ships in the antiinflammatory steroids. In addition to determining the contribution each individual substituent makes to potency, we predicted a synergistic effect to be in operation between certain pairs of substituents. These results allow the medicinal chemist to adopt a more rational approach to the design of potent antiinflammatory steroids.

Acknowledgment. Financial support by Otsuka Pharmaceutical Co. is gratefully acknowledged. A.J.H. is grateful for the financial support provided by the University of Florida.

Registry No. 1, 25122-46-7; 2, 50-02-2; 3, 5534-09-8; 4, 50-03-3; 5, 67-73-2; 6, 50-23-7; 7, 127-31-1; 8, 52-21-1; 9, 3093-35-4; 10, 25122-47-8; 11, 50-22-6; 12, 50-24-8; 13, 13609-67-1; 14, 356-12-7; 15, 37926-91-3; 16, 37926-78-6; 17, 913-42-8; 18, 59198-70-8; 19, 152-97-6; 20, 2002-29-1; 21, 312-93-6; 22, 2022-55-1; 23, 1524-88-5; 24, 76-25-5; 25, 5635-85-8; 26, 2152-44-5; 27, 987-24-6; 28, 378-44-9; 29, 53-36-1; 30, 84099-84-3; 31, 84099-85-4; 32, 4524-39-4; 33, 37926-75-3; 34, 37926-79-7; 35, 52619-01-9; 36, 52510-15-3; 37, 53-33-8; 38, 56933-60-9; 39, 84108-26-9; 40, 49697-38-3; 41, 37926-90-2; 42, 2240-28-0; 43, 5534-12-3; 44, 84099-86-5; 45, 29379-86-0; 46, 23640-97-3; 47, 23641-10-3; 48, 124-94-7; 49, 1177-87-3; 50, 37792-94-2; 51, 15180-00-4; 52, 37926-92-4; 53, 2693-06-3; 54, 4419-39-0; 55, 1597-82-6; 56, 23641-05-6; 57, 25122-48-9; 58, 302-25-0; 59, 37926-95-7; 60, 37927-21-2; 61, 37926-89-9; 62, 5534-14-5; 63, 75883-07-7; 64, 57524-89-7; 66, 638-94-8; 67, 514-36-3; 68, 83-43-2; 69, 84099-87-6; 70, 52510-28-8; 71, 25092-07-3; 72, 84099-88-7; 73, 37927-23-4; 74, 23641-03-4; 75, 37792-93-1; 76, 23674-85-3; 77, 806-29-1; 78, 37792-98-6; 79, 37926-93-5; 80, 382-67-2; 81, 641-77-0; 82, 5593-20-4; 83, 37926-96-8; 84, 4351-48-8; 85, 84099-89-8; 86, 84099-90-1; 87, 15845-96-2; 88, 84099-91-2; 89, 23640-96-2; 90, 42363-29-1; 91, 53-34-9; 92, 28971-62-2; 93, 2802-11-1; 94, 37926-76-4; 95, 84099-92-3; 96, 749-69-9; 97, 23674-86-4; 98, 25450-34-4; 99, 16463-74-4; 100, 2668-66-8; 101, 82034-75-1; 102, 5534-13-4; 103, 3863-59-0; 104, 84099-93-4; 105, 23641-07-8; 106, 84099-94-5; 107, 807-38-5; 108, 23641-01-2; 109, 630-44-4; 110, 25122-41-2; 111, 23641-09-0; 112, 23641-02-3; 113, 5534-18-9; 114, 23640-96-2; 116, 84099-95-6; 117, 72064-79-0; 118, 23641-08-9; 119, 37792-97-5; 120, 360-63-4; 121, 84099-96-7; 122, 25122-45-6.

Structure–Activity Studies of Configurationally Rigid Arylprostaglandins

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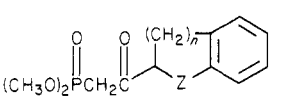
Potent, albeit nonselective, smooth-muscle stimulant activity has been previously reported for 16-phenoxy- and 17-phenylprostaglandins, a finding that led to the design and development of the tissue-selective uterine stimulant sulprostone. As an extension of this work, analogues incorporating the 16-phenoxy and 17-phenyl substituents into the rigid indanyl, tetrahydronaphthyl, dihydrobenzofuryl, and dihydrobenzopyranyl ring systems were prepared and evaluated for uterine stimulant activity in vitro and diarrheal effects in vivo. Since these cyclic groups, with the exception of the indanyl, contain a chiral center, both optical antipodes were prepared. These studies demonstrate that ring size, heteroatom, and absolute configuration at C-16 are important determinants for potency and selectivity.

The lack of tissue selectivity and metabolic stability of the natural prostaglandins has prompted the synthesis of numerous analogues.[1] As part of a systematic investigation of structure–activity relationships, we previously reported that the 17-phenyl-ω-trinor- and 16-phenoxy-ω-tetranorprostaglandins exhibit potent, albeit relatively nonselective, smooth-muscle stimulant activity, a finding that was an important consideration in the design of the selective uterine stimulant sulprostone.[2] As an extension of this work, the flexible 17-phenyl and 16-phenoxy groups were incorporated into the rigid indanyl, tetrahydronaphthyl, dihydrobenzofuryl, and dihydrobenzopyranyl structures.[3] Since these cyclic substituents, with the exception of the indanyl, contain a chiral center, congeners containing each of the optical antipodes were prepared from resolved precursors. The synthesis and structure–activity relationships of these analogues are the subject of this paper.

Chemistry. The Corey synthesis,[4] which is ideally suited for the synthesis of PGE_2 and $PGF_{2\alpha}$ analogues modified in the *n*-amylcarbinol side chain, was used in the preparation of our analogues (Scheme I). Since the cyclic substituents were introduced by means of appropriately substituted, optically active phosphonates (Table I), it was necessary to resolve the acid precursors. Thus, sodium ethyl *tert*-butylmalonate[5] was condensed with xylylene dibromide to provide 2-(carboxyethyl)-2-carboxy-*tert*-butylindan, which was treated without purification with

Table I. Optical Rotation of Chiral Phosphonates



compd	Z	*n*	config	$[\alpha]_D$, deg (solv, *c*)
2a	CH_2	1		*a*
2b	CH_2	2	d[b]	+46.2 (MeOH, 1.00)
2c	CH_2	2	*l*[b]	−43.2 (MeOH, 1.00)
2d	O	1	d[b]	+32.4 (C_6H_6, 6.11)
2e	O	1	*l*[b]	−34.8 (C_6H_6, 6.11)
2f	O	2	*l*[b]	−57.3 ($CHCl_3$, 1.00)
2g	O	2	d[b]	+54.9 ($CHCl_3$, 1.17)

[a] Phosphonate is achiral. [b] Configuration of chiral carbon (pro C-16); designation refers to carboxylic acid precursor of phosphonates.

[†] Pfizer, Inc.
[‡] Schering A.G.

(1) A portion of this work has been previously presented: Johnson, M. R.; Schaaf, T. K.; Bindra, J. S.; Hess, H.-J. Abstracts: Fourth International Prostaglandin Conference, Washington, DC, May 17–31, 1979, p 56.
(2) Schaaf, T. K.; Bindra, J. S.; Eggler, J. F.; Plattner, J. J.; Nelson, A. J.; Johnson, M. R.; Elger, W.; Constantine, J. W.; Hess, H.-J. *J. Med. Chem.* **1981**, *24*, 1353, and references therein.
(3) For other configurationally restricted 17-phenyl congeners, see Fletcher, D. G.; Gibson, K. H.; Moss, H. R.; Sheldon, D. R.; Walker, E. R. H. *Prostaglandins* **1976**, *12*, 493.

