Structural Assignment of Nitrostyrenes 20 and 21. A few milligrams of the yellow isomer (mp 102–103.5 °C) were reduced with AlH_3 as described for the reduction of nitrostyrene 6. Sodium hydroxide (1 mL of 10%) and Raney nickel alloy (50 mg) were added to the crude product. The mixture was heated to a boil and then cooled to room temperature and acidified with HCl to dissolve all solids. About 0.1 mL of the clear solution was made basic with NaOH and extracted with 1 mL of ether. The ether layer was separated and evaporated to dryness, and the amine was converted to its heptafluorobutyryl (HFB) derivative by heating with heptafluorobutyric anhydride (50 μL) in 2 mL of toluene for 15 min at about 120 °C in a tightly capped culture tube in the presence of a few milligrams of anhydrous K_2CO_3. GC analysis on a 2 m SP2100 column at 170 °C revealed a peak with a retention time of 1.85 min and only traces of minor peaks. The retention times of the HFB derivatives of authentic 3,4-dimethoxyphenethylamine (**25**)[14] and 2,3-dimethoxyphenethylamine (**24**)[14] were 1.85 and 1.36 min, respectively.

A few milligrams of the orange, lower melting (70–71 °C) nitrostyrene was reduced with AlH_3 and disulfurized with Raney nickel to give a product which, after conversion to its HFB derivative, had a retention time of 1.35 min.

2,3-Dimethoxy-4-(methylthio)phenethylamine (22). The orange nitrostyrene, mp 70–71 °C (**20**), 0.9 g, was reduced with AlH_3 as described for the reduction of 14. The crude free base was distilled bulb to bulb at 100–115 °C (0.3 mmHg) to give 0.45 g of free base, which yielded 0.45 g (48%) of the hydrochloride salt, mp 212–213 °C. Anal. ($C_{11}H_{18}ClNO_2S{\cdot}H_2O$) C, H, N.

3,4-Dimethoxy-2-(methylthio)phenethylamine (23). The yellow nitrostyrene, mp 102–103.5 °C (**21**), 4.4 g, was reduced with AlH_3 to give, after distillation (100–115 °C, 0.3 mmHg) and conversion to the hydrochloride salt, 3.2 g (70%) of white crystalline solid (platelets), mp 183–184 °C. Anal. ($C_{11}H_{18}ClNO_2S{\cdot}0.25H_2O$) C, H, N.

Incubations with MAO. Solutions of the amines (50 μM) in 0.1 M phosphate buffer (pH 7.4) were treated with 0.01 unit bovine plasma MAO (E.C. 1.4.3.4, Sigma) in a total volume of 200 μL. Incubations were carried out at 37 °C in 13 × 100 mm culture tubes. Duplicate incubations were carried out for each amine. After 1 h the incubations were stopped by the addition of 0.5 mL of 0.5 N NaOH. An appropriate internal standard (substrate, internal standard: **1**, **25**; **2**, **25**; **7**, **12**; **12**, **7**; **15**, **12**; **22**, **12**; **23**, **12**; **25**, **1**) was added, and the mixture was extracted with 2 mL of CH_2Cl_2. The organic layer was separated, dried over anhydrous K_2CO_3, treated with 10 μL of heptafluorobutyric anhydride, and heated at 60 °C for 10 min. The solvent was evaporated under a current of nitrogen, and the residue was reconstituted with 0.5 mL of ethyl acetate. GC analysis was carried out on a 2 m × 2 mm i.d. column packed with 3% OV-101 on 100–120 mesh Chromosorb W.-HP, with a column-oven temperature of 185 °C. Quantitation was achieved using peak height ratios, employing standards prepared in an identical fashion without enzyme present. Retention times for the heptafluorobutyryl derivatives were (amine, retention time in minutes): **1**, 2.00; **2**, 1.49; **7**, 3.01; **12**, 4.19; **15**, 3.55; **22**, 2.62; **23**, 2.68; **25**, 1.33.

Incubations of amines **1**, **2**, **23**, and **25** were carried out in the presence of semicarbazide (50 μM), since this compound has been shown to inhibit the deamination of mescaline but not tyramine.[14]

Psychopharmacologic Assays. Effective human levels of action were determined in normal healthy adult subjects (age range 32–65 years, all experienced with a broad spectrum of psychotropic drugs) employing spaced trials (about 1 week separation) of small increments of chemical (1.6:1), starting with 2 mg of the hydrochloride orally. With the establishment of threshold levels, complete studies at fully active levels were conducted with both **12** (9 subjects, 16 trials, dosage range 16–40 mg) and **7** (9 subjects, 13 trials, dosage range 60–100 mg). Seven subjects were common to trials with both compounds. The same protocol was used with **2**, **15**, **22**, and **23** (4, 5, 7, and 8 trials, respectively, at dosage maxima of 400, 240, 160, and 240 mg, respectively). No central disturbance of any kind was observed. See ref 11 for complementary findings with **2**.

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N-(Methanesulfonyl)-16-phenoxyprostaglandincarboxamides: Tissue-Selective, Uterine Stimulants†

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In an effort to develop tissue-selective prostaglandin analogues resistant to the metabolic inactivating pathways of the natural materials, hybrid compounds modified both at C-1 with a sulfonimide moiety and in the *n*-amylcarbinol side chain with substituted phenoxy groups were synthesized and evaluated in a variety of in vitro and in vivo models. Several of these analogues exhibited potent, tissue-selective, uterine stimulant activity, a finding subsequently confirmed in clinical studies with one member of this series, *N*-(methanesulfonyl)-16-phenoxy-ω-tetranor-PGE_2-carboxamide (CP-34 089/ZK-57 671, sulprostone).

Widespread clinical use of prostaglandins, both the natural materials and analogues, for a variety of obstetric and gynecological uses has been limited by a lack of tissue selectivity and metabolic stability. In an attempt to circumvent these shortcomings, we sought to design congeners resistant to metabolic inactivation (i.e., C_{15}-dehydrogenation and β-oxidation).[1] It was reasoned that, in so doing, analogues would be found that would also exhibit pharmacological selectivity. We initially focused our attention on carboxyl-terminus modified analogues, among which *N*-(methanesulfonyl)-PGE_2-carboxamide displayed selective uterine stimulant activity.[2] In parallel, we explored modifications of the *n*-amylcarbinol side chain, an

† Compounds were synthesized in the laboratories of Pfizer Inc. and jointly evaluated at Pfizer Inc. and Schering A.G., Berlin, Germany.

(1) Hess, H.-J.; Bindra, J. S.; Constantine, J. W.; Elger, W.; Loge, O.; Schillinger, E.; Losert, W. *Experientia* 1977, 33, 1076.
(2) Schaaf, T. K.; Hess, H.-J. *J. Med. Chem.* 1979, 22, 1340.

