Prostaglandin Analogues Possessing Antinidatory Effects. 2. Modification of the α Chain

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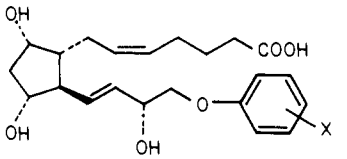
Additional double bonds were introduced into the α chain in 16-phenoxy-, 16-(3-chlorophenoxy)-, 16-[3-(trifluoromethyl)phenoxy]-, and 16-(4-chlorophenoxy)-17,18,19,20-tetranorprostaglandins which have antinidatory effects. Of these analogues, the Δ^3-cis-Δ^5 analogue **23b** is 1200 times more potent than prostaglandin $F_{2\alpha}$ in antinidatory effect in the rat and more potent than any other known prostaglandin analogues.

Prostaglandin $F_{2\alpha}$ is ca. 10 times more active than prostaglandin $F_{1\alpha}$ in antinidatory effect.[1] Since the structural characteristic which distinguishes the former from the latter is the presence of the cis double bond at C_5–C_6 in the α chain (the upper chain), it can be presumed that this feature is an important factor for increasing the antinidatory effect. From this point of view, it was considered very interesting to know the structure–bioactivity relationship of antinidatory effects of analogues in which one or more double bonds are introduced into other positions in the α chain.

We have synthesized novel prostaglandin analogues containing a variety of double bonds in the α chain and have examined their antinidatory effects in comparison with 16-(aryloxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$

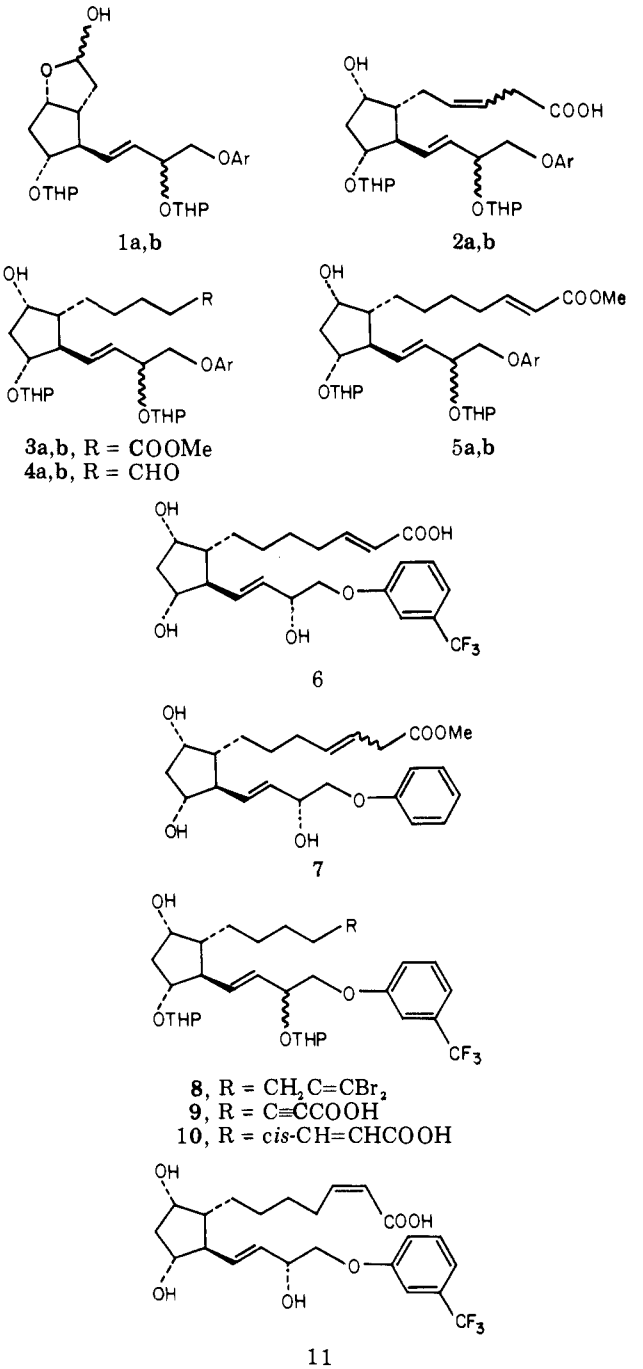


X = H, *m*-Cl, *m*-CF_3, or *p*-Cl

which was known to have a high antinidatory effect.[2] As a result of this research, a remarkably active prostaglandin analogue has been found, which was 1200 times more potent than prostaglandin $F_{2\alpha}$ in antinidatory effect. Some 16-(aryloxy) groups in the ω chain (the lower chain) were selected from phenoxy, *m*-chlorophenoxy, *m*-(trifluoromethyl)phenoxy, and *p*-chlorophenoxy functions, and we prepared trans-Δ^2, cis-Δ^2, Δ^3, and trans-Δ^5 analogues containing the monoene in the α chain; trans-Δ^2-cis-Δ^5, Δ^3-cis-Δ^5, trans-Δ^3-cis-Δ^5, cis-Δ^3-cis-Δ^5, trans-Δ^2-trans-Δ^4, trans-Δ^2-trans-Δ^5, and trans-Δ^3-trans-Δ^5 analogues having the diene; and also trans-Δ^2-trans-Δ^4-trans-Δ^6 analogues possessing the triene in the α chain.

Chemistry. Starting with the readily available lactols **1a,b**,[2] 16-(aryloxy)prostaglandin analogues **6**, **7**, and **11** containing a double bond in the α chain were synthesized (see Chart I). The Wittig reaction of **1a,b** with the unstable ylide prepared from (β-carboxyethyl)triphenylphosphonium bromide[3] and sodiomethylsulfinyl carbanide ($NaCH_2SOCH_3$) in dimethyl sulfoxide (Me_2SO) afforded the corresponding β,γ-unsaturated acids **2a,b** in ca. 64% yield. Selective hydrogenation of the double bond in the α chain in **2a,b** with 5% palladium on carbon as a catalyst, followed by esterification with diazomethane, gave the esters **3a,b** in 87% yield, which were converted to the aldehydes **4a,b** quantitatively by diisobutylaluminum hydride (DIBAL) at −78 °C in toluene. The aldehydes **4a,b** were condensed by the Wittig reaction with the stable ylide, (carbomethoxymethylene)triphenylphosphorane,[4] to

Chart I[a]



1a,b **2a,b**

3a,b, R = COOMe
4a,b, R = CHO

5a,b

6

7

8, R = $CH_2C{=}CBr_2$
9, R = C≡CCOOH
10, R = *cis*-CH=CHCOOH

11

[a] For 1a-5a, Ar = *m*-(trifluoromethyl)phenyl; 1b-5b, Ar = phenyl.

(1) K. Matsumoto, unpublished data.
(2) (a) D. Binder, J. Bowler, E. D. Brown, N. S. Crossley, J. Hutton, M. Senior, L. Wilkinson, and N. C. A. Wright, *Prostaglandins*, **6**, 87 (1974); (b) N. S. Crossley, *ibid.*, **10**, 5 (1975).
(3) (a) H. Wakatsuka, S. Kori, and M. Hayashi, *Prostaglandins*, **8**, 341 (1974); (b) H. S. Coery, J. R. D. McCormick, and W. E. Swensen, *J. Am. Chem. Soc.*, **86**, 1844 (1964).

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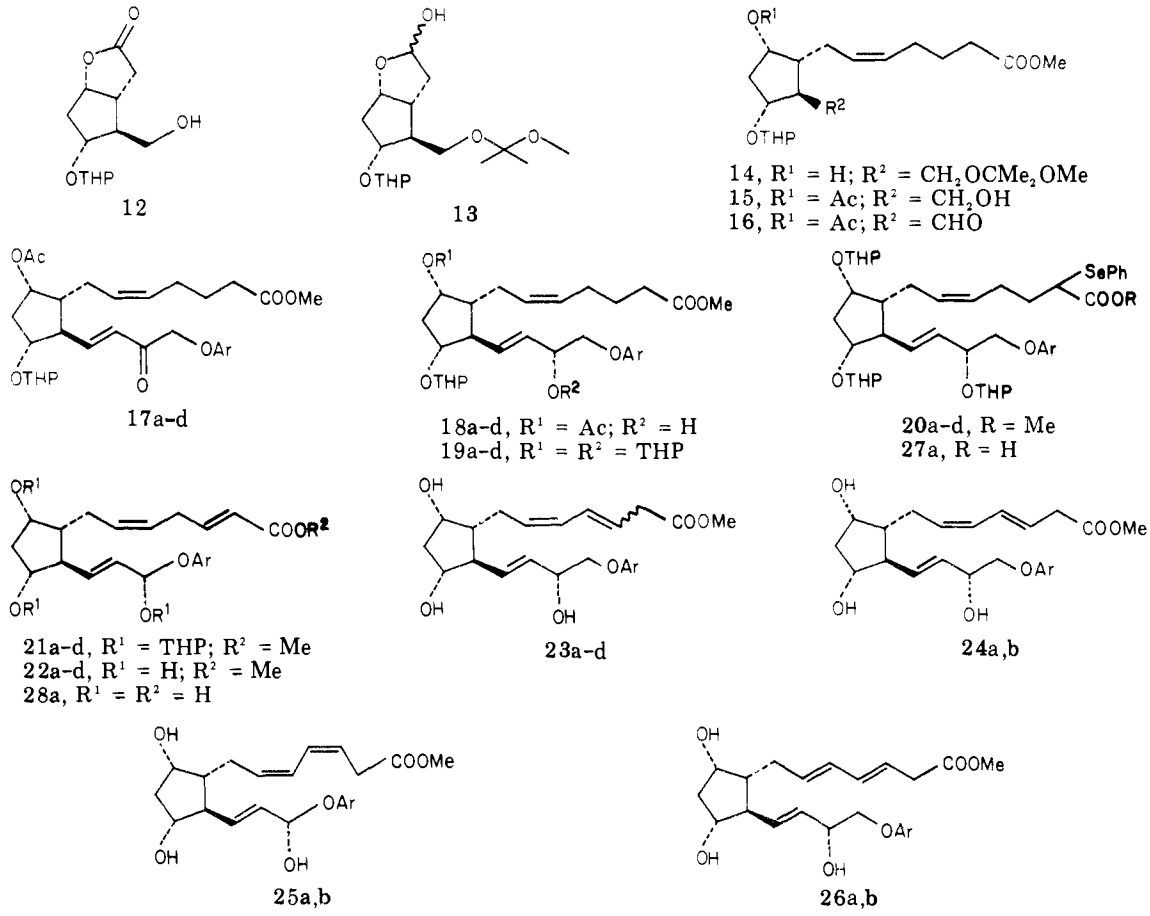
Chart II[a]



[a] For 17a-28a, Ar = *m*-chlorophenyl; 17b-26b, Ar = phenyl; 17c-23c, Ar = *m*-(trifluoromethyl)phenyl; 17d-23d, Ar = *p*-chlorophenyl.

form the trans α,β-unsaturated esters **5a,b** in 95% yield. Deprotection of the tetrahydropyranyl (THP) groups in **5a** with 1 N hydrochloric acid, followed by saponification with potassium hydroxide in aqueous ethanol, furnished the desired 16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{1\alpha}$ (**6**) in 34% yield. In the purification of **6**, the 15β-hydroxy isomer,[5] which had contaminated the starting material **1a**, could be separated easily by column chromatography on silica gel.

Double bond isomerization from C_2–C_3 to C_3–C_4 in α,β-unsaturated ester **5b** was achieved by treatment with lithium diisopropylamide (LDA)[6] in tetrahydrofuran and hexamethylphosphoric triamide (9:1) at −78 °C. Removal of the THP units with 65% aqueous acetic acid produced in 26% yield from **5b** the desired 16-phenoxy-17,18,19,20-tetranor-3,4-didehydroprostaglandin $F_{1\alpha}$ methyl ester (**7**), which was a 1:1 mixture of C_3–C_4 cis and trans double-bond isomers.

The Wittig reaction of the aldehyde **4a** with the ylide[7] derived from triphenylphosphine, zinc powder, and carbon tetrabromide yielded the dibromide **8**, which was treated with *n*-butyllithium followed by carbon dioxide gas to give the acid **9** containing the triple bond in 12% yield.[8] Partial hydrogenation of the triple bond in **9** over a Lindlar catalyst furnished the C_2–C_3 cis olefinic carboxylic acid **10** in 76% yield. The desired 16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,3-*cis*-didehydroprostaglandin $F_{1\alpha}$ (**11**) was obtained from **10** by deprotection of the THP groups using 1 N hydrochloric acid. Similarly, the 15β-hydroxy isomer was removed by chromatography in the purification of **11**.

