mol) of **15** in 10 mL of hot HOAc was added over a period of 15 min. After an additional hour at reflux, the hot mixture was filtered. The cooled filtrate was diluted with $H_2O$ and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with saturated $NaHCO_3$ solution and then with $H_2O$ and dried. The solution was concentrated, and the residue was suspended in ether, filtered, and recrystallized from ethanol to give microcrystals: mp 157–160 °C; yield 2.5 g (46%). Anal. ($C_{12}H_{12}BrNO_2$) C, H, N.

**4-[(4′-Amino-1′-pentyl)amino]-1,2-dimethoxy-6-bromonaphthalene Fumarate (17a).** A mixture of 2.5 g (0.009 mol) of **16**, 3.04 g (0.009 mol) of *N*-(4-iodo-1-methylbutyl)phthalimide,[9] and 2.5 mL of triethylamine was heated at 140 °C for 4 h. The mixture was worked up as usual and chromatographed on silica gel with benzene/ether (4:3) as the eluant. An oil was obtained, which crystallized under ether. After recrystallization from $C_2H_5OH$ the yellow crystals melted at 138–140 °C, yield 1.8 g (54%). Anal. ($C_{25}H_{25}BrN_2O_4$) C, H, N.

A solution of 1.7 g (0.0034 mol) of the above and 3.2 mL of 85% $H_2NNH_2 \cdot H_2O$ in 50 mL of $C_2H_5OH$ was refluxed under $N_2$ for 2 h and worked up as usual to furnish the desired amine as a brown oil, yield 1.1 g (88%). The fumarate was prepared in $C_2H_5OH$ and was obtained as gray microcrystals, mp 209–210 °C. Anal. ($C_{17}H_{23}BrN_2O_2 \cdot 0.5C_4H_4O_4$) C, H, N.

**4-[(4′-Amino-1′-methylbutyl)amino]-1,2-dimethoxy-6-bromonaphthalene Fumarate (17b).** A mixture of 2.2 g of **16**, 2.3 g (0.0079 mL) of *N*-(4-bromopentyl)phthalimide,[9] and 2 mL of triethylamine was heated at 150 °C for 4 h. After the usual workup, the crude material was chromatographed on a silica gel column using benzene/ether (3:7) as the eluant. The combined fractions were concentrated to leave an oil, which crystallized under ether at 0 °C. Recrystallization from $C_2H_5OH$–ether gave 0.39 g (10%) of a crystalline solid, mp 144–146 °C. Anal. ($C_{25}H_{25}BrNO_4$) C, H, N.

A solution of 1.7 g (0.0034 mol) of the above phthalimide and 3.2 mL of 85% $H_2NNH_2 \cdot H_2O$ in 50 mL of $C_2H_5OH$ was refluxed for 2 h and then worked up as usual to give 1.2 g (89%) of the free base as a brown oil. The fumarate salt, prepared in $C_2H_5OH$, crystallized after standing overnight in the cold, mp 174–177 °C. Anal. ($C_{17}H_{23}BrN_2O_2 \cdot C_4H_4O_4$) C, H, N.

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# Prostaglandin Analogues Possessing Antinidatory Effects. 1. Modification of the ω Chain

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Novel prostaglandin analogues modified in the ω chain were prepared by the reaction of the vinyl aldehydes **1a–e** with a variety of organometallic reagents as a key step of the syntheses. Compared with the natural prostaglandin $F_{2\alpha}$ in antinidatory effect, the analogues **4**, **7**, and **10** were 40 times more potent and the analogue **11** was 50–100 times more potent in the rat.

Prostaglandin $F_{2\alpha}$ has a high luteolytic effect and is of interest because it is effective in controlling the reproduction of animals by synchronization of the sex cycle.[1] In order to develop new prostaglandin analogues which have more potent antinidatory effects than that of prostaglandin $F_{2\alpha}$, we synthesized novel analogues modified in the ω chain (the lower chain) by the reaction of the vinyl aldehydes[2] with a variety of organometallic reagents as a key step of these syntheses. Some analogues were found to show considerably higher antinidatory effects in the rat. We report herein the syntheses of these novel prostaglandin analogues and their antinidatory effects.