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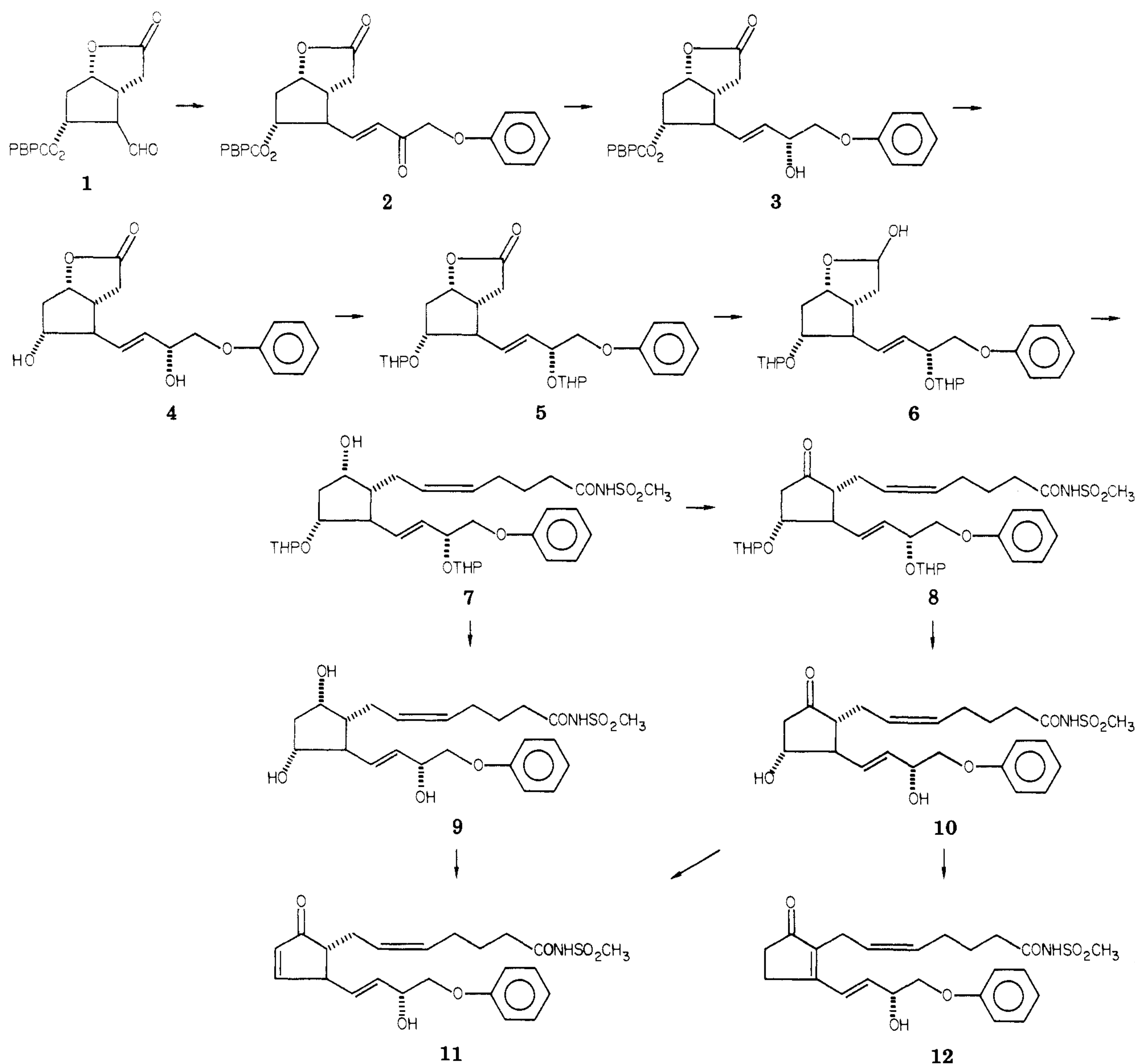
Scheme I



effort which led to the discovery that 16-phenoxy-ω-tetranor-PGE_2 is a potent, albeit nonselective, uterine stimulant.[3] This report describes the synthesis and structure–activity relationships of prostaglandin analogues incorporating both of these structural modifications.

Chemistry. The Corey synthesis[4] is ideally suited for the preparation of PGE_2 analogues modified in either side chain (Scheme I). Thus, condensation of the optically active aldehyde **1**[5] with the sodium salt of the requisite dimethyl 3-substituted-2-oxopropylphosphonate[6] in THF provided the enones **2**. Reduction of **2** with lithium triethylborohydride in THF at −78 °C afforded a mixture of C-15 epimers, which was separated by silica gel chromatography. By analogy with the synthesis of the natural prostaglandins,[5] the less polar epimers were tentatively identified as the desired 15α-hydroxy congeners **3**.[7] Cleavage of **3** with potassium carbonate in MeOH, followed by treatment with dihydropyran in CH_2Cl_2 containing *p*-toluenesulfonic acid and reduction with diisobutylaluminum hydride in toluene at −78 °C, provided the hemiacetals **6**. Condensation of **6** with the Wittig reagent derived from 5-(triphenylphosphono)pentanoic acid[4] or the corresponding sulfonimides[2] and sodium methylsulfinylcarbanide in Me_2SO gave the corresponding $PGF_{2\alpha}$ 11,15-tetrahydropyranyl ethers **7**. Hydrolysis of **7** with a mixture of acetic acid–water provided the $PGF_{2\alpha}$ analogues **10** (Table I). Oxidation of **7** with Jones reagent at −20 °C, followed by hydrolysis of the tetrahydropyranyl ethers with a mixture of acetic acid–water, afforded the PGE_2 analogues **9** (Table I). Dehydration of **9** with acetic acid at 76 °C gave the PGA_2 congener **11** (Table I). Treatment of **9** with ethanolic KOH afforded the PGB_2 derivative **12** (Table I).

(3) Hess, H.-J.; Schaaf, T. K.; Bindra, J. S.; Johnson, M. R.; Constantine, J. W. In "International Sulprostone Symposium"; Friebel, K.; Schneider, A.; Würfel, H., Ed.; Medical Scientific Department, Schering, A.G.: Berlin and Bergkamen, 1979; p 29.

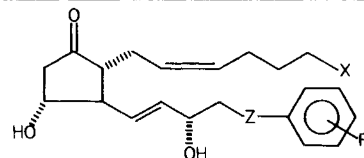
(4) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(5) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491.

(6) Prepared by treating the known methyl phenoxyacetates with the lithium salt of dimethyl methylphosphonate in THF at −78 °C.