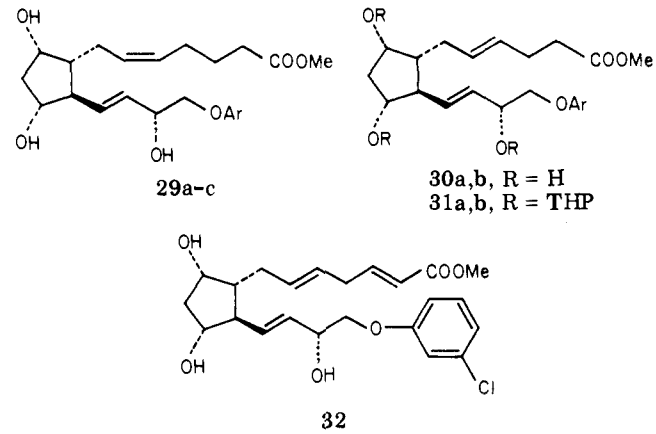
The preparation of 16-(aryloxy)prostaglandin analogues **22a–d**, **23a–d**, **24a,b**, **25a,b**, **26a,b**, and **28** containing two double bonds in the α chain was developed starting with the readily available lactones **12**[9] (Chart II). The hydroxy group in **12** was protected with the methoxyisopropyl unit, by treatment with 2-methoxypropene[10] and a catalytic amount of *p*-toluenesulfonic acid in methylene chloride, since the methoxyisopropyl unit could be easily deprotected by acid in the presence of the THP group. Re-

(4) H. O. House, V. K. Jones, and G. A. Frank, *J. Org. Chem.*, **29**, 3327 (1964).
(5) For assignment of C-15 configuration, see M. Hayashi, H. Miyake, S. Kori, T. Tanouchi, H. Wakatsuka, Y. Arai, Y. Yamato, I. Kajiwara, Y. Konishi, T. Tsuda, and K. Matsumoto, *J. Med. Chem.*, **23**, preceding paper in this issue (1980).
(6) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).
(7) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769 (1972).
(8) In the Wittig reaction, the hydroxy function in the cyclopentane ring was eliminated, and the dehydrated compound was the major product. On treatment of the resulting Wittig reaction product with *n*-butyllithium, followed by CO_2 gas, a large amount of 2α-(5-hexynyl)-3β-[4-[3-(trifluoromethyl)-phenoxy]-3$\alpha\beta$-(tetrahydropyran-2-yloxy)-1-*trans*-butenyl]-4α-(tetrahydropyran-2-yloxy)cyclopentan-1-ol was produced.
(9) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Am. Chem. Soc.*, **93**, 1491 (1971).
(10) (a) M. S. Newman and M. C. Vander Zwan, *J. Org. Chem.*, **38**, 2910 (1973); (b) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972).

duction with DIBAL gave the lactol **13** in quantitative yield. The Wittig reaction of the lactol **13** with the unstable ylide prepared in situ from (4-carboxybutyl)triphenylphosphonium bromide and $NaCH_2SOCH_3$ in Me_2SO produced the 5-cis olefinic carboxylic acid, which was converted to the methyl ester **14** with methyl iodide and potassium carbonate in acetone in 85% yield. After the protection of the C_9-hydroxy function with an acetyl group, selective deprotection of the methoxyisopropyl unit at C_{13} was accomplished using 0.5 N hydrochloric acid in THF at 0 °C to form the alcohol **15** in 89% yield, which was oxidized to the aldehyde **16** by the sulfur trioxide–pyridine complex[11] in Me_2SO in 90% yield. The aldehyde **16** is stable enough to be stored below 0 °C for a long time. Since the C_9-hydroxy function is protected with an acetyl group which can be deprotected with base and since the C_{11}-hydroxy function is blocked with a THP unit which can be removed by acid, the aldehyde **16** is a very useful intermediate for the preparation of prostaglandin $F_{2\alpha}$ or prostaglandin E_2 type analogues modified in the ω chain.

The aldehyde **16** was transformed to the α,β-unsaturated ketone **17a–d** by the Horner–Emmons reaction[2] using the carbanions from the appropriate dimethyl 3-(aryloxy)-2-oxopropylphosphonates [**a**, 3-chlorophenoxy; **b**, phenoxy; **c**, 3-(trifluoromethyl)phenoxy; **d**, 4-chlorophenoxy] in 43–64% yield. Sodium borohydride reduction of the resulting enones afforded the allylic alcohols **18a–d** in 36% yield, the $C_{15\beta}$-hydroxy isomers[5] being easily separated by column chromatography on silica gel. Deacetylation of **18a–d** with potassium carbonate in methanol, followed by tetrahydropyranylation, resulted in the formation of the corresponding tris(THP) compounds **19a–d** in 91% yield. Conversion of **19a–d** to the desired corresponding 16-(aryloxy)-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ methyl esters **22a–d** was effected by the sequence:[12] (1) treatment with LDA; (2) exposure of the resulting carbanions to diphenyl diselenide to form 2-phenylselenyl esters **20a–d** in 64% yield; (3) oxidative elimination with 30% hydrogen peroxide to yield the corresponding α,β-unsaturated esters **21a–d** in 85% yield from **19a–d**; and (4) tetradehydropyranylation with 65% aqueous acetic acid in 71% yield. Exposure of **22a–d** to potassium carbonate in methanol at 0 °C[13] transformed the C_2–C_3 trans olefinic bond into the C_3–C_4 olefinic bond to give 16-(aryloxy)-17,18,19,20-tetranor-3,4-didehydroprostaglandin $F_{2\alpha}$ methyl esters **23a–d** in 95% yield. According to NMR analysis, **23a–d** were mixtures of C_3–C_4 trans and C_3–C_4 cis double-bond isomers, and the ratios were determined to be 2:1 by the integral ratios of C_2 methylene protons: δ 3.11 (d, J = 7 Hz) assigned to the C_2 methylene proton next to the C_3–C_4 trans double bond and δ 3.21 (d, J = 7 Hz) assigned to that next to C_3–C_4 cis double bond, respectively. On this treatment with base, only a trace of the thermodynamically more stable α,β,-γ,δ-conjugated dienoic ester **36** was produced as a byproduct. The geometrical isomers **23a,b** could be separated into 16-(aryloxy)-17,18,19,20-tetranor-3,4-*trans*-didehydroprostaglandin $F_{2\alpha}$ methyl esters **24a,b** and their 3,4-cis isomers **25a,b** by silver nitrate impregnated preparative thin-layer chromatography. **23a,b** were irradiated by the diffused sunlight[14] through a Pyrex filter in carbon tetrachloride in the presence of iodine as a sensitizer to produce 16-(aryloxy)-17,18,19,20-tetranor-3,4-*trans*-5,6-*trans*-tetradehydroprostaglandin $F_{1\alpha}$ methyl esters **26a,b** in which the double bonds were not shifted and their configurations were all trans. In this case, C_9-hydroxy functions were protected with the THP units to prevent the ring closure to form the iodo ether moiety[15] by a C_6 olefinic carbon and C_9-hydroxy unit. Since the C_2–C_3 double bond was shifted by base, the preparation of 16-(3-chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ containing carboxylic acid was realized by the following sequence: (1) saponification of the selenide **20a** with potassium hydroxide in aqueous methanol to give the selenylcarboxylic acid **27a**; (2) oxidative elimination of the phenylselenyl group with hydrogen peroxide; and (3) tetradehydropyranylation.

Chart III[a]



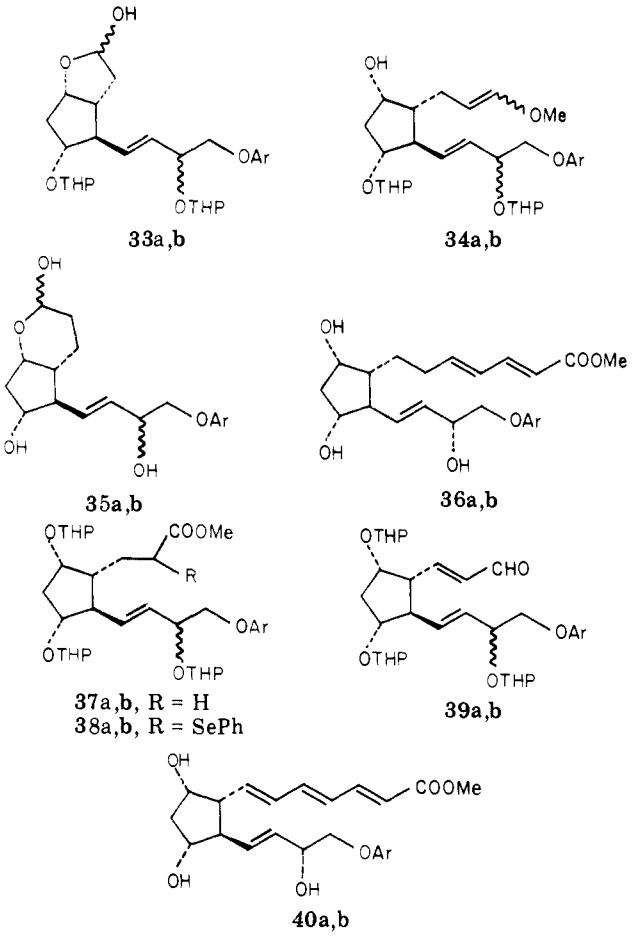
[a] For **29a–31a**, Ar = *m*-chlorophenyl; **29b,30b**, Ar = phenyl; **29c**, Ar = *m*-(trifluoromethyl)phenyl.

16-(Aryloxy)-17,18,19,20-tetranor-5,6-*trans*-didehydroprostaglandin $F_{1\alpha}$ methyl esters **30a,b** were obtained from 16-(aryloxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl esters **29a,b**[2] by irradiation with a high-pressure mercury lamp in the presence of diphenyl sulfide as a sensitizer to isomerize the C_5–C_6 cis double bond to the C_5–C_6 trans double bond[16] (Chart III). The starting material was removed by column chromatography on silver nitrate impregnated silica gel. The hydroxy groups in **30a** were protected with the THP functions to produce **31a**, which was converted to 16-(3-chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*,5,6-*trans*-tetradehydroprostaglandin $F_{1\alpha}$ methyl ester (**32**) by the similar sequence to **19** → **20** → **21** → **22**: (1) selenylation; (2) oxidative elimination; and (3) tetradehydropyranylation.

Preparation of 16-phenoxy-17,18,19,20-tetranorprostaglandin analogues **36a,b** and **40a,b** containing the conjugated dienoic ester or conjugated trienoic ester was achieved starting with the lactols **33a,b** (**33b** = **1b**) (Chart IV). The Wittig reaction of the lactols **33a,b** with the ylide derived from (methoxymethyl)triphenylphosphonium chloride and $NaCH_2SOCH_3$ led to the vinyl ethers **34a,b**, which were hydrolyzed with 65% aqueous acetic acid to afford α-lactols **35a,b** in 51% yield from **33a,b**.[17] The

(11) J. R. Parikh and W. E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).
(12) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 1637 (1973).
(13) G. P. Chiusoli, *Angew. Chem.*, **72**, 750 (1960).
(14) W. D. Celmer and I. A. Solomous, *J. Am. Chem. Soc.*, **75**, 3430 (1953).
(15) K. C. Nicolaou, W. E. Barnette, G. P. Gasic, R. L. Magolda, and W. J. Sipio, *J. Chem. Soc., Chem. Commun.*, 630 (1977).
(16) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *J. Am. Chem. Soc.*, **94**, 2124 (1972).
(17) (a) R. A. Johnson and E. G. Nidy, *Adv. Prostaglandin Thromboxane Res.*, **2**, 873 (1976); (b) E. W. Yankee, D. E. Ayer, G. L. Bundy, F. H. Lincoln, W. L. Miller, and G. A. Youngdale, *ibid.*, 1, 195 (1976).

Chart IV[a]



[a] 33a-40a, Ar = *p*-chlorophenyl; 33b-40b, Ar = phenyl.

desired 16-(aryloxy)-17,18,19,20-tetranor-2,3-*trans*,4,5-*trans*-tetradehydroprostaglandin methyl esters **36a,b** were obtained from **35a,b** by the Wittig reaction with the stable ylide (3-carbomethoxy-2-propenyl)triphenylphosphorane[18] in 37% yield. Oxidation of δ-lactols **35a,b** with silver oxide prepared in situ from silver nitrate and sodium hydroxide, followed by saponification, afforded the hydroxy acids, which were immediately esterified by diazomethane and then treated with dihydropyran to produce the tris(THP) ethers **37a,b** in 68% yield. Unless esterification, followed by tetrahydropyranylation, was carried out immediately, a considerable amount of δ-lactones was produced as by-products. **37a,b** were transformed to the α,β-unsaturated aldehydes **39a,b** by the following sequence: (1) selenylation to form **38a,b**, (2) oxidative elimination to give α,β-unsaturated esters, (3) reduction of the ester groups with DIBAL to afford allylic alcohols, and (4) oxidation with manganese dioxide. The Wittig reaction of **39a,b** with (3-carbomethoxy-2-propenyl)triphenylphosphorane led to the conjugated trienoic esters. The THP groups were removed with acid to form the desired 16-(aryloxy)-17,18,19,20-tetranor-2,3-*trans*,4,5-*trans*,6,7-*trans*-hexadehydroprostaglandin $F_{1\alpha}$ methyl esters **40a,b** in 31% yield. 15β-Hydroxy isomers[5] were removed easily by column chromatography on silica gel at the final steps.