0022-2623/83/1826-0328$01.50/0

Scheme I

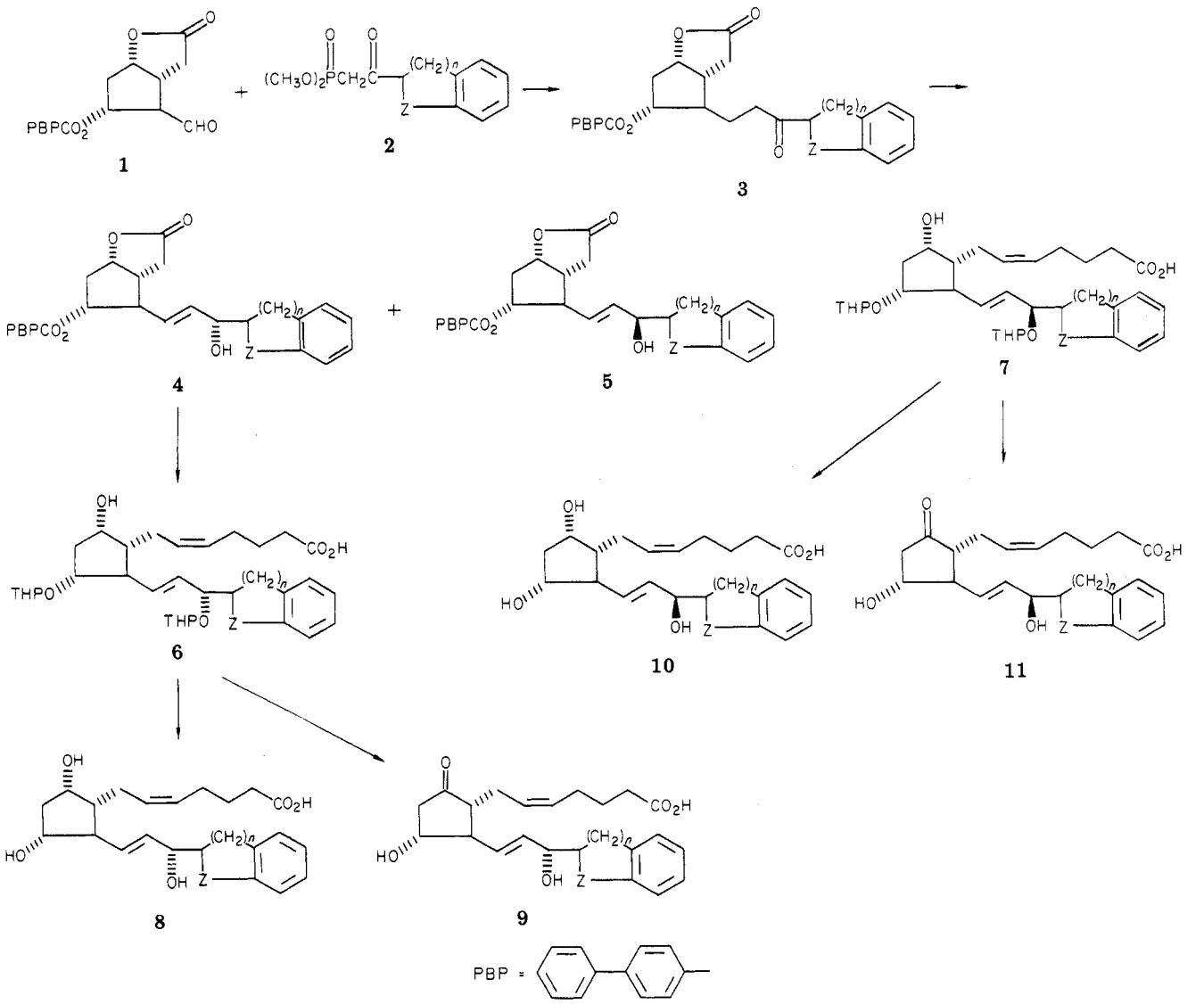
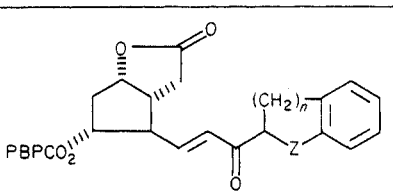


Table II. Physical Properties of Enone Intermediates



compd	Z	*n*	config	mp, °C	$[\alpha]_D$, deg (solv, *c*)
3a	CH_2	1		170-172 (IPA/CH_2Cl_2)	−145 ($CHCl_3$, 1.00)
3b	CH_2	2	d[a]	136-138 (CH_2Cl_2/hex)	−112 ($CHCl_3$, 1.00)
3c	CH_2	2	*l*[a]	147-148 (CH_2Cl_2/hex)	−160 ($CHCl_3$, 1.00)
3d	O	1	d[a]	159.5-160.5 (Et_2O/EtOAc)	−15.1 (C_6H_6, 2.26)
3e	O	1	*l*[a]	173-173.5	−10.2 (C_6H_6, 1.36)
3f	O	2	*l*[a]	121-125 (Et_2O/EtOAc)	−86.6 ($CHCl_3$, 1.00)
3g	O	2	d[a]	167-170 (EtOAc)	−126.9 ($CHCl_3$, 1.00)

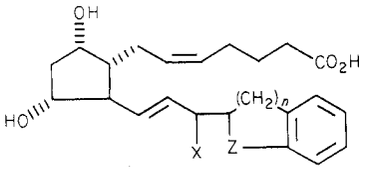
[a] Configuration of pro C-16 chiral carbon; designation refers to carboxylic acid precursor of phosphonates.

p-TsOH in refluxing benzene to give 2-(carboxyethyl)-indan-2-carboxylic acid. The crude acid was heated at 190–200 °C under reduced pressure, and the desired ethyl indan-2-carboxylate was collected by distillation.

1,2,3,4-Tetrahydro-2-naphthoic acid[6] was resolved by recrystallization of the corresponding *l*-amphetamine salt to provide the *d*-acid[7] and by recrystallization of the *d*-amphetamine salt to afford the *l*-acid. 2,3-Dihydro-2-benzofuroic acid[8] was resolved by recrystallization of the

(4) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
(5) Strube, P. E. In "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 417.
(6) Cohen, S. G.; Milovanovic, A.; Schultz, R. M.; Weinstein, S. Y. *J. Biol. Chem.* **1969**, *244*, 2664.
(7) The *d*-acid has been assigned the *R* absolute configuration.[6]

Table III. Structure and Biological Activities of Configurationally Rigid Arylprostaglandin $F_{2\alpha}$ Analogues



compd	X	Z	n	config	$[\alpha]_D$, deg (solv, c)	effects: uterine[a]	effects: diarrheal[b]
17-Ph-$PGF_{2\alpha}$	≡OH					15	220
15-*epi*-17-Ph-$PGF_{2\alpha}$	◄OH					0.02	*c*
8a	≡OH	CH_2	1		+20.7 (MeOH, 0.33)	0.3	50
10a	◄OH	CH_2	1		+13.9 (MeOH, 0.33)	0.07	*c*
8b	≡OH	CH_2	2	d[d]	+49.4 (MeOH, 0.33)	18	40
10b	◄OH	CH_2	2	d[d]	+38.0 (MeOH, 0.33)	0.1	
8c	≡OH	CH_2	2	*l*[d]	−7.6 (MeOH, 0.33)	2	10
10c	◄OH	CH_2	2	*l*[d]	−23.5 (MeOH, 0.33)	0.1	
16-PhO-$PGF_{2\alpha}$	≡OH					15	150
15-*epi*-16-PhO-$PGF_{2\alpha}$	◄OH						300
8d	≡OH	O	1	d[d]	+12.9 (MeOH, 1.23)	0.2	10
8e	≡OH	O	1	*l*[d]	+22.5 (MeOH, 0.54)	5	190
10e	◄OH	O	1	*l*[d]	+10.6 (MeOH, 0.76)	0.3	15
8f	≡OH	O	2	*l*[d]	+3.3 ($CHCl_3$, 1.02)	19	310
10f	◄OH	O	2	*l*[d]	−21.5 ($CHCl_3$, 1.33)	0.8	
8g	≡OH	O	2	d[d]	+54.3 ($CHCl_3$, 1.16)	25	1100
10g	◄OH	O	2	d[d]	+40.2 ($CHCl_3$, 1.28)	0.4	

