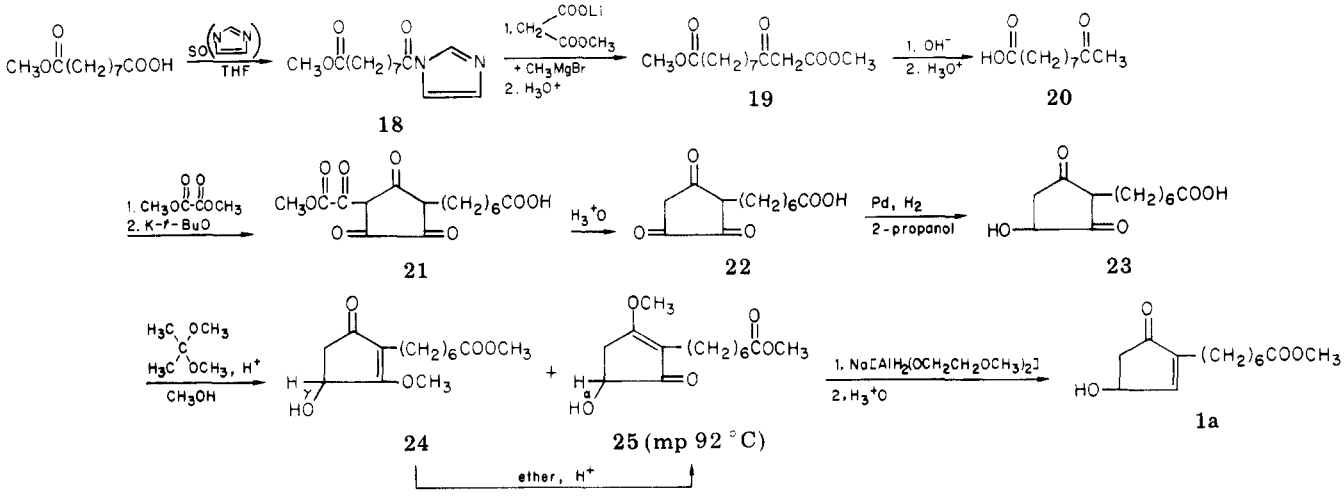


generate the vinyllithium species, we have found that 1 equiv of *n*-butyllithium gives more rapid and just as complete conversion of the vinyl iodide to its lithium counterpart.

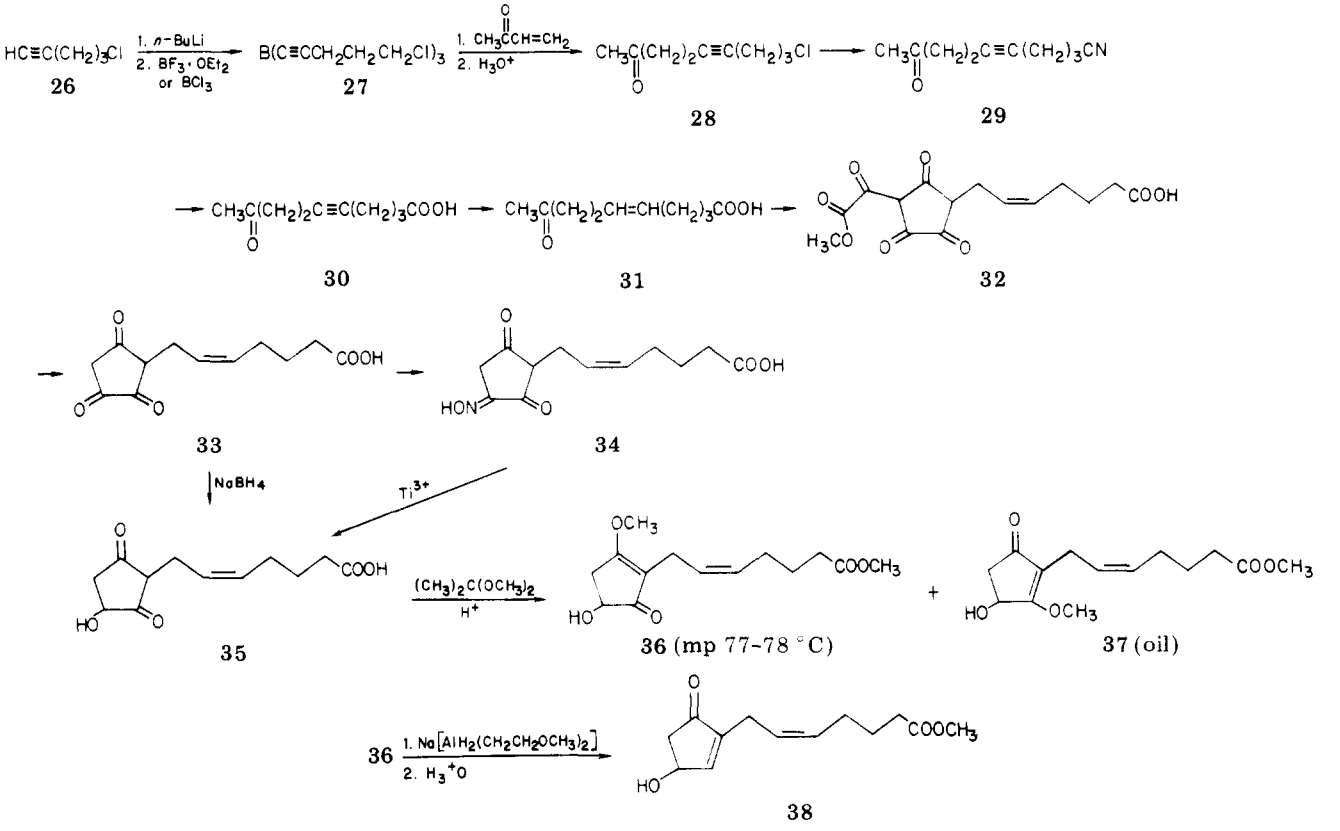
Compounds 7–12 and 15–17 (Table I) were prepared in an analogous fashion from the appropriate cyclopentenones and vinyl iodides. The synthetic sequence for the preparation of the hydroxy cyclopentenone **1a**[4] is shown in Scheme III. Conversion of monomethyl azelate with thionyldiimidazole in tetrahydrofuran to its imidazolide (**18**) was followed by condensation with the lithium salt of monomethyl malonate in the presence of methylmagnesium bromide to give the keto ester **19**. Alkaline hydrolysis and decarboxylation after acidification yielded 9-oxodecanoic acid **20**. This preparation of **20** was patterned after the work of Bram and Vilkas.[7] A distinct improvement over their method was the use of the lithium salt of monomethyl malonate. In our hands the large-scale purification of malonic acid monomethyl ester by distillation was difficult due to its instability. On the other hand, the crystalline lithium salt of this acid is easily prepared and purified. It can be stored indefinitely without decomposition. We recommend the use of this salt whenever it is possible to substitute it for the corresponding acid. Condensation of **20** with dimethyl oxalate in the presence of excess potassium *tert*-butoxide led to the glyoxalate derivative **21** which on treatment with refluxing 2 N hydrochloric acid yielded the enolic triketone **22**. Selective catalytic hydrogenation of **22** in 2-propanol in the presence of 5% palladium on carbon yielded the hydroxydione 23. Treatment of **23** with 2,2-dimethoxypropane and hydrogen chloride in methanol resulted in two isomeric enol ethers, **24** and **25**. The preponderant product was the undesired oily isomer **24**. Fortunately the desired isomer **25** was crystalline and could be obtained in good yield by treating the mixture of **24** and **25** in ether with a trace of methanolic hydrogen chloride and allowing **25** to precipitate from solution, thus disturbing the equilibrium and allowing almost complete conversion of **24** to **25**. Recently we discovered an improved technique for obtaining **25**. The reaction mixture was stripped to dryness and a small volume of ether was added to the residue which still contained traces of HCl. When allowed to stand at room temperature for 1–2 days, the mixture slowly crystallized to give exclusively **25**. Reduction of **25** with lithium aluminum hydride or, preferably, with sodium dihydrobis(2-methoxyethoxy)aluminate in toluene at −60 °C, followed by acidification, gave **1a**.