(7) In accord with this assignment, the 15β-congener of **9a**, prepared from the more polar epimer, exhibited 50-fold less uterine stimulant activity in vitro than **9a**.

Table I. Structures and Biological Activities of *N*-(Methanesulfonyl)-16-phenoxyprostaglandincarboxamides



					effects					
compd	PG type	X	Z	R	uterine in vitro[a]	abortifacient[b]	bronchodilator[c]	blood pressure[d]	diarrhea[e]	antisecretory[f]
PGE_2					100	100	100	100 (–)	100	100
9	PGE_2	$CONHSO_2CH_3$	O	H	115	3000	10	0.5 (–)	80	450
9a	PGE_2	CO_2H	O	H	75	300	9	10 (–)	150	530[g]
9b	PGE_2	$CONHSO_2CH_3$	CH_2	H	75	<100	0	2.5 (–)	2.5	NT[h]
9c	PGE_2	$CONHSO_2CH_2CH_3$	O	H	85	3000	9	1 (–)	45	NT[h]
9d	PGE_2	$CONHSO_2C_6H_5$	O	H	5	1000	13	<0.5	100	370
9e	PGE_2	$CONHSO_2CH_3$	O	*p*-OCH_3	10	<1000[i]	13	<0.5	27	600
9f	PGE_2	$CONHSO_2CH_3$	O	*m*-OCH_3	1	<1000[i]	25	<0.5	*j*	0[g]
9g	PGE_2	$CONHSO_2CH_3$	O	*p*-Cl	90	10000	9	0.5 (–)	190	1200
9h	PGE_2	$CONHSO_2CH_3$	O	*m*-Cl	46	1000	28	NT[h]	10	140
9i	PGE_2	$CONHSO_2CH_3$	O	*p*-F	120	3000	3	NT[h]	150	NT[h]
9j	PGE_2	$CONHSO_2CH_3$	O	*m*-CH_3	4	<1000[i]	44	0.5 (–)	*i*	125[g]
9k	PGE_2	$CONHSO_2CH_3$	O	*m*-CF_3	0.5	<100	16	<0.5	*i*	NT[h]
9l	PGE_2	$CONHSO_2CH_3$	O	C_4H_3S[k]	50	300	28	0.5 (–)	100	NT[h]
10	$PGF_{2\alpha}$[m]	$CONHSO_2CH_3$	O	H	10	1000	3	10 (+)	>200	NT[h]
11	PGA_2[m]	$CONHSO_2CH_3$	O	H	0.2	<100	9	2.5 (–)	10	200
12	PGB_2[m]	$CONHSO_2CH_3$	O	H	1.2	<100	0	10 (+)	60	80
16,16-dimethyl-PGE_2					33	<100[l]	41	10 (–)	5300	400
15(*S*)-methyl-$PGF_{2\alpha}$ Me ester					7	300	NT[h]	10 (+)	181	NT[h]

[a] Relative spasmogenic potency from concentration–response curves (0.1–10 μg/mL) for at least three individual guinea pig uteri. [b] Relative potency (PGE_2, 1.0 mg/kg, sc) causing abortion in at least 1/3 conscious guinea pigs. [c] Percent protection from histamine-induced bronchoconstriction in a group of eight conscious guinea pigs by a 2.85×10^{-4} M aerosol solution. [d] Relative threshold dose (PGE_2, 0.1 μg/kg, iv) for effects on blood pressure from at least two PGE_2 responsive anesthetized dogs (–, depressor; +, pressor). [e] Relative potency estimated from concentration–response curves (PGE_2, 0.3–3.0 mg/kg, iv) for induction of diarrhea in a group of six conscious mice. [f] Relative potency (50 μg/kg, iv) for inhibition of pentagastrin-stimulated gastric acid secretion in anesthetized rats. [g] Compound tested at 10 μg/kg vs. PGE_2 at 50 μg/kg. [h] NT = not tested. [i] No effect was observed at one-tenth the minimum effective dose for PGE_2; no other doses were tested. [j] No effect at 10 times the ED_{50} for PGE_2. [k] The phenyl ring was replaced with the α-thienyl group. [l] Potent abortifacient activity has been reported in the hamster.[14] [m] See Scheme I for the structures of these compounds.

Biology. The determination of the tissue selectivity of prostaglandins necessitates a variety of biological tests. Uterine stimulant and abortifacient effects, which are indicative of potential applications in obstetrics and gynecology, were assessed using the isolated guinea pig uterus[2] and the pregnant guinea pig. Other activities, including the clinically limiting diarrheal side effects and blood pressure, gastric antisecretory, and bronchodilator effects, were evaluated by published procedures.[2] A monkey lung C_{15}-hydroxyprostaglandin dehydrogenase preparation was utilized to assess susceptibility to C_{15} dehydrogenation.

Results and Discussion

The importance of metabolic stability of the prostaglandins for potency in vivo is exemplified by the enhanced abortifacient activity of 15(*S*)-methyl-$PGF_{2\alpha}$ methyl ester, which is resistant to oxidation by C_{15}-hydroxyprostaglandin dehydrogenase, compared with its natural congener.[8] However, the report that the half-life of 15(*S*)-methyl-$PGF_{2\alpha}$ is still relatively short[9] suggests that β-oxidation plays an important additional role in the catabolism of prostaglandins; we therefore sought analogues resistant to both modes of metabolic inactivation. Toward this end, systematic structural modification of both the carboxyl terminus[2] and *n*-amylcarbinol side chain[3] of PGE_2 was undertaken, which provided a series of hybrid analogues displaying potent, selective uterine stimulant effects in vitro and abortifacient activity in vivo (Table I).

Replacement of a methylene group in the *n*-amylcarbinol side chain of PGE_2 with an oxygen atom provided the 17-, 18-, and 20-oxa derivatives. Within this series, the 17-oxa-PGE_2 displayed the highest uterine stimulant activity in vitro and reduced blood pressure, bronchodilator, and diarrheal effects.[10] Concurrently, successive substitution of the *n*-amylcarbinol side chain with a phenyl group afforded the 16-phenyl-ω-tetranor-, 17-phenyl-ω-trinor- and 18-phenyl-ω-dinor-PGE_2 analogues.[11,12] Of these compounds, the 17-phenyl-ω-trinor-PGE_2 exhibited the most potent uterine stimulant effects in vitro.[13] Having identified two *n*-amylcarbinol side-chain substituents exhibiting favorable uterine stimulant effects in vitro, both modifications were incorporated into the same compound, providing 16-phenoxy-ω-tetranor-PGE_2 (**9a**). Although it was relatively nontissue selective, this analogue displayed potent uterine stimulant activity (Table I). The enhanced activity in vivo compared to PGE_2 may be ascribed to the stability of **9a** toward C_{15}-hydroxyprostaglandin dehydrogenase.[14]

In a parallel synthetic pursuit, replacement of the carboxyl terminus of PGE_2 with the methanesulfonimide group gave a compound which manifested selectivity for uterine tissue, both in vitro and in vivo.[2] This suggested, as a logical extension, substitution of the carboxylic acid function of **9a** with the methanesulfonimide to provide **9**.