In this report the antinidatory effect induced by prostaglandins was examined as an indication of the luteolytic effect.[3] The antinidatory effect means a loss of pregnancy in the implantation process. Animals were sacrificed on day 11 (day 0 = sperm confirmation) in order to examine the number of implantation sites. The test group was compared with the control group.

**Chemistry.** As shown in Scheme I, treatment of the versatile vinyl aldehyde **1** previously reported by us[2] with a variety of organometallic reagents easily afforded the intermediates **3**, in some of which the hydroxy function at $C_9$ or $C_{11}$ was protected with an acetyl or a tetrahydropyranyl (THP) group. Since the vinyl aldehyde **1** contains not only an aldehyde unit but also an ester function in the same molecule, the reaction conditions must be carefully controlled in order to avoid side reactions. The selective reaction of the aldehyde unit in **1** with organometallic reagents was realized under the following conditions. Using tetrahydrofuran (THF) as solvent, the vinyl aldehyde **1** was treated with Grignard reagents at 0 °C or alkyllithium reagents at −78 to −40 °C. When the reaction temperature was raised to higher than that required for optimum results, a byproduct was produced in which the methyl ester group was alkylated.

Because the vinyl aldehydes **1a,c,d** possess free hydroxy functions, an excess of organometallic reagent corresponding to the equivalent of the hydroxy functions was required. Therefore, it was better to protect these hydroxy functions with the acetyl or the THP group. When the intermediates **3** were converted to the final products, the THP group in **3d,e** and the acetyl group in **3b,c,e** were removed by acidic treatment (65% aqueous AcOH, 40 °C, 1 h) and basic treatment ($K_2CO_3$ in MeOH, 50 °C, 30 min), respectively. The stability of the ω chain under these conditions was considered in the selection of suitable vinyl aldehydes, **1a–e**. Summarized in Table I are the combination of various vinyl aldehydes and organometallic reagents, the yields of the intermediates **3** (as the mixture

(1) B. B. Pharris and L. J. Wyngarden, *Proc. Soc. Exp. Biol. Med.*, **130**, 92 (1969).

(2) (a) H. Wakatsuka, Y. Konishi, S. Kori, and M. Hayashi, *Chem. Lett.*, 141 (1978); (b) H. Miyake, T. Tanouchi, Y. Yamato, T. Okada, Y. Konishi, H. Wakatsuka, S. Kori, and M. Hayashi, *ibid.*, 145 (1978).

(3) Labhsetwar observed the luteolytic effect from the antinidatory effect of prostaglandin $E_1$; see A. P. Labhsetwar, *Biol. Reprod.*, **8**, 103 (1973).

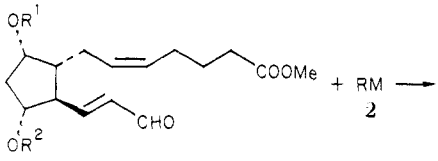
0022-2623/80/1823-0519$01.00/0 

Table I. Reaction of Vinyl Aldehydes with Organometallic Anions and the Antinidatory Effects in the Rat of Synthesized Prostaglandin $F_{2\alpha}$ Analogues Relative to That of Prostaglandin $F_{2\alpha}$