The synthesis of the *cis*-$\Delta^{5,6}$-hydroxycyclopentenone **38**[8] which was utilized in the preparation of **7** and **17** is outlined in Scheme IV. The required keto acid **30** was prepared by a novel approach based on our experience[4] on conjugate additions of 1-alkynes to α,β-unsaturated ketones. Treatment of commercially available 5-chloropentyne **26** with *n*-butyllithium followed by boron tri-

Scheme III



Scheme IV

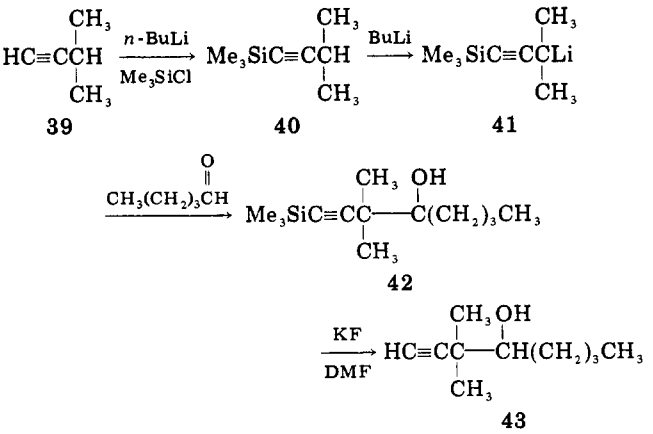


fluoride etherate or boron trichloride gave the trialkynylboron reagent **27**. The resulting mixture was treated with methyl vinyl ketone to give the desired chloro ketone **28**. Initially we had tried a dimethylalkynylalane derived from dimethylaluminum chloride and the lithium salt of 5-chloropentyne **26** using the procedure of Hooz.[9] When methyl vinyl ketone was treated with this reagent, a 1:1 mixture of the 1,2 and 1,4 addition products was obtained. Refluxing **28** with sodium cyanide in aqueous ethanol gave the nitrile **29** which was hydrolyzed to the acid **30**. Hydrogenation of **30** with palladium on barium sulfate yielded the cis-olefinic acid **31**. Conversion of **31** to the triketone **33** was carried out in a manner similar to that employed in the E_1 series. Thus **31** was condensed with dimethyl oxalate in the presence of potassium *tert*-butoxide to yield the glyoxalate derivative **32**. Treatment of **32** with refluxing aqueous hydrochloric acid gave the triketo acid **33** which was purified either by chromatography or via the corresponding monooxime **34**. Selective reduction of **33** with aqueous sodium borohydride gave the hydroxydione **35**. Alternatively **34** could be reduced with titanium trichloride in aqueous acetic acid buffered with sodium acetate to give **35**, the intermediate trione **33** being reduced further by the reagent. Conversion of **35** to the desired enol ether **36** was accomplished by the same technique employed in the E_1 series. Reduction of **36** with sodium dihydrobis(2-methoxyethoxy)aluminate followed by acid treatment yielded **38**.

The cyclopentenone required for the synthesis of **12** (Table I) was supplied by the Unilever Co. A method for its preparation has been described.[10]

The *trans*-vinyl iodides utilized in the synthesis of **7–12**, **16**, and **17** were prepared from the corresponding acetylenic alcohols by use of either the catechol borane/

Scheme V



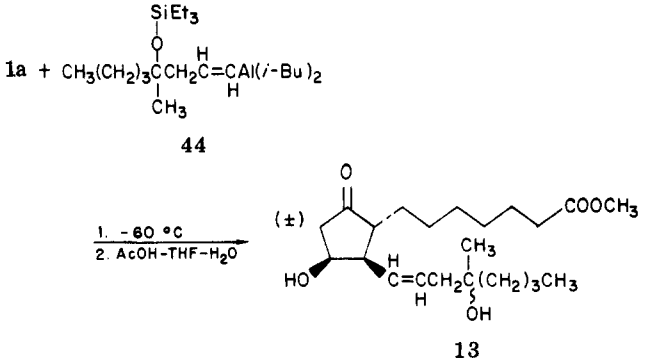
iodine–sodium hydroxide approach or by the diisobutylaluminum hydride/iodine technique.[11] The choice of the protecting group of the acetylenic alcohols was very critical to the success of these reactions. In the case of the addition of catechol borane to 1-octyn-4-ol, the use of the relatively small trimethylsilyl group or groups containing the mixed acetal function such as a tetrahydropyranyl ether resulted in either slight reaction or cleavage of the protecting group. When larger groups were employed such as *tert*-butyldimethylsilyl, reaction proceeded smoothly. With diisobutylaluminum hydride only the bulky triphenylmethyl derivative of 1-octyn-4-ol reacted cleanly. With all other protecting groups, either a mixture of products or cleavage of the protecting group was observed.

