Articles

Synthesis and Gastric Antisecretory Properties of 4,5-Unsaturated Derivatives of 15-Deoxy-16-hydroxy-16-methylprostaglandin E_1[1,2]

Paul W. Collins,* Esam Z. Dajani, Raphael Pappo,[2] Alan F. Gasiecki, Robert G. Bianchi, and Emmett M. Woods

Departments of Medicinal Chemistry and Biological Research, G. D. Searle & Co., Chicago, Illinois 60680.
Received July 6, 1982

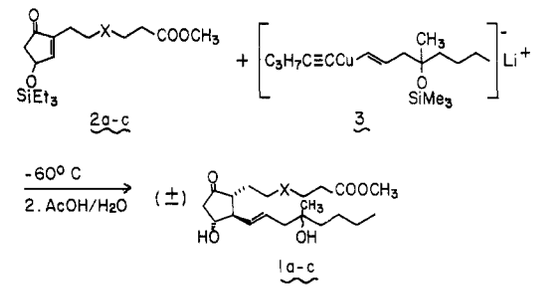
The synthesis and gastric antisecretory activities of the $\Delta^{4,5}$-cis, $\Delta^{4,5}$-trans, and 4,5-acetylenic analogues of 15-deoxy-16-hydroxy-16-methyl prostaglandin E_1 methyl ester are described. The key step in the preparation of these compounds involved the stereospecific conjugate addition of a cuprate reagent to the appropriate cyclopentenones. Although the trans and acetylenic derivatives were weak inhibitors of gastric acid secretion, the cis olefin was more potent and longer acting than the saturated parent compound. Selectivity with respect to unwanted diarrheagenic effects was found to be improved over that of both the parent 16-hydroxy compound and the reference standards, (15*S*)-15-methyl- and 16,16-dimethylprostaglandin E_2.

Recent publications[3-5] have described the effects of inserting a 4,5 cis double bond into various prostaglandin structures. Metabolic inactivation via β oxidation of the upper side chain is impeded by this relatively simple modification, and, depending on metabolic susceptibility of other sites in the molecule, the half-life of the resulting compounds may be increased. Improved separation of gastric antisecretory activity from undesired diarrheagenic properties also has been observed with this functionality.[6]

We were prompted by these reports to investigate the influence of a 4,5 cis double bond on the metabolic and pharmacological characteristics of our previously reported gastric antisecretory agent, 15-deoxy-16-hydroxy-16-methyl prostaglandin E_1 methyl ester **19**.[7,8a] The corresponding $\Delta^{4,5}$-trans and 4,5-acetylenic derivatives also became synthetic targets because the influence of these modifications on β oxidation of prostaglandins have not been described, and they were easily accessible by the preparative pathway that we utilized.

Chemistry. The key step in the synthesis of these compounds is the well-established[8a-c] stereospecific conjugate addition of the cuprate species **3** to the cyclopentenones **2a–c**, followed by mild acid hydrolysis of protecting groups and chromatographic purification (Scheme I) to give **1a–c**. It should be noted that these prostaglandin derivatives exist as a mixture of two racemates, since racemic starting materials are employed.