[a] Relative spasmogenic potency (PGE_2 = 100) from concentration-response curves (0.1–10 μg/mL) for at least three guinea pig uteri. [b] Relative potency (PGE_2 = 100) estimated from concentration-response curves (0.3–3.0 mg/kg, iv) for induction of diarrhea in a group of six conscious mice. [c] No effect at 10 times the ED_{50} for PGE_2. [d] Configuration of C-16; designation refers to carboxylic acid precursors of phosphonates.

corresponding *d*-amphetamine salt to give the *d*-acid,[9] and by recrystallization of the *l*-amphetamine salt to provide the *l*-acid. Resolution of 2,3-dihydro-2-benzopyranoic acid (chroman-2-carboxylic acid)[10] was accomplished by recrystallization of the corresponding *l*-amphetamine salt to afford the *l*-acid and by recrystallization of the *d*-amphetamine salt to give the *d*-acid.

The acids were esterified (MeOH, H_2SO_4), and the resultant esters were treated with lithium dimethyl methylphosphonate in THF at −78 °C to afford the desired phosphonates (Table I). Condensation of the optically active aldehyde **1**[11] with the lithium salts of **2** in DME provided enones **3** (Table II). That epimerization of the chiral center at C-16 did not take place during the Wittig reaction is supported by the recovery of unchanged **2e** after treatment with *n*-butyllithium in DME and quenching with acetic acid.

Reduction of **3** with zinc borohydride in DME afforded a mixture of C-15 epimers (**4** and **5**), which was separated by silica gel chromatography. By analogy with the synthesis of the natural prostaglandins,[11] the less polar epimers were tentatively identified as the 15α-hydroxy congeners. That epimerization at C-16 had not occurred to this point is supported by the observation that the diastereomers **4f,g** and **5f,g** were cleanly separated by TLC and were each homogeneous.[12] Cleavage of **4** and **5** with potassium carbonate in MeOH, treatment of the resultant diol lactones with dihydropyran in CH_2Cl_2 containing *p*-TsOH, and reduction of the lactone with diisobutylaluminum hydride in toluene at −78 °C, followed by condensation of the resultant hemiacetals with the Wittig reagent derived from 5-(triphenylphosphonio)pentanoic acid[3] and sodium methylsulfinylcarbanide in Me_2SO provided the corresponding $PGF_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether) **6** and **7**.

Hydrolysis of **6** and **7** with a mixture of acetic acid–water provided the $PGF_{2\alpha}$ analogues **8** and **10** (Table III). Oxidation of **6** and **7** with Jones reagent at −10 °C, followed by hydrolysis of the tetrahydropyranyl ethers with a mixture of acetic acid–water, afforded the PGE_2 analogues **9** and **11** (Table IV).

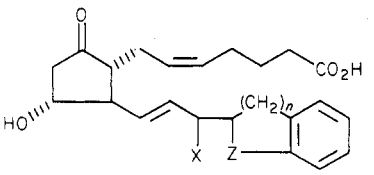
Biology. Widespread clinical use of the prostaglandins in obstetrics and gynecology as uterine stimulants has been limited by a lack of tissue selectivity, reflected as gastrointestinal side effects. Accordingly, the analogues described were evaluated by published procedures on the isolated guinea pig uterus[13,14] and for diarrheal activity in mice[13] as measures of these effects.

Results and Discussion

As an extension of our previous studies, series of prostaglandins incorporating the 17-phenyl and 16-phenoxy substituents into rigid cyclic structures were prepared. The results in Tables III and IV indicate that both activity and selectivity of these analogues is strongly dependent on the

(8) Bowen, D. M.; DeGraw, Jr., J. I.; Shah, V. R.; Bonner, W. A. *J. Med. Chem.* **1963**, *6*, 315.
(9) The *d*-acid has been assigned the *R* absolute configuration. Bonner, W. A.; Burke, N. I.; Fleck, W. E.; Hill, R. K.; Joule, J. A.; Sjoberg, B.; Zalkow, J. H. *Tetrahedron* **1964**, *20*, 1419.
(10) Witiak, D. T.; Strafford, E. S.; Nazareth, R.; Wagner, G.; Feller, D. R. *J. Med. Chem.* **1971**, *14*, 758.
(11) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491.
(12) R_f (Ethyl acetate/cyclohexane; 3:1, v/v, 4 passes): **4f**, 0.20; **5f**, 0.29; **4g**, 0.17; **5g**, 0.24.
(13) Schaaf, T. K.; Hess, H.-J. *J. Med. Chem.* **1979**, *22*, 1340.
(14) Clegg, P. C.; Hopkinson, P.; Pickles, V. R. *J. Physiol.* **1963**, *167*, 1.

Table IV. Structure and Biological Activities of Configurationally Rigid Arylprostaglandin E_2 Analogues



compd	X	Z	*n*	config	$[\alpha]_D$, deg (solv, *c*)	effects: uterine[a]	effects: diarrheal[b]
17-Ph-PGE_2	≡OH					100	10
15-*epi*-17-Ph-PGE_2	◄OH					0.2	10
9a	≡OH	CH_2	1		−60.7 (MeOH, 0.33)	6	25
11a	◄OH	CH_2	1		−71.2 (MeOH, 0.33)	0.3	*c*
9b	≡OH	CH_2	2	d[d]	−24.6 (MeOH, 0.33)	36	40
11b	◄OH	CH_2	2	d[d]	−22.0 (MeOH, 0.33)	2	
9c	≡OH	CH_2	2	*l*[d]	−93.8 (MeOH, 0.33)	44	*c*
11c	◄OH	CH_2	2	*l*[d]	−112 (MeOH, 0.33)	0.1	*c*
16-PhO-PGE_2	≡OH					75	150
15-*epi*-16-PhO-PGE_2	◄OH					1	<10
9d	≡OH	O	1	d[d]	−64.4 (MeOH, 1.76)	0.1	*c*
9e	≡OH	O	1	*l*[d]	−33.0 (MeOH, 0.80)	18	>250
11e	◄OH	O	1	*l*[d]	−73.2 (MeOH, 0.68)	19	15
9f	≡OH	O	2	*l*[d]	−96.1 ($CHCl_3$, 2.02)	66	270
11f	◄OH	O	2	*l*[d]	−99.1 ($CHCl_3$, 2.30)	3	
9g	≡OH	O	2	d[d]	−25.4 ($CHCl_3$, 2.02)	130	730
11g	◄OH	O	2	d[d]	−33.4 ($CHCl_3$, 1.18)	7	

[a] Relative spasmogenic potency (PGE_2 = 100) from concentration-response curves (0.1-10 μg/mL) for at least three guniea pig uteri. [b] Relative potency (PGE_2 = 100) estimated from concentration-response curves (0.3-3.0 mg/kg, iv) for induction of diarrhea in a group of six conscious mice. [c] No effect at 10 times the ED_{50} for PGE_2. [d] Configuration of C-16; designation refers to carboxylic acid precursors of phosphonates.

ring size, heteroatom, and absolute configuration of the substituents at C-15 and C-16. Within the carbon series, the 15-indanyl analogues **8a**, **10a**, **9a**, and **11a** are uniformly weak uterine stimulants but exhibit diarrheal activity comparable to their acyclic congeners. Thus, these cyclic analogues are less selective uterine stimulants than their acyclic counterparts. In contrast, the activity pattern of the more flexible 15-tetrahydronaphthyl analogues **8b,c**, **9b,c**, **10b,c**, and **11b,c** is less uniform. Among the $PGF_{2\alpha}$ analogues, for example, **8b** exhibits potent uterine stimulant effects in vitro and is more selective than 17-phenyl-ω-trinorprostaglandin $F_{2\alpha}$, while among the PGE_2 congeners, the C_{16}-enantiomer **9c** is more selective than 17-phenyl-ω-trinorprostaglandin E_2. Thus, there is an opposite chiral preference at C-16 for selective uterine stimulant effects between PGE_2 and $PGF_{2\alpha}$ in the tetrahydronaphthyl series.