In the case of the more hindered alcohols such as 4-methyl-1-octyn-4-ol, both diisobutylaluminum hydride and catechol borane gave poor results when either the trimethylsilyl or tetrahydropyranyl groups were utilized, whereas more bulky groups such as *tert*-butyldimethylsilyl and triethylsilyl provided the products in good yield. The triethylsilyl-protecting group was preferred because the conditions required to remove the *tert*-butyldimethylsilyl group caused excessive elimination of the 11-hydroxy group. Similar reaction characteristics were noted during our earlier studies with 1-alkyn-3-ols.[12]

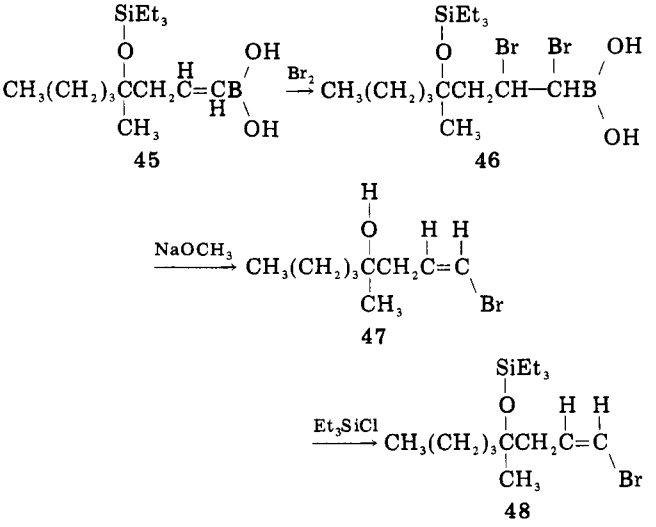
The 1-alkyn-4-ols were prepared by reaction of the appropriate carbonyl compound with the Grignard reagent derived from propargyl bromide. Synthesis of 3,3-dimethyl-1-octyn-4-ol (**43**), which was used in the preparation of **9**, required a different approach (Scheme V). Commercially available 3-methyl-1-butyne (**39**) in ether was treated successively with *n*-butyllithium and trimethylchlorosilane to generate **40** which was not isolated. A second equivalent of *n*-butyllithium was added and the solution was refluxed 24 h to generate the lithio derivative **41**. Addition of valeraldehyde followed by overnight stirring, acid work-up, and fractional distillation gave **42**. The trimethylsilyl group was removed by treatment with potassium fluoride in dimethylformamide[13] to yield **43**.

Treatment of **1a** with the diisobutylaluminum hydride adduct of 4-methyl-4-triethylsilyloxy-1-octyne (**44**) at −60 °C followed by acid hydrolysis and chromatography gave **13** (Scheme VI). Previously[1] we had found that the corresponding C-13,14 acetylenic prostaglandin could be prepared by reaction of the appropriate dialkylalkynylalane (4-methyl-4-triethylsilyloxy-1-octynylalane) with **1a**. These two reactions are in contrast to the findings of Hooz[9] that transoid α,β-unsaturated ketones do not react with alanes in a conjugate addition mode. We believe that our results can be explained on the basis of participation of the hydroxy function of **1a**. Removal or blockage of this

Scheme VI



Scheme VII



hydroxy group renders the resulting unsaturated ketones incapable of conjugate addition with the alane reagents.

Catalytic hydrogenation of **8** yielded **14** (Table I). The *cis*-vinyl bromide **48** (Scheme VII) utilized in the synthesis of **15** was prepared by the procedure of Brown et al.[14] The boronic acid derivative **45** obtained by reaction of catechol borane on the acetylene followed by hydrolysis was treated with bromine to give the dibromo compound **46**. Addition of sodium methoxide resulted in stereospecific elimination to give **47**. The strong alkaline conditions of the reaction caused the cleavage of the triethylsilyl-protecting group. However, **47** was readily reprotected to give **48**. In order to effect complete halogen–metal exchange, it was necessary to treat **48** with 2 equiv of *t*-BuLi[6] rather than the usual 1 equiv of *n*-BuLi.

Results and Discussion

Unlike PGE_1 and PGE_1ME[15] which are single isomers, all prostaglandins in this work were synthesized and tested (except compound **12** which is a single racemate) as a mixture of two racemates, i.e., a 1:1 mixture of (±)-15-deoxy-16α- and (±)-15-deoxy-16β-hydroxyprostaglandin E_1 and E_2 derivatives. It has been established that many racemic prostaglandins possess half the biological potency of the naturally occurring enantiomers.[16-18] In our studies, if it can be assumed that only a single isomer is responsible for the gastric antisecretory effect, then clearly the single isomer would be four times more potent than a mixture of two racemates. Central to this hypothesis, however, is the assumption that the other isomers present in these prostaglandins are biologically inert and have no intrinsic activity of their own. As is evident from Table I, compound **3** was found to be equipotent to PGE_1ME. This

implies that the transposition of the C-15 hydroxy group of PGE_1 to the adjacent C-16 position significantly increased the gastric antisecretory potency.

The introduction of alkyl groups in the proximity of the side-chain hydroxy group profoundly influenced the activity of the resulting prostaglandins. On the one hand, the introduction of a methyl group at the C-16 position as in **8** markedly increased the potency. On the other hand, the introduction of methyl groups adjacent to the C-16 hydroxy function at the C-15 (**9**) or C-17 (**10**) position markedly reduced or totally eliminated the antisecretory properties of the resulting prostaglandins. This latter result was rather surprising in view of the enhanced biological activities that are observed with natural prostaglandins methylated at the carbon (C-16) adjacent to the 15-hydroxy group.[19,20] It is interesting to note that the size of alkyl group at C-16 also significantly affected the potency of the resulting prostaglandin. Compound **8** which has a methyl group at C-16 was significantly more potent than **11** which has an ethyl group in the C-16 position. The reason for this decreased potency is not known, but it is probable that the larger ethyl group sterically interferes with receptor interaction.

The introduction of a cis double bond at carbons 5,6 did not appreciably affect the gastric antisecretory activity of either **3** or **8**. For example, the E_2 analogues **7** and **17** were equipotent to their respective E_1 counterparts **3** and **8**.