As anticipated, compound **9** exhibited potent, uterine stimulant activity in vitro, and, based on a comparison of abortifacient and diarrheal activity in vivo, **9** is at least 30 times more selective than PGE_2. Futhermore, **9** displayed minimal bronchodilator and hypotensive effects in vivo. Since **9** is not a substrate for C_{15}-hydroxyprostaglandin dehydrogenase, the markedly increased abortifacient activity of **9** (approximately 30 times PGE_2) compared with that of **9a** may be attributed to the additional metabolic stability toward β-oxidation conferred by the methanesulfonimide moiety. The importance for in vivo activity of inhibiting both C_{15}-dehydrogenation and β-oxidation is supported by the activity of the 17-phenyl sulfonimide **9b**. This C_{16}-carbon isostere of **9**, which is readily metabolized at C-15,[15] displays potent uterine stimulant effects in vitro but very weak abortifacient activity in vivo.

Replacement of the methanesulfonimide group of **9** by either the ethane- or benzenesulfonimide moieties (**9c** and **9d**) maintained potent, selective abortifacient activity, although the uterine stimulant effect in vitro of **9d** was diminished. Substitution of the phenoxy moiety of **9** in the meta position with methoxy (**9f**), methyl (**9j**), or trifluoromethyl (**9k**) led to a substantial reduction in both abortifacient and uterine stimulant effects. The *p*-methoxy derivative (**9e**) also exhibited less overall uterine activity. In contrast, the *p*-chloro (**9g**), *m*-chloro (**9h**), and *p*-fluoro (**9i**) analogues displayed potent abortifacient and uterine stimulant activity. The selectivity of **9g–i**, however, was no greater than that exhibited by **9**. Replacement of the phenyl ring of **9** with an α-thienyl group (**9l**) led to a decrease of abortifacient but not uterine stimulant effects. Potent, selective uterine stimulant activity is confined to PGE analogues, since the PGA_2 (**11**) and PGB_2 (**12**) analogues lacked significant uterine stimulant effects, and the $PGF_{2\alpha}$ analogue (**10**), while exhibiting potent uterine effects, was significantly less tissue selective than the PGE_2 congener (**9**).

The biological profile of several members of this series compares favorably not only with that of the natural prostaglandins but also with that of two widely studied analogues, 16,16-dimethyl-PGE_2 and 15(*S*)-methyl-$PGF_{2\alpha}$ methyl ester (Table I). The nonproprietary (USAN) name sulprostone (CP-34 089/ZK-57 671) has been assigned to one of these compounds, **9**. Its activity has been confirmed in clinical trials, which demonstrate that it is one of the most potent and best tolerated prostaglandin uterine stimulants reported to date.[16–19]

Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. ^1H NMR spectra, obtained on a Varian T-60 or A-60 spectrometer, were recorded in $CDCl_3$ unless otherwise noted, and data are reported as δ values with respect to Me_4Si. IR spectra, obtained on a Perkin-Elmer 237B spectrophotometer, were recorded in $CHCl_3$ unless otherwise noted, and data are reported in reciprocal centimeters. High-resolution mass spectra were obtained on an AEI-MS30 coupled with a DS-50 system.

Column chromatography was carried out on Mallinckrodt SilicAR CC-7 or EM Reagents silica gel 60. Thin-layer chro-

(8) Weeks, J. R.; DuCharme, D. W.; Magee, W. E.; Miller, W. L. *J. Pharmacol. Exp. Ther.* **1973**, *186*, 67.
(9) Hansson, G.; Granstrom, E. *Biochem. Med.* **1977**, *18*, 420.
(10) Johnson, M. R.; Hess, H.-J. Abstracts: Fourth International Prostaglandin Conference, Washington, DC, May 27–31, 1979; p 56.
(11) Johnson, M. R.; Schaaf, T. K.; Constantine, J. W.; Hess, H.-J. In ref 10; p 56.
(12) Johnson, M. R.; Schaaf, T. K.; Constantine, J. W.; Hess, H.-J. *Prostaglandins* **1980**, *20*, 515.
(13) For an independent report of the activity of this compound, see Miller, W. L.; Weeks, J. R.; Lauderdale, J. W.; Kirton, K. T. *Prostaglandins* **1975**, *9*, 9.
(14) Sun, F. F.; Armour, S. B.; Bockstanz, V. R.; McGuire, J. C. *Adv. Prostaglandin Thromboxane Res.* **1976**, *1*, 163.
(15) Powell, W. S.; Hammarstrom, S.; Samuelsson, B.; Miller, W. L.; Sun, F. F.; Fried, J.; Lin, C. H.; Jarabak, J. *Eur. J. Biochem.* **1975**, *59*, 271.
(16) Karim, S. M. M.; Choo, H. T.; Lim, A. L.; Yeo, K. C.; Ratnam, S. S. *Prostaglandins* **1978**, *15*, 1063.
(17) Schuessler, B.; Schmidt-Gollwitzer, K.; Hoebick, D.; Schmidt-Gollwitzer, M. *Contraception* **1979**, *19*, 29.
(18) Csapo, A. I.; Peskin, E. G.; Sauvage, J. P.; Pulkkinen, M. O.; Lampe, L.; Godeny, A.; Laajoki, V.; Kivikoski, A. *Lancet* **1980**, 90.
(19) Ulbrich, I.; Bartels, H. In ref 3, p 61.

matography (TLC) was used to monitor column fractions and to establish homogeneity of products. TLC was performed on EM Reagents silica gel 60F-254 plates (250-μm thick). Spots were located by spraying with vanillin in EtOH–phosphoric acid, followed by charring at 200 °C. All analogues were homogeneous using a standard solvent system of 10% MeOH in CH_2Cl_2.

Chromatographed products were prepared for analysis and biological testing by heating at 56 °C in vacuo for 8 h. When analyses are indicated only by the symbols of the elements, the analytical results obtained were within 0.4% of the theoretical values. Satisfactory high-resolution mass values were obtained for the peaks indicated.

Anhydrous $MgSO_4$ was used to dry organic extracts. Since optically active starting materials were employed, the absolute configuration of all chiral centers are identical with those found in the natural prostaglandins.