Similar to the carbocyclic series, the activity and selectivity of the oxygen isosteres are also strongly affected by the absolute configuration at C-15 and C-16 (Tables III and IV). The 15-dihydrobenzofuryl congeners **9d,e**, **11e**, **8d,e**, and **10e** generally display weak uterine stimulant effects and are less tissue selective than the acyclic analogues. As in the carbocyclic series, the more flexible six-membered 15-dihydrobenzopyran compounds **8f,g**, **9f,g**, **10f,g**, and **11f,g** are generally more potent than the corresponding five-membered ring congeners. Particularly noteworthy are the potent uterine stimulant effects of **9f,g** and **8f,g**, although these compounds are less tissue selective than 16-phenoxy-ω-tetranorprostaglandins $F_{2\alpha}$ and E_2.

In contrast to the potent uterine stimulant activity and increased selectivity of sulprostone compared to its corresponding carboxylic acid analogue,[2] the C_1-methanesulfonimides of **9f,g** display 50–100 times less uterine stimulant activity in vitro[15] than the parent acids. Furthermore, **9b** and the crystalline *p*-biphenyl esters of **9c,f,g** exhibit at least 100 times less abortifacient activity than sulprostone in guinea pigs.[16]

In conclusion, incorporation of the acyclic 16-phenoxy and 17-phenyl groups into rigid cyclic structures provided series of prostaglandin analogues, the activity of which strongly depends on ring size, heteroatom, and absolute configuration at C-16. None of these compounds, however, displays an activity profile as favorable as the selective uterine stimulant sulprostone.

Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. ^1H NMR spectra, obtained on Varian T-60 or A-60 spectrometers, 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. Optical activity was determined on a Perkin-Elmer 141 polarimeter.

(15) The relative spasmogenic potency (PGE_2 = 100) from concentration–response curves (0.1–10 μg/mL) for at least three guinea pig uteri was 1.5 and 0.9 for the C_1 methanesulfonimides of **9f** and **9g**, respectively.

(16) Sulprostone causes abortions in at least 1/3 conscious guinea pigs at 0.03 mg/kg, sc.[2] A comparable minimum effective dose for **9b** is 3.0 mg/kg, sc, while the *p*-biphenyl esters of **9c,f,g** are without effect at this dose. (Data provided by Dr. W. Elger, Research Laboratories, Schering A.G., Berlin, Germany.)

(17) Pickard, R. H.; Yates, J. *J. Chem. Soc.* **1906**, *89*, 1101.

Column chromatography was carried out on Mallinckrodt SilicAR CC-7 or EM Reagents silica gel 60. Thin-layer chromatography (TLC) was used to monitor column fractions and to establish homogeneity of products. TLC was performed on EM Reagent 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 with a standard solvent system of 10% MeOH in CH_2Cl_2.

Chromatographed oils 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 are within 0.4% of the theoretical values. Satisfactory high-resolution mass values were obtained for the peaks indicated.

All reactions were performed under an atmosphere of dry nitrogen. Anhydrous $MgSO_4$ was used to dry organic extracts. Since optically active starting materials were employed, the absolute configuration of all chiral centers is identical with those found in the natural prostaglandins.

15-(2-Indanyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (8a and 9a). To a stirred suspension of 57% NaH in mineral oil (25.2 g, 0.60 mol) in THF (560 mL) was added dropwise ethyl *tert*-butyl malonate (54.4 g, 0.30 mol). The mixture was stirred for 30 min, and then a solution of xylylene dibromide (78.5 g, 0.30 mol) in THF (360 mL) was added dropwise. After being stirred for 1.5 h, the reaction mixture was concentrated, and the residue was dissolved in water. The aqueous mixture was extracted with ethyl acetate, and the organic extracts were washed with brine, dried, and concentrated to afford 85.2 g (98%) of 2-(ethoxycarbonyl)-2-(*tert*-butoxycarbonyl)indan as an oil, which was used without purification.

A solution of the diester prepared above (85.2 g, 0.29 mL) and *p*-toluenesulfonic acid hydrate (5.0 g, 29.3 mmol) in benzene (850 mL) was heated at reflux for 3.5 h with azeotropic removal of water. The reaction mixture was let cool, washed with water, dried, and concentrated to provide 68 g (100%) of 2-[(ethoxycarbonyl)indanyl]-2-carboxylic acid as a white solid, which was used without purification.

The acid prepared above (68 g, 0.29 mol) was heated at 190–200 °C, and the product was collected by distillation under reduced pressure [bp 120–154 °C (1 mmHg)]. Redistillation of the crude product gave 26.4 g (48%) of ethyl indan-2-carboxylate: bp 85–92 °C (0.3 mmHg); NMR δ 7.16 (4 H, s, aromatic), 4.62 (1 H, s, CH), 4.16 (2 H, q, OCH_2), 3.22 (4 H, s, CH_2), 1.23 (3 H, s, CH_3).

To a solution, cooled to −78 °C, of dimethyl methylphosphonate (20.4 g, 164 mmol) in THF (200 mL) was added a 2.25 M solution of *n*-butyllithium in hexane (82.6 mL) dropwise over a period of 20 min. After being stirred an additional 5 min at −78 °C, ethyl indane-2-carboxylate (14.0 g, 73.5 mmol) was added dropwise at a rate that kept the reaction temperature less than −70 °C (20 min). After being stirred for 1.0 h at −78 °C, the reaction mixture was allowed to warm, neutralized with acetic acid (20 mL), and concentrated. The residue was diluted with water, and the aqueous layers extracted with CH_2Cl_2. The organic extracts were washed with water, dried, and concentrated to provide 17.0 g (86%) of **2a** as a colorless oil (Table I): bp 150–160 °C (0.1 mmHg); NMR δ 7.15 (4 H, s, aromatic), 3.76 (6 H, d, J = 11 Hz, OCH_3), 3.25 (4 H, s, CH_2), 3.18 (1 H, d, J = 23 Hz, CH_2P), 3.13 (1 H, t, J = 2 Hz, CH).

To a solution, cooled in ice, of 1.90 M *n*-butyllithium in hexane (17.2 mL) in DME (150 mL) was added dropwise **2a** (9.2 g, 34.5 mmol). The solution was stirred in the cold for 10 min, and then the aldehyde **1** (11.9 g, 33.5 mmol) was added. The ice bath was removed, and the mixture was stirred for 1.0 h and then quenched by the addition of glacial acetic acid (pH ~5). The reaction mixture was concentrated, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with water, saturated $NaHCO_3$, and brine, dried, and concentrated to afford 6.85 g (43%) of **3a** as a white solid (Table II): mp 170–172 °C (isopropyl alcohol–CH_2Cl_2); IR 1775 (lactone C=O), 1710 (ester C=O), 1670 and 1625 (ketone C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.73 (9 H, m, C_6H_4–C_6H_5), 7.16 (4 H, s, C_6H_4), 6.98 (1 H, dd, J = 7 and 16 Hz) and 6.35 (1 H, d, J = 16 Hz, trans CH=CH), 3.26 (4 H, s, benzylic CH_2).