All the intermediates and final products of these syntheses are viscous oils that retain solvents tenaciously. It was impossible to remove the solvents and water completely from these compounds, since they decomposed partially under the drying conditions suitable for elemental analysis (heated at ca. 50 °C under high vacuum for long periods). The structures of all products are supported by their NMR, IR, UV, and high-resolution mass spectra. The purity was checked by TLC, and the final compounds were confirmed to be homogeneous by TLC.

(18) F. Bohlman, *Chem. Ber.*, **90**, 1519 (1957).

Table I. Relative Antinidatory Effects in the Rat of 16-(Aryloxy)-17,18,19,20-tetranorprostaglandin Analogues with the Modified α Chain

compd	chart	double bond in α chain	X in C_6H_4-X	ANE[a] ($F_{2\alpha}$ = 1)
		monoene		
6[b]	I	trans-Δ^2	*m*-CF_3	4
11[b]	I	cis-Δ^2	*m*-CF_3	2-4
7	I	Δ^3(cis/trans = 1:1)	H	40
30b	II	trans-Δ^5	H	20-40
		2,4-diene		
36a	IV	trans-Δ^2-trans-Δ^4	*m*-Cl	4-8
36b	IV	trans-Δ^2-trans-Δ^4	H	20
		2,5-diene		
22a	II	trans-Δ^2-cis-Δ^5	*m*-Cl	200
22b	II	trans-Δ^2-cis-Δ^5	H	200-400
22c	II	trans-Δ^2-cis-Δ^5	*m*-CF_3	100
22d	II	trans-Δ^2-cis-Δ^5	*p*-Cl	100
28a[b]	II	trans-Δ^2-cis-Δ^5	*m*-Cl	200
32	III	trans-Δ^2-trans-Δ^5	*m*-Cl	100
		3,5-diene		
23a	II	Δ^3(trans/cis = 2:1)-cis-Δ^5	*m*-Cl	600
24a	II	trans-Δ^3-cis-Δ^5	*m*-Cl	800
25a	II	cis-Δ^3-cis-Δ^5	*m*-Cl	400
23b	II	Δ^3(trans/cis = 2:1)-cis-Δ^5	H	1200
24b	II	trans-Δ^3-cis-Δ^5	H	800
25b	II	cis-Δ^3-cis-Δ^5	H	400-600
23c	II	Δ^3(trans/cis = 2:1)-cis-Δ^5	*m*-CF_3	100
23d	II	Δ^3(trans/cis = 2:1)-cis-Δ^5	*p*-Cl	200-400
26a	II	trans-Δ^3-trans-Δ^5	*m*-Cl	100-200
26b	II	trans-Δ^3-trans-Δ^5	H	200
		2,4,6-triene		
20a	IV	trans-Δ^2-trans-Δ^4-trans-Δ^6	*m*-Cl	1
20b	IV	trans-Δ^2-trans-Δ^4-trans-Δ^6	H	2
		$F_{2\alpha}$ type		
29a	III	cis-Δ^5	*m*-Cl	200
29b	III	cis-Δ^5	H	200-400
29c	III	cis-Δ^5	*m*-CF_3	100

[a] Antinidatory effects in the rat. The activities relative to that of prostaglandin $F_{2\alpha}$ were calculated based on the ED_{50} values. The ED_{50} value of prostaglandin $F_{2\alpha}$ is 1.3 (0.90-1.87) mg/kg and its confidence limit is 95%. [b] This analogue is the carboxylic acid type.

Pharmacological Results and Discussion

The abortifacient effect in pregnant rats is currently regarded as being an indication of observing the luteolytic effect of prostaglandins. In this report, the antinidatory effect induced by prostaglandins was examined for the purpose of screening for the effect on the corpus luteum in early pregnancy. The antinidation of 50% of the animals was achieved by 1.3-mg doses of prostaglandin $F_{2\alpha}$ (b.i.d., 3 days), and the average number of implantation sites of the test group in comparison with the control group was about 50% for the same dose of prostaglandin $F_{2\alpha}$. A significant decrease in the uterine-fetal weights and in progesterone values in the peripheral blood was observed. This action was inhibited by the intramuscular injection of progesterone (2 mg, single dose, 3 days), and the number

of implantation sites and the uterine-fetal weights were not significantly different from those of the control group. From these results, it was considered that this experimental system could be applied to the indication of the luteolytic effect of prostaglandins.

Summarized in Table I are the relative antinidatory effects in the rat of a variety of prostaglandin analogues to that of prostaglandin $F_{2\alpha}$. For reference, the relative activities of 16-(aryloxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl esters **29a,b,c**, which were not modified in α chains, are shown. In regard to the 16-substituent groups, the relative activities of the analogues were increased with a sequence of phenoxy > *m*-chlorophenoxy > *m*-(trifluoromethyl)phenoxy (**29b** > **29a** > **29c**), and this inclination of the activities was also shown in the analogues which were modified in the α chain.

In the monoene-type analogues, trans-Δ^2 analogue **6** and cis-Δ^2 analogue **11** were only four times and two to four times more active than prostaglandin $F_{2\alpha}$, respectively.[19] However, Δ^3 analogue **7**, which was a 1:1 mixture of trans and cis double bonds in the α chains, and trans-Δ^5 analogue **30b** showed much higher activities (**7** and **30b** were 40 and 20–40 times more potent than prostaglandin $F_{2\alpha}$, respectively), while the activity of **30b** containing the C_5–C_6 trans double bond was one-tenth that of **29b**, which had the C_5–C_6 cis double bond. These results demonstrate that the position and geometry of the double bond in the α chain have an important influence on the antinidatory effect.

In the diene-type analogues, although the 2,4-diene analogues **36a** and **36b** were 4–20 times more active than prostaglandin $F_{2\alpha}$, the activities of the 2,5-diene analogues **22a–d**, **28a**, and **32** were increased to 100–400 times that of prostaglandin $F_{2\alpha}$. Furthermore, the 3,5-diene analogues **23a–d**, **24a,b**, **25a,b**, and **26a,b** exhibited 100–1200 times more active antinidatory effects than prostaglandin $F_{2\alpha}$. In the Δ^3-cis-Δ^5 analogues, the trans-Δ^3-type analogues were more active than the cis-Δ^3-type analogues, **24a** > **25a**, **24b** > **25b**, in antinidatory effect. **23a** or **23b** was a 2:1 mixture of the trans-Δ^3-cis-Δ^5 analogues **24a** or **24b** and cis-Δ^3-cis-Δ^5 analogues **25a** or **25b**, respectively. The potency of the 16-*m*-chlorophenoxy analogue **23a** displayed the geometrical mean value of those of its components, while the 16-phenoxy analogue **23b** was more potent than its components **24b** and **25b** and 1200 times more active than prostaglandin $F_{2\alpha}$. It is presumed that this markedly high potency of **23b** which had not been seen in the other prostaglandin analogues resulted from the synergism of its components. With respect to the C_5–C_6 double bond, the cis analogues **24a** and **24b** were approximately five times more potent than the corresponding trans analogues **26a** and **26b**. In the case of the 2,5-diene analogues, a similar relationship was also observed: **22a** was twofold more active than **32**. The activity of **30b**, which has a C_5–C_6 trans double bond, was one-tenth that of the cis isomer **29b**, and approximately the same potency was observed by the introduction of a C_3–C_4 trans double bond in **30b**, giving **26b**.

It is also of interest that the activities of 3,5-diene-type analogues were dependent upon the phenyl substituents in the ω chain.

The activities of the triene-type analogues **40a** and **40b** were remarkably decreased. In this case, it is assumed that the α chain was fixed rigidly and, consequently, the proper conformation could not be maintained at the receptor sites.

(19) Analogues **6** and **11** were not the esters but the free acids. In this series of the investigation, there was no significant difference between the esters and the acids in antinidatory effect.

Additionally, uterine contractile activities of these prostaglandin analogues in the rat[20] were examined, which were less potent than their antinidatory effect. The most potent analogue in uterine contractile activity was **23b** (10–20 times more potent than prostaglandin $F_{2\alpha}$), and the others were much less potent than **23b**.

As mentioned previously, it was found that the antinidatory effect of 16-(aryloxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ was subject to the influence of the numbers, position, and geometry of the double bonds in α chains.

Experimental Section

^1H NMR spectra were taken on a JEOL PMX-60 or a Varian XL-100 spectrometer in $CDCl_3$ or CCl_4 under the supervision of A. Ishihara. Chemical shifts are reported as parts per million relative to Me_4Si as an internal standard. IR spectra were recorded on a Hitachi EPI-G2 model, and UV spectra were measured by a Hitachi 124 type double-beam spectrophotometer. Mass spectra were obtained on a JMS-01SG double-focusing mass spectrometer under the supervision of S. Takaoka. Molecular ion peaks of some analogues were too weak to be detected because of their low volatility. In these cases, the molecular weights and the molecular formulas were determined by their dehydration peaks.

For TLC analysis, throughout this work Merck TLC plates (silica gel 60 F_{254} precoated, layer thickness 0.2 mm) were used. Column chromatography was carried out on silica gel (Merck, particle size 0.063–0.20 mm, or Mallinckrodt, Silic AR CC-7 special). Unless otherwise specified, all reactions were carried out under an atmosphere of argon.

(5*Z*,*E*)-16-[3-(Trifluoromethyl)phenoxy]-2,3,17,18,19,20-hexanorprostaglandin $F_{2\alpha}$ 11,15αβ-Bis(tetrahydropyran-2-yl ether) (2a). A 2 M solution of sodiomethylsulfinyl carbanion (285 mL, 0.57 mol) in dry Me_2SO was dropped into a stirred solution of (β-carboxyethyl)triphenylphosphonium bromide (125 g, 0.3 mol) in dry Me_2SO (240 mL) at such a rate as to maintain the solution at 25 °C to yield the red solution of the ylide. Immediately, a solution of 2-oxo-6-*syn*-[3αβ-(tetrahydropyran-2-yloxy)-4-[3-(trifluoromethyl)phenoxy]-1-*trans*-butenyl]-7-*anti*-(tetrahydropyran-2-yloxy)-*cis*-bicyclo[3.3.0]octan-3-ol (**1a**; 34.5 g, 63.7 mmol) in dry Me_2SO (150 mL) was added to the ylide, and then the resulting solution was stirred at 25 °C for 2 h. The mixture was poured into cold water (3.5 L) containing anhydrous K_2CO_3 (ca. 50 g) and extracted with AcOEt–ether (1:1; 2 L × 3). The aqueous phase was acidified with oxalic acid to pH 3 and was extracted with pentane–ether (1:1). The acidic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to leave the crude product, which was column chromatographed on silica gel (Merck, 1 kg) with 5% EtOH in benzene elution to obtain **2a** (24.4 g, 64% yield): R_f 0.46 (CH_2Cl_2–MeOH, 19:1); IR (film) 3450 (OH), 1735 (COOH), 1595 (phenyl), 980 (trans olefin) cm^{-1}.

16-[3-(Trifluoromethyl)phenoxy]-2,3,17,18,19,20-hexanorprostaglandin $F_{1\alpha}$ Methyl Ester 11,15αβ-Bis(tetrahydropyran-2-yl ether) (3a). **2a** (24.7 g, 41 mmol) was hydrogenated with 5% Pd on charcoal catalyst (5 g) in MeOH (300 mL) at atmospheric pressure at 25 °C. When hydrogen (41 mmol) had been absorbed, the catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was dissolved in ether (300 mL) and a solution of diazomethane in ether was added until a yellow color persisted. The ether was evaporated in vacuo, and the residue was column chromatographed on silica gel (Merck, 600 g) with AcOEt–cyclohexane (1:3) elution to obtain **3a** (14.8 g, 87% yield): R_f 0.40 (CH_2Cl_2–MeOH, 19:1); IR (film) 3450 (OH), 1740 (ester), 1600 (phenyl), 1490, 980 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.50–6.70 (4 H, m, aromatic H), 5.80–5.35 (2 H, m, olefinic H).

16-[3-(Trifluoromethyl)phenoxy]-2,3,17,18,19,20-hexanorprost-13-en-1-al 11,15αβ-Bis(tetrahydropyran-2-yl ether) (4a).