Scheme I

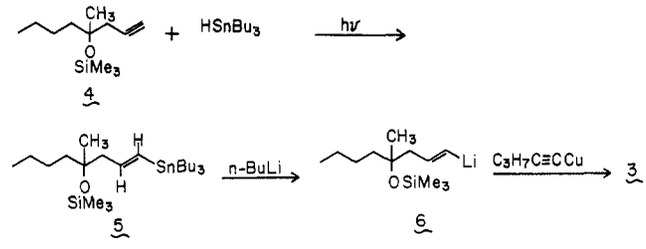


1a and 2a; X = -C≡C-

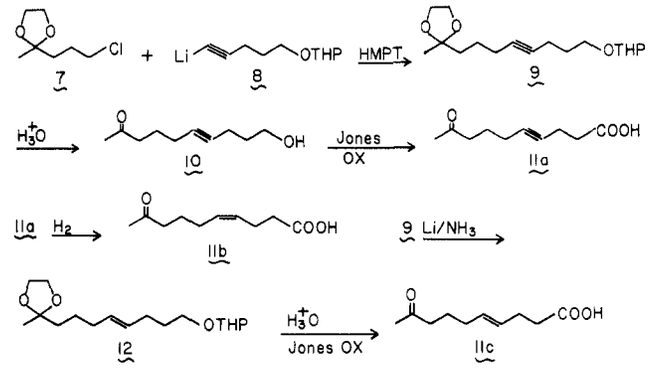
1b and 2b; X = -CH=CH Cis

1c and 2c; X = -CH=CH Trans

Scheme II



Scheme III

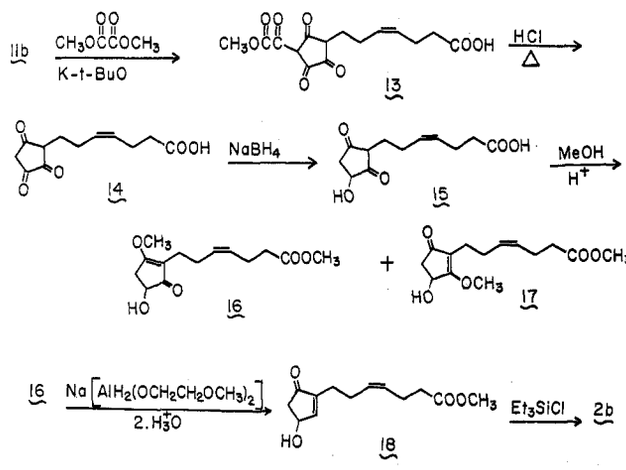


The cuprate reagent **3** was prepared (Scheme II) as previously described.[9] Thus, irradiation with a sunlamp

(1) Portions of this work were presented at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, Mar 1982. See P. W. Collins et al. in "Abstract of Papers", American Chemical Society, Washington, DC, 1982, Abstr MEDI 62.
(2) Present address: International Plant Research Institute, San Carlos, CA 94070.
(3) K. Green, B. Samuelson, and B. J. Magerlein, *Eur. J. Biochem.* **62**, 527 (1976).
(4) E. G. Nidy and R. A. Johnson, *J. Org.* Chem., **45**, 1121 (1980).
(5) W. G. Tarpley and F. F. Sun, *J. Med. Chem.*, **21**, 288 (1978).
(6) E. R. H. Walker "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids", Pergamon Press, Elmsford, NY, 1979, p 326.
(7) E. Z. Dajani, D. R. Driskill, R. G. Bianchi, P. W. Collins, and R. Pappo, *Am. J. Dig. Dis.*, **21**, 1049 (1976).
(8) (a) P. W. Collins, E. Z. Dajani, D. R. Driskill, M. S. Bruhn, C. J. Jung, and R. Pappo, *J. Med. Chem.*, **20**, 1152 (1977); (b) C. J. Sih, J. B. Heather, R. Goal, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, *J. Am. Chem. Soc.*, **97**, 865 (1975); (c) J. S. Skotnicki, R. E. Schaub, M. J. Weiss, and F. Dessy, *J. Med. Chem.*, **20**, 1042 (1977).

0022-2623/83/1826-0786$01.50/0

Scheme IV

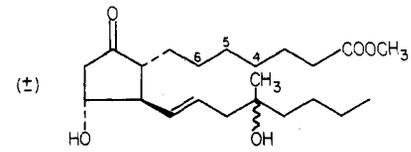


of an undiluted mixture of the protected acetylenic alcohol **4** and tri-*n*-butyltin hydride for 2 h at room temperature and then for 2 h at about 55 °C effected a smooth conversion to the *trans*-vinylstannane **5**.[10] Treatment of **5** with 1 equiv of *n*-butyllithium at −50 °C for about 1 h provided the *trans*-vinyllithium species **6**, which was converted in situ to the cuprate reagent **3** by addition of an ethereal solution of copper 1-pentyne solubilized with 2 equiv of hexamethylphosphorus triamde.[11]

The primary task in this synthesis, therefore, was the construction of the requisite cyclopentenones **2a–c**. Our synthetic strategy involved generation of the appropriate keto acids **11a–c** (Scheme III), which then could be converted to **2a–c** by a pathway (Scheme IV) previously reported[8a] and well known to us. Condensation of 5-chloro-2-pentanone ethylene ketal **7**[12] with the lithium salt of the tetrahydropyranyl ether of 1-pentyn-4-ol **8**[13] (generated in situ from the corresponding acetylene and *n*-butyllithium) in THF was effected at reflux in the presence of hexamethylphosphoric triamide (HMPT) to give **9**. Alternately, we found that the corresponding 5-bromo derivative of **7** would react at room temperature, again, in the presence of HMPT. Exposure of **9** to a tetrahydrofuran, methanol, and 1 N hydrochloric acid mixture at room temperature hydrolyzed both protecting groups to provide **10**. Without purification, **10** was oxidized with Jones reagent at 0 °C to afford **11a** following an acid–base extractive workup. The corresponding cis keto acid **11b** was obtained by hydrogenation of **11a** with a quinoline poisoned Pd on $BaSO_4$ catalyst. Alternatively, **11b** could be prepared by catalytic reduction of **9**, followed by hydrolysis and oxidation. Reduction of **9** with lithium metal in liquid ammonia gave the trans product **12**. Hydrolysis and oxidation of **12** provided the trans keto acid **11c**. The coupling constants of the olefinic protons of **11b** and **11c** were determined by utilization of the shift reagent Eu(fod)$_3$.[14]

The conversion of the cis keto acid **11b** to the corresponding cyclopentenone **2b** is outlined in Scheme IV.