To a solution of **3a** (6.73 g, 14 mmol) in THF (67 mL) was added dropwise 0.05 M zinc borohydride in DME (14 mL). After being stirred for 1.5 h, a saturated sodium bitartrate solution was added dropwise until hydrogen evolution ceased. The reaction mixture was allowed to stir for 5 min and then was diluted with CH_2Cl_2, dried, and concentrated. Purification of the residue by column chromatography with mixtures of ether in ethyl acetate as eluants provided 2.21 g (33%) of **4a** as a viscous oil [IR 1770 (lactone C=O), 1705 (ester C=O), 970 (trans CH=CH) cm^{-1}] and 1.79 g (27%) of **5a** as a viscous oil [IR 1770 (lactone C=O), 1705 (ester C=O), 970 (trans CH=CH) cm^{-1}].

A heterogeneous mixture of **4a** (2.21 g, 4.46 mmol), THF (40 mL), MeOH (40 mL), and potassium carbonate (0.61 g) was stirred for 1 h and then cooled in ice. To the cooled solution was added 1.0 N aqueous HCl (4.46 mL). After being stirred at 0 °C for an additional 10 min, water (75 mL) was added with concomitant formation of methyl *p*-phenylbenzoate which was collected by filtration. The filtrate was concentrated and then extracted with ethyl acetate. The organic extracts were dried and concentrated to give 924 mg (66%) of 2-[3α,5α-dihydroxy-2β-[3α-hydroxy-3-(2-indanyl)-*trans*-1-propen-1-yl]cyclopent-1α-yl]acetic acid γ-lactone as a viscous oil: IR 1770 (lactone C=O), 970 (trans CH=CH) cm^{-1}.

A solution of the crude diol prepared above (0.92 g, 2.94 mmol), dihydropyran (0.86 mL), and *p*-toluenesulfonic acid hydrate (trace) in CH_2Cl_2 (49 mL) was stirred for 15 min and then was diluted with ether, washed with saturated $NaHCO_3$ and brine, dried, and concentrated to give 1.38 g (98%) of 2-[5α-hydroxy-3α-[(tetrahydropyran-2-yl)oxy]-2β-[3α-[(tetrahydropyran-2-yl)oxy]-3-(2-indanyl)-*trans*-1-propen-1-yl]cyclopent-1α-yl]acetic acid γ-lactone as a viscous oil, which was used without purification: IR 1775 (lactone C=O), 965 (trans CH=CH) cm^{-1}.

To a solution, cooled to −78 °C, of the crude bis(THP ether) prepared above (1.38 g, 1.9 mmol) in toluene (20 mL) was added 20% diisobutylaluminum hydride in hexane (4.2 mL). After being stirred for 30 min, the reaction was quenched by the dropwise addition of MeOH until gas evolution ceased. The mixture was then concentrated, and the residue was slurried with MeOH and filtered. Concentration of the filtrate, followed by purification of the residue by column chromatography with mixtures of benzene in ethyl acetate as eluants afforded 1.17 g (84%) of 2-[5α-hydroxy-3α-[(tetrahydropyran-2-yl)oxy]-2β-[3α-[(tetrahydropyran-2-yl)oxy]-3-(2-indanyl)-*trans*-1-propen-1-yl]cyclopent-1α-yl]acetaldehyde γ-hemiacetal as a viscous oil: IR 975 (trans CH=CH) cm^{-1}.

To a solution of (4-carbohydroxy-*n*-butyl)triphenylphosphonium bromide (3.21 g, 7.24 mmol) in Me_2SO (6 mL) was added 6.96 mL of 2.01 M sodium methylsulfinylmethide in Me_2SO. To this red ylide solution was added dropwise a solution of the hemiacetal prepared above (1.16 g, 2.41 mmol) in Me_2SO (2 mL). After being stirred for 2 h, the reaction mixture was poured onto ice–water. The basic aqueous solution was acidified to pH ~3 with 10% HCl and extracted with ethyl acetate. The combined organic extracts were washed with water, dried, and concentrated. The solid residue was triturated with ether and filtered. The filtrate was concentrated to provide 1.99 g (>100%) of **6a** as a viscous oil, which was used without further purification: NMR δ 7.08 (4 H, s, C_6H_4), 5.43 (4 H, m, cis and trans CH=CH), 4.70 (2 H, m, OCHO); IR 1710 (acid C=O), 970 (trans CH=CH) cm^{-1}.

A solution of **6a** (620 mg, 1.0 mmol) in 10 mL of 65% aqueous HOAc was stirred at room temperature for 18 h and then was concentrated. Purification of the residue by column chromatography with mixtures of $CHCl_3$ in ethyl acetate as eluants gave 156 mg (39%) of **8a** as a white solid (Table II): mp 114–115 °C from ethyl acetate; IR (KBr) 1733 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR (MeOH-d_4) δ 7.10 (4 H, s, C_6H_4), 5.47 (4 H, m, cis and trans CH=CH), 3.96 (3 H, m, CHO); $[\alpha]_D$ +20.7° (MeOH, *c* 0.33). Anal. ($C_{24}H_{32}O_5$) C, H.

To a solution, cooled to −10 °C, of **6a** (1.32 g, 2.34 mmol) in acetone (15 mL) was added 1.17 mL of Jones reagent. After being stirred for 15 min, the reaction was quenched with isopropyl alcohol (1.17 mL), diluted with ethyl acetate, washed with water, dried, and concentrated to give 1.11 g (84%) of 15-(2-indanyl)-ω-pentanorprostaglandin E_2 11,15-bis(tetrahydropyranyl ether) as a viscous oil, which was used immediately without purification.

A solution of the crude bis(THP ether) prepared above (1.11 g, 2.0 mmol) in 15 mL of 65% aqueous HOAc was stirred at room

temperature for 18 h and then was concentrated. Purification of the residue by column chromatography with mixtures of ethyl acetate in $CHCl_3$ as eluants provided 288 mg (37%) of **9a** as a white solid (Table IV): mp 110–112 °C (ethyl acetate–hexane); IR (KBr) 1760 (ketone C=O), 1712 (acid C=O), 976 (trans CH=CH) cm^{-1}; NMR (MeOH-d_4) δ 7.07 (4 H, s, C_6H_4), 5.62 (2 H, m, trans CH=CH), 5.31 (2 H, m, cis CH=CH), 3.99 (2 H, m, OCHO); $[\alpha]_D$ −60.7° (MeOH, *c* 0.33). Anal. ($C_{24}H_{30}O_5$) C, H.

15-*epi*-15-(2-Indanyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (10a and 11a). The 15β-alcohol **5a** was subjected to the reaction sequence described above to give **10a** as a viscous oil (Table III) [IR 1712 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR (MeOH-d_4) δ 7.08 (4 H, s, C_6H_4), 5.36 (4 H, m, cis and trans CH=CH), 4.07 (3 H, m, OCH); $[\alpha]_D$ +13.9° (MeOH, *c* 0.33); MS ($C_{24}H_{28}O_3$, P − $2H_2O$) calcd, 364.2038; found, 364.2099] and **11a** as white solid (Table IV) [mp 66–68 °C (ethyl acetate–hexane); IR (KBr) 1740 (ketone C=O), 1710 (acid C=O), 970 (trans CH=CH) cm^{-1}; NMR δ 7.09 (4 H, s, C_6H_4), 5.62 (2 H, m, trans CH=CH), 5.32 (2 H, m, cis CH=CH), 4.06 (2 H, m, OCH); $[\alpha]_D$ −71.2° (MeOH, *c* 0.33). Anal. ($C_{24}H_{30}O_5$) C, H].