(20) M. Hayashi, H. Miyake, S. Kori, T. Tanouchi, H. Wakatsuka, Y. Arai, T. Yamato, I. Kajiwara, Y. Konishi, T. Tsuda, and K. Matsumoto, *J. Med. Chem.*, **23**, preceding paper in this issue (1980).

To a stirred solution of **3a** (2.63 g, 4.3 mmol) in toluene (10 mL) was added dropwise a 25% solution of diisobutylaluminum hydride (DIBAL; 9.9 mL, 17.1 mmol) in toluene at −78 °C under a nitrogen atmosphere. After the solution was stirred for 30 min at −78 °C, the excess reagent was decomposed by the addition of MeOH at −78°C until gas evolution had ceased. The mixture was warmed up to 0 °C. Water (2 mL) was added and the mixture was stirred at 25 °C until the gel-like mass had turned crystalline (ca. 45 min). The mixture was then filtered, the filtrate was extracted with AcOEt, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford **4a** (2.51 g, 100% yield): R_f 0.24 (CH_2Cl_2–MeOH, 19:1); IR (film) 3450 (OH), 1720 (CHO), 1595 (phenyl), 980 (trans olefin) cm^{-1}; NMR (CCl_4) δ 9.61 (1 H, br s, CHO), 7.56–6.74 (4 H, m, aromatic H), 5.86–5.36 (2 H, m, olefinic H).

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{1\alpha}$ Methyl Ester 11,15αβ-Bis(tetrahydropyran-2-yl ether) (5a). **4a** (2.51 g, 4.3 mmol) and (carbomethoxymethylene)triphenylphosphorane (3.3 g, 10 mmol) were dissolved in $CHCl_3$ (50 mL) and stirred at 25 °C for 5 h. The solvent was evaporated in vacuo and the residue was column chromatographed with AcOEt–cyclohexane (1:2) on silica gel (Merck, 70 g) to provide **5a** (2.60 g, 95% yield): R_f 0.26 (CH_2Cl_2–MeOH, 19:1); IR (film) 3450 (OH), 1720 (ester), 1660 (conjugated olefin), 1500 (phenyl), 980 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.61–6.35 (5 H, m, aromatic H and C_3 H), 5.77–5.23 (3 H, m, olefinic H), 3.70 (3 H, s, COOMe).

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{1\alpha}$ (6). A mixture of **5a** (2.30 g, 3.58 mmol), THF (50 mL), and 1 N hydrochloric acid (20 mL) was stirred at 45 °C for 1 h. The mixture was diluted with AcOEt (300 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in a mixture of EtOH (50 mL) and 2 N aqueous KOH (20 mL). The mixture was stirred at 25 °C for 2 h, then acidified with 1 N hydrochloric acid, and diluted with AcOEt (300 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 70 g) with AcOEt–cyclohexane (1:1) to give the desired **6** [525 mg, 32%; R_f 0.15 (AcOEt–HCOOH 80:1)], the $C_{15\beta}$-hydroxy isomer [492 mg, 30%; R_f 0.18 (AcOEt–HCOOH, 80:1)], and their mixture (246 mg, 15%). **6**: IR (film) 3400 (OH), 1700 (COOH), 1650 (conjugated olefin), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.60–7.05 (4 H, m, aromatic H), 6.94 (1 H, dt J = 15.5 and 7.0 Hz, C_3 H), 5.95–5.35 (3 H, m, olefinic H). High-resolution MS for $C_{23}H_{27}O_5F_3$ (dehydration peak from molecular ion): calcd, m/e 440.18136; found, 440.18361.

16-Phenoxy-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{1\alpha}$ Methyl Ester 11,15αβ-Bis(tetrahydropyran-2-yl ether) (5b). **5b** was prepared in four steps starting with the Wittig reaction of 2-oxa-6-*syn*-[3αβ-(tetrahydropyran-2-yloxy)-4-phenoxy-1-*trans*-butenyl]-7-*anti*-(tetrahydropyran-2-yloxy)-*cis*-bicyclo[3.3.0]octan-3-ol (1b). **5b**: R_f 0.26 (CH_2Cl_2–MeOH, 19:1); IR (film) 3470 (OH), 1725 (ester), 1658 (conjugated olefin), 1600 (phenyl), 978 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.47–6.68 (6 H, m, aromatic H and C_3 H), 6.00–5.44 (3 H, m, C_2, C_{13}, and C_{14} H), 3.70 (3 H, s, COOMe).

***16*-Phenoxy-17,18,*19,20*-tetranor-3,*4*-*trans*,*cis*-didehydroprostaglandin $F_{1\alpha}$ Methyl Ester (7).** To a solution of diisopropylamine (0.212 mL, 2.12 mmol) in dry THF (8 mL) cooled at −78 °C was added dropwise a 1.5 M solution of *n*-butyllithium (0.95 mL, 1.43 mmol) in hexane. The mixture was stirred at −78 °C for 30 min to give lithium diisopropylamide (1.43 mmol) containing excess diisopropylamine. Hexamethylphosphoric triamide (0.27 mL) was added and then a solution of **5b** (368 mg, 0.642 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h. The reaction was quenched by the addition of AcOH (0.1 mL) at −78 °C. The mixture was diluted with ether (50 mL), washed with saturated aqueous $NaHCO_3$, water, and brine in succession, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in THF (0.5 mL) and 65% aqueous AcOH (5 mL). The mixture was stirred at 70 °C for 10 min, then diluted with AcOEt (25 mL), washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was column chromatographed on silica gel (Mallinckrodt, 10 g) with AcOEt–benzene (1:2) to give the desired **7** [57 mg, 22%; R_f 0.24 (AcOEt)], the $C_{15\beta}$-hydroxy isomer [60 mg, 23%; R_f 0.27 (AcOEt)], and their mixture (36 mg, 15%). **7**: IR (film) 3400 (OH), 1736 (ester), 1600 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.38–6.80 (5 H, m, aromatic H), 5.72–5.40 (4 H, m, olefinic H), 4.58–4.45 (1 H, m, C_{15} H), 4.27–3.84 (4 H, m, C_9, C_{11}, and C_{16} H), 3.65 and 3.64 (total 3 H, 1:1, each s, COOMe), 3.06 and 2.99 (total 2 H, 1:1, each d, C_2 H). High-resolution MS for $C_{23}H_{30}O_5$ (dehydration peak from molecular ion): calcd, m/e 386.20932; found, 386.20786.

2α-(6,6-Dibromo-5-hexenyl)-3β-[4-[3-(trifluoromethyl)phenoxy]-3αβ-(tetrahydropyran-2-yloxy)-1-*trans*-butenyl]-4α-(tetrahydropyran-2-yloxy)cyclopentan-1-ol (8). To a stirred solution of triphenylphosphine (32.3 g, 123 mmol) and zinc powder (8 g, 123 mmol) in dry CH_2Cl_2 (400 mL) in an ice–water bath was added a solution of carbon tetrabromide (40.8 g, 123 mmol) in dry CH_2Cl_2 (40 mL). The mixture was stirred at 25 °C overnight to yield a ylide solution. To this solution was added a solution of **4a** (7.2 g, 12.3 mmol) in dry CH_2Cl_2 (100 mL). After it was stirred for 5 min at 25 °C, the mixture was poured into cold water (3 L) containing anhydrous K_2CO_3 (12 g, 87 mmol) and extracted with AcOEt (1 L × 2). The solid that appeared was removed by filtration through a pad of Celite. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 500 g) with AcOEt–benzene (1:8) to provide **8** (3.1 g, 34% yield): R_f 0.80 (AcOEt–benzene, 1:1); IR (film) 3450 (OH), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.66–6.79 (4 H, m, aromatic H), 6.36 (1 H, 5, $CH{=}CBr_2$), 5.79–5.25 (2 H, m, olefinic H).

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,2,3,3-tetradehydroprostaglandin $F_{1\alpha}$ 11,15αβ-Bis(tetrahydropyran-2-yl ether) (9). To a stirred solution of **8** (3.1 g, 4.2 mmol) in dry THF (30 mL) at −78 °C was added dropwise a 1.5 M solution of *n*-butyllithium (10.4 mL, 15.6 mmol) in hexane. The mixture was stirred at −78 °C for 30 min and then carbon dioxide gas was introduced at −78 °C for 5 h. The mixture was poured into cold water (150 mL) containing anhydrous K_2CO_3 (ca. 1 g) and extracted with ether (75 mL × 3). The aqueous layer was acidified with oxalic acid and extracted with ether–pentane (1:1, 200 mL × 3). These extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 100 g) with AcOEt–cyclohexane (5:8) to afford **9** (876 mg, 34% yield): R_f 0.39 ($CHCl_3$–THF–AcOH, 10:2:1); IR (film) 3400 (OH), 2600 (COOH), 2225 (C≡C), 1710 (COOH), 1595 (phenyl), 980 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.51–6.79 (4 H, m, aromatic H), 6.75–6.33 (2 H, m, OH), 5.75–5.32 (2 H, m, olefinic H).

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,3-*cis*-didehydroprostaglandin $F_{1\alpha}$ 11,15αβ-Bis(tetrahydropyran-2-yl ether) (10). A mixture of **9** (535 mg, 0.841 mmol), 5% Pd/$BaSO_4$ catalyst (200 mg), pyridine (0.5 mL), and MeOH (8 mL) was stirred under a hydrogen atmosphere until hydrogen (25 mL) was absorbed. Ether (30 mL) and $NaHSO_4{\cdot}H_2O$ (2.7 g) were added, and the mixture was stirred for 5 min. The solid was filtered off. The filtrate was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 30 g) with 5% EtOH in benzene to give **10** (400 mg, 76% yield): R_f 0.73 ($CHCl_3$–THF–AcOH, 10:2:1); IR (film) 3450 (OH), 1700 (COOH), 1640 (conjugated olefin), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.23–6.57 (4 H, m, aromatic H), 6.54–5.09 (6 H, m, OH and olefinic H).

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,3-*cis*-didehydroprostaglandin $F_{1\alpha}$ (11). A mixture of **10** (400 mg, 0.64 mmol), THF (4 mL), and 1 N hydrochloric acid (4 mL) was stirred at 45 °C for 1.5 h. The mixture was diluted with AcOEt (30 mL), washed with water and brine, and dried over $MgSO_4$. The solvents were evaporated in vacuo, and the residue was column chromatographed on silica gel (Mallinckrodt, 12 g) with 2.5% EtOH in benzene to give the desired **11** [85 mg, 29%; R_f 0.17 (AcOEt–HCOOH, 80:1)], the $C_{15\beta}$-hydroxy isomer [79 mg, 27%; R_f 0.20 (AtOEt–HCOOH, 80:1)], and their mixture (45 mg, 15%). **11**: IR (film) 3400 (OH), 1700 (COOH), 1640 (conjugated olefin), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR (acetone-d_6) δ 7.65–7.11 (4 H, m, aromatic H), 6.26 (1 H, dt, J = 11.7 and 7.3

Hz, C_3 H), 5.86–5.60 (3 H, m, C_1, C_{13}, and C_{14} H), 4.60–4.40 (1 H, m, C_{15} H).

2-Oxa-6-*syn*-(2,4-dioxa-3,3-dimethylpentyl)-7-*anti*-(tetrahydropyran-2-yloxy)-*cis*-bicyclo[3.3.0]octan-3-ol (13). A solution of *p*-toluenesulfonic acid (7 mg) in dry CH_2Cl_2 (3 mL) and THF (1 drop) was added to a stirred solution of 2-oxo-6-*syn*-(hydroxymethyl)-7-*anti*-(tetrahydropyran-2-yloxy)-*cis*-bicyclo[3.3.0]octan-3-one (**12**; 19.1 g, 74.5 mmol) and 2-methoxypropene (15.7 g, 218 mmol) in dry CH_2Cl_2 (20 mL) in an ice–water bath. The mixture was stirred below 15 °C for 15 min. The reaction was quenched by the addition of triethylamine (0.1 mL), and the mixture was concentrated in vacuo. The residue was dissolved in toluene (500 mL) and cooled to −78 °C. To this solution was added dropwise a 25% solution of DIBAL (55 mL, 97 mmol) in toluene. The mixture was stirred at −78 °C for 20 min, and the excess reagent was decomposed by the addition of MeOH at −78 °C until gas evolution had ceased. The mixture was warmed up to 0 °C and then water (30 mL) was added. The mixture was stirred at 25 °C until the gel-like solid had turned crystalline (ca. 45 min). The mixture was filtered and the solid was washed with AcOEt (300 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield **13** (24.2 g, 98% yield): R_f 0.54 (AcOEt–benzene, 2:1); IR (film) 3400 (OH); NMR ($CDCl_3$) δ 5.70–5.34 (1 H, m, OC*H*OH), 4.82–4.53 (2 H, m, OC*H*O in THP unit and CHO in five-membered ring), 3.20 (3 H, s, OMe), 1.32 (6 H, s, CMe_2).