Table I. Comparative Gastric Antisecretory Actions of 16-Hydroxyprostaglandins in Dogs



no.	struct diff from 19	approx. ED_{50}'s, μg/kg iv[a]	ig[b]
19		0.3–1.0[d]	5.5–10.0[d]
20	5,6-*cis*-olefin	0.3–1.0[d]	4.5–10.0[d]
1a	4,5-acetylene	>100	ND[c]
1b	4,5-*cis*-olefin	0.1–0.3[d]	0.3–1.0[d]
1c	4,5-*trans*-olefin	10	ND[c]

[a] Determined in histamine-stimulated Heidenhain pouch dogs. [b] Determined in histamine-stimulated gastric fistula dogs. [c] Not determined. [d] Number at the end of range represents the lowest dose at which the mean percent inhibition of total acid output was significantly greater than 50% by Student's *t* test with $p = 0.05$.

Condensation of **11b** with dimethyl oxalate in the presence of excess potassium *tert*-butoxide in refluxing *tert*-butyl alcohol gave the glyoxalate derivative **13**. The glyoxalate moiety was removed by refluxing **13** in 1 N HCl to afford the triketone **14**. Reduction of **14** with sodium borohydride in ethanol and water at 0 °C cleanly yielded the hydroxy dione **15**. Esterification of **15** to a mixture of isomeric enol ethers **16** and **17** was carried out in methanol containing hydrochloric acid and the water scavenger 2,2-dimethoxypropane. The desired isomer **16** is crystalline (**17** is an oil) and was obtained in good yield by the following technique.[8a] 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 **16**. Reduction of **16** with sodium dihydrobis(2-methoxyethoxy)aluminate in toluene at −60 °C, followed by acidic workup, gave **18**. Conversion of **18** to its triethylsilyl ether **2b** was carried out with triethylchlorosilane in dimethylformamide and imidazole as base at room temperature.[15] In previous work[8a] we had utilized the tetrahydropyranyl group for protection of the hydroxycyclopentanones. More recently, we have found the triethylsilyl ether to be superior because of the ease and completeness of its removal following the cuprate reaction. In a similar manner, the keto acids **11a** and **11c** were converted to the corresponding cyclopentenones **2a** and **2c**.

Results and Discussion

The intravenous (iv) and intragastric (ig) antisecretory activities of these derivatives were determined in histamine-stimulated Heidenhain pouch (HP) and gastric fistula (GF) dogs, respectively. Comparison is made with the saturated parent compound **19**, as well as the corresponding 5,6-cis derivative **20** in Table I. As previously reported,[8a] insertion of the 5,6 cis double bond into **19** has little, if any, effect on the potency of **19** either by iv or ig administration (compare **19** with **20** in Table I).

In the present work we have found that the introduction of a cis double bond between the 4 and 5 positions of **19** results in marked improvement in potency and duration of action. Compound **1b** is approximately three times more potent than **19** when administered iv to HP dogs and

(9) P. W. Collins, C. J. Jung, A. F. Gasiecki, and R. Pappo, *Tetrahedron Lett.*, 3187 (1978).
(10) This reaction actually gives a 85:15 equilibrium mixture of trans/cis isomers. See ref 9 for details.
(11) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
(12) Available from Aldrich Chemical Co.
(13) The alcohol is available from Farchan Laboratories. The THP ether was prepared by standard methods.
(14) R. E. Rondeau and R. E. Sievers, *J. Am. Chem. Soc.*, **93**, 1522 (1971).
(15) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **91**, 6190 (1972).

Table II. Comparative Oral Gastric Antisecretory and Diarrheal Effects of (*E*)-Prostaglandin Analogues

compound	ED_{50}, μg/kg ig: gastric antisecretory effects in dogs[a]	ED_{50}, μg/kg ig: diarrheal effects in rats[b] (mean ± SE)	therapeutic index: ED_{50} Diarrhea / ED_{50} Antisecretory
(15*S*)-15-Me-PGE_2 Me ester	6.5-10.0[c]	27 ± 6	4.2
16,16-Me_2-PGE_2 Me ester	2.4-3.0[c]	10 ± 4.0	4.2
19	5.5-10.0[c]	366 ± 70	66.5
20	4.5-10.0[c]	124 ± 33	27.6
1b	0.3-1.0[c]	62 ± 11	208

[a] Determined in the histamine-stimulated gastric fistula dogs. [b] Adult male rats, fasted 24 h prior to the test, were administered logarithmically graded doses of the prostaglandins. Diarrhea was assessed at hourly intervals after prostaglandin administration on an all or none basis. [c] Number at the end of range respresents the lowest dose at which the mean percent inhibition of total acid output was significantly greater than 50%, by Student's *t* test with $p = 0.05$.