15-(*d*-1,2,3,4-Tetrahydro-2-naphthyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (8b and 9b). *l*-Amphetamine (42.2 g, 0.312 mol) was added to a solution of 1,2,3,4-tetrahydro-2-naphthoic acid (54.9 g, 0.312 mol) in ether (500 mL), and the resultant salt was collected by filtration. Recrystallization of this salt from acetone–hexane (5 times) to constant rotation provided 25.5 g (52%) of the resolved salt: mp 136–137 °C; $[\alpha]_D$ +30.1° (MeOH, *c* 1.00). A solution of the resolved salt (25.5 g, 82 mmol) in water (200 mL) was acidified with 10% HCl (pH ~2) and extracted with CH_2Cl_2. The combined extracts were washed with water, dried, and concentrated to provide 13.4 g (93%) of *d*-1,2,3,4-tetrahydro-2-naphthoic acid as a white solid: mp 100–101 °C from hexane: $[\alpha]_D$ +52.1° (MeOH, *c* 1.00).

The resolved acid was esterified (MeOH, H_2SO_4), and the resultant ester was converted to the phosphonate **2b** as described above (Table I). Reaction of **2b** with the aldehyde **1** afforded enone **3b** (Table II). Reduction of **3b**, followed by chromatographic separation of the epimeric alcohols, provided **4b** [oil; $[\alpha]_D$ −60.6° ($CHCl_3$, *c* 1.00)] and **5b** [oil; $[\alpha]_D$ −76.6° ($CHCl_3$, *c* 1.00)].

The 15α-alcohol **4b** was subjected to the reaction sequence described above to give **8b** as a white solid (Table III) [mp 105–105.5 °C (ethyl acetate); IR (KBR) 1710 (acid C=O), 970 (trans CH=CH) cm^{-1}; NMR δ 7.00 (4 H, s, C_6H_4), 5.55 (4 H, m, cis and trans CH=CH), 3.91 (3 H, m, CHO); $[\alpha]_D$ +49.4° (MeOH, *c* 0.33). Anal. ($C_{25}H_{34}O_5$) C, H] and **9b** as a white solid (Table IV) [mp 103–104 °C (ethyl acetate–hexane); IR (KBr) 1730 (ketone C=O), 1712 (acid C=O), 965 (trans CH=CH) cm^{-1}; NMR δ 7.04 (4 H, s, C_6H_4), 5.63 (2 H, m, trans CH=CH), 5.40 (2 H, m, cis CH=CH), 3.97 (2 H, m, OCH); $[\alpha]_D$ −24.6° (MeOH, *c* 0.33). ($C_{25}H_{32}O_5$) C, H].

15-*epi*-15-(*d*-1,2,3,4-Tetrahydro-2-naphthyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (10b and 11b). The 15β-alcohol **5b** was subjected to the reaction sequence described above to give **10b** as a viscous oil (Table III) [IR 1710 (acid C=O), 970 (trans CH=CH) cm^{-1}; NMR δ 7.09 (4 H, s, C_6H_4), 5.60 (2 H, m, trans CH=CH), 5.39 (2 H, m, cis CH=CH), 4.02 (3 H, m, OCH); $[\alpha]_D$ +38.0° (MeOH, *c* 0.33); MS ($C_{25}H_{32}O_4$, P − H_2O) calcd, 396.2301; found, 396.2305] and **11b** as a viscous oil (Table IV) [IR 1732 (ketone C=O), 1711 (acid C=O), 965 (trans CH=CH) cm^{-1}; NMR δ 7.08 (4 H, s, C_6H_4), 5.67 (2 H, m, trans CH=CH), 5.36 (2 H, m, cis CH=CH), 4.04 (2 H, m, OCH); $[\alpha]_D$ −22.0° (MeOH, *c* 0.33); MS ($C_{25}H_{30}O_4$, P − H_2O) calcd, 394.2144; found, 394.2172].

15-(*l*-1,2,3,4-Tetrahydro-2-naphthyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (8c and 9c). *d*-Amphetamine (23.1 g, 0.171 mol) was added to a solution of partially resolved *l*-1,2,3,4-tetrahydro-2-naphthoic acid (30.1 g, 0.171 mol), which was recovered from the mother liquors of the resolution of the *d* antipode, in ether (300 mL), and the resultant salt was collected by filtration. Recrystallization of this salt from acetone (3 times) to constant rotation afforded 26.1 g of the resolved salt: mp 135–136 °C; $[\alpha]_D$ −30.7° (MeOH, *c* 1.00). A solution of the resolved salt (26.1 g, 84 mmol) in water (200 mL) was acidified with 10% HCl (pH ~2) and extracted with CH_2Cl_2. The combined extracts were washed with water, dried, and concentrated to provide 13.5 g (91%) of *l*-1,2,3,4-tetrahydro-2-naphthoic acid as a white solid: mp 100–101 °C (hexane); $[\alpha]^{25}_D$ −52.5° (MeOH, *c* 1.00) [lit.[17] mp 99 °C; $[\alpha]_D$ −51.8° ($CHCl_3$, *c* 1.40)].

The resolved acid was esterified (MeOH, H_2SO_4), and the resultant ester was converted to the phosphonate **2c** as described above (Table I). Reaction of **2c** with the aldehyde **1** afforded enone **3c** (Table II). Reduction of **3c**, followed by chromatographic separation of the epimeric alcohols, provided **4c** [mp 113–114 °C (ethyl acetate–hexane); $[\alpha]_D$ −125° ($CHCl_3$, *c* 1.00)] and **5c** [mp 159.5–160.5 °C (CH_2Cl_2–hexane); $[\alpha]_D$ −145° ($CHCl_3$, *c* 1.00)].

The 15α-alcohol **4c** was subjected to the reaction sequence described above to give **8c** as a white solid (Table III) [mp 127–127.5 °C (ethyl acetate–hexane); IR (KBr) 1712 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.10 (4 H, s, C_6H_4), 5.56 (4 H, m, cis and trans CH=CH), 4.08 (3 H, m, OCH); $[\alpha]_D$ −7.6° (MeOH, *c* 0.33). Anal. ($C_{25}H_{34}O_5$) C, H] and **9c** as a white solid (Table IV) [mp 72–73.5 °C (ethyl acetate–hexane); IR (KBr) 1737 (ketone C=O), 1710 (acid C=O), 970 (trans CH=CH) cm^{-1}; NMR δ 7.12 (4 H, s, C_6H_4), 5.66 (2 H, m, trans CH=CH), 5.37 (2 H, m, cis CH=CH), 4.08 (2 H, m, OCH); $[\alpha]_D$ −93.8° (MeOH, *c* 0.33). Anal. ($C_{25}H_{32}O_5$) C, H].

15-*epi*-15-(*l*-1,2,3,4-Tetrahydro-2-naphthyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (10c and 11c). The 15β-alcohol **5c** was subjected to the reaction sequence described above to give **10c** as a viscous oil (Table III) [IR 1708 (acid C=O), 970 (trans CH=CH) cm^{-1}; NMR δ 7.10 (4 H, s, C_6H_4), 5.57 (4 H, m, cis and trans CH=CH), 4.08 (3 H, m, OCH); $[\alpha]_D$ −23.5° (MeOH, *c* 0.33); MS ($C_{25}H_{30}O_3$, P − H_2O) calcd, 378.2195; found, 378.2232] and **11c** as a white solid (Table IV) [mp 80–81 °C (ethyl acetate–hexane); IR (KBr) 1736 (ketone C=O), 1701 (acid C=O), 966 (trans CH=CH) cm^{-1}; NMR (MeOH-d_4) δ 7.12 (4 H, m, C_6H_4), 5.80 (2 H, m, trans CH=CH), 5.42 (2 H, m, cis CH=CH), 4.03 (2 H, m, OCH); $[\alpha]_D$ −112° (MeOH, *c* 0.33). Anal. ($C_{25}H_{32}O_5$) C, H].