N-(Methanesulfonyl)-16-phenoxy-ω-tetranor-PGE$_2$-carboxamide (9). To a stirred suspension of 57% NaH in mineral oil (1.3 g, 30.9 mmol) in THF (120 mL) was added dropwise a solution of dimethyl 2-oxo-3-phenoxypropylphosphonate (8.4 g, 32.5 mmol) in THF (30 mL). The mixture was stirred under nitrogen for 90 min and then a solution of 1 (9.5 g, 27.1 mmol) in THF (50 mL) was added. After being stirred for 30 min, the reaction was quenched with acetic acid (2.5 mL) and then concentrated. The residue was diluted with ethyl acetate, washed with water and brine, dried, and concentrated. Purification of the crude product by column chromatography using mixtures of ethyl acetate in benzene as eluants provided 9.5 g (72%) of 2 as a white powder: mp 124–125 °C after trituration with ether; NMR δ 8.08–6.34 (16 H, m, trans CH═CH and aromatic), 5.48–4.84 (2 H, m, CHOCO), 4.10 (2 H, s, CH_2O); IR (KBr) 1776 (lactone C═O), 1727 (ester C═O), 1647 and 1616 (ketone C═O) cm^{-1}.

To a solution, cooled under nitrogen to −78 °C, of 2 (9.5 g, 19.6 mmol) in THF (150 mL) was added dropwise 20.6 mL of a 1 M solution of lithium triethylborohydride in THF (Superhydride, Aldrich). After being stirred for 30 min, the reaction was quenched with 10% aqueous acetic acid (25 mL) and concentrated. The residue was diluted with ethyl acetate, washed with brine, dried, and concentrated. Purification of the crude product by column chromatography using mixtures of ethyl acetate in benzene as eluants gave 2.4 g (25%) of 3 as a white solid: mp 125–129 °C after trituration with ether; NMR δ 8.03–6.57 (14 H, m, aromatic), 5.80–5.62 (2 H, m, trans CH═CH), 5.32–4.82 (2 H, m, CHOCO), 4.70–4.36 (1 H, m, CHOH), 3.93–3.68 (2 H, m, CH_2O); IR 1775 (lactone C═O), 1720 (ester C═O), 970 (trans CH═CH) cm^{-1}.

A heterogeneous mixture of 3 (4.54 g, 9.4 mmol), MeOH (35 mL), THF (35 mL), and potassium carbonate (1.3 g, 9.4 mmol) was stirred under nitrogen for 2.5 h and then was cooled in ice. To the cold mixture was added 1 N HCl (18.8 mL) and water (50 mL) with the concomitant formation of a solid, which was collected by filtration. The filtrate was concentrated to remove the MeOH and THF and extracted with ethyl acetate. The organic extracts were dried and concentrated to afford 2.65 g (93%) of oily 4, which was used without purification: NMR δ 7.31–6.64 (5 H, m, aromatic), 5.67–5.46 (2 H, m, trans CH═CH), 4.92–4.61 (1 H, m, CHOCO), 4.53–4.20 (2 H, m, CHOH); IR (mull) 1755 (lactone C═O), 970 (trans CH═CH) cm^{-1}.

A solution of crude 4 (2.65 g, 8.7 mmol), dihydropyran (5 mL), and p-toluenesulfonic acid (27 mg) in CH_2Cl_2 (75 mL) was stirred under nitrogen for 30 min, then was washed with saturated $NaHCO_3$, dried, and concentrated. Purification of the residue by silica gel chromatography using mixtures of $CHCl_3$ in ethyl acetate as eluants gave 3.90 g (95%) of 5 as a viscous oil: NMR δ 7.47–6.78 (5 H, m, aromatic), 5.78–5.50 (2 H, m, trans CH═CH), 5.06–4.82 (1 H, m, CHOCH), 4.82–4.58 (2 H, m, OCHO); IR (mull) 1770 (lactone C═O), 970 (trans CH═CH) cm^{-1}.

To a solution, cooled under nitrogen to −78 °C, of 5 (3.90 g, 8.3 mmol) in toluene (40 mL) was added 9.6 mL of a 20% solution of diisobutylaluminum hydride in hexane (Alfa). After being stirred for 20 min, the reaction was quenched by the dropwise addition of MeOH until gas evolution ceased. The mixture was then concentrated, and the residue was triturated with hot MeOH. Concentration of the MeOH followed by purification of the residue by silica gel chromatography using mixtures of $CHCl_3$ in ethyl acetate as eluants provided 3.05 g (79%) of 6 as a viscous oil: NMR δ 7.41–6.72 (5 H, m, aromatic), 5.85–5.38 (2 H, m, trans CH═CH); IR 965 (trans CH═CH) cm^{-1}.

To a solution of [4-(methanesulfonimido)-n-butyl]triphenylphosphonium bromide (6.91 g, 13.3 mmol) in Me_2SO (15 mL) was added 14.4 mL of a 18.1 M solution of sodium methylsulfinylcarbanide in Me_2SO. To the resultant red ylide solution was added 6 (1.52 g, 3.2 mmol) in Me_2SO (4 mL). After being stirred for 2 h, the reaction mixture was poured onto a mixture of ice–water and ethyl acetate. The aqueous layer was acidified with 10% HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, and concentrated. Purification of the residue by silica gel chromatography using mixtures of $CHCl_3$ in ethyl acetate as eluants gave 1.39 g (68%) of 7 as a viscous oil: NMR δ 7.38–6.76 (5 H, m, aromatic), 5.88–5.25 (4 H, m, cis and trans CH═CH), 3.29 (3 H, s, SO_2CH_3); IR 1725 (C═O), 975 (trans CH═CH) cm^{-1}.

To a solution, cooled under nitrogen to −20 °C, of 7 (2.14 g, 3.36 mmol) in acetone (20 mL) was added 1.4 mL of Jones reagent. After being stirred for 5 min, the reaction was quenched with isopropyl alcohol (1.4 mL), diluted with ethyl acetate, washed with water and brine, dried, and concentrated to provide 1.80 g (84%) of 8 as a viscous oil, which was used immediately without further purification.

A solution of 8 (1.83 g, 2.89 mmol) in 50 mL of 65% aqueous acetic acid was stirred under nitrogen at room temperature for 14 h and then was concentrated. Purification of the residue by silica gel chromatography using mixtures of ethyl acetate in $CHCl_3$ as eluants afforded 571 mg (43%) of 9 as a white solid: mp 78.5–79.5 °C after trituration with ether–ethyl acetate; NMR δ 7.45–6.75 (5 H, m, aromatic), 5.90–5.68 (2 H, m, trans CH═CH), 5.49–5.16 (2 H, m, cis CH═CH), 3.24 (3 H, s, SO_2CH_3); IR (KBr) 1733 (carbonyls), 972 (trans CH═CH) cm^{-1}. Anal. ($C_{23}H_{31}NO_7S$) C, H, N.