| class | entry | vinyl aldehydes | RM (ref) | % yield of 3 | final products (% yield[a]) | R in final products | ANE[b] ($PGF_{2\alpha}$ = 1) |
|---|---|---|---|---|---|---|---|
| A | 1 | 1a | $C_6H_5COCH_2Li$ (8) | 86 | 4 (86) | $-CH_2COC_6H_5$ | 40 |
| | 2 | 1a | *m*-Cl-$C_6H_4COCH_2Li$ (8) | 83 | 5 (83) | $-CH_2COC_6H_4$-Cl-*m* | 10 |
| | 3 | 1a | *p*-Cl-$C_6H_4COCH_2Li$ (8) | 79 | 6 (79) | $-CH_2COC_6H_4$-Cl-*p* | 4-8 |
| B | 4 | 1b | $C_6H_5C{\equiv}CLi$ (9) | 82 | 7 (98) | $-C{\equiv}CC_6H_5$ | 40 |
| | 5 | 1b | *m*-Cl-$C_6H_4C{\equiv}CLi$ (9) | 76 | 8 (89) | $-C{\equiv}CC_6H_4$-Cl-*m* | 40-80 |
| | 6 | 1b | *p*-Cl-$C_6H_4C{\equiv}CLi$ (9) | 79 | 9 (87) | $-C{\equiv}CC_6H_4$-Cl-*p* | 1 |
| C | 7 | 1b | 2-benzo[*b*]thienyllithium (10) | 80 | 10 (80) | 2-benzo[*b*]thienyl | 40 |
| | 8 | 1b | 2-benzofuranyllithium (10) | 80 | 11 (85) | 2-benzofuranyl | 50-100 |
| | 9 | 1a | 1-indenyllithium (11) | 75 | 12 (75) | 1-indenyl | <5 |
| D | 10 | 1a | $C_6H_5Si(Me)_2CH_2MgBr$ (12) | 79 | 13 (79) | $-CH_2Si(Me)_2C_6H_5$ | <1 |
| | 11 | 1a | $C_6H_5OCHLiCOOMe$ (13) | 86 | 14 (86) | $-CH(COOMe)OC_6H_5$ | <4 |
| | 12 | 1a | *o*-MeO-$C_6H_4MgBr$ | 82 | 15[c] (82) | $-C_6H_4$-OMe-*o* | <2 |
| | 13 | 1c | 1-(phenylthio)cyclopropyllithium (14) | 83 | 16 (78) | 1-(phenylthio)cyclopropyl | <2 |
| | 14 | 1e | (cyclohex-1-enylthio)methyllithium (15) | 95 | 17 (85) | (cyclohex-1-enylthio)methyl | 10 |
| | 15 | 1d | *t*-$BuOCOCH_2Li$ (13) | 96 | 18 (20) | $-CH_2COOC_6H_5$ | <1 |
| | 16 | 1a | $C_6H_5OC{\equiv}CLi$ (16) | 95 | 19 (75) | $-C{\equiv}COC_6H_5$ | <2-4 |

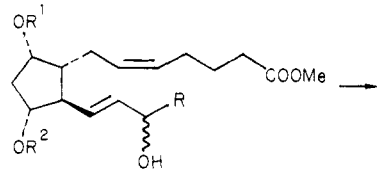
[a] As a mixture of $C_{15}$-epimeric isomers. [b] Antinidatory effects in the rat. The activities relative to that of prostaglandin $F_{2\alpha}$ were calculated based on the $ED_{50}$ values by the Litchfield-Wilcoxin method. The $ED_{50}$ value of prostaglandin $F_{2\alpha}$ is 1.3 (0.90-1.87) mg/kg and its confidence limit is 95%. [c] A mixture of $C_{15}$-epimeric isomers.

Scheme I

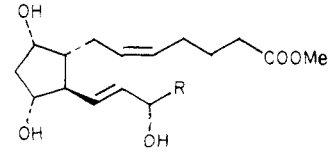



2

1a-e
1a, $R^1 = R^2 = H$
b, $R^1 = R^2 = Ac$
c, $R^1 = Ac$; $R^2 = H$
d, $R^1 = H$; $R^2 = THP$
e, $R^1 = Ac$; $R^2 = THP$




3a-e
3a, $R^1 = R^2 = H$
b, $R^1 = R^2 = Ac$
c, $R^1 = Ac$; $R^2 = H$
d, $R^1 = H$; $R^2 = THP$
e, $R^1 = Ac$; $R^2 = THP$




4-19 (final product)[a]

[a] For R, see Table I.

of $C_{15}$-hydroxy isomers), the structures of final products, and their antinidatory effects.