about 18 times more potent than **19** by ig administration to GF dogs. At equally active iv or ig doses, the duration of the gastric antisecretory effects of **1b** was significantly longer than that achieved with **19**.[16] The basis for the potent and prolonged gastric antisecretory effects of **1b** has not been established, but it is quite possible that the reported[3-5] metabolic stabilizing influence of the 4,5 cis double bond is responsible. Metabolic studies with radiolabeled **1b** are currently in progress to address this issue. Another interesting finding was that the ratio of ig to iv antisecretory ED_{50} doses for the saturated parent **19** is about 18, while the same ratio for **1b** is only 3. This fact suggests that **1b** has greater bioavailability than **19** due to either improved absorption or decreased metabolic degradation. Another possibility is that **1b** has a more pronounced topical effect on the gastric mucosa than does **19**. Further studies are needed, however, to determine potential local actions of either compound on gastric mucosa.

In contrast to the 4,5 cis double bond, the introduction of a 4,5 trans double bond into **19** reduces activity by approximately 30-fold, while, surprisingly, the acetylenic derivative **1a** was found to be totally devoid of gastric antisecretory activity at the highest dose tested (100 μg/kg). These findings demonstrate that small changes in the upper side chain of prostaglandins can significantly affect pharmacological activities, as well as susceptibility, to β oxidation. Although the influence on metabolic stability of these latter modifications remains unidentified, it is interesting to speculate that the diminsihed gastric antisecretory effects shown by these analogues are due to distortion of a preferred shape or geometry of the α chain, which is necessary for optimal receptor interaction.

Diarrhea is a side effect that has been consistently observed with administration of natural and synthetic prostaglandins to animals[17,18] and man.[19-21] In order to provide a better perspective concerning the selectivity of our synthetic prostaglandins, we have evaluated the diarrheagenic potential of these compounds in relationship to their gastric antisecretory properties in animals. The diarrheal effects of **19**, **20**, and **1b** were determined in rats by using (15*S*)-15-Me-PGE_2 methyl ester[22] and 16,16-Me_2-PGE_2 methyl ester[23] as reference standards. The data in Table II indicate that, by ig administration, the antisecretory effects of the reference standards were comparable to those of **19** and **20**. In sharp contrast, **1b** showed significantly higher potency as an inhibitor of gastric secretion. Examination of the diarrheal ED_{50} values in Table II shows that the two reference standards exhibited the greatest ability to induce diarrhea, while **19** was the weakest in this respect. Computation of therapeutic indexes of diarrheal to antisecretory ED_{50}'s reveals that the 15-hydroxyprostaglandins display poor separation of desired antisecretory effects from unwanted diarrheagenic actions. In fact, these compounds consistently produced diarrhea in histamine-stimulated dogs when administered at maximally effective antisecretory doses. In comparison, the 16-hydroxyprostaglandin E_2 analogue **20** is about seven times more selective, and the parent compound of this series (**19**) is approximately 16 times more selective than the 15-hydroxyprostaglandins. However, the highest degree of selectivity was shown by **1b**, whose therapeutic index was 50 times higher than those of the 15-hydroxyprostaglandin standards and about 3 times greater than that of **19**. Interestingly, none of these 16-hydroxyprostaglandins induces diarrhea in histamine-stimulated dogs at maximally effective antisecretory doses. Furthermore, species differences do not appear to exist because both **19** and **1b** produced diarrhea in dogs at dosage levels corresponding to those found in rats.[16] Indeed, it is reasonable to expect that both **19** and **1b** will exhibit a good degree of selectivity in man.

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 NMR spectra were recorded on either a Varian Model A-60 or XL-100 spectrometer in $CDCl_3$ with Me_4Si as internal standard. Where elemental analyses are given, results obtained were within ±0.4% of the theoretical values. Solvents were removed under reduced pressure on a rotary evaporator. Temperatures are given in degrees centigrade.

2-[8-[(2-Tetrahydropyranyl)oxy]-4-octynyl]-2-methyl-1,3-dioxolane (9). A solution of 18.5 g (0.11 mol) of the tetrahydropyranol ether of 4-pentyn-1-ol[13] in 125 mL of THF (freshly distilled from $LiAlH_4$) was cooled under N_2 to −30 °C and treated with 46 mL of *n*-butyllithium (2.4 M in hexane). The solution was allowed to come to room temperature for about 30 min and then was treated with 18.2 g (0.11 mol) of 5-chloro-2-pentanone ethylene ketal **7** and 50 mL of hexamethylphosphoric triamide. The resulting solution was refluxed for 16 h under N_2. The reaction mixture was cooled to room temperature and poured into a mixture of ether and 1 N HCl. The organic layer was washed with water twice, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on silica gel (10% EtOAc in hexane) to give 18.4 g (60%) of a colorless viscous oil: ^1H NMR δ 1.31 (s, C_{10}), 3.94 (s, ketal).