After having discovered the potent and prolonged gastric antisecretory actions of the 16-methyl analogue **8**,[21] attempts were made to identify the factors influencing its activity. The removal of the C-11 hydroxy group from **8** (compound **12**) reduced the potency. Likewise, epimerization of the C-11 hydroxy group (**13**) markedly decreased the potency.

The trans double bond at C-13,14 is also important. For example, the reduction of the double bond of **8** to the saturated analogue **14** yielded a biologically less active compound. This observation is in contrast to that of Lippman[22] who found a fivefold increase in biological activity in a saturated analogue (11-deoxyprostaglandin E_1) when compared to the unsaturated derivative. Likewise, the replacement of the trans-13,14 double bond of **8** with a cis-13,14 double bond in **15** significantly reduced the activity. Finally, the ω-homologation of the lower side chain of **8** did not affect potency as is evident from the activity of **16**.

From these studies, it appears that **8**, **16**, and **17** possess optimum gastric antisecretory effects in this series of synthetic prostaglandins.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The UV spectra were recorded on a Beckman ACTA CV instrument in methanol. The IR spectra were taken on a Beckman IR-12 instrument in $CHCl_3$. The NMR spectra were recorded on either a Varian Model A-60 or XL-100 spectrometer in $CDCl_3$, unless otherwise noted, with Me_4Si as internal standard. Where elemental analyses are given, results obtained were within ±0.4% of the theoretical values.

(±)-1-Octyn-4-ol. Powdered (50 mesh) magnesium metal (14 g, 0.6 mol) was suspended in 80 mL of ether and activated with $HgCl_2$ (200 mg). A solution of valeraldehyde (25 g, 0.3 mol) and propargyl bromide (36.6 g, 0.31 mol) in 120 mL of ether and 50 mL of benzene was added dropwise at a rate which produced gentle reflux. After the addition was complete, the reaction mixture was stirred for several hours and then poured into 500 mL of cold 5% H_2SO_4. The organic layer was washed with H_2O two times, dried (Na_2SO_4), and stripped of solvent under reduced pressure and the residue was distilled under vacuum to give 23 g (60%) of a colorless liquid: bp 33–34 °C (0.2 mm); ^1H NMR δ 2.05 (C_1, t).

(±)-4-*tert*-Butyldimethylsilyloxy-1-octyne (4). A stirred solution of 5 g (40 mmol) of 1-octyn-4-ol and 6.8 g (100 mmol) of imidazole in 10 mL of DMF was treated with 6.6 g (44 mmol) of *tert*-butyldimethylchlorosilane.[23] The mixture was stirred for 2 h at room temperature and then poured into a mixture of ether and H_2O. The ether layer was washed three times with H_2O, dried (Na_2SO_4), stripped of solvent under reduced pressure, and vacuum distilled to give 7.2 g (75%) of a colorless liquid: bp 64 °C (0.2 mm); ^1H NMR δ 0.87 (s, *t*-Bu protons).

(±)-4-*tert*-Butyldimethylsilyloxy-*trans*-1-octenylboronic Acid (5). To 2.4 g (10 mmol) of acetylene **4** was added 1.3 g (11 mmol) of catechol borane. The mixture was allowed to stand at room temperature for 24 h and then was poured into cold H_2O with vigorous stirring. The mixture was extracted with hexane, and the hexane solution was extracted five times with 1 N KOH to remove the catechol. The hexane solution was then extracted three to four times with Claisen's alkali (MeOH–H_2O–KOH, 100:25:35). The extracts were combined, cooled to 5 °C, and carefully acidified with 2 N HCl. The solution was extracted with ether, and the ether extract was washed with H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure to give 1.7 g (60%) of a brown oil **5**: ^1H NMR δ 0.86 (s, *t*-Bu protons), 5–6 ($C_{1\text{-}2}$, m).

(±)-4-*tert*-Butyldimethylsilyloxy-*trans*-1-octenyl Iodide (6). A solution of 1.16 g (4 mmol) of **5** in 10 mL of MeOH was cooled to 0 °C and treated with a solution of 320 mg (8 mmol) of NaOH in 3 mL of H_2O. A solution of iodine (1.01 g, 4 mmol) in 20 mL of MeOH was added dropwise to this solution. The mixture was diluted with ether, washed with H_2O, dried (Na_2SO_4), stripped of solvent under reduced pressure, and chromatographed on silica gel with hexane as eluent to give 1.1 g (75%) of a light red liquid **6**: ^1H NMR δ 6.58 (C_2, m), 6.01 [C_1, d(15)]. Anal. ($C_{14}H_{29}OSiI$) I.

(±)-15-Deoxy-16α,β-hydroxyprostaglandin E_1 Methyl Ester (3). A solution of **6** (3.7 g, 10 mmol) in 10 mL of dry ether was treated under N_2 at –60 °C with 4.7 mL of *n*-butyllithium (2.14 M in hexane, 10 mmol). After 15 min a solution of copper 1-pentyne (1.3 g, 10 mmol) and hexamethylphosphorous triamide (3.2 g, 20 mmol) in 10 mL of ether was added. After 10–15 min a solution of **1b** (1.6 g, 5 mmol) in 5 mL of ether was added dropwise. The reaction mixture was stirred for 1 h at –60 °C and then poured into a mixture of ether and 1 N HCl. The ether layer was washed with H_2O, filtered, dried (Na_2SO_4), stripped of solvent, and chromatographed (silica gel, 30% EtOAc in hexane).

The residue (2 g) was not characterized but was dissolved in 50 mL of an AcOH–H_2O–THF mixture (3:1:1)[23] and kept at room temperature overnight. The solution was diluted with ether, washed five to six times with H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure and the residue chromatographed (silica gel, 100% EtOAc) to give 1 g (55%) of **3** as a light yellow oil: ^1H NMR δ 5.74 [C_{14}, d (15.5), t (7.0)], 5.4 [C_{13}, d (15.5), d (7.3)], 4.06 [C_{11}, t (9.2), d (7.5)]. Anal. ($C_{21}H_{36}O_5$) C, H.