15-(*d*-2,3-Dihydro-2-benzofuryl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (8d and 9d). *d*-Amphetamine (50.0 g, 0.37 mol) was added to a solution of 2,3-dihydrobenzo-2-furoic acid (60 g, 0.37 mol) in CH_2Cl_2 (300 mL), and the resultant solid was collected by filtration. Recrystallization of this salt from water (2 times) to constant rotation afforded 37.5 g (68%) of the resolved salt: mp 184.5–185.5 °C. A portion of the resolved salt was converted as described above into the resolved free acid: mp 116 °C; $[\alpha]_D$ +22.6° (EtOH, *c* 7.3).

The resolved salt was esterified (MeOH, H_2SO_4), and the resultant ester was converted to the phosphonate **2d** as described above (Table I). Reaction of **2d** with the aldehyde **1** afforded enone **3d** (Table II). Reduction of **3d**, followed by chromatographic separation of the epimeric alcohols, provided **4d**: mp 150–152 °C after trituration with ether; $[\alpha]_D$ −89.5° (C_6H_6, *c* 3.03).

The 15α-alcohol **4d** was subjected to the reaction sequence described above to give **8d** as a viscous oil (Table III) [IR 1708 (acid C=O), 970 (trans CH=CH); $[\alpha]_D$ +12.9° (MeOH, *c* 1.23); MS ($C_{22}H_{28}O_5$, P − H_2O) calcd, 384.1937; found, 384.1998] and **9d** as a viscous oil (Table IV) [IR 1735 (ketone C=O), 1700 (acid C=O), 965 (trans CH=CH) cm^{-1}; $[\alpha]_D$ −64.4° (MeOH, *c* 1.76); MS ($C_{22}H_{26}O_5$, P − H_2O) calcd, 382.1780; found, 382.1784].

15-(*l*-2,3-Dihydro-2-benzofuryl-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (8e and 9e). *l*-Amphetamine (30 g, 0.22 mol) was added to a solution of partially resolved *l*-2,3-dihydrobenzo-2-furoic acid (37 g, 0.22 mol), which was recovered from the mother liquors of the resolution of the *d* antipode, in CH_2Cl_2 (500 mL), and the salt was collected by filtration. Recrystallization of this salt from water (1 time) to constant rotation afforded 39 g of the resolved salt: mp 187–188 °C. A portion of the resolved salt was converted as described above into the resolved free acid: mp 115 °C; $[\alpha]_D$ −20.8° (EtOH, *c* 7.26).

The resolved salt was esterified (MeOH, H_2SO_4), and the resultant ester converted to the phosphonate **2e** as described above (Table I). Reaction of **2e** with the aldehyde **1** afforded enone **3e** (Table II). Reduction of **3e**, followed by chromatographic separation of the epimeric alcohols, provided **4e** [mp 119–121 °C; $[\alpha]_D$ −120° (C_6H_6, *c* 6.06)] and **5e** [mp 135–137 °C; $[\alpha]_D$ −123° (C_6H_6, *c* 6.04)].

The 15α-alcohol **4e** was subjected to the reaction sequence described above to give **8e** as a viscous oil (Table III) [IR 1700 (acid C=O), 965 (trans CH=CH) cm^{-1}; $[\alpha]_D$ +22.5° (MeOH, *c* 0.54); MS ($C_{23}H_{28}O_5$, P − H_2O) calcd, 384.1937; found 384.1998] and **9e** as a viscous oil (Table IV) [IR 1730 (ketone C=O), 1700

(acid C=O), 965 (trans CH=CH) cm^{-1}; $[\alpha]_D$ -33.0° (MeOH, c 0.80); MS ($C_{23}H_{26}O_5$, P - H_2O) calcd, 382.1780; found, 382.1866].

15-*epi*-15-(*l*-2,3-Dihydro-2-benzofuryl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (10e and 11e). The 15β-alcohol **5e** was subjected to the reaction sequence described above to give **10e** as a viscous oil (Table III) [IR 1700 (acid C=O), 965 (trans CH=CH) cm^{-1}; $[\alpha]_D$ +10.6° (MeOH, c 0.75); MS ($C_{23}H_{30}O_6$) calcd, 402.2042; found; 402.2016] and **11e** as a viscous oil (Table IV) [IR 1735 (ketone C=O), 1700 (acid C=O), 965 (trans CH=CH) cm^{-1}; $[\alpha]_D$ -73.2° (MeOH, c 0.68); MS ($C_{23}H_{26}O_5$, P - H_2O) calcd, 382.1780; found, 382.1866].

15-(*l*-2,3-Dihydro-2-benzopyranyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (8f and 9f). *l*-Amphetamine (97.5 g, 0.72 mol) was added to a solution of 2,3-dihydrobenzopyran-2-carboxylic acid (117 g, 0.66 mol) in CH_2Cl_2 (465 mL), and the resultant solid was collected by filtration. Recrystallization of this salt from water (3 times) to constant rotation provided 15 g of the resolved salt: mp 170–174 °C; $[\alpha]_{365}$ -100° ($CHCl_3$, c 1.00).

The resolved salt was esterified (MeOH, H_2SO_4), and the resultant ester was converted to the phosphonate **2f** as described above (Table I). Reaction of **2f** with the aldehyde **1** afforded enone **3f** (Table II). Reduction of **3f**, followed by chromatographic separation of the epimeric alcohols, provided **4f** [mp 157–159 °C; $[\alpha]_D$ -121° ($CHCl_3$, c 1.00)] and **5f** [mp 134–136 °C; $[\alpha]_D$ -135° ($CHCl_3$, c 1.00)].

The 15α-alcohol **4f** was subjected to the reaction sequence described above to give **8f** as a viscous oil (Table III) [IR 1710 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.12 (4 H, m, C_6H_4), 5.58 (4 H, m, cis and trans CH=CH); $[\alpha]_D$ +3.3° ($CHCl_3$, c 1.02); MS ($C_{24}H_{32}O_6$) calcd, 416.2199; found, 416.2202] and **9f** as a viscous oil (Table IV) [IR 1740 (ketone C=O), 1710 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.06 (4 H, m, C_6H_4), 5.84 (2H, m, trans CH=CH), 5.42 (2 H, m, cis CH=CH); $[\alpha]_D$ -96.1° ($CHCl_3$, c 2.02); MS ($C_{24}H_{30}O_6$) calcd, 414.2044; found, 414.2034].

15-*epi*-15-(*l*-2,3-Dihydro-2-benzopyranyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (10f and 11f). The 15β-alcohol **5f** was subjected to the reaction sequence described above to give **10f** as a viscous oil (Table III) [IR 1710 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.00 (4 H, m, C_6H_4), 5.53 (4 H, m, cis and trans CH=CH); $[\alpha]_D$ -21.5° ($CHCl_3$, c 1.33); MS ($C_{24}H_{32}O_6$) calcd, 416.2199; found, 416.2135] and **11f** as a viscous oil [IR 1740 (ketone C=O), 1710 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.00 (4 H, m, C_6H_4), 5.82 (2 H, m, trans CH=CH), 5.45 (2 H, m, cis CH=CH); $[\alpha]_D$ -99.1° ($CHCl_3$, c 2.30); MS ($C_{24}H_{28}O_5$, P - H_2O) calcd, 396.1937; found, 396.1895].

15-(*d*-2,3-Dihydro-2-benzopyranyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (8g and 9g). *d*-Amphetamine (21.6 g, 0.16 mol) was added to a solution of partially resolved *d*-2,3-dihydrobenzopyran-2-carboxylic acid (28.6 g, 0.16 mol), which was recovered from the mother liquors of the resolution of the *l* antipode, in CH_2Cl_2 (150 mL), and the salt was collected by filtration. Recrystallization of this salt from isopropyl alcohol (7 times) to constant rotation afforded 36.6 g of the resolved salt: mp 173–175 °C; $[\alpha]_{365}$ +106° ($CHCl_3$, c 1.00).