10-Hydroxy-6-decyn-2-one (10). A solution of 30 g (0.1 mol) of **9** in 150 mL of 1 N HCl, 200 mL of THF, and 50 mL of MeOH

(16) E. Z. Dajani, unpublished results. The details of the studies concerned with duration of activity will be presented in a separate publication.
(17) K. E. Eakins and J. H. Sanner, *Prostaglandins: Prog. Res.*, 263 (1972).
(18) E. Z. Dajani, E. A. W. Roge, and R. E. Bertermann, *Eur. J. Pharmacol.* **34**, 105 (1975).
(19) E. W. Horton, I. H. M. Main, C. J. Thompson, and P. M. Wright, *Gut*, **9**, 655 (1968).
(20) J. J. Misiewicz, S. L. Waller, N. Kiley, and E. W. Horton, *Lancet*, 1, 648 (1969).
(21) S. M. M. Karim and J. J. Amy, *Prostaglandins*, **7**, 293 (1974).
(22) E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974).
(23) B. J. Magerlein, D. W. Ducharme, W. E. Magee, W. L. Miller, A. Robert, and J. R. Weeks, *Prostaglandins*, **4**, 143 (1973).

was allowed to stand at room temperature for about 24 h. The reaction mixture was neutralized by portionwise addition of solid potassium carbonate, evaporated to about one-half its volume, diluted with water, and extracted with ether twice and then twice with EtOAc. The extracts were combined, dried (Na_2SO_4), and evaporated to give 20 g of crude product, which was used without characterization or purification in the next step.

9-Oxo-4-decynoic Acid (11a). A solution of 20 g of crude **10** in 200 mL of acetone was cooled to 0 °C and treated dropwise with stirring with 90 mL of 2.67 M Jones reagent (chromic acid in aqueous sulfuric acid). After the addition was complete, the acetone solution was decanted from the solid chromium salts, which were washed with additional acetone. The acetone solutions were combined, evaporated to about one-half of their volume, and poured into a mixture of ether and water. The organic layer was separated, washed once with water, and extracted three times with 5% K_2CO_3 solution. The alkaline extracts were combined, extracted once with ether, acidified with 2 N HCl, and extracted twice with ether and twice with EtOAc. The extracts were combined, dried (Na_2SO_4), and evaporated to give 10.7 g (55% from **9**) of **11a**: mp 41–43 °C; ^1H NMR δ 2.17 (s, C_{10}). Anal. ($C_{10}H_{14}O_3$) C, H.

9-Oxo-4(*Z*)-decenoic Acid (11b). The acid **11a** (10 g, 55 mol) was hydrogenated at room temperature and atmospheric pressure in toluene containing about 0.5% quinoline with 5% Pd on $BaSO_4$ as catalyst. The toluene solution was filtered, washed with 1 N HCl and then water, dried (Na_2SO_4), and evaporated to give about 10 g of **11b** as a yellow oil: ^1H NMR δ 5.4 (olefinic protons, J = 11 Hz). Anal. ($C_{10}H_{16}O_3$) C, H.

2-[8-[(2-Tetrahydropyranyl)oxy]-4(*E*)-octenyl]-2-methyl-1,3-dioxolane (12). Lithium metal (2 g, 0.285 mol) was dissolved in 200 mL of anhydrous ammonia in a flask fitted with a dry ice condenser. To this stirred solution was added dropwise a mixture of 30 g (0.1 mol) of **9** and 10 mL of *t*-BuOH. The reaction mixture was stirred for 2 h at refluxing temperature and then carefully quenched by the portionwise addition of solid ammonium chloride. The condenser was removed, and 200 mL of ether was added dropwise, followed by 100 mL of water. This mixture was diluted with more ether, washed twice with 1 N HCl and then twice with water, dried (Na_2SO_4), and evaporated to give 29 g (97%) of **12**. This material was used directly in the next step without further purification.

9-Oxo-4(*E*)-decenoic Acid (11c). As described for the preparation of **11a** from **9**, the protected keto alcohol **12** was converted to the corresponding keto acid **11c**: ^1H NMR δ 5.4 (olefinic protons, J = 15 Hz). Anal. ($C_{10}H_{16}O_3$) C, H.

7-(2,3,5-Trioxo-4-methoxalylcyclopentyl)-4(*Z*)-heptenoic Acid (13). To a mechanically stirred, refluxing solution of potassium metal (3.2 g, 80 mmol) in 60 mL of dry *tert*-butyl alcohol (distilled from CaH_2) was added dropwise a solution of 2.52 g (13.5 mmol) of **11b** and 4.85 g of dimethyl oxalate in 25 mL of *tert*-butyl alcohol. The reaction mixture was refluxed for 2 h, cooled to room temperature, and filtered. The orange filter cake was added to a mixture of $CHCl_3$ and 1 N HCl. The $CHCl_3$ layer was washed with water, dried (Na_2SO_4), and evaporated. The reddish-black viscous oil (4 g) so obtained was used without characterization in the next step.