(±)-4-Methyl-4-triethylsilyloxy-*trans*-1-octenyl Iodide. To a solution of 2.54 g (10 mmol) of (±)-4-methyl-4-triethylsilyloxy-1-octyne in 10 mL of hexane at 0 °C was added 8 g (10 mmol) of a 20% solution of diisobutylaluminum hydride in toluene. The resulting mixture was allowed to stand at room temperature overnight. A solution of iodine (1.26 g, 10 mmol) in 5 mL of THF was added dropwise at 0 °C. The reaction mixture was diluted with ether, washed successively with dilute sodium sulfite solution and H_2O, dried (Na_2SO_4), stripped of solvent under reduced pressure, and chromatographed (silica gel, hexane as eluent) to afford 2.0 g (52%) of a pink liquid.

(±)-15-Deoxy-16-methyl-16α,β-hydroxyprostaglandin E_1 Methyl Ester (8). Following the procedure for the preparation of **3**, **(±)-4-methyl-4-triethylsilyloxy-*trans*-1-octenyl iodide** (1.9 g, 5 mmol) was converted to a mixed cuprate reagent and reacted with **1b** (2.5 mmol) to produce 475 mg (50%) of **8**: ^1H NMR δ 4.07 [C_{11}, d (8.2), t (7.5)], 2.73 [C_{10}, d (18.0), d (7.5)], 1.19 (CH_3 at C_{16}, s). Anal. ($C_{22}H_{38}O_5$) C, H.

(±)-15-Deoxy-16-methyl-16α,β-hydroxyprostaglandin E_2 Methyl Ester (17). As described for the preparation of **3** the tetrahydropyranyl ether of **38** (2.5 mmol) was allowed to react with the cuprate species derived from **(±)-4-methyl-4-triethylsilyloxy-*trans*-1-octenyl iodide** (1.9 g, 5 mmol) to give 430 mg (45%) of **17**: ^1H NMR δ 1.19 (s), 1.68 (p), 2.75 (dd), 4.09 (q). Anal. ($C_{22}H_{36}O_5$) C, H.

Lithium Monomethyl Malonate. A solution of 15 g (114 mmol) of dimethyl malonate in 50 mL of MeOH was cooled to 15 °C and treated dropwise over a 2-h period with a solution of 4.2 g (100 mmol) of $LiOH \cdot H_2O$ in 20 mL of H_2O. The mixture was stirred for 30 min after the addition was completed and then stripped of solvent in vacuo. The residue was taken up in hot MeOH; the solution was cooled to room temperature and filtered. The filtrate was stripped in vacuo almost to dryness. The residue was dissolved in 100 mL of toluene and stripped further to remove any remaining MeOH. The solution was cooled to room temperature and the precipitate collected by filtration to give 10.6 g (75%) of a white solid: ^1H NMR (D_2O) δ 3.32 (s, 2 H), δ 3.75 (s, 3 H). Anal. ($C_4H_5O_4Li$) Li.

Dimethyl 3-Ketoundecadioate (19). Imidazole (54.4 g, 0.8 mol) was dissolved in 400 mL of THF and thionyl chloride (23.8 g, 0.2 mol) in 100 mL of THF was added dropwise with stirring and cooling. The mixture was allowed to stir for 1.5 h and then was filtered under N_2 and treated with monomethyl azelate (40.4 g, 0.2 mol).

In a separate flask 25.6 g (0.2 mol) of lithium monomethyl malonate was suspended in a mixture of 75 mL of hexamethylphosphoric amide and 200 mL of THF and treated with 67 mL of methylmagnesium bromide (3 M in ether, 0.2 mol) with cooling. The imidazolide solution described above was added, and the mixture was stirred for 2 h at room temperature and poured into a mixture of ice and 50 mL of concentrated HCl. The mixture was extracted with benzene and the organic layer was washed (H_2O, 5% Na_2CO_3, H_2O), dried (Na_2SO_4), and stripped of solvent under reduced pressure. Distillation in vacuo gave 36 g (70%) of a yellow oil: bp 57 °C (0.004 mm); ^1H NMR δ 3.65 (s, 3 H), 3.68 (s, 3 H). Anal. ($C_{13}H_{22}O_5$) C, H.

9-Oxodecanoic Acid (20). To a solution of 77.4 g (0.3 mol) of **19** in 225 mL of MeOH was added a solution of 40 g (1 mol) of NaOH in 225 mL of H_2O and the mixture was allowed to stand at room temperature overnight. The solution was heated on a steam bath for 30 min, cooled, extracted with ether–benzene (1:1), acidified with 2 N HCl, and placed on a steam bath for 30 min. The mixture was cooled and extracted with ether–benzene (1:1). The organic layer was dried (Na_2SO_4) and stripped of solvent under reduced pressure and the residue was recrystallized from hexane–ether (2:1) to give 47 g (85%) of **20**: mp 45–46 °C. Anal. ($C_{10}H_{18}O_3$) C, H.

2,3,5-Trioxo-4-methoxalylcyclopentaneheptanoic Acid (21). To a mechanically stirred, refluxing solution of potassium metal (56.5 g, 1.4 mol) in 1 L of dry *tert*-butyl alcohol was added dropwise a solution of 55.8 g (0.3 mol) of **20** and 102 g (0.86 mol) of dimethyl oxalate in 150 mL of *tert*-butyl alcohol. Refluxing was continued for 2 h after the addition was complete. The reaction mixture was cooled and filtered under N_2. The filter cake was added to 1 N HCl and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was crystallized from hexane–ether (1:1) to give 49 g (50%) of **21**, mp 127–129 °C. Anal. ($C_{15}H_{18}O_8$) C, H, O.

2,3,5-Trioxocyclopentaneheptanoic Acid (22). A mixture of 50 g (0.153 mol) of **21** and 3 L of 2 N HCl was refluxed under N_2 for 2 h, cooled, and decolorized with Darco. The filtrate was stripped of solvent, and the residue was dissolved in EtOAc. The solution was washed with saturated NaCl solution (three times) and water (two times), dried (Na_2SO_4), and stripped of solvent under reduced pressure. Crystallization of the residue from H_2O yielded 28.5 g (78%) of **22**, mp 106–108 °C. Anal. ($C_{12}H_{16}O_5$) C, H, O.

(±)-2,5-Dioxo-3-hydroxycyclopentaneheptanoic Acid (23). The trione **22** (2.4 g, 10 mmol) was hydrogenated at atmospheric pressure in 70% aqueous 2-propanol (50 mL) with 5% palladium-on-carbon catalyst. The mixture was filtered, and the filtrate was stripped of solvent under reduced pressure. Recrystallization of the residue from H_2O afforded 1.9 g (80%) of **23**, mp 127–129.5 °C. Anal. ($C_{12}H_{18}O_5$) C, H, O.