The resolved salt was esterified (MeOH, H_2SO_4), and the resultant ester was converted into the phosphonate **2g** as described above (Table I). Reaction of **2g** with the aldehyde **1** afforded enone **3g** (Table II). Reduction of **3g**, followed by chromatographic separation of the epimeric alcohols, provided **4g** [mp 157–159 °C; $[\alpha]_D$ -68.2° ($CHCl_3$, c 1.00)] and **5g** [mp 147–150 °C; $[\alpha]_D$ -81.3° ($CHCl_3$, c 1.00)].

The 15α-alcohol **4g** was subjected to the reaction sequence described above to give **8g** as a viscous oil (Table III) [IR 1710 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.00 (4 H, m, C_6H_4), 5.58 (4 H, m, cis and trans CH=CH); $[\alpha]_D$ +54.3° ($CHCl_3$, c 1.16); MS ($C_{24}H_{30}O_5$, P - H_2O) calcd, 398.2088; found, 398.2106] and **9g** as a viscous oil (Table IV) [IR 1740 (ketone C=O), 1710 (acid C=O), 970 (trans CH=CH) cm^{-1}; NMR δ 6.96 (4 H, m, C_6H_4), 5.68 (2 H, m, trans CH=CH), 5.38 (2 H, m, cis CH=CH); $[\alpha]_D$ -25.4° ($CHCl_3$, c 2.02); MS ($C_{24}H_{28}O_5$, P - H_2O) calcd, 396.1937; found, 396.1916].

15-*epi*-15-(*d*-2,3-Dihydro-2-benzopyranyl)-ω-pentanorprostaglandins $F_{2\alpha}$ and E_2 (10g and 11g). The 15β-alcohol **5g** was subjected to the reaction sequence described above to give **10g** as a viscous oil (Table III) [IR 1710 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 7.05 (4 H, m, C_6H_4), 5.56 (4 H, m, cis and trans CH=CH); $[\alpha]_D$ +40.2° ($CHCl_3$, c 1.28); MS ($C_{24}H_{32}O_6$) calcd, 416.2199; found, 416.2134] and **11g** as a viscous oil (Table IV) [IR 1740 (ketone C=O), 1710 (acid C=O), 975 (trans CH=CH) cm^{-1}; NMR δ 6.95 (4 H, m, C_6H_4), 5.72 (2 H, m, trans CH=CH), 5.34 (2H, m, cis CH=CH); $[\alpha]_D$ -33.4° ($CHCl_3$, c 1.18); MS ($C_{24}H_{28}O_5$, P - H_2O) calcd, 396.1937; found, 396.1998].

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Registry No. **1**, 38754-71-1; **2a**, 53273-26-0; **2b**, 53319-32-7; **2c**, 53319-33-8; **2d**, 66598-85-4; **2e**, 66598-84-3; **2f**, 66598-86-5; **2g**, 66598-87-6; **3a**, 53273-41-9; **3b**, 83721-30-6; **3c**, 83780-43-2; **3d**, 66673-51-6; **3e**, 66673-50-5; **3f**, 66598-88-7; **3g**, 66701-39-1; **4a**, 53273-46-4; **4b**, 83721-31-7; **4c**, 83780-44-3; **4d**, 66673-55-0; **4e**, 66673-53-8; **4f**, 66673-56-1; **4g**, 66701-40-4; **5b**, 83780-42-1; **5c**, 83780-45-4; **5e**, 66673-52-7; **5f**, 66598-89-8; **5g**, 66673-57-2; **6a**, 71358-62-8; **8a**, 53273-81-7; **8b**, 83780-36-3; **8c**, 83780-38-5; **8d**, 66673-74-3; **8e**, 66673-73-2; **8f**, 66598-93-4; **8g**, 66673-75-4; **9a**, 53273-97-5; **9b**, 83721-27-1; **9c**, 83780-32-9; **9d**, 66673-83-4; **9e**, 66673-82-3; **9f**, 66598-97-8; **9g**, 66673-84-5; **10a**, 55221-27-7; **10b**, 83780-37-4; **10c**, 83780-39-6; **10e**, 83780-41-0; **10f**, 66673-76-5; **10g**, 66673-77-6; **11a**, 54483-42-0; **11b**, 83780-31-8; **11c**, 83780-33-0; **11e**, 83780-35-2; **11f**, 66673-85-6; **11g**, 66673-86-7; ethyl *tert*-butyl malonate, 32864-38-3; xylylene dibromide, 91-13-4; 2-(ethoxycarbonyl)-2-(*tert*-butoxycarbonyl)indan, 83721-28-2; 2-[(ethoxycarbonyl)indanyl]-2-carboxylic acid, 83721-29-3; ethyl indan-2-carboxylate, 81290-34-8; dimethyl methylphosphonate, 756-79-6; 2-[3α,5α-dihydroxy-2β-[3α-hydroxy-3-(2-indanyl)-*trans*-1-propen-1-yl]cyclopent-1α-yl]acetic acid γ-lactone, 53273-61-3; dihydropyran, 110-87-2; 2-[5α-hydroxy-3α-[(tetrahydropyran-2-yl)oxy]-2β-[3α-[(tetrahydropyran-2-yl)oxy]-3-(2-indanyl)-*trans*-1-propen-1-yl]cyclopent-1α-yl]acetic acid γ-lactone, 71358-53-7; 2-[5α-hydroxy-3α-[(tetrahydropyran-2-yl)oxy]-2β-[3α-[(tetrahydropyran-2-yl)oxy]-3-(2-indanyl)-*trans*-1-propen-1-yl]cyclopent-1α-yl]acetaldehyde γ-hemiacetal, 53273-57-7; (4-carbohydroxy-*n*-butyl)triphenylphosphonium bromide, 17814-85-6; 15-(2-indanyl)-ω-pentanorprostaglandin E_2 11,15-bis(tetrahydropyranyl ether), 71358-71-9; 1,2,3,4-tetrahydro-2-naphthoic acid, 53440-12-3; *d*-1,2,3,4-tetrahydro-2-naphthoic acid, 38157-15-2; *d*-1,2,3,4-tetrahydro-2-naphthoic acid methyl ester, 53319-10-1; *l*-1,2,3,4-tetrahydro-2-naphthoic acid, 83721-32-8; *l*-1,2,3,4-tetrahydro-2-naphthoic acid methyl ester, 53319-11-2; *d*-2,3-dihydrobenzo-2-furoic acid, 77341-31-2; *d*-2,3-dihydrobenzo-2-furoic acid methyl ester, 17332-01-3; *l*-2,3-dihydrobenzo-2-furoic acid, 63559-46-6; *l*-2,3-dihydrobenzo-2-furoic acid methyl ester, 24758-34-7; *l*-2,3-dihydrobenzopyran-2-carboxylic acid, 83780-46-5; methyl *l*-2,3-dihydrobenzopyran-2-carboxylate, 66598-81-0; *d*-2,3-dihydrobenzopyran-2-carboxylic acid, 83780-47-6; methyl *d*-2,3-dihydrobenzopyran-2-carboxylate, 66598-82-1; 17-Ph-ω-trinor-$PGF_{2\alpha}$, 38344-08-0; 15-*epi*-17-Ph-ω-trinor-$PGF_{2\alpha}$, 41639-71-8; 16-PhO-ω-tetranor-$PGF_{2\alpha}$, 51705-19-2; 15-*epi*-16-PhO-ω-tetranor-$PGF_{2\alpha}$, 83780-40-9; 17-Ph-ω-trinor-PGE_2, 38315-43-4; 15-*epi*-17-Ph-ω-trinor-PGE_2, 83780-30-7; 16-PhO-ω-tetranor-PGE_2, 54382-74-0; 15-*epi*-16-PhO-ω-tetranor-PGE_2, 83780-34-1.