7-(2,3,5-Trioxocyclopentyl)-4(*Z*)-heptenoic Acid (14). The viscous oil (4 g) from the previous reaction was suspended in 100 mL of 1 N HCl and refluxed with stirring under N_2 for 2 h. The reaction mixture was cooled to room temperature and extracted three times with EtOAc. The extracts were combined, washed twice with saturated NaCl solution, dried (Na_2SO_4), and evaporated. The reddish-black oily residue was chromatographed (60% EtOAc, 39% hexane, 1% AcOH as eluent) on silica gel to give 2 g of **14** (63% from **11b**) as a pale yellow solid: mp 78–80 °C; UV λ_{max} (MeOH/1 N HCl) 278 nm (ϵ 11 000). Anal. ($C_{12}H_{14}O_5$) C, H.

7-(2,3,5-Trioxocyclopentyl)heptyn-4-oic Acid (19). In a similar manner, **11a** was converted to the title compound, mp 118–120 °C, in 75% yield from **11a**. Anal. ($C_{12}H_{12}O_5$) C, H.

7-(2,3,5-Trioxocyclopentyl)-4(*E*)-heptenoic Acid (20). In a similar manner, **11c** was converted to the title compound, mp 94–96 °C, in 60% yield from **11c**. Anal. ($C_{12}H_{14}O_5$) C, H.

(±)-7-(3-Hydroxy-2,5-dioxocyclopentyl)-4(*Z*)-heptenoic Acid (15). A solution of 1.1 g (4.6 mmol) of **14** in 30 mL of EtOH and 30 mL of H_2O was cooled to 0 °C and treated dropwise with a solution of 550 mg of $NaBH_4$ in 5 mL of H_2O. After the addition was complete, the solution was stirred at 0 °C for 30 min and then quenched with 1 N HCl. The aqueous layer was extracted three times with EtOAc. The extracts were combined, washed once with saturated NaCl solution, dried (Na_2SO_4), and evaporated to dryness to give 1 g of **15** as a viscous oil. This material was used without further purification in the next step.

(±)-Methyl 7-(4-Hydroxy-2-methoxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate (16). To a solution of 1 g (4.2 mmol) of **15** in 20 mL of dry MeOH was added 5 mL of 2,2-dimethoxypropane and 2 drops of concentrated HCl. The mixture was allowed to stand at room temperature for 48 h and then evaporated to dryness. About 2 mL of ether was added to the residue, and the mixture was stoppered and allowed to stand at room temperature for 48 h. The solidified mixture was taken up in toluene containing 1% Et_3N, and the solution was washed sucessively with dilute K_2CO_3 solution and H_2O, dried (Na_2SO_4), and evaporated. The residue crystallized upon addition of ether to give 675 mg (60%) of **16** as a white solid, mp 82–84 °C. Anal. ($C_{14}H_{20}O_5$) C, H.

(±)-Methyl 7-(4-Hydroxy-2-methoxy-5-oxo-1-cyclopenten-1-yl)heptyn-4-oate (21). In a similar manner, **19** was converted to the title compound, mp 108–109 °C, in 55% yield from **19**. Anal. ($C_{14}H_{18}O_5$) C, H.

(±)-Methyl 7-(4-Hydroxy-2-methoxy-5-oxo-1-cyclopenten-1-yl)-4(*E*)-heptenoate (22). In a similar manner, **20** was converted to the title compound, mp 92–93°, in 65% yield from **20**. Anal. ($C_{14}H_{20}O_5$) C, H.

(±)-Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate (18). Dry toluene (6 mL) was placed in a three-necked flash and cooled to −70 °C in an *i*-PrOH–dry ice bath under N_2. In separate dropping funnels were placed 0.4 mL of a 3.1 M solution of sodium dihydrobis(2-methoxyethoxy)aluminate diluted with 4 mL of toluene and a solution of 300 mg (1.1 mmol) of **16** in 4 mL of toluene. The two solutions were added dropwise and simultaneously to the flask with stirring. The mixture was stirred at −70 °C for about 3 h and then at 0 °C for 15 min, and it was finally quenched with a solution of MeOH in toluene. The reaction mixture was washed with 1 N HCl twice and then H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (70% EtOAc, 30% hexane) to give 110 mg (40%) of **18** as a viscous oil: UV λ_{max} 221 nm (ϵ 8900); ^1H NMR δ 3.65 (s, me ester), 5.35 (m, C_3), 7.15 (d, C_2). Anal. ($C_{13}H_{18}O_4$) C, H.

(±)-Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)heptyn-4-oate (23). In a similar manner, **21** was converted to the title compound, a viscous oil, in 50% yield from **21**. Anal. ($C_{13}H_{16}O_4$) C, H.

(±)-Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*E*)-heptenoate (24). In a similar manner, **22** was converted to the title compound, a viscous oil, in 45% yield from **22**. Anal. ($C_{13}H_{18}O_4$) C, H.