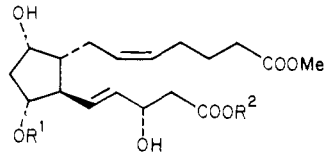
When the final product was stable to base and acid (entry 14; final product 17), the vinyl aldehyde 1e was selected in which the hydroxy functions at $C_9$ and $C_{11}$ were protected with the acetyl group and the THP unit, respectively. As already reported,[2b] 3e could be converted to not only prostaglandin $F_{2\alpha}$ analogues but also prostaglandin $E_2$ analogues (9-oxo type), since the hydroxy functions at $C_9$ and $C_{11}$ were blocked with different protecting groups. The vinyl aldehyde 1a containing the free hydroxy functions was selected in the reaction when the dehydration of $C_{15}$-allylic hydroxy functions in the final products under the acidic or basic condition led undesirably to the conjugated dienoic type (entries 1, 2, and 3; final products 4, 5, and 6), the conjugated fulvene type (entry 9; final product 12), or the conjugated dienoic ester type (entry 11; final product 14). The treatment of 1a with the corresponding alkyllithium reagents at -78 °C, followed by quenching the reaction at -78 °C, furnished **3a**, which was subjected to column chromatography on silica gel to separate the $C_{15\alpha}$- and $C_{15\beta}$-hydroxy isomers,[4] respectively. The vinyl aldehyde 1a was also used when hydrolysis of the protecting groups to the final product containing the C-Si bond with base or acid caused desilylation (entry 10; final product **13**).[5]

In the preparation of the acetylenic analogues (entries 4, 5, 6, and 16; final products **7**, **8**, **9**, and **19**) and the bicyclic aromatic analogues (entries 7 and 8; final products **10** and **11**), **1b**, in which the hydroxy functions are protected not with the THP units but with the acetyl groups, was selected, since the final products were stable to base, whereas under acidic conditions a considerable amount of the $C_{13}$-hydroxy byproduct was produced by the 1,3 rearrangement of the $C_{15}$-allylic alcohol. Similarly, in the preparation of an analogue having a cyclopropyl ring (entry 13; final product **16**), the vinyl aldehyde **1c** was selected, where the $C_9$-hydroxy group was protected with the acetyl function. When the Grignard reagent could be easily prepared, although the final product was stable to base (entry 12; product **15**), the vinyl aldehyde 1a, whose hydroxy functions are free, was selected.

(4) Assignment of the $C_{15}$ configuration based on relative TLC mobility has generally been accepted as correct: in the final products, the more polar isomer is the $C_{15\alpha}$-hydroxy compound and the less polar one is the $C_{15\beta}$-hydroxy one, which is biologically less active. In these prostaglandin analogues, the more polar isomers were determined to be $C_{15\alpha}$-hydroxy isomers by comparison of biological activities of $C_{15}$ isomers.

(5) P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464 (1975), and references cited therein.

Since it was difficult to prepare the phenyl acetate anion, $LiCH_2COOPh$, the preparation of analogue **18** was achieved by the following sequence: (1) reaction of the $C_{11}$-OTHP vinyl aldehyde **1d** with the *tert*-butyl acetate anion, $LiCH_2COO$-*t*-Bu; (2) separation of the desired $C_{15\alpha}$-hydroxy isomer **20** from the $C_{15}$ epimer;[4] (3) hydrolysis of the *tert*-butyl ester group and the THP unit at the same time by treatment with trifluoroacetic acid–THF (7:3) to afford the intermediate **21**; and (4) esterification of **21** with phenol in the presence of dicyclohexylcarbodiimide to the final product **18**.