(±)-Methyl 7-(4-Hydroxy-2-methoxy-5-oxocyclopent-1-ene)heptanoate (25). To a solution of 2.4 g (10 mmol) of **23** in 35 mL of MeOH was added 10 mL of acetone dimethyl acetal and 4 mL of 1% methanolic HCl. The mixture was allowed to stand at room temperature 48 h and then was stripped to dryness at room temperature and under reduced pressure. About 4 mL of ether was added and the mixture was allowed to stand at room temperature for 48 h. The solidified mixture was taken up in benzene containing 1% triethylamine and the solution was washed successively with dilute K_2CO_3 and H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue crystallized upon addition of ether to give 2.2 g (80%) of a white solid **25**, mp 92 °C. Anal. ($C_{14}H_{22}O_5$) C, H.

(±)-Methyl 7-(3-Hydroxy-5-oxocyclopent-1-ene)heptanoate (1a). Dry toluene (100 mL) was placed in a three-necked flask and cooled to −70 °C in an *i*-PrOH–dry ice bath. In separate dropping funnels were placed 15.5 mL (1.83 M solution, 28.4 mmol) of sodium dihydrobis(2-methoxyethoxy)aluminate diluted with 100 mL of toluene and a solution of **25** (6.92 g, 25.6 mmol) in 200 mL of toluene. The two solutions were added dropwise and simultaneously to the flask over a 15-min period. The temperature of the reaction mixture was not allowed to exceed −60 °C during the additions. The mixture was stirred at −70 °C for 3.5 h and at 0 °C for 15 min, quenched with MeOH (5 mL in 10 mL of toluene), and acidified with 1 N HCl (150 mL). The organic layer was separated, washed successively with dilute $KHCO_3$ and H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was dissolved in 250 mL of THF, treated with 30 mL of 1 N HCl, and placed in the refrigerator overnight. The THF was evaporated and the residue was diluted with EtOAc. The organic layer was separated, washed successively with dilute $KHCO_3$ and H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was crystallized from ether to give a white solid, **1a** (4.78 g, 78%): mp 50–51 °C; λ_{max} 222 (9400). Anal. ($C_{13}H_{20}O_4$) C, H.

(±)-Methyl 7-[3-(2-Tetrahydropyranyloxy)-5-oxocyclopent-1-ene]heptanoate (1b). A solution of **1a** (2.4 g, 10 mmol) and dihydropyran (0.9 g, 11 mmol) in 10 mL of ether was treated with 50 mg of *p*-toluenesulfonic acid, and the resulting solution was allowed to stand at room temperature overnight. The solution was diluted with ether, washed with dilute $KHCO_3$, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was taken up in hexane–ether (10:1) and placed in the refrigerator overnight. The precipitate was collected and recrystallized from hexane to give 2.7 g (84%) of a white solid, **1b**: mp 49–50 °C; λ_{max} 222 (9700). Anal. ($C_{18}H_{28}O_5$) C, H.

9-Chloro-5-nonyn-2-one (28). Under a N_2 atmosphere, *n*-BuLi (68.2 mL, 2.31 M in hexane, 0.158 mol) was added to a cold (−25 °C) solution of 14.8 g (0.144 mol) of 5-chloro-1-pentyne (**26**) in 250 mL of toluene. After 15 min, 6.87 g (0.048 mol) of boron trifluoride etherate was added and the mixture was stirred for 2.5 h at −25 °C and allowed to stand overnight at −10 °C. Methyl vinyl ketone (10.14 g, 1.44 mol) was added at −40 °C and the solution was stirred overnight at −20 °C, diluted with H_2O, acidified with 3 N HCl, and extracted with toluene. After successive washings with dilute NaOH and H_2O, the solution was dried (Na_2SO_4), the solvent evaporated under reduced pressure, and the residue distilled to give 11.8 g (48%) of **28**: bp 80 °C (0.11 mm); ^1H NMR δ 2.12 (s), δ 3.61 (t). Anal. ($C_9H_{13}OCl$) C, H, Cl.

9-Cyano-5-nonyn-2-one (29). A solution of 2.77 g (16 mmol) of **28** in 8 mL of EtOH was added to a solution of 2.8 g (56 mmol) of NaCN in 4 mL of H_2O and refluxed for 18 h. The solution was cooled and diluted with 20 mL of ether and 20 mL of 5% NaOH. The layers were separated, and the ether portion was washed (H_2O). The solution was dried (Na_2SO_4) and the solvent removed by evaporation under reduced pressure to give 1.9 g (72%) of **29**. An analytically pure sample was obtained by distillation: bp 122–126 °C (0.03 mm); ν_{max} 2250 cm^{-1}. Anal. ($C_{10}H_{13}NO$) C, H, N.

9-Oxo-5-decynoic Acid (30). A solution of 1.79 g (11 mmol) of **29** in 5 mL of EtOH and 5 mL of 5% NaOH was refluxed for 6 h, cooled, and extracted with $CHCl_3$ to remove any starting material. The aqueous phase was acidified with dilute HCl and extracted with $CHCl_3$. The organic layer was washed (H_2O) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give 1.5 g (76%) of **30**, bp 139–142 °C (0.05–0.07 mm), which crystallized upon refrigeration. Anal. ($C_{10}H_{14}O_3$) C, H.

9-Oxo-5-*cis*-decenoic Acid (31). A solution of 23.6 g (128 mmol) of **30** in 1 L of benzene and 221.4 mL of benzene containing 1% quinoline was hydrogenated over 5% palladium on barium sulfate at room temperature and a pressure of 2 psi. The catalyst was removed by filtration and the solution washed successively

with dilute HCl and H_2O and dried (Na_2SO_4), and the solvent was removed in vacuo to give 22.4 g (95%) of a colorless oil, **31**: ^1H NMR δ 2.12 (s), δ 5.38 (t). Anal. ($C_{10}H_{16}O_3$) C, H.

7-(2,3,5-Trioxo-4-methoxalylcyclopentane)hept-5-*cis*-enoic Acid (32). Potassium metal (32 g, 0.82 mol) was dissolved in 184 mL of dry refluxing *t*-BuOH under N_2, and a solution of 25.2 g (0.137 mol) of **31** and 48.5 g (0.41 mol) of dimethyl oxalate in 30 mL of *t*-BuOH was added slowly to the resulting solution. After 2.5 h, the reaction mixture was cooled slightly and filtered under N_2. The filter cake was acidified with 1 N HCl and extracted thoroughly with $CHCl_3$. The organic phase was washed with saturated NaCl and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded 18.1 g (41%) of the crude product **32** which was used without further purification.