16-Phenoxy-ω-tetranor-PGE$_2$ (9a). The hemiacetal 6 (613 mg, 1.29 mmol) was caused to react with the ylide of 5-(triphenylphosphono)pentanoic acid followed by oxidation, hydrolysis, and purification as described above to give 210 mg (42% from 6) of 9a as a white solid: mp 89–91 °C after trituration with ether; IR (mull) 1730 (carbonyls), 965 (trans CH═CH) cm^{-1}; NMR δ 7.40–6.70 (5 H, m, aromatic), 5.88–5.70 (2 H, m, trans CH═CH), 5.55–5.20 (2 H, m, cis CH═CH), 4.70–4.51 (2 H, m, CHOH). Anal. ($C_{22}H_{28}O_5$) C, H.

N-(Methanesulfonyl)-17-phenyl-ω-trinor-PGE$_2$-carboxamide (9b). The aldehyde 1 (10 g, 28.6 mmol) was caused to react with dimethyl 2-oxo-4-phenylbutylphosphonate as described above to afford 7.47 g (54%) of 2b as a white solid: mp 129–129.5 °C after recrystallization from CH_2Cl_2–hexane; NMR δ 8.10–7.00 (9 H, m, C_6H_5–C_6H_4), 7.17 (5 H, s, C_6H_5), 6.65 (1 H, 2 d, J = 6 and 16 Hz, CH═CH), 6.12 (1 H, d, J = 16 Hz, CH═CH), 5.44–4.89 (2 H, m, CHOCO); IR 1775 (lactone C═O), 1710 (ester C═O), 1670 and 1630 (ketone C═O) cm^{-1}.

Reduction of 2b, chromatographic separation of the resultant epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above afforded 6b (45% from 2b) as a viscous oil. The hemiacetal 6b was caused to react with the ylide of [4-(methanesulfonimido)-n-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to give 9b (46% from 6b) as a white solid: mp 125–125.5 °C after recrystallization from ethyl acetate–hexane; IR (KBr) 1724 (carbonyls), 976 (trans CH═CH) cm^{-1}; NMR (CD_3OD) δ 7.26 (5 H, s, aromatic), 5.77–5.60 (2 H, m, trans CH═CH), 5.64–5.30 (2 H, m, cis CH═CH), 3.23 (3 H, s, SO_2CH_3). Anal. ($C_{24}H_{33}NO_6S$) C, H, N.

N-(Ethanesulfonyl)-16-phenoxy-ω-tetranor-PGE$_2$-carboxamide (9c). The hemiacetal 6 (331 mg, 0.7 mmol) was caused to react with the ylide of [4-(ethanesulfonimido)-n-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to provide 146 mg (43% from 6) of 9c as a viscous oil: NMR δ 7.43–6.72 (5 H, m, aromatic), 5.88–5.59 (2 H, m, trans CH═CH), 5.42–5.10 (2 H, m, cis CH═CH), 3.39 (2 H, q, SO_2CH_2), 1.34 (3 H, t, CH_3); IR 1735 (ketone C═O), 1715 (imide C═O), 970 (trans CH═CH) cm^{-1}; MS ($C_{24}H_{31}NO_6S$, P − H_2O) calcd, 461.1875; found, 461.1816.

N-(Benzenesulfonyl)-16-phenoxy-ω-tetranor-PGE$_2$-carboxamide (9d). The hemiacetal 6 (331 mg, 0.7 mmol) was caused to react with the ylide of [4-(benzenesulfonimido)-n-bu-

tyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to give 113 mg (30% from 6) of **9d** as a viscous oil: NMR δ 8.13–6.76 (10 H, m, aromatic), 5.87–5.61 (2 H, m, trans CH=CH), 5.37–5.06 (2 H, m, cis CH=CH); IR 1732 (ketone C=O), 1717 (imide C=O), 965 (trans CH=CH) cm^{-1}; MS ($C_{21}H_{24}NO_5S$, P − $CH_2OC_6H_5$ and H_2O) calcd, 402.1378; found, 402.1368.

***N*-(Methanesulfonyl)-16-(*p*-methoxyphenoxy)-ω-tetranor-PGE$_2$-carboxamide (9e).** The aldehyde 1 (6.0 g, 17 mmol) was caused to react with dimethyl 2-oxo-3-(*p*-methoxyphenoxy)propylphosphonate as described above to afford 4.4 g (50%) of **2e** as a white solid: mp 133–135 °C after recrystallization from CH_2Cl_2–hexane. Reduction of **2e**, chromatographic separation of the resultant epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above gave **6e** (18% from **2e**) as a viscous oil. The hemiacetal **6e** (1.67 g, 3.3 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to afford 250 mg (15% from **6e**) of **9e** as a viscous oil: NMR δ 6.83 (4 H, s, aromatic), 5.84–5.67 (2 H, m, trans CH=CH), 5.45–5.17 (2 H, m, cis CH=CH), 3.88 (3 H, s, OCH_3), 3.20 (3 H, s, SO_2CH_3); IR 1730 (carbonyls), 965 (trans CH=CH) cm^{-1}; MS ($C_{24}H_{33}NO_8S$) calcd, 495.1937; found, 495.1923.

***N*-(Methanesulfonyl)-16-(*m*-methoxyphenoxy)-ω-tetranor-PGE$_2$-carboxamide (9f).** The aldehyde 1 (4.9 g, 23 mmol) was caused to react with dimethyl 2-oxo-3-(*m*-methoxyphenoxy)propylphosphonate as described above to provide 2.54 g (29%) of **2f** as a viscous oil: NMR δ 8.10–6.28 (15 H, m, aromatic and trans CH=CH), 5.19–4.80 (2 H, m, CHOCO), 4.66 (2 H, s, CH_2O), 3.77 (3 H, s, OCH_3).

Reduction of **2f**, chromatographic separation of the epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above provided **6f** (11% from **2f**) as a viscous oil. The hemiacetal **6f** (346 mg, 0.69 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to give 38 mg (11% from **6f**) of **9f** as a viscous oil: NMR δ 7.74–6.34 (4 H, m, aromatic), 5.83–5.56 (2 H, m, trans CH=CH), 5.44–5.10 (2 H, m, cis CH=CH), 3.70 (3 H, s, OCH_3), 3.18 (3 H, s, SO_2CH_3); IR 1730 (carbonyls), 965 (trans CH=CH) cm^{-1}; MS ($C_{24}H_{31}NO_7S$, P − H_2O) calcd, 477.1826; found, 477.1789.