**18**, $R^1$ = H; $R^2$ = Ph
**20**, $R^1$ = THP; $R^2$ = *t*-Bu
**21**, $R^1$ = $R^2$ = H

Although the intermediate **3** was generally a 1:1 mixture of epimeric $C_{15\alpha}$- and $C_{15\beta}$-hydroxy isomers, the $C_{15\alpha}$-hydroxy isomer was obtained fairly selectively in the Grignard reaction of the vinyl aldehyde **1a** with the silyl reagent, $PhSi(Me)_2CH_2MgBr$, in a ratio of $C_{15\alpha}$-OH/$C_{15\beta}$-OH = ca. 3:2 (entry 10). In general, $C_{15}$ isomers[4] were separated at the final step by column chromatography on silica gel, while some intermediates, **3b–d** (entries 7, 8, and 13–15), could be easily separated by chromatography. Exceptionally, in the case of the analogue **15**, it was impossible to separate the $C_{15}$-hydroxy isomers, and the bioactivity of the $C_{15}$ mixture was measured.

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 were supported by their NMR, IR, and high-resolution mass spectra. The purity was checked by TLC, and the final products were confirmed to be homogeneous by TLC.

## Pharmacological Results and Discussions

The abortifacient effect in pregnant rats is currently regarded as being an indication of the luteolytic effect of prostaglandins.[3] 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 approximately 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 the novel prostaglandin $F_{2\alpha}$ analogues modified in the ω chain.

The hydroxy group at $C_{15}$ is an important function for biological activities of prostaglandins, which are greatly influenced by the steric and electronic effects of substituents near $C_{15}$ and by their position. The interesting biological results were anticipated by the introduction of a phenyl group into the ω chain.[6] These prostaglandin analogues were grouped into four classes, A–D, and are shown in Table I with their antinidatory effects relative to that of prostaglandin $F_{2\alpha}$. Class A consists of analogues containing a phenylcarbonyl moiety. Class B is composed of analogues having a triple bond and a phenyl group. The aromatic bicyclic analogues containing the hetero atom, or not, make up class C. The other analogues modified in the ω chain belong to class D.

The analogues **4–6** in class A exhibited higher antinidatory effects as compared with that of prostaglandin $F_{2\alpha}$, and the phenyl analogue **4** was 40 times more potent than prostaglandin $F_{2\alpha}$. In class B, the *p*-chlorophenyl analogue **9** showed the same potency as that of prostaglandin $F_{2\alpha}$, while the phenyl analogue **7** and *m*-chlorophenyl analogue **8** were 40 and 40–80 times more active than prostaglandin $F_{2\alpha}$, respectively. In classes A and B, there was a marked tendency that phenyl analogues **4**, **7**, and **8** were considerably more potent. In class C, although the potency of the indenyl analogue **12** was lower than that of prostaglandin $F_{2\alpha}$, the benzothienyl analogue **10** and benzofuranyl analogue **11** were 40 and 50–100 times more active than prostaglandin $F_{2\alpha}$, respectively. In class D, the thiocyclohexenyl analogue **17** and the phenoxy acetylenic analogue **19** exhibited 10 and 2–4 times greater potency than that of prostaglandin $F_{2\alpha}$, respectively, whereas the others were less potent than prostaglandin $F_{2\alpha}$.

When the phenyl group was attached to $C_{17}$ or the corresponding hetero atom, the potency of the analogues was increased (**4–8**, **10**, and **11**). Although the analogues **13**, **14**, and **16** are analogous compounds, they are less potent probably because of the steric hindrance of other substituents near by. It is not clear why the potency of analogue **9** was not increased.

Additionally, the uterine contractile activities in the rat[7] of these prostaglandin analogues were examined: exceptionally, analogue **11** was 5–10 times more potent than prostaglandin $F_{2\alpha}$, whereas the others were less potent than it.