7-(2,3,5-Trioxocyclopentane)hept-5-*cis*-enoic Acid (33). A solution of 11 g (34 mmol) of **32** in 490 mL of dilute HCl was refluxed for 3 h, cooled, and extracted with EtOAc. The organic layer was washed with saturated NaCl solution and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel, 20% EtOAc–PhH) to give 1.54 g (19%) of **33** as pale yellow crystals, mp 84–85 °C. Anal. ($C_{12}H_{14}O_5$) C, H.

7-(2,5-Dioxo-3-hydroxyiminocyclopentane)hept-5-*cis*-enoic Acid (34). A solution of 476 mg (2 mmol) of crude **33** in 4 mL of pyridine was treated with 153 mg (2.2 mmol) of $HONH_2$·HCl and allowed to stir overnight at room temperature. The solution was diluted with EtOAc and washed with an ice-cold mixture of concentrated HCl–H_2O and then with H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was crystallized from H_2O to give 233 mg (46%) of **34**, mp 163–164 °C (H_2O). Anal. ($C_{12}H_{15}O_5N$) C, H, N.

(±)-7-(2,5-Dioxo-3-hydroxycyclopentane)hept-5-*cis*-enoic Acid (35). Method A. At 58 °C, under an N_2 atmosphere, 1.95 g of $TiCl_3$ in 14.5 mL of aqueous AcOH (1:1) was added dropwise and very slowly to a solution of 255 mg (1 mmol) of **34** in 13 mL of aqueous AcOH (1:1) and 1.64 g of NaOAc in 5 mL of H_2O until a green color persisted. The solution was concentrated on a rotary evaporator, acidified with 1 N HCl, and extracted with EtOAc. The organic layer was washed (H_2O), dried (Na_2SO_4), and evaporated under reduced pressure leaving 185 mg (77%) of a crystalline product: mp 83–85 °C; ^1H NMR (D_2O) δ 5.45 (t), 4.75 (s), 4.63 (dd), 2.85 (d), 2.94 (dd), 2.32 (dd). Anal. ($C_{12}H_{15}O_5$) C, H.

Method B. To a solution of 1.15 g (4.8 mmol) of **33** in a mixture of 37 mL of EtOH and 46 mL of H_2O was added, at 0–5 °C, a solution of 548 mg (14.3 mmol) of $NaBH_4$ in 2 mL of H_2O. The solution was stirred for 30 min and quenched with 1 N HCl. The solution was extracted with EtOAc (three times). The extracts were combined, washed (saturated NaCl), dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give 900 mg (79%) of **35**.

(±)-Methyl 7-(4-Hydroxy-2-methoxy-5-oxocyclopent-1-ene)hept-5-*cis*-enoate (36). Except that the residue from the reaction mixture and the ether were allowed to stand 2–3 days in the refrigerator rather than at room temperature, the method used for the preparation of **25** was employed to convert 2.4 g (10 mmol) of **35** to 1.88 g (70%) of **36**, mp 77–78 °C. Anal. ($C_{14}H_{20}O_5$) C, H.

(±)-Methyl 7-(3-Hydroxy-5-oxocyclopent-1-ene)hept-5-*cis*-enoate (38).[8] The procedure for the preparation of **1a** was used to convert 2.38 g (10 mmol) of **36** to 1.45 g (61%) of **38** obtained as a colorless oil following chromatography (silica gel, 40% EtOAc–PhH). Anal. ($C_{13}H_{18}O_4$) C, H.

1-Trimethylsilyl-3,3-dimethyl-1-octyn-4-ol (42). A solution of 3-methyl-1-butyne (**39**) (Farchan Labs) (6.8 g, 100 mmol) in 50 mL of ether was cooled to −40 °C in a dry ice–2-propanol bath and treated with *n*-butyllithium (47 mL, 2.17 M in hexane, 100 mmol). The mixture was allowed to warm to room temperature and then was treated with trimethylchlorosilane (10.8 g, 100 mmol) to give **40**. Another equivalent of *n*-butyllithium (47 mL) was added and the mixture was refluxed for 24 h to generate the anion **41**. The reaction mixture was cooled to −10 °C and valeraldehyde (8.5 g, 100 mmol) was added. The mixture was allowed to rise to room temperature and was poured into cold 1 N HCl. The organic layer was separated, washed with H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was chromatographed on silica gel with 10% EtOAc in benzene as eluent to give 3.4 g (15%) of **42**: ^1H NMR δ 1.20, 1.25 (s, methyl groups), 2.4 (m, C_4).

3,3-Dimethyl-1-octyn-4-ol (43). A mixture of 3 g of **42** and 6 g of powdered KF in 75 mL of DMF was stirred vigorously at room temperature for 4–5 h. The mixture was poured into H_2O and extracted with ether. The ether layer was washed with H_2O (five times), dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was chromatographed on silica gel with 10% EtOAc in benzene as eluent to give 1.6 g (80%) of **43**: ^1H NMR δ 2.15 (s, C_1); IR 3322 cm^{-1}.

(±)-11-Epi-15-deoxy-16-methyl-16α,β-hydroxyprostaglandin E_1 Methyl Ester (13). A solution of 2 g (8 mmol) of (±)-4-methyl-4-triethylsilyloxy-1-octyne in 5 mL of hexane was treated with 5.6 g of a 20% by weight solution of diisobutylaluminum hydride in toluene (8 mmol) at 0 °C. The solution was allowed to stand at room temperature overnight. The solution was cooled to −60 °C and treated with an ether solution of 960 mg (4 mmol) of **1a**. The reaction mixture was stirred at −60 °C for 2 h and then poured into 1 N HCl. The organic layer was washed with H_2O, dried (Na_2SO_4), and stripped under reduced pressure, and the residue was chromatographed (silica gel, 30% EtOAc–PhH). The product (1.1 g) was not characterized but was dissolved in 25 mL of an AcOH–H_2O–THF mixture (3:1:1) and kept at room temperature overnight. The solution was diluted with ether, washed with H_2O (five to six times), dried (Na_2SO_4), stripped under reduced pressure, and chromatographed (silica gel, 100% EtOAc) to give 0.53 g (35%) of **13** as a light yellow oil: ^1H NMR δ 4.37 (C_{11}, m, $W_{1/2}^{max}$ = 8 Hz), δ 6.68 (C_{13} and C_{14}, m). Anal. ($C_{22}H_{38}O_5$) C, H.