2-*syn*-(6-Carbomethoxy-2-*cis*-hexenyl)-3-*anti*-(2,4-dioxa-3,3-dimethylpentyl)-4-*syn*-(tetrahydropyran-2-yloxy)cyclopentan-1-ol (14). A 2 M solution of sodiomethylsulfinyl carbanion (164 mL, 328 mmol) in dry Me_2SO was dropped into a stirred solution of (4-carboxybutyl)triphenylphosphonium bromide (72.5 g, 164 mmol) in dry Me_2SO (150 mL) at such a rate as to maintain the temperature at 20–25 °C to yield the red solution of the ylide. Immediately, a solution of **13** (24.2 g, 73.4 mmol) in dry Me_2SO (180 mL) was added to the ylide. The mixture was stirred at 25 °C for 40 min and then at 55 °C for 1 h, poured into cold water containing anhydrous K_2CO_3 (10 g), and extracted with ether–AcOEt (1:1, 1 L × 3). To the aqueous layer was added ether (2 L) and ice (400 g), and then the solution was acidified to pH 5 by the slow addition of oxalic acid under vigorous stirring. The ethereal layer was separated and the aqueous layer was extracted with ether (1.5 L). The combined ethereal layers were washed with water and brine and dried over $MgSO_4$. After $MgSO_4$ was removed by filtration, to the ethereal filtrate was added anhydrous K_2CO_3 (30.8 g, 223 mmol) and ether was evaporated in vacuo to yield the potassium salt as a gummy solid. Acetone (500 mL) and methyl iodide (106 g, 745 mmol) were added, and the mixture was refluxed weakly for 50 min. Most of the acetone and excess methyl iodide was removed by evaporation in vacuo and then saturated aqueous NH_4Cl (200 mL) was added. The mixture was extracted with ether (300 mL × 2), and the combined ethereal layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 800 g) with AcOEt–cyclohexane–Et_3N (100:100:0.1) to provide **14** (26.7 g, 85.1% yield): R_f 0.59 (AcOEt–cyclohexane, 1:1); IR (film) 3520 (OH), 1740 (ester) cm^{-1}; NMR ($CDCl_3$) δ 5.87–5.11 (2 H, m, olefinic H), 4.67 (1 H, m, OCHO), 3.60 (3 H, s, COOMe), 3.20 (3 H, s, OMe), 1.33 (6 H, s, CMe_2).

2-*syn*-(6-Carbomethoxy-2-*cis*-hexenyl)-3-*anti*-(hydroxymethyl)-4-*syn*-(tetrahydropyran-2-yloxy)cyclopent-1-yl Acetate (15). Acetic anhydride (40 mL, 415 mmol) was dropped into a stirred solution of **14** (35.5 g, 88 mmol) in pyridine (70 mL, 830 mmol) cooled in an ice–water bath, and the resulting solution was stirred at 20 °C for 15 h. The mixture was poured into cold water (500 mL) and extracted with AcOEt (300 mL × 2). The extracts were washed with 0.5 N hydrochloric acid (×2) and concentrated in vacuo. The residue was dissolved in THF (150 mL) and cooled to 5 °C. Cold 0.5 N hydrochloric acid (80 mL) was dropped into the stirred solution at 5 °C while the reaction was monitered by TLC. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (150 mL) and the mixture was extracted with AcOEt (500 mL × 2). The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 1 kg) with AcOEt–cyclohexane (2:1) to give **15** (29.4 g, 89% yield): R_f 0.32 (AcOEt–benzene, 1:2); IR (film) 3450 (OH), 1740 (ester), 975 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 5.63–5.10 (2 H, m, olefinic H), 5.10–4.83 (1 H, m, C*H*OAc), 4.73–4.40 (1 H, m, OC*H*O), 3.60 (3 H, s, COOMe), 2.00 (3 H, s, MeCOO).

2-*syn*-(6-Carbomethoxy-2-*cis*-hexenyl)-3-*anti*-formyl-4-*syn*-(tetrahydropyran-2-yloxy)cyclopent-1-yl Acetate (16). To a stirred solution of **15** (29.3 g, 73.6 mmol) and Et_3N (61.5 mL, 442 mmol) in dry Me_2SO (300 mL) at 20 °C was added a solution of a SO_3–pyridine complex (35.2 g, 221 mmol) in dry Me_2SO (350 mL). The mixture was stirred at 20 °C for 15 min, poured into cold saturated aqueous NH_4Cl (1 L), and extracted with AcOEt–ether (1:1, 500 mL × 3). The extracts were washed with water (×3) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 1 kg) with AcOEt–cyclohexane (1:3) to give **16** (26.2 g, 90% yield): R_f 0.66 (AcOEt–benzene, 1:2); IR (film) 2725 (CHO), 1738 (CHO and esters) cm^{-1}; NMR ($CDCl_3$) δ 9.60 (1 H, t, CHO), 5.82–5.11 (2 H, m, olefinic H), 5.00–4.95 (1 H, m, C*H*OAc), 3.60 (3 H, s, COOMe), 2.00 (3 H, s, MeCOO).

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-15-dehydroprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester 11-(Tetrahydropyran-2-yl ether) (17a). To a stirred suspension of NaH (649 mg, 27 mmol) in dry THF (120 mL) was added at 25 °C dropwise a solution of dimethyl 3-(3-chlorophenoxy)-2-oxopropylphosphonate (8.74 g, 30 mmol) in dry THF (40 mL). After the solution was stirred at 25 °C for 20 min, a solution of **16** (4.16 g, 10.5 mmol) in dry THF (40 mL) was added. The mixture was allowed to stirr at 25 °C for 1.5 h, at 45 °C for 1 h, and at 60 °C for 2 h, and the reaction was quenched by the addition of AcOH (ca. 2 mL). The precipitate that appeared was removed by filtration through a pad of silica gel, and the filtrate was concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 120 g) with AcOEt–benzene (1:15 → 1:10 → 1:8) to give **17a** (2.94 g, 50% yield): R_f 0.78 (AcOEt–benzene, 1:2); IR (film) 1740 (esters), 1695 (conjugated ketone), 1625 (conjugated olefin), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.45–6.43 (6 H, m, aromatic and conjugated olefinic H), 5.75–5.25 (2 H, m, cis olefinic H), 4.80 (2 H, s, C_{16} H), 4.75–4.44 (1 H, m, OC*H*O), 3.70 (3 H, s, COOMe), 2.10 (3 H, s, MeCOO).

16-Phenoxy-17,18,19,20-tetranor-15-dehydroprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester 11-(Tetrahydropyran-2-yl ether) (17b). **17b** was prepared analogously from dimethyl 3-phenoxy-2-oxopropylphosphonate and **16** in 64% yield. **17b**: R_f 0.78 (AcOEt–benzene, 1:2); IR (film) 1737 (esters), 1685 (conjugated ketone), 1620 (conjugated olefin) cm^{-1}; NMR (CCl_4) δ 7.50–6.30 (7 H, m, aromatic and conjugated olefinic H), 5.62–5.13 (2 H, m, cis olefinic H), 5.13–4.86 (1 H, m, C_9 H), 4.59 (2 H, s, C_{16} H), 3.59 (3 H, s, COOMe), 2.00 (3 H, s, MeCOO).

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-15-dehydroprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester 11-(Tetrahydropyran-2-yl ether) (17c). **17c** was prepared analogously from dimethyl 3-[3-(trifluoromethyl)phenoxy]-2-oxopropylphosphonate and **16** in 43% yield. **17c**: R_f 0.78 (AcOEt–benzene, 1:2); IR (film) 1730 (esters), 1690 (conjugated ketone), 1617 (conjugated olefin) cm^{-1}; NMR (CCl_4) δ 7.50–6.20 (6 H, m, aromatic and conjugated olefinic H), 5.50–5.19 (2 H, m, cis olefinic H), 5.19–4.80 (1 H, m, C_9 H), 4.62 (2 H, s, C_{16} H), 3.55 (3 H, s, COOMe), 1.99 (3 H, s, MeCOO).

16-(4-Chlorophenoxy)-17,18,19,20-tetranor-15-dehydroprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester 11-(Tetrahydropyran-2-yl ether) (17d). **17d** was prepared analogously from dimethyl 3-(4-chlorophenoxy)-2-oxopropylphosphonate and **16** in 53% yield. **17d**: R_f 0.78 (AcOEt–benzene, 1:2); IR (film) 1735 (esters), 1695 (conjugated ketone), 1620 (conjugated olefin) cm^{-1}; NMR (CCl_4) δ 7.40–6.35 (6 H, m, aromatic and conjugated olefinic H), 5.50–5.17 (2 H, m, cis olefinic H), 5.17–4.90 (1 H, m, C_9 H), 4.60 (2 H, s, C_{16} H), 3.62 (3 H, s, COOMe), 2.02 (3 H, s, MeCOO).

16-(3-Chlorophenoxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester 11-(Tetrahydropyran-2-yl ester) (18a). To a stirred solution of **17a** (2.87 g, 5.12 mmol) in MeOH (25 mL) and THF (25 mL) at −45 °C was added slowly $NaBH_4$ (760 mg, 20 mmol). The reaction was quenched by the addition of acetic acid until the solution became pH 4. The mixture was concentrated in vacuo and the residue was dissolved in AcOEt (150 mL) and water (30 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine in succession, dried

over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 100 g) with AcOEt–benzene (1:3) to give the desired **18a** [1.05 g, 36%; R_f 0.38 (AcOEt–benzene, 1:2)], the $C_{15\beta}$-hydroxy isomer [1.01 g, 34%; R_f 0.45 (AcOEt–benzene, 1:2)], and their mixture (430 mg, 14%). **18a**: IR (film) 3430 (OH), 1740 (esters), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.43–6.77 (4 H, m, aromatic H), 5.95–5.65 (2 H, m, trans olefinic H), 5.65–5.30 (2 H, m, cis olefinic H), 5.33–4.95 (1 H, m, C_9 H), 4.91–4.44 (2 H, m, C_{15} H and OC*H*O), 4.05 (2 H, d, C_{16} H), 3.72 (3 H, s, COOMe), 2.10 (3 H, s, MeCOO).

16-(3-Chlorophenoxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Methyl Ester 9,11,15-Tris(tetrahydropyran-2-yl ether) (19a). A mixture of anhydrous K_2CO_3 (250 mg, 1.8 mmol), **18a** (845 mg, 1.5 mmol), and MeOH (10 mL) was stirred at 50 °C for 1 h. The mixture was neutralized with acetic acid; diluted with AcOEt (200 mL); washed with water, saturated aqueous $NaHCO_3$, and brine; dried over $MgSO_4$; and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and dihydropyran (0.4 mL, 4.4 mmol) and *p*-toluenesulfonic acid (3 mg) was added. The mixture was stirred at 25 °C for 20 min and poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with AcOEt (20 mL × 3), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 30 g) with AcOEt–benzene (1:9) to give **19a** (937 mg, 91% yield): R_f 0.52 (AcOEt–benzene, 1:2); IR (film) 1740 (ester), 1600 (phenyl) cm^{-1}; NMR (CCl_4) δ 7.45–6.50 (4 H, m, aromatic H), 5.95–5.10 (4 H, m, olefinic H), 5.00–4.30 (4 H, m, C_{15} H and OC*H*O), 3.70 (3 H, s, COOMe).

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2-(phenylselenyl)prostaglandin $F_{2\alpha}$ Methyl Ester 9,11,15-Tris(tetrahydropyran-2-yl ether) (20a). To a stirred solution of diisopropylamine (0.45 mL, 3.2 mmol) in dry THF (10 mL) at −78 °C was added dropwise a 1.4 M solution of *n*-butyllithium (2 mL, 2.8 mmol) in hexane. The mixture was stirred at −78 °C for 20 min. To this LDA solution was added slowly during 20 min a solution of **19a** (937 mg, 1.36 mmol) in dry THF (5 mL), and the mixture was stirred at −78 °C for 20 min. A solution of diphenyldiselenide (900 mg, 2.88 mmol) in dry THF (3 mL) was added at −78 °C, and the mixture was stirred at −78 °C for 30 min and then at 20 °C for 30 min. The mixture was poured into saturated aqueous NH_4Cl (30 mL) and extracted with AcOEt (100 mL × 2). The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 40 g) with AcOEt–benzene (1:9) to give **20a** (736 mg, 64% yield): R_f 0.57 (AcOEt–benzene, 1:3); IR (film) 1735 (ester), 1597 (phenyl), 980 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.72–6.45 (9 H, m, aromatic H), 6.00–5.02 (4 H, m, olefinic H), 5.02–4.28 (4 H, m, C_{15} H and OC*H*O), 3.72 (3 H, s, COOMe).