As previously mentioned, the preparation of the novel types of prostaglandin analogues and examination of their antinidatory effects resulted in the discovery of some highly potent analogues containing the phenyl ketone, the phenylacetylene, or the aromatic bicyclic ring moiety in the molecule.

## 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. 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, and 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 0.25 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.

(6) D. Binder, J. Bowler, E. D. Brown, N. C. Crassley, J. Hutton, M. Senior, L. Slater, P. Wilkinson, and N. C. A. Wright, *Prostaglandins*, **6**, 87 (1974).

(7) An increase of intrauterine pressure in the rat on day 20 of pregnancy under urethane anesthesia was observed by the threshold dose of each prostaglandin analogue (prostaglandin $F_{2\alpha}$ = 20 μg/kg).

**17-Oxo-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (4).** To a stirred solution of the aldehyde **1a** (915 mg, 3.1 mmol) in dry THF (30 mL) at −78 °C was added dropwise a solution of the anion ($LiCH_2COPh$;[8] 4.5 equiv) in dry THF which had been prepared from lithium diisopropylamide and acetophenone. After stirring at −78 °C for 1 h, the reaction was quenched by the addition of AcOH (2 mL), and the mixture was diluted with AcOEt (150 mL). The solution was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of $C_{15\alpha}$ and $C_{15\beta}$ alcohols. They were column chromatographed on silica gel (Mallinckrodt, 40 g) with 0–40% cyclohexane in AcOEt to provide **4** [$R_f$ 0.19 (AcOEt); 389 mg, 30%], the $C_{15\beta}$ isomer [$R_f$ 0.28 (AcOEt); 374 mg, 29%], and their mixture (347 mg, 27%). **4**: IR (film) 3400 (OH), 1740 (ester), 1685 (phenyl ketone) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.10–7.83 (2 H, m, aromatic H), 7.73–7.33 (3 H, m, aromatic H), 5.80–5.55 (2 H, m, trans olefinic H), 5.55–5.20 (2 H, m, cis olefinic H), 4.30–3.84 (2 H, m, $C_9$ and $C_{11}$ H), 3.66 (3 H, s, $COOCH_3$), 3.22 (2 H, d, $C_{16}$ H); $[\alpha]^{20}_D$ (*c* 1.6, $CHCl_3$) +9.3°. High-resolution MS for $C_{24}H_{30}O_5$ (dehydration peak from molecular ion): calcd, *m/e* 398.20931; found, 398.20865.

The analogues **5** and **6** were prepared from the aldehyde **1a** and the corresponding anions by the same method as applied for the preparation of **4**.

**17-Oxo-17-(3-chlorophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (5).** Column chromatography gave **5** ($R_f$ 0.25; 35%), the $C_{15}$ epimer [$R_f$ 0.34 (AcOEt); 30%], and their mixture (18%). **5**: IR (film) 3400 (OH), 1740 (ester), 1680 (phenyl ketone) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.00–7.73 (2 H, m, aromatic H), 7.63–7.30 (2 H, m, aromatic H), 5.72–5.54 (2 H, m, trans olefinic H), 5.54–5.20 (2 H, m, cis olefinic H), 4.90–4.58 (1 H, m, $C_{15}$ H), 4.32–3.85 (2 H, m, $C_9$ and $C_{11}$ H), 3.64 (3 H, s, COOMe), 3.30–3.05 (2 H, m, $C_{16}$ H). High-resolution MS for $C_{24}H_{29}O_5Cl$ (dehydration peak from molecular ion): calcd, *m/e* 432.17033; found, 432.17020.