(±)-Methyl 7-[3-[(Triethylsilyl)oxy]-5-oxo-1-cyclopenten-1-yl]-4(*Z*)-heptenoate (2b). A solution of 238 mg (1 mmol) of **18** in 3 mL of DMF was treated successively with 100 mg of imidazole and 180 mg (1.2 mmol) of triethylchlorosilane. The solution was stirred for 1 h at room temperature, diluted with ether, washed with H_2O four times, dried (Na_2SO_4), and evaporated to give **2b** as an oil, which was purified by chromatography (silica gel; 10% EtOAc in hexane).

(*E*)-1-(Tri-*n*-butylstannyl)-4-methyl-4-[(trimethylsilyl)oxy]-1-octene (5). A mixture of 2.12 g (10 mmol) of **4**[8a] and 2.91 g (10 mmol) of tri-*n*-butyltin hydride[24] contained in a Pyrex round-bottomed flask was irradiated under argon with a General Electric sunlamp for 2 h at room temperature (a circulating water bath is required) and then at about 55 °C (heat generated by lamp) for 2 h. The resulting product was used directly in the next step.

(±)-15-Deoxy-16-methyl-16-hydroxy-4(*Z*)-didehydroprostaglandin E_1 Methyl Ester (1b). A solution of 1 g (2 mmol) of **5** in 4 mL of dry THF was cooled to −50 °C under argon and

(24) The tributyltin hydride should be freshly distilled prior to use for best results. Argon is preferred to nitrogen for this reaction.

treated with 0.87 mL of a 2.3 M solution of *n*-BuLi in hexane. The solution was stirred for 1 h at −50 °C, cooled to −60 °C, and treated with an ether solution (4 mL) of 260 mg of copper 1-pentyne and 640 mg of hexamethylphosphorous triamide. The reaction mixture was stirred for 10 min at −60 °C, and then an ether solution (2 mL) of 350 mg (1 mmol) of **2b** was added dropwise. The solution was stirred for 1 h and then poured into a mixture of ether and 1 N HCl. The mixture was shaken well, after which the organic layer was separated, washed with H_2O three times, and filtered, and the filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give the protected prostaglandin. This material (500 mg) was dissolved with stirring in about 20 mL of a 3:1:1 mixture of AcOH/THF/H_2O[15] and allowed to stand at room temperature for approximately 1 h. The solution was diluted with ether, washed four times with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (80% EtOAc, 20% hexane) to give 230 mg (60%) of **1b** as a colorless, viscous oil: ^{1}H NMR δ 1.19 (s, 16-CH_3), 4.09 (q, C_{11}), 5.39 (m, $C_{4,5}$), 5.42 (dd, C_{13}), 5.79 (dt, C_{14}). Anal. ($C_{22}H_{36}O_5$) C, H.

Compounds **1a** and **1c** were prepared in an analogous manner from the corresponding cyclopentenones **23** and **24**. **1a** Anal. ($C_{22}H_{34}O_5$) C, H. **1c** Anal. ($C_{22}H_{36}O_5$) C, H.

Gastric Antisecretory Studies.[25,26] Adult female mongrel dogs (15–18 kg)) surgically prepared with Heidenhain pouches (HP) and adult female Beagles (4.5–7 kg) prepared with simple gastric fistulas (GF) were used in these experiments. The dogs were trained to stand quietly in Pavlov supports and were conscious during all studies. The animals were not used more than once per week.

All prostaglandins were dissolved in absolute ethanol stock solution (1 mg/mL) and stored at −10 °C when not in use. Appropriate dilutions of the stock solution were carried out with an isoosmotic phosphate buffer so that the final alcohol concentration did not exceed 20%.

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 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 stimulatory dose of 1.0 mg/h. The rate of infusion was kept at approximately 13.0 mL/h for the HP dogs and 6.5 mL/h for the GF dogs. Approximately 1 h after the start of histamine infusion, a steady-state plateau of gastric secretion was obtained. At this time, in the HP dogs, the prostaglandin was administered by a single intravenous bolus injection using a total volume not exceeding 3.0 mL. The iv doses usually ranged from 0.1 to 100 μg/kg and were logarithmically spaced. At least two dogs were employed at each dose.

The GF dogs were used for the intragastric administration of the prostaglandins. At the steady-state plateau of gastric secretion, the PG's were administered directly into the stomach through a specially constructed dosage plug, and the cannula was closed for 30 min to allow sufficient contact with the gastric mucosa. At the end of 30 min, gastric juice collections were resumed.

Gastric samples were measured for total acidity by titration with 0.1 N sodium hydroxide solution to pH 7.0 (Radiometer, Copenhagen). ED_{50} values were calculated from the degree of maximum inhibition of total acid output. The ED_{50} is defined as the dose that caused 50% inhibition of total acid output in the series of dogs.