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester 9,11,15-Tris(tetrahydropyran-2-yl ether) (21a). H_2O_2 (0.70 mL, 6.2 mmol), 30%, was added to a stirred solution of **20a** (736 mg, 0.87 mmol) in AcOEt (6 mL) and MeOH (4 mL). The mixture was stirred at 40 °C for 20 min and diluted with AcOEt (100 mL). The solution was washed with saturated aqueous $NaHCO_3$, water, and brine in succession, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 30 g) with AcOEt–benzene (1:9) to provide **21a** (510 mg, 85% yield): R_f 0.50 (AcOEt–benzene, 1:3); IR (film) 1730 (ester), 1655 (conjugated olefin), 1595 (phenyl), 985 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.40–6.50 (5 H, m, aromatic and C_3 H), 6.00–5.10 (5 H, m, other olefinic H), 4.93–4.30 (4 H, m, C_{15} H and OC*H*O), 3.72 (3 H, s, COOMe).

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (22a). A mixture of **21a** (510 mg, 0.742 mmol), 65% aqueous AcOH (10 mL), and THF (1 mL) was stirred at 70 °C for 20 min. The mixture was diluted with AcOEt (70 mL); washed with water, saturated aqueous $NaHCO_3$, and brine in succession; dried over $MgSO_4$; and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 20 g) with AcOEt–cyclohexane (3:2) to give **22a** (230 mg, 71% yield): R_f 0.26 (AcOEt); IR (film) 3400 (OH), 1720 (ester), 1655 (conjugated olefin), 1600 (phenyl), 975 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.40–6.60 (5 H, m, aromatic and C_3 H), 4.80 (1 H, d, J = 15.5 Hz, C_2 H), 5.72–5.24 (4 H, m, C_9, C_{11}, and C_{16} H), 3.69 (3 H, s, COOMe), 2.95 (2 H, t, C_4 H); UV (EtOH) λ_{max} 205, 220, 267, 274, 282 nm. High-resolution MS for $C_{23}H_{27}O_5Cl$ (dehydration peak from molecular ion): calcd, m/e 418.15468; found, 418.15775.

16-Phenoxy-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (22b). **22b** was prepared starting with the reduction of **17b** by the same five steps as applied for the preparation of **22a**. **22b**: R_f 0.26 (AcOEt); IR (film) 3400 (OH), 1725 (ester), 1655 (conjugated olefin), 1600 (phenyl), 975 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.45–6.66 (6 H, m, aromatic and C_3 H), 5.80 (1 H, d, J = 15.5 Hz, C_2 H), 5.72–5.24 (4 H, m, other olefinic H), 4.63–4.35 (1 H, m, C_{15} H), 4.25–3.78 (4 H, m, C_9, C_{11}, and C_{16} H), 3.69 (3 H, s, COOMe), 2.95 (2 H, t, C_4 H); UV (EtOH) λ_{max} 206, 218, 265, 271, 278 nm. High-resolution MS for $C_{23}H_{28}O_5$ (dehydration peak from molecular ion): calcd, m/e 384.19366; found, 384.19206.

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (22c). **22c** was prepared starting with the reduction of **17c** by the same five steps as applied for the preparation of **22a**. **22c**: R_f 0.27 (AcOEt); IR (film) 3380 (OH), 1720 (ester), 1658 (conjugated olefin), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.00 (4 H, m, aromatic H), 6.92 (1 H, dt, J = 15.5 and 6.0 Hz, C_3 H), 5.81 (1 H, d, J = 15.5 Hz, C_2 H), 5.76–5.30 (4 H, m, other olefinic H), 4.64–4.40 (1 H, m, C_{15} H), 4.23–3.84 (4 H, m, C_9, C_{11}, and C_{16} H), 3.70 (3 H, s, COOMe), 2.96 (2 H, t, C_4 H). High-resolution MS for $C_{24}H_{27}O_5F_3$ (dehydration peak from molecular ion): calcd, m/e 452.18103; found, 452.17815.

16-(4-Chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (22d). **22d** was prepared starting with the reduction of **17d** by the same five steps as applied for the preparation of **22a**. **22d**: R_f 0.26 (AcOEt); IR (film) 3400 (OH), 1720 (ester), 1655 (conjugated olefin), 1600 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.21 (2 H, d, J = 9 Hz, C_3 and C_5 H in aromatic ring), 6.82 (2 H, d, J = 9 Hz, C_2 and C_6 H in aromatic ring), 6.92 (1 H, dt, J = 16.0 and 6.5 Hz, C_3 H), 5.80 (1 H, d, J = 16.0 Hz, C_2 H), 5.72–5.30 (4 H, m, other olefinic H), 4.58–5.37 (1 H, m, C_{15} H), 4.23–3.80 (4 H, m, C_9, C_{11}, and C_{16} H), 3.70 (3 H, s, COOMe), 2.95 (2 H, t, C_4 H). High-resolution MS for $C_{23}H_{27}C_5Cl$ (dehydration peak from molecular ion): calcd, m/e 418.15468; found, 418.15444.

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-3,4-*trans*,*cis*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (23a). A mixture of **22a** (400 mg, 2.17 mmol), anhydrous K_2CO_3, and MeOH (10 mL) was stirred at 0 °C for 1.5 h. The mixture was neutralized with AcOH. Most of MeOH was removed by evaporation in vacuo, and the residue was dissolved in AcOEt (40 mL). The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 20 g) with AcOEt–benzene (1:1 → 2:1) to give **23a** (380 mg, 95% yield): R_f 0.26 (AcOEt); IR (film) 3400 (OH), 1740 (ester), 1600 (phenyl), 980 (trans olefinic H) cm^{-1}; NMR ($CDCl_3$) δ 7.35–6.72 (4 H, m, aromatic H), 6.65–5.25 (6 H, m, olefinic H), 4.60–4.35 (1 H, m, C_{15} H), 4.25–3.79 (4 H, m, C_9, C_{11}, and C_{16} H), 3.67 and 3.66 (total 3 H, s, COOMe), 3.19 (2 H × 0.33, d, C_2 H in 3-cis isomer), 3.12 (2 H × 0.66, d, C_2 H in 3-trans isomer). High-resolution MS for $C_{23}H_{27}O_5Cl$ (dehydration peak from molecular ion): calcd, m/e 418.15469; found, 418.15754.

16-Phenoxy-17,18,19,20-tetranor-3,4-*trans*,*cis*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (23b). **23b** was prepared by the same method as applied for the preparation of **23a** in 97% yield. **23b**: R_f 0.26 (AcOEt); IR (film) 3380 (OH), 1730 (ester), 1600 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.37–6.80 (5 H, m, aromatic H), 6.64–5.26 (6 H, m, olefinic H), 4.60–4.38 (1 H, m, C_{15} H), 4.20–3.80 (4 H, m, C_9, C_{11}, and C_{16} H), 3.66 (3 H, s, COOMe), 3.18 (2 H × $^1/_3$, d, C_2 H in 3-cis isomer), 3.10 (2 H × $^2/_3$, d, C_2 H in 3-trans isomer). High-resolution MS for $C_{23}H_{30}O_6$ (molecular ion peak): calcd, m/e 402.20422; found, 402.20322.

16-[3-(Trifluoromethyl)phenoxy]-17,18,19,20-tetranor-3,4-*trans*,*cis*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (23c). **23c** was prepared analogously as described above from **22c** in 93% yield. **23c**: R_f 0.27 (AcOEt); IR (film) 3380 (OH), 1740 (ester), 1597 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.00 (4 H, m, aromatic H), 6.65–5.30 (6 H, m, olefinic H), 4.65–4.40 (1 H, m, C_{15} H),

4.27–3.80 (4 H, m, C_9, C_{11}, and C_{16} H), 3.67 (3 H, s, COOMe), 3.18 (2 H × $^1/_3$, d, C_2 H in 3-cis isomer), 3.11 (2 H × $^2/_3$, d, C_2 H in 3-trans isomer); UV (EtOH) λ_{max} 226 nm. High-resolution MS for $C_{24}H_{29}O_6F_3$ (dehydration peak from molecular ion): calcd, *m/e* 452.18103; found, 452.18001.

16-(4-Chlorophenoxy)-17,18,19,20-tetranor-3,4-*trans*,*cis*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (23d). **23d** was prepared analogously as previously described from **22d** in 94% yield. **23d**: R_f 0.27 (AcOEt); IR (film) 3420 (OH), 1740 (ester), 1600 (phenyl), 978 (trans olefin); NMR ($CDCl_3$) δ 7.21 (2 H, d, *J* = 9 Hz, C_3 and C_5 H in aromatic ring), 6.82 (2 H, d, *J* = 9 Hz, C_2 and C_6 H in aromatic ring), 6.61–5.25 (6 H, m, olefinic H), 4.55–4.36 (1 H, m, C_{15} H), 4.20–3.80 (4 H, m, C_9, C_{11}, and C_{16} H), 3.67 and 3.66 (total 3 H, s, COOMe), 3.19 (2 H × $^1/_3$, d, C_2 H in 3-cis isomer), 3.10 (2 H × $^2/_3$, d, C_2 H in 3-trans isomer). High-resolution MS for $C_{23}H_{27}O_5Cl$ (dehydration peak from molecular ion): calcd, *m/e* 418.15469; found, 418.15503.

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-3,4-*trans*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (24a) and 16-(3-Chlorophenoxy)-17,18,19,20-tetranor-3,4-*cis*-didehydroprostaglandin $F_{2\beta}$ Methyl Ester (25a). Preparative TLC of **23a** (110 mg) on a $AgNO_3$-impregnated silica gel plate by development twice with $CHCl_3$–MeOH (5:1) afforded the crude **24a** (45 mg) and the crude **25a** (25 mg) by acetone elution. $AgNO_3$-impregnated silica gel plates were prepared as follows: the preparative TLC plates (Merck, silica gel, Art 5745, 20 × 20 cm, thickness 2 mm) were immersed in a 10% solution of $AgNO_3$ in CH_3CN–EtOH (1:1) during 1 min and dried at 20 °C for 3 h. Each of the crude **24a** and **25a** was further purified by the same preparative TLC and then column chromatographed on silica gel (Mallinckrodt, 3 g) with AcOEt–benzene (1:2) to yield **24a** (13 mg) and **25a** (13 mg), respectively. **24a**: R_f 0.51 (on silica gel impregnated with $AgNO_3$; development twice with $CHCl_3$–MeOH, 5:1); NMR ($CDCl_3$) δ 7.35–6.65 (4 H, m, aromatic H), 6.65–5.30 (6 H, m, olefinic H), 4.60–4.35 (1 H, m, C_{15} H), 4.30–3.75 (4 H, m, C_9, C_{11}, and C_{16} H), 3.67 (3 H, s, COOMe), 3.11 (2 H, d, C_2 H); UV (EtOH) λ_{max} 205, 226, 268, 274, 282 nm; MS *m/e* 418 ($M^+ - H_2O$), 400 ($M^+ - 2H_2O$), 382, 368, 295, 291, 277, 273, 259, 245, 241, 227. High-resolution MS for $C_{23}H_{27}O_5Cl$ (dehydration peak from molecular ion): calcd, *m/e* 418.15469; found, 418.15658. **25a**: R_f 0.43 (on silica gel impregnated with $AgNO_3$; development twice with $CHCl_3$–MeOH, 5:1); NMR ($CDCl_3$) δ 7.35–6.65 (4 H, m, aromatic H), 6.65–5.30 (6 H, m, olefinic H), 4.60–4.35 (1 H, m, C_{15} H), 4.30–3.75 (4 H, m, C_9, C_{11}, and C_{16} H), 3.69 (3 H, s, COOMe), 3.21 (2 H, d, C_2 H); UV (EtOH) λ_{max} 205, 227, 269, 275, 282 nm; MS *m/e* 418 ($M^+ - H_2O$), 400 ($M^+ - 2H_2O$), 268, 295, 291, 277, 273, 259, 245, 241, 227, 223. High-resolution MS for $C_{23}H_{27}O_5Cl$ (dehydration peak from molecular ion): calcd, *m/e* 418.15469; found, 418.15632.

16-Phenoxy-17,18,19,20-tetranor-3,4-*trans*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (24b) and 16-Phenoxy-17,18,19,20-tetranor-3,4-*cis*-didehydroprostaglandin $F_{2\alpha}$ Methyl Ester (25b). **24b** and **25b** were separated by the same method as applied for the separation of **24a** and **25a** in 15 and 10% yield, respectively. **24b**: R_f 0.31 (on silica gel impregnated with $AgNO_3$, development twice with $CHCl_3$–EtOH, 5:1); NMR ($CDCl_3$) δ 7.34–6.87 (5 H, m, aromatic H), 6.64–5.28 (6 H, m, olefinic H), 4.62–4.33 (1 H, m, C_{15} H), 4.23–3.91 (4 H, m, C_9, C_{11}, and C_{16} H), 3.66 (3 H, s, COOMe), 3.10 (2 H, d, C_2 H). High-resolution MS for $C_{23}H_{30}O_6$ (molecular ion peak): calcd, *m/e* 402.20422; found, 402.20333.