**17-Oxo-17-(4-chlorophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (6).** Column chromatography gave **6** ($R_f$ 0.19; 29%), the $C_{15}$ epimer [$R_f$ 0.30 (AcOEt); 22%], and their mixture (28%). **6**: IR (film) 3400 (OH), 1740 (ester), 1680 (phenyl ketone) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.03–7.80 (2 H, m, aromatic H), 7.58–7.30 (2 H, m, aromatic H), 5.78–5.55 (2 H, m, trans olefinic H), 5.55–5.20 (2 H, m, cis olefinic H), 4.90–4.55 (1 H, m, $C_{15}$ H), 4.29–3.80 (2 H, m, $C_9$ and $C_{11}$ H), 3.65 (3 H, s, $COOCH_3$), 3.30–3.05 (2 H, m, $C_{16}$ H). High-resolution MS for $C_{24}H_{29}O_5Cl$ (dehydration peak from molecular ion): calcd, *m/e* 432.17033; found, 432.16838.

**16,16,17,17-Tetradehydro-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ 9,11-Diacetate Methyl Ester (3b; R = C≡CPh).** To a stirred solution of the aldehyde **1b** (1.05 g, 2.8 mmol) in dry THF (10 mL) at −78 °C was added dropwise a solution of lithiophenylacetylene[9] (1.3 equiv) in THF. After stirring at −78 °C for 1 h, the mixture was poured into saturated aqueous $NH_4Cl$ (20 mL) and extracted with AcOEt (30 mL × 3). 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, 50 g) with 10% AcOEt in benzene to afford **3b** (R = C≡CPh; 1.097 g, 82%). The $C_{15}$ epimer could not be separated by chromatography. **3b** (R = C≡CPh): TLC $R_f$ 0.40 (AcOEt–benzene, 1:2); IR (film) 3400 (OH), 1740 (ester), 1590 (phenyl) $cm^{-1}$; NMR ($CCl_4$) $\delta$ 7.65–7.03 (5 H, m, aromatic H), 5.95–5.60 (2 H, m, trans olefinic H), 5.55–5.17 (2 H, m, cis olefinic H), 5.17–4.60 (3 H, m, $C_9$, $C_{11}$, and $C_{15}$ H), 3.60 (3 H, s, $COOCH_3$), 2.05 (3 H, s, $CH_3COO$), 2.00 (3 H, s, $CH_3COO$).

The following intermediates **3b** (R = C≡$CC_6H_4$-Cl-*m*, C≡$CC_6H_4$-Cl-*p*, and C≡COPh) were prepared from the aldehyde **1b** and the corresponding anions by the same method as applied for the preparation of **3b** (R = C≡CPh). They were mixtures of $C_{15\alpha}$- and $C_{15\beta}$-hydroxy isomers which could not be separated by chromatography.

**16,16,17,17-Tetradehydro-17-(3-chlorophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ 9,11-diacetate methyl ester (3b; R = C≡$CC_6H_4$-Cl-*m*):** 76% yield; TLC $R_f$ 0.41 (benzene–AcOEt, 2:1); IR (film) 3450 (OH), 1740 (ester), 1600 (phenyl) $cm^{-1}$; NMR ($CCl_4$) $\delta$ 7.60–7.26 (4 H, m, aromatic H), 6.00–5.68 (2 H, m, trans olefinic H), 5.65–5.28 (2 H, m, cis olefinic H), 5.28–4.60 (3 H, m, $C_9$, $C_{11}$, and $C_{15}$ H), 3.67 (3 H, s, $COOCH_3$), 2.05 (3 H, $CH_3COO$), 2.02 (3 H, s, $CH_3COO$).

**16,16,17,17-Tetradehydro-17-(4-chlorophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ 9,11-diacetate methyl ester (3b; R = C≡$CC_6H_4$-Cl-*p*):** 79% yield; TLC $R_f$ 0.42 (benzene–AcOEt 2:1); IR (film) 3430 (OH), 1740 (ester) $cm^{-1}$; NMR ($CCl_4$) $\delta$ 7.45–7.10 (4 H, m, aromatic H), 5.97–5.68 (2 H, m, trans olefinic H), 5.60–5.22 (2 H, m, cis olefinic H), 5.22–4.67 (3 H, $C_9$, $C_{11}$, and $C_{15}$ H), 3.65 (3 H, s, $COOCH_3$), 2.05 (3 H, s, $CH_3COO$), 2.01 (3 H, s, $CH_3COO$).