Diarrheal Studies. Adult Charles River male rats weighing 210–230 g were individually housed and fasted for 24 h prior to the test. The animals (N = 6–12) were orally administered logarithmically graded doses of the prostaglandin. Immediately after administration, the animals were returned to their cages, and diarrhea, if any, was assessed on an all or none basis up to 8 h after drug treatment. The ED_{50} and relative potency values were calculated by the logistic method of Berkson.[27,28]

Acknowledgment. The authors thank Ms. E. L. Phillips and Jackie Casler for technical assistance in the antisecretory and diarrheal studies, David Calhoun for statistical assistance, the group of A. J. Damascus for spectral data, Dr. R. Bible, Ms. L. Swenton, and Ms. P. Finnegan for assistance in interpretation of spectral data, the group of E. Zielinski for microanalyses, and Dr. P. H. Jones for helpful discussions during the preparation of this manuscript.

Registry No. (±)-**1a** (isomer 1), 85168-35-0; (±)-**1a** (isomer 2), 85168-55-4; (±)-**1b** (isomer 1), 78908-16-4; (±)-**1b** (isomer 2), 78908-15-3; (±)-**1c** (isomer 1), 78908-27-7; (±)-**1c** (isomer 2), 78908-26-6; (±)-**2a**, 85168-36-1; (±)-**2b**, 78908-11-9; (±)-**2c**, 85168-37-2; (±)-**3**, 85201-89-4; (±)-**4**, 66792-28-7; (±)-**5**, 66792-29-8; (±)-**6**, 85185-20-2; **7**, 5978-08-5; **8**, 85168-38-3; **9**, 78908-03-9; **10**, 61448-22-4; **11a**, 78908-04-0; **11b**, 78908-05-1; **11c**, 85168-39-4; **12**, 78908-28-8; **12** (keto alcohol), 85168-50-9; **13**, 78908-06-2; (±)-**14**, 85168-40-7; **15**, 78908-08-4; **15**-yne, 85168-53-2; (*E*)-**15**, 85168-54-3; (±)-**16**, 78908-09-5; (±)-**17**, 85168-41-8; (±)-**17**-yne, 85168-45-2; (±)-(*E*)-**17**, 85168-47-4; (±)-**18**, 78908-10-8; (±)-**19**, 85168-42-9; **19** (4-methoxalyl derivative), 85168-51-0; (±)-**20**, 85168-43-0; **20** (4-methoxalyl derivative), 85168-52-1; (±)-**21**, 85168-44-1; (±)-**22**, 85168-46-3; (±)-**23**, 85168-48-5; (±)-**24**, 85168-49-6; 4-pentyn-1-ol THP ether, 62992-46-5.

(25) E. Z. Dajani, D. R. Driskill, R. G. Bianchi, and P. W. Collins, *Prostaglandins*, **10**, 205 (1975).
(26) E. Z. Dajani, L. F. Rozek, J. H. Sanner, and M. Miyano, *J. Med. Chem.*, **19**, 1007 (1976).
(27) D. J. Finney, "Statistical Methods in Biological Assay", 2nd ed., Harper Publishing Co., New York, 1964, Chapters 4–6.
(28) J. Berkson, *Am. Stat. Assoc. J.*, **48**, 565 (1953).

Synthesis and Platelet Aggregation Inhibiting Activity of Prostaglandin D Analogues

Gordon L. Bundy,* D. R. Morton, D. C. Peterson, E. E. Nishizawa, and W. L. Miller

Departments of Experimental Science I, Diabetes and Atherosclerosis Research and Fertility Research, The Upjohn Company, Kalamazoo, Michigan 49001. *Received September 27, 1982*

Several prostaglandin D (PGD) analogues have been synthesized, incorporating the following variations: (a) varying degrees of side-chain unsaturation, (b) C-9 hydroxy removed or in the unnatural 9β configuration, (c) metabolically stabilized analogues (e.g., 15-methyl, 16,16-dimethyl, 17-phenyl, etc.), and (d) Δ^{12} isomers resulting from decomposition of PGD_2. With regard to their ability to inhibit adenosine diphosphate (ADP) induced human platelet aggregation: (a) $PGD_3 \geq PGD_2 > PGD_1 >$ 13,14-dihydro-PGD_1, (b) the 9β- and 9-deoxy-PGD_2 analogues are more potent than PGD_2, (c) metabolically stabilized analogues with bulky substituents at or near C-15 have substantially reduced antiaggregatory activity relative to PGD_2 and (d) the Δ^{12} isomers of PGD_2 are much less active than PGD_2.

Like the more thoroughly studied prostaglandins of the E series (PGE_1, PGE_2), PGD_1 and PGD_2 are important metabolic products of homo-γ-linolenic acid and arachidonic acid, respectively, via the endoperoxide pathway.[1-3]

0022-2623/83/1826-0790$01.50/0