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-3,4-*trans*-5,6-*trans*-tetradehydroprostaglandin $F_{1\alpha}$ Methyl Ester (26a). A mixture of **23a** (52 mg, 0.12 mmol), dihydropyran (0.1 mL, 1 mmol), *p*-toluenesulfonic acid (0.1 mg), and dry CH_2Cl_2 (2 mL) was stirred at 25 °C for 15 min, then poured into saturated aqueous $NaHCO_3$, and extracted with ether (10 mL × 2). The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude tris(THP) compound, which was purified by column chromatography on silica gel (Merck, 5 g) with AcOEt–benzene (1:4). To a solution of this tris(THP) compound in CCl_4 (2 mL) was added a 0.1 M solution of iodine in CCl_4 (0.012 mL). The mixture was irradiated with diffused sunlight in a Pyrex flask at 25 °C for 25 h and concentrated in vacuo. The residue was dissolved in MeOH (2 mL) and *p*-toluenesulfonic acid (0.1 mg) was added. After it was stirred at 25 °C for 30 min, the mixture was diluted with AcOEt (20 mL). The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 5 g) with AcOEt–benzene (1:2) to yield **26a** (28 mg, 53% yield): R_f 0.42 ($CHCl_3$–EtOH, 5:1) and 0.25 (AcOEt); IR (film) 3400 (OH), 1731 (ester), 1596 (phenyl), 997 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.35–6.70 (4 H, m, aromatic H), 6.54–5.30 (6 H, m, olefinic H), 4.56–4.35 (1 H, m, C_{15} H), 4.26–3.80 (4 H, m, C_9, C_{11}, and C_{16} H), 3.65 (3 H, s, COOMe), 3.14 (2 H, d, *J* = 7.0 Hz, C_2 H); UV (EtOH) λ_{max} 205, 226, 269, 275, 282 nm. High-resolution MS for $C_{23}H_{29}O_6Cl$ (molecular ion peak): calcd, *m/e* 436.16525; found, 436.16463.

16-Phenoxy-17,18,19,20-tetranor-3,4-*trans*,5,6-*trans*-tetradehydroprostaglandin $F_{1\alpha}$ Methyl Ester (26b). **26b** was prepared from **23b** by the same method as described previously in 55% yield. **26b**: R_f 0.42 ($CHCl_3$–MeOH, 5:1) and 0.24 (AcOEt); IR ($CHCl_3$) 3420 (OH), 1733 (ester), 1601 (phenyl), 974 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.36–7.12 (2 H, m, C_1 and C_5 H in aromatic ring), 7.04–6.80 (3 H, m, C_2, C_4, C_6 H in aromatic ring), 6.45–5.31 (6 H, m, olefinic H), 4.56–3.37 (1 H, m, C_{15} H), 4.22–3.80 (4 H, m, C_9, C_{11}, and C_{16} H), 3.65 (3 H, s, COOMe), 3.14 (2 H, d, *J* = 7.0 Hz, C_2 H); UV (EtOH) λ_{max} 205, 222, 237, 264, 270, 277 nm. High-resolution MS for $C_{23}H_{28}O_5$ (dehydration peak from molecular ion): calcd, *m/e* 384.19366; found, 384.19426.

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2-(phenylselenyl)prostaglandin $F_{2\alpha}$ 9,11,15-Tris(tetrahydropyran-2-yl ether) (27a). **20a** (486 mg, 0.574 mmol) was dissolved in a mixture of KOH (96.4 mg, 1.72 mmol), water (4 mL), and MeOH (10 mL). The mixture was stirred at 50 °C for 3 h, then acidified with 1 N HCl, and diluted with AcOEt (100 mL). The solution was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 20 g) with AcOEt–benzene (1:3) to yield **27a** (360 mg, 75% yield): R_f 0.34 (CH_2Cl_2–MeOH, 19:1); NMR ($CDCl_3$) δ 8.72 (1 H, br s, COOH), 7.70–6.68 (9 H, m, aromatic H), 5.80–5.10 (4 H, m, olefinic H).

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*-didehydroprostaglandin $F_{2\alpha}$ (28a). **27a** was oxidized and subsequently deprotected with 1 N HCl by the same method as described previously to provide **28a** in 52% yield: R_f 0.15 (AcOEt–HCOOH, 80:1); IR (film) 3480 (OH), 2670 (COOH), 1700 (COOH), 1650 (conjugated olefin), 1600 (phenyl), 975 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.30–6.70 (5 H, m, aromatic H and C_3 H), 5.86–5.20 (5 H, m, other olefinic H), 2.98 (2 H, t, C_4 H). High-resolution MS for $C_{22}H_{27}O_6Cl$ (molecular ion peak): calcd, *m/e* 402.20422; found, 402.20322.

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-5,6-*trans*-didehydroprostaglandin $F_{1\alpha}$ Methyl Ester (30a). 16-(3-Chlorophenoxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester (**29a**; 1.3 g, 30 mmol) and diphenyl sulfide (1.04 mL, 6.26 mmol) were dissolved in a mixture of MeOH (14 mL) and benzene (138 mL). The solution was irradiated through a Pyrex filter with a high-pressure mercury lamp for 22 h with stirring in a water bath. After concentration in vacuo, the residue was column chromatographed on silica gel (Mallinckrodt, 50 g) with AcOEt–cyclohexane (2:1) to remove diphenyl sulfide. The starting material **29a** and the product **30a** were separated from each other by column chromatography on $AgNO_3$-impregnated silica gel (Mallinckrodt, 70 g) with AcOEt–cyclohexane (2:1). The pure **30a** (790 mg, 61% yield) was obtained by subsequent column chromatography on silica gel (Mallinckrodt, 50 g) with AcOEt–cyclohexane (2:1): R_f 0.27 (R_f of **29a** 0.19; AcOEt, silica gel impregnated with $AgNO_3$); IR (film) 3400 (OH), 1740 (ester), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.28–6.70 (4 H, m, aromatic H), 5.73–5.34 (4 H, m, olefinic H), 4.58–4.36 (1 H, m, C_{15} H), 4.25–3.80 (4 H, m, C_9, C_{11}, and C_{16} H), 3.65 (3 H, s, COOMe).

16-Phenoxy-17,18,19,20-tetranor-5,6-*trans*-prostaglandin $F_{1\alpha}$ Methyl Ester (30b). **30b** was prepared analogously from 16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester (**29b**) in 63% yield. **30b**: R_f 0.42 (R_f of **29b** 0.35; AcOEt, silica gel impregnated with $AgNO_3$); IR (film) 3380 (OH), 1740 (ester), 1600 (phenyl), 975 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.40–6.70 (5 H, m, aromatic H), 5.78–5.23 (4 H, m, olefinic H), 4.62–4.33 (1 H, m, C_{15} H), 4.32–3.73 (4 H, m, C_9, C_{11}, and C_{16} H), 3.64 (3

H, s, COOMe). High-resolution MS for $C_{23}H_{30}O_5$ (dehydration peak from molecular ion): calcd, m/e 386.20931; found, 386.21112.

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-5,6-*trans*-dihydroprostaglandin $F_{2\alpha}$ Methyl Ester 9,11,15-Tris(tetrahydropyran-2-yl ether) (31a). Tetrahydropyranylation of **30a** was carried out similarly as described above in 95% yield. **31a**: R_f 0.37 (AcOEt–cyclohexane, 1:3); IR (film) 1745 (ester), 1600 (phenyl), 980 (trans olefin) cm^{-1}.

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*,5,6-*trans*-tetradehydroprostaglandin $F_{1\alpha}$ Methyl Ester (32). **32** was prepared in 43% yield from **31a** by the same three steps as applied for the preparation of **22a** from **19a**. **32**: R_f 0.20 (AcOEt–cyclohexane–THF, 7:3:3; development twice) and 0.27 (AcOEt); IR (film) 3400 (OH), 1730 (ester), 1650 (conjugated olefin), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.25–6.70 (5 H, m, aromatic and C_3 H), 5.82 (1 H, d, J = 15.5 Hz, C_2 H), 5.77–5.60 (2 H, m, C_{13} and C_{14} H), 5.60–5.37 (2 H, m, C_5 and C_6 H), 4.60–4.35 (1 H, m, C_{15} H), 4.27–3.85 (4 H, m, C_9, C_{11}, and C_{16} H), 3.72 (3 H, s, COOMe), 3.06 (3 H, br s, OH), 2.88 (2 H, br s, C_4 H); UV (EtOH) λ_{max} 205, 220, 268, 275, 282 nm. High-resolution MS for $C_{23}H_{27}O_5Cl$ (dehydration peak from molecular ion): calcd, m/e 418.15468; found, 418.15395.

2-*syn*-(3-Methoxy-2-*cis*,*trans*-propenyl)-3-*anti*-[3$\alpha\beta$-(tetrahydropyran-2-yloxy)-4-(3-chlorophenoxy)-1-*trans*-butenyl]-4-*syn*-(tetrahydropyran-2-yloxy)cyclopentan-1-ol (34a). A 2 M solution of sodiomethylsufinyl carbanion in Me_2SO (7 mL, 14 mmol) was added slowly during 30 min to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (5.1 g, 14.9 mmol) in dry Me_2SO (50 mL) and dry THF (50 mL) at 5 °C. The mixture was stirred for an additional 30 min in an ice–water bath to yield the ylide. To this ylide solution was added dropwise during 30 min a solution of 2-oxa-6-*syn*-[3$\alpha\beta$-(tetrahydropyran-2-yloxy)-4-(3-chlorophenoxy)-1-*trans*-butenyl]-7-*anti*-(tetrahydropyran-2-yloxy)-*cis*-bicyclo[3.3.0]octan-3-ol (33a; 3.15 g, 6.2 mmol) in dry Me_2SO (15 mL) and dry THF (15 mL). The mixture was stirred at 5 °C for 1 h and then at 25 °C for 1 h. THF was removed by evaporation in vacuo, and the mixture was poured into cold water (200 mL). The solution was extracted with ether–pentane (1:1; 500 mL × 3), and the extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 200 g) with AcOEt–benzene (1:4) to give **34a** (2.61 g, 88% yield): R_f 0.36 (AcOEt–benzene, 1:2); IR (film) 3470 (OH), 1657 (C=COMe), 1600 (phenyl) cm^{-1}; NMR (CCl_4) δ 7.28–6.70 (4 H, m, aromatic H), 6.34 (1 H × $^2/_3$, d, J = 13 Hz, trans C=C*H*OMe), 5.96 (1 H × $^1/_3$, d, J = 6 Hz, cis C=C*H*OMe), 5.87–5.45 (2 H, m, olefinic H in ω chain), 3.63 (3 H × $^1/_3$, s, OMe in cis isomer), 3.48 (3 H × $^2/_3$, s, OMe in trans isomer).

2-Oxo-7-*syn*-[3$\alpha\beta$-hydroxy-4-(3-chlorophenoxy)-1-*trans*-butenyl]-8-*anti*-hydroxy-*cis*-bicyclo[4.3.0]nonan-3-ol (35a). A mixture of **34a** (2.61 g, 5.43 mmol), 65% aqueous AcOH (70 mL), and THF (5 mL) was stirred at 60 °C for 3 h and then concentrated in vacuo. The residue was dissolved in AcOEt (500 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 80 g) with AcOEt–benzene (1:1) to give **35a** (1.11 g, 58% yield): R_f 0.22 (AcOEt); IR (film) 3400 (OH), 1600 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.55–6.70 (4 H, m, aromatic H), 5.95–5.50 (2 H, m, olefinic H), 5.40–5.15 (1 H, m, OC*H*O).

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*,4,5-*trans*-tetradehydroprostaglandin $F_{1\alpha}$ Methyl Ester (36a). A solution of **35a** (355 mg, 1 mmol) and (3-carbomethoxy-2-propenyl)triphenylphosphorane (720 mg, 2 mmol) in CH_2Cl_2 (10 mL) was refluxed for 12 h. CH_2Cl_2 was removed by evaporation in vacuo, and the residue was column chromatographed on silica gel (Mallinckrodt, 50 g) with AcOEt–benzene (1:1) and then purified by chromatography with a Lober prepacked column (Merck, Art 10401, Grösse B) using the same eluent to afford **26a** [123 mg, 28%; R_f 0.23 (AcOEt)], the $C_{15\beta}$-hydroxy isomer [130 mg, 30%; R_f 0.26 (AcOEt)], and their mixture (75 mg, 17%). **36a**: IR (film) 3400 (OH), 1710 (ester), 1640 (conjugated olefin), 1620 (conjugated olefin), 1600 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 7.30–6.50 (5 H, m, aromatic and C_3 H), 6.15–5.85 (2 H, m, C_4 and C_5 H), 5.80–5.35 (3 H, m, C_2, C_{13}, and C_{14} H), 3.75 (3 H, s, COOMe); UV (EtOH) λ_{max} 204, 221, 262 nm. High-resolution MS for $C_{23}H_{27}O_5Cl$ (dehydration peak from molecular ion): calcd, m/e 418.15468; found, 418.15300.