***N*-(Methanesulfonyl)-16-(*p*-chlorophenoxy)-ω-tetranor-PGE$_2$-carboxamide (9g).** The aldehyde 1 (6.0 g, 17 mmol) was caused to react with dimethyl 2-oxo-3-(*p*-chlorophenoxy)propylphosphonate as described above to give 4.4 g (50%) of **2g** as a white solid: mp 134–135 °C after recrystallization from CH_2Cl_2–hexane; NMR δ 8.08–6.36 (15 H, m, aromatic and trans CH=CH), 5.53–4.91 (2 H, m, CHOCO), 4.61 (2 H, s, CH_2O).

Reduction of **2g**, chromatographic separation of the epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above provided **6g** (14% from **2g**) as a viscous oil. The hemiacetal **6g** (794 mg, 1.6 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to afford 144 mg (18% from **6g**) of **9g** as a viscous oil: NMR δ 7.37–6.74 (4 H, m, aromatic), 5.87–5.65 (2 H, m, trans CH=CH), 5.44–5.21 (2 H, m, cis CH=CH), 3.19 (3 H, s, SO_2CH_3); IR 1735 (carbonyls), 970 (trans CH=CH) cm^{-1}; MS ($C_{16}H_{24}NO_6S$, P − H_2O and $CH_2OC_6H_4Cl$) calcd, 358.1329; found, 358.1333.

***N*-(Methanesulfonyl)-16-(*m*-chlorophenoxy)-ω-tetranor-PGE$_2$-carboxamide (9h).** The aldehyde 1 (4.0 g, 11.4 mmol) was caused to react with dimethyl 2-oxo-3-(*m*-chlorophenoxy)propylphosphonate as described above to give 3.16 g (61%) of **2h** as a white solid: mp 162–163 °C; NMR δ 7.90–6.10 (15 H, m, aromatic and trans CH=CH), 5.26–4.68 (2 H, m, CHOCO), 4.40 (2 H, s, CH_2O).

Reduction of **2h**, chromatographic separation of the epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above afforded **6h** (17% from **2h**) as a viscous oil. The hemiacetal **6h** (171 mg, 0.34 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to provide 42 mg (23% from **6h**) of **9h** as a viscous oil: NMR δ 7.33–6.60 (4 H, m, aromatic), 5.90–5.54 (2 H, m, trans CH=CH), 5.50–5.12 (2 H, m, cis CH=CH), 3.28 (3 H, s, SO_2CH_3); IR 1720 (carbonyls), 965 (trans CH=CH) cm^{-1}; MS ($C_{23}H_{28}ClNO_6S$, P − H_2O) calcd, 481.1329; found, 481.1359.

***N*-(Methanesulfonyl)-16-(*p*-fluorophenoxy)-ω-tetranor-PGE$_2$-carboxamide (9i).** The aldehyde (3.54 g, 10.1 mmol) was caused to react with dimethyl 2-oxo-3-(*p*-fluorophenoxy)propylphosphonate as described above to give 1.86 g (37%) of **2i** as a viscous oil: NMR δ 8.16–6.36 (15 H, m, aromatic and trans CH=CH), 5.49–4.88 (2 H, m, CHOCO), 4.67 (2 H, s, CH_2O).

Reduction of **2i**, chromatographic separation of the epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above afforded **6i** (15% from **2i**) as a viscous oil. The hemiacetal **6i** (380 mg, 0.77 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to give 35 mg (9% from **6i**) of **9i** as a viscous oil: NMR δ 7.20–6.80 (4 H, m, aromatic), 5.87–5.55 (2 H, m, trans CH=CH), 5.43–5.12 (2 H, m, cis CH=CH), 3.19 (3 H, s, SO_2CH_3); IR 1739 (carbonyls), 971 (trans CH=CH) cm^{-1}; MS ($C_{16}H_{24}NO_6S$, P − H_2O and $CH_2OC_6H_4F$) calcd, 358.1329; found, 358.1351.

***N*-(Methanesulfonyl)-16-(*m*-methylphenoxy)-ω-tetranor-PGE$_2$-carboxamide (9j).** The aldehyde 1 (5.0 g, 22.8 mmol) was caused to react with dimethyl 2-oxo-3-(*m*-methylphenoxy)propylphosphonate as described above to afford 2.3 g (36%) of **2j** as a white solid: mp 113–115 °C; NMR δ 8.20–6.16 (15 H, m, aromatic and trans CH=CH), 5.53–4.90 (2 H, m, CHOCO), 2.30 (3 H, s, CH_3).

Reduction of **2j**, chromatographic separation of the epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above gave **6j** (17% from **2j**) as a viscous oil. The hemiacetal **6j** (625 mg, 1.28 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to provide 260 mg (43% from **6j**) of **9j** as a viscous oil: NMR δ 7.42–6.67 (4 H, m, aromatic), 5.96–5.76 (2 H, m, trans CH=CH), 5.56–5.11 (2 H, m, cis CH=CH), 3.27 (3 H, s, SO_2CH_3), 2.15 (3 H, s, CH_3); IR 1750 (ketone C=O), 1730 (imide C=O), 975 (trans CH=CH) cm^{-1}; MS ($C_{24}H_{31}NO_6S$) calcd, 461.1875; found, 461.1895.

***N*-(Methanesulfonyl)-16-[*m*-(trifluoromethyl)phenoxy]-ω-tetranor-PGE$_2$-carboxamide (9k).** The aldehyde 1 (4.0 g, 11.4 mmol) was caused to react with dimethyl 2-oxo-3-[*m*-(trifluoromethyl)phenoxy]propylphosphonate as described above to give 3.39 g (54%) of **2k** as a white solid: mp 104–108 °C; NMR δ 8.23–6.48 (15 H, m, aromatic and trans CH=CH), 5.60–5.03 (2 H, m, CHOCO), 4.80 (2 H, s, CH_2O).

Reduction of **2k**, chromatographic separation of the epimers followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above provided **6k** (26% from **2k**) as a viscous oil. The hemiacetal **6k** (300 mg, 0.56 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to give 40 mg (14% from **6k**) of **9k** as a viscous oil: NMR (CD_3OD) δ 7.49–7.18 (4 H, m, aromatic), 5.90–5.70 (2 H, m, trans CH=CH), 5.45–5.19 (2 H, m, cis CH=CH), 2.95 (3 H, s, SO_2CH_3); IR 1735 (carbonyls), 9.65 (trans CH=CH) cm^{-1}.

***N*-(Methanesulfonyl)-16-(α-thienyloxy)-ω-tetranor-PGE$_2$-carboxamide (9l).** The aldehyde 1 (4.9 g, 13.9 mmol) was caused to react with dimethyl 2-oxo-3-(α-thienyloxy)propylphosphonate as described above to give 4.5 g (66%) of **2l** as a pale yellow foam: NMR δ 8.20–6.20 (14 H, m, aromatic and trans CH=CH), 5.57–5.00 (2 H, m, CHOCO), 4.70 (2 H, s, CH_2O).