(±)-15-Deoxy-13,14-dihydro-16-methyl-16α,β-hydroxyprostaglandin E_1 Methyl Ester (14). A solution of 96 mg (0.25 mmol) of **8** in 10 mL of 2-propanol was hydrogenated at atmospheric pressure and room temperature with 5% palladium-on-carbon catalyst. The mixture was filtered, and the filtrate was stripped of solvent under reduced pressure to give **14** as a colorless oil: ^1H NMR no olefinic protons present. Anal. ($C_{22}H_{40}O_5$) C, H.

(±)-4-Hydroxy-4-methyl-*cis*-1-octenyl Bromide (47). A solution of 5.7 g (20 mmol) of (±)-4-triethylsilyloxy-4-methyl-*trans*-1-octenylboronic acid (**45**) in 20 mL of ether was treated at −30 °C with a solution of 3.2 g (20 mmol) of bromine in 20 mL of CH_2Cl_2. The solution was allowed to rise to room temperature for 15 min and then recooled to −30 °C. Sodium methoxide (1.1 g) in 20 mL of MeOH was added and the mixture again allowed to come to room temperature. The reaction mixture was poured into 1 N HCl and extracted with ether. The organic layer was washed with H_2O, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The residue was chromatographed on silica gel (10% EtOAc in PhH as eluent) to give 2.5 g (60%) of **47** as a colorless oil: ^1H NMR δ 6.1–6.45 (m, J = 7 Hz, C_1 and C_2).

Gastric Antisecretory Studies.[24,25] Adult female mongrel dogs with Heidenhain pouches and weighing between 15 and 18 kg were used in these experiments. The dogs had been trained to stand quietly in a Pavlov support and were conscious during all studies. The surgery was done about 1 year before these studies were started. The animals were not used more than once per week.

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 (iv) with 0.15 M NaCl solution. Gastric pouch secretion was collected at 15-min intervals and measured for volume to the nearest 0.1 mL. After 15–30 min basal secretion, the dogs were infused with histamine solution at the submaximal dose of 1.0 mg/h. This dose, which was approximately equivalent to 60 μg/kg/h, was chosen from predetermined dose–response curves to represent 75% of maximal stimulation in this series of dogs. The volume of infusion was kept at approximately 13.0 mL/h. Approximately 1 h after the start of histamine infusion, a steady-state plateau of gastric secretion was obtained. At this time the prostaglandin was administered by a single intravenous bolus injection using a total volume not exceeding 3.0 mL/dog. The doses usually ranged from 0.1 to 100 μg/kg and were logarithmically spaced. At least two dogs were employed at each test dose.

Gastric samples were measured for total acidity by titration with 0.1 N sodium hydroxide solution to pH 7.0 (Radiometer,

Copenhagen). ID_{50} values and relative potencies of the compounds were calculated[26,27] from the degree of maximum inhibition of total acid output. The ID_{50} is defined as the dose which caused 50% inhibition of total acid output in this series of dogs.

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Orally Active Esters of Cephalosporin Antibiotics. Synthesis and Biological Properties of Acyloxymethyl Esters of 7-(D-2-Amino-2-phenylacetamido)-3-[5-methyl-(1,3,4-thiadiazol-2-yl)thiomethyl]-3-cephem-4-carboxylic Acid

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The synthesis of the acetoxymethyl (AOM), pivaloyloxymethyl (POM), and phthalidyl (PHTH) esters of 7-[D-(−)-2-amino-2-phenylacetamido]-3-[5-methyl-(1,3,4-thiadiazol-2-yl)thiomethyl]-3-cephem-4-carboxylic acid (**1a**), a broad-spectrum semisynthetic cephalosporin antibiotic, is described. These esters were examined as potential orally active antibiotic prodrugs. The superior oral absorption of the three esters relative to the unesterified parent, **1a**, is demonstrated by differential blood levels as well as measurement of the rate at which doses of the ester leave the gastrointestinal tract and appear in the urine. A study of the decreased stability of the three esters relative to **1a** at pH 4.5, 6.5, and 7.5 is also presented.

Sodium cephalothin [sodium 7-(2-thienylacetamido)-3-acetoxymethyl-3-cephem-4-carboxylate, KEFLIN, Lilly], the first cephalosporin antibiotic available for clinical use, was marketed in the U.S. in 1964. The remarkable safety and efficacy of this parenteral antibiotic prompted a major medicinal chemistry effort to prepare analogues which were well absorbed orally in addition to having high antimicrobial potency and broad spectra. As a result, cephaloglycin [7-(D-2-amino-2-phenylacetamido)-3-acetoxymethyl-3-cephem-4-carboxylic acid, KAFOCIN, Lilly][1] and cephalexin [7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid, cephalexin monohydrate, KEFLEX, Lilly][2] were made available as safe, effective, orally absorbed antibiotics. While cephaloglycin is more potent than cephalexin,[3] the latter is more efficiently absorbed orally.[4] Recently, however, Binderup and coworkers reported that administration of acetoxymethyl and pivaloyloxymethyl esters of cephaloglycin resulted in more efficient oral absorption of cephaloglycin in both rats and man.[5] These esters are enzymatically degraded to cephaloglycin both during the process of absorption from the gastrointestinal tract and after absorption occurs.

Esters of ampicillin [6-(D-2-amino-2-phenylacetamido)penicillanic acid][6] and carbenicillin [6-(2-carboxyl-2-phenylacetamido)penicillanic acid; disodium carbenicillin, Geopen, Roerig][7] are well absorbed orally giving higher blood levels than the unesterified parent compound in both laboratory animals and humans. Reports on the clinical efficacy of pivampicillin (the pivaloyloxymethyl ester of ampicillin) are numerous.[8–10] The phthalidyl ester of ampicillin is efficiently absorbed orally in both laboratory animals and man.[11,12] Bacampicillin (the ethoxycarbonyloxyethyl ester of ampicillin) is rapidly converted to ampicillin in vivo in rats, dogs, and man.[13] Oral administration of bacampicillin results in earlier and higher peak blood levels of ampicillin than when an equimolar