16-Phenoxy-17,18,19,20-tetranor-2,3-*trans*,4,5-*trans*-tetradehydroprostaglandin $F_{1\alpha}$ Methyl Ester (36b). **36b** was prepared starting with the Wittig reaction of **33b** (=**1b**) by the three steps described for **36a**. **36b**: R_f 0.22 (AcOEt; R_f of the $C_{15\beta}$-hydroxy isomer 0.26); IR (film) 3400 (OH), 1700 (ester), 1640 and 1620 (conjugated olefin), 1600 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.44–6.76 (6 H, m, aromatic and C_3 H), 6.32–5.45 (5 H, m, other olefinic H), 3.75 (3 H, m, COOMe); UV (EtOH) λ_{max} 202, 221, 263 nm. High-resolution MS for $C_{23}H_{28}O_5$ (dehydration peak from molecular ion): calcd, m/e 384.19366; found, 384.19400.

1-*syn*,4-*syn*-Bis(tetrahydropyran-2-yloxy)-2-*syn*-(2-carbomethoxyethyl)-3-*anti*-[3$\alpha\beta$-(tetrahydropyran-2-yloxy)-4-(3-chlorophenoxy)-1-*trans*-butenyl]cyclopentane (37a). A solution of $AgNO_3$ (1.1 g, 6.5 mmol) in water (4 mL) was added to a stirred solution of **35a** (1.1 g, 3.1 mmol) in MeOH (30 mL) and then 0.5 N NaOH (28 mL, 14 mmol) was added slowly at 25 °C. After it was stirred at 25 °C for 2 h, the mixture was filtered through a glass filter over Celite. Two-thirds of the filtrate was evaporated in vacuo, the residue was acidified with cold 10% HCl to pH 2 in an ice–water bath, and the solution was extracted with AcOEt (200 mL). The extracts were washed with brine and dried over $MgSO_4$. To this solution cooled to 5 °C was added a solution of diazomethane in ether until a yellow color persisted, and the solvents were evaporated in vacuo. The residue was dissolved in dry CH_2Cl_2 (5 mL) and dihydropyran (2.5 mL, 25 mmol). *p*-Toluenesulfonic acid (ca. 10 mg) was added to this solution cooled to 10 °C. After it was stirred at 10 °C for 15 min, the mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with AcOEt (50 mL × 3). The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 30 g) with AcOEt–benzene (1:7) to obtain **37a** (1.28 g, 68% yield): R_f 0.66 (AcOEt–benzene, 1:2); IR (film) 1740 (ester), 1600 (phenyl), 980 (trans olefin) cm^{-1}; NMR (CCl_4) δ 7.60–6.78 (4 H, m, aromatic H), 6.00–5.52 (2 H, m, olefinic H), 3.66 (3 H, s, COOMe).

1-*syn*,4-*syn*-Bis(tetrahydropyran-2-yloxy)-2-*syn*-[2-carbomethoxy-2-(phenylselenyl)ethyl]-3-*anti*-[3$\alpha\beta$-(tetrahydropyran-2-yloxy)-4-(3-chlorphenoxy)-1-*trans*-butenyl]-cyclopentane (38a). To a stirred solution of diisopropylamine (0.16 g, 1.57 mmol) in dry THF (10 mL) cooled at −40 °C was added dropwise a 1.5 M solution of *n*-butyllithium in hexane (1.0 mL, 1.5 mmol). The mixture was stirred for 20 min at −40 °C. To this LDA solution cooled at −78 °C was added slowly during 20 min a solution of **37a** (770 mg, 1.21 mmol) in dry THF (4 mL). After this solution was stirred at −78 °C for 30 min, a solution of diphenyldiselenide (500 mg, 1.6 mmol) in dry THF (2 mL) was added. The mixture was stirred at −78 °C for 40 min and then at 5 °C for 30 min, poured into saturated aqueous NH_4Cl (30 mL), and extracted with AcOEt (150 mL × 2). The extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 30 g) with AcOEt–benzene (1:6) to give **38a** (790 mg, 82% yield): R_f 0.71 (AcOEt–benzene, 1:2); IR (film) 1730 (ester), 1600 (phenyl), 985 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 8.00–6.71 (9 H, m, aromatic H), 6.00–5.52 (2 H, m, olefinic H), 3.68 and 3.66 (total 3 H, each s, COOMe).

1-*syn*,4-*syn*-Bis(tetrahydropyran-2-yloxy)-2-*syn*-(2-formyl-1-*trans*-ethenyl)-3-*anti*-[3$\alpha\beta$-(tetrahydropyran-2-yloxy)-4-(3-chlorophenoxy)-1-trans-butenyl]cyclopentane (39a). To a solution of **38a** in AcOEt (10 mL) and THF (10 mL) was added dropwise 35% H_2O_2 (1 mL, 33 mmol). The mixture was stirred at 35 °C for 5 min and was diluted with water (30 mL). The solution was extracted with AcOEt (100 mL × 3). The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to yield the crude α,β-unsaturated ester (630 mg). To a solution of the ester in dry toluene (30 mL) cooled to −78 °C was added dropwise a 25% solution of DIBAL in toluene (2 mL, 3.5 mmol), and the mixture was stirred at −78 °C for 10 min. After the reaction was quenched by the addition of MeOH (ca. 2 mL), the mixture was warmed up to 0 °C and water (5 mL) was added. After the mixture was stirred at 25 °C for 1 h, $Al(OH)_3$ appeared, which was filtered off. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield the

crude allylic alcohol (580 mg). A mixture of the allylic alcohol, manganese dioxide (4.0 g), and CH_2Cl_2 (20 mL) was stirred at 25 °C for 2 h and filtered. The filtrate was concentrated in vacuo to give **39a** (540 mg, 88% yield): R_f 0.46 (AcOEt–benzene, 1:2); IR (film) 1690 (CHO), 1600 (phenyl), 975 (trans olefin); NMR (CCl_4) δ 10.0–9.66 (1 H, m, CHO), 7.35–6.52 (5 H, m, aromatic H and C*H*=CC=O), 6.32–5.34 (3 H, m, olefin in the ω chain and C=C*H*C=O).

16-(3-Chlorophenoxy)-17,18,19,20-tetranor-2,3-*trans*,4,5-*trans*,6,7-*trans*-hexadehydroprostaglandin $F_{1\alpha}$ Methyl Ester (40a). A mixture of **39a** (150 mg, 0.24 mmol), (3-carbomethoxy-2-propenyl)triphenylphosphorane (360 mg, 1.0 mmol), and CH_2Cl_2 (5 mL) was refluxed for 12 h and concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 10 g) with AcOEt–benzene (1:7) to give the tris(THP) conjugated ester. A mixture of this ester, THF (2 mL), and 1 N HCl (2 mL) was stirred at 45 °C for 1 h, diluted with AcOEt (5 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 15 g) with AcOEt–benzene (1:1) to afford **40a** [28 mg, 26%; R_f 0.22 (AcOEt)], the C_{15S}-hydroxy isomer [26 mg, 24%; R_f 0.26 (AcOEt)], and their mixture (14 mg, 13%). **40a**: IR (film) 3400 (OH), 1702 (ester), 1615 (conjugated olefin), 1593 (phenyl), 978 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.72–5.92 (9 H, m, aromatic H and conjugated olefinic H, except for C_2 H), 5.97–5.53 (3 H, m, C_2, C_{13}, and C_{14} H), 4.43 (1 H, m, C_{15} H), 3.73 (3 H, s, COOMe); UV (EtOH) λ_{max} 306 nm. High-resolution MS for $C_{23}H_{25}O_5Cl$ (dehydration peak from molecular ion): calcd, *m/e* 416.13904; found, 416.13996.

16-Phenoxy-17,18,19,20-tetranor-2,3-*trans*,4,5-*trans*,6,7-*trans*-hexadehydroprostaglandin $F_{1\alpha}$ Methyl Ester (40b). **40b** was prepared by starting with the Wittig reaction of **33b** (=**1b**) by the same six steps as described for **40a**. **40b**: R_f 0.20 (AcOEt, R_f of the C_{15S}-hydroxy isomer 0.26); IR 3380 (OH), 1710 (ester), 1615 (conjugated olefin), 1600 (phenyl), 972 (trans olefin) cm^{-1}; NMR ($CDCl_3$) δ 7.44–5.23 (13 H, m, aromatic H and olefinic H), 4.67–4.31 (1 H, m, C_{15} H), 4.34–3.71 (4 H, m, C_9, C_{11}, and C_{16} H), 3.73 (3 H, s, COOMe); UV (EtOH) λ_{max} 306 nm. High-resolution MS for $C_{23}H_{28}O_6$ (molecular ion peak): calcd, *m/e* 400.18858; found, 400.19194.

Biological Procedure. Antinidatory Effect. By the same biological procedure as described in the preceding paper in this issue,[20] the antinidatory effects of prostaglandin analogues were examined.

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2,4-Diamino-5-benzylpyrimidines as Antibacterial Agents. 4. 6-Substituted Trimethoprim Derivatives from Phenolic Mannich Intermediates. Application to the Synthesis of Trimethoprim and 3,5-Dialkylbenzyl Analogues[1]

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The preparation of a wide variety of 6-substituted trimethoprim analogues was readily accomplished by the reaction of 2,4-diamino-6-substituted-pyrimidines with 2,6-dimethoxy-4-[(*N*,*N*-dimethylamino)methyl]phenol at 120–160 °C. The less reactive 2,6-dialkyl-4-[(*N*,*N*-dimethylamino)methyl]phenols reacted successfully with 2,4-diamino-6-(alkylthio)pyrimidines to give 5-(substituted benzyl)pyrimidines. The phenolic groups of the products were alkylated in high yield when a nonreactive 6-substituent was present in the pyrimidine ring. 6-(Alkylthio) groups were easily removed with Raney nickel. Trimethoprim was thus obtained in high yield from its 6-(methylthio) counterpart. The 6-substituted trimethoprim analogues all had low activity as inhibitors of *Escherichia coli* dihydrofolate reductase and as antibacterial agents.

A previous paper in this series[2] described the synthesis of trimethoprim (**18**), a broad-spectrum antibacterial agent,[3] from 2,4-diaminopyrimidine and phenolic Mannich bases. This route had limited applicability to the preparation of benzylpyrimidine analogues; it was not useful with 3,5-dialkylphenolic Mannich bases. However, the highly successful condensation of 2,4-diaminopyrimidin-6(1*H*)-one and 2,4-diamino-6-methylpyrimidine with Mannich bases[2] suggested that a wide gamut of 6-substituted derivatives might be prepared by this approach. This paper describes such analogues and their biological activity. Furthermore, it presents a synthesis of 3,5-dialkyl-4-hydroxy- and 3,5-dialkyl-4-methoxybenzyl analogues of trimethoprim which utilizes the readily reactive 2,4-diamino-6-(methylthio)pyrimidine as an intermediate.[1,4]

A study of the effect of 6-substitution on the biological activity of trimethoprim was considered of importance. Its 6-methyl derivative[2] had less antibacterial activity and dihydrofolate reductase (DHFR) inhibitory activity (*E. coli* and *P. berghei*) than did the parent. However, related 6-alkyl-2,4-diamino-5-benzylpyrimidines[5] had high antimalarial activity.[6] It seemed plausible that appropriate 6-modification, such as lengthening the chain and introducing an aromatic or conceivably a polar substituent, would provide useful activity and perhaps yield information about the interaction of these compounds with DHFR derived from different species.

(1) (a) A portion of this paper dealing with trimethoprim geometry and 6-substitution was presented at the 164th American Chemical Society Meeting. See "Abstracts of Papers", 164th National Meeting of the American Chemical Society, New York, N.Y., Aug 1972, American Chemical Society, Washington, D.C., Abstr MEDI 23. (b) B. Roth, U.S. Patent 3 772 289 (1973). (c) B. Roth, U.S. Patent 3 822 264 (1974).
(2) For paper 2 in this series, see B. Roth, J. Z. Strelitz, and B. S. Rauckman, *J. Med. Chem.*, **23**, 379 (1980).
(3) (a) B. Roth, E. A. Falco, G. H. Hitchings, and S. R. M. Bushby, *J. Med. Pharm. Chem.*, **5**, 1103 (1962). (b) *Drugs*, 1, 7 (1971), and references therein. (c) Symposium on Trimethoprim-Sulfamethoxazole, *J. Infect. Dis.*, **128**, supplement (Nov, 1973).
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