Reduction of **2l**, chromatographic separation of the epimer followed by treatment of the 15α epimer with potassium carbonate, dihydropyran, and diisobutylaluminum hydride and purification as described above provided **6l** (23% from **2l**) as a viscous oil.

The hemiacetal 61 (950 mg, 1.98 mmol) was caused to react with the ylide of [4-(methanesulfonimido)-*n*-butyl]triphenylphosphonium bromide followed by oxidation, hydrolysis, and purification as described above to give 85 mg (10% from 61) of 91 as a viscous oil: NMR δ 6.78–6.12 (3 H, m, aromatic), 5.84–5.58 (2 H, m, trans CH=CH), 5.41–5.13 (2 H, m, cis CH=CH), 3.21 (3 H, s, SO_2CH_3); IR 1735 (carbonyls), 965 (trans CH=CH) cm^{-1}; MS ($C_{21}H_{27}NO_6S_2$, P – H_2O) calcd, 453.1280; found, 453.1289.

***N*-(Methanesulfonyl)-16-phenoxy-ω-tetranor-$PGF_{2\alpha}$-carboxamide (10).** A solution of 7 (636 mg, 1.0 mmol) in 7 mL of 65% aqueous acetic acid was stirred under nitrogen for 14 h and then was concentrated. Purification of the residue by silica gel chromatography using mixtures of ethyl acetate in $CHCl_3$ as eluants provided 187 mg (40%) of 10 as a viscous oil: IR 1720 (carbonyls), 975 (trans CH=CH) cm^{-1}; NMR δ 7.63–6.68 (5 H, m, aromatic), 5.72–5.17 (4 H, m, trans and cis CH=CH), 3.18 (3 H, s, SO_2CH_3); MS ($C_{23}H_{29}NO_5S$, P – $2H_2O$) calcd, 431.1763; found, 431.1781.

***N*-(Methanesulfonyl)-16-phenoxy-ω-tetranor-PGA_2-carboxamide (11).** A solution of 9 (110 mg, 0.24 mmol) in acetic acid (6 mL) was heated under nitrogen at 76 °C for 18 h and then concentrated. Purification of the crude product by silica gel chromatography using $CHCl_3$ as eluant provided 106 mg (99%) of 11 as a viscous oil: NMR δ 7.63–7.44 and 6.27–6.07 (2 H, m, CH=CHCO), 7.44–6.73 (5 H, m, aromatic), 5.88–5.68 (2 H, m, trans CH=CH), 5.50–5.20 (2 H, m, cis CH=CH), 4.67–4.33 (1 H, m, C*H*OH), 3.22 (3 H, m, SO_2CH_3); IR 1700 (carbonyls), 970 (trans CH=CH) cm^{-1}; MS ($C_{23}H_{29}NO_6S$) calcd, 447.1719; found, 447.1752.

***N*-(Methanesulfonyl)-16-phenoxy-ω-tetranor-PGB_2-carboxamide (12).** A solution of 9 (202 mg, 0.435 mmol), EtOH (20 mL), and 40% KOH (0.5 mL) was stirred at room temperature under nitrogen for 5 min, cooled in ice, acidified with 10% HCl, and concentrated. The residue was dissolved in ethyl acetate, washed with water and brine, dried, and concentrated. Purification of the crude product by silica gel chromatography using mixtures of $CHCl_3$ in ethyl acetate as eluants afforded 84 mg (43%) of 12 as a viscous oil: NMR δ 7.51–6.23 (7 H, m, aromatic and trans CH=CH), 5.46–5.16 (2 H, m, cis CH=CH), 4.92–4.63 (1 H, m, C*H*OH), 3.22 (3 H, s, SO_2CH_3); IR 1715 (imide C=O), 1685 (ketone C=O), 975 (trans CH=CH) cm^{-1}; MS ($C_{23}H_{29}NO_6S$) calcd, 447.1719; found, 447.1733.

Monkey Lung C_{15}-Hydroxyprostaglandin Dehydrogenase. All steps were performed at 0–4 °C. A 30-g portion of tissue (two lungs) was freed of adjacent tissue, cut into small pieces, and homogenized in 60 mL of buffer [5 mM potassium phosphate, 1 mM EDTA, and 20% (v/v) glycerol, pH 7.4]. The preparation was centrifuged at 10 000*g* for 45 min, and the supernatant was immediately decanted. Solid ammonium sulfate was then added to 65% saturation (430 g/L), and the mixture was stirred for 3–4 h and then centrifuged at 10000*g* for 45 min. The precipitate was collected, suspended in a minimum amount of buffer [5 mM potassium phosphate, 1 mM EDTA, and 20% (v/v) glycerol, pH 7.4], and stored in aliquots at –20 °C.

PGE_2 served as a standard to determine correct enzyme dilutions for further studies. A mixture consisting of 100 μL of buffer (0.05 M Tris-HCl, pH 9.0), 100 μL of Cleland's solution (1 mM), 100 μL of prostaglandin (3% methanol in 0.05 M Tris-HCl, pH 9.0) at the desired concentration, and 100 μL of enzyme solution was vortexed and read in a fluorometer (Turner Model 111). A 100-μL portion of 1 mM NAD solution was added and vortexed, and the solution was read in a fluorometer after 30 min. Under these conditions, (–)-PGE_2 was oxidized at a concentration of 1×10^{-9}, whereas 9 was unreactive at 1×10^{-7} M.

Test for In Vivo Uterine Stimulation. In guinea pigs, placental production of progesterone is sufficient to maintain pregnancy after 25 days, and, consequently, pregnancy can be interrupted after this time by direct effects on the uterus but not by luteolysis.[20] Pregnancy in guinea pigs (Wellcome, 700–1000 g) was determined by assigning the 2nd day of vaginal opening as the 1st day of pregnancy and was confirmed by palpation prior to the start of the experiment. Animals were maintained at a standard temperature (20 °C) and illumination (12 h dark, 12 h light) and received vitamin C rich pellets (Altromin), fresh lettuce, and water ad libitum.

On days 43 and 44 of pregnancy, animals were administered subcutaneously a solution (0.4 mL) of PGE_2 or prostaglandin analogues in a 1:3 mixture of benzyl benzoate and castor oil. The cages were repeatedly inspected for occurrence of abortion during and after treatment. The fetus and placenta were usually expelled within a few hours after the first or second dose. The data presented in Table I are the relative minimum effective doses (PGE_2, 1.0 mg/kg = 100) causing abortion in at least one of three animals.

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(20) Deanesly, R. *J. Endocrinol.* **1960**, *21*, 235.