**16,16,17,17-Tetradehydro-17-phenoxy-18,19,20-trinorprostaglandin $F_{2\alpha}$ 9,11-diacetate methyl ester (3b; R = C≡COPh):** 95% yield; TLC $R_f$ 0.39 (benzene–AcOEt, 2:1); IR (film) 3740 (OH), 2275 (C≡C), 1740 (ester), 1590 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.68–7.00 (5 H, m, aromatic H), 6.02–5.70 (2 H, m, trans olefinic H), 5.70–5.28 (2 H, m, cis olefinic H), 5.28–4.75 (3 H, m, $C_9$, $C_{11}$, and $C_{15}$ H), 3.69 (3 H, s, $COOCH_3$), 2.10 (3 H, s, $CH_3COO$), 2.05 (3 H, s, $CH_3COO$).

**16,16,17,17-Tetradehydro-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (7).** A mixture of the compound **3b** (R = C≡CPh; 1.09 g, 2.26 mmol), anhydrous $K_2CO_3$ (830 mg, 6 mmol), and absolute MeOH (10 mL) was stirred at 40 to 45 °C for 1 h. The reaction was quenched at 5 °C by the addition of AcOH to neutralize the solution, and then the mixture was poured into water (50 mL). After extraction with AcOEt (30 mL × 3), the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to yield the $C_{15\alpha}$ alcohol **7** and the $C_{15\beta}$ isomer. Column chromatography on silica gel (Mallinckrodt, 60 g) with 30% AcOEt in benzene–40% AcOEt in cyclohexane gave **7** [$R_f$ 0.31 (AcOEt); 342 mg, 38%], the $C_{15\beta}$ isomer [$R_f$ 0.35 (AcOEt); 288 mg, 32%], and their mixture (252 mg, 28%). **7**: IR (film) 3350 (OH), 2220 (C≡C), 1740 (ester), 1605 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.60–7.10 (5 H, m, aromatic H), 5.99–5.63 (2 H, m, trans olefinic H), 5.63–5.22 (2 H, m, cis olefinic H), 5.22–4.93 (1 H, m, $C_{15}$ H), 4.33–3.82 (2 H, m, $C_9$ and $C_{11}$ H), 3.64 (3 H, s, $COOCH_3$); $[\alpha]^{18}_D$ (*c* 1.5, $CHCl_3$) +6.3°. High-resolution MS for $C_{24}H_{28}O_4$ (dehydration peak from molecular ion): calcd, *m/e* 380.19875; found, 380.20026.

**16,16,17,17-Tetradehydro-17-(3-chlorophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (8).** Column chromatography gave **8** ($R_f$ 0.31; 27%), the $C_{15}$ epimer [$R_f$ 0.36 (AcOEt); 33%], and their mixture (27%). **8**: IR (film) 3400 (OH), 1735 (ester), 1550 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.50–7.15 (4 H, m, aromatic H), 5.91–5.66 (2 H, m, trans olefinic H), 5.66–5.26 (2 H, m, cis olefinic H), 5.14–4.98 (1 H, m, $C_{15}$ H), 4.30–2.80 (2 H, m, $C_9$ and $C_{11}$ H), 3.65 (3 H, s, $COOCH_3$). High-resolution MS for $C_{24}H_{27}ClO_4$ (dehydration peak from molecular ion): calcd, *m/e* 414.15977; found, 414.15953.

**16,16,17,17-Tetradehydro-17-(4-chlorophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (9).** Column chromatography gave **9** ($R_f$ 0.32; 26%), the $C_{15}$ epimer [$R_f$ 0.38 (AcOEt); 31%], and their mixture (30%). **9**: IR (film) 3400 (OH), 2220 (C≡C), 1740 (ester), 1580 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.55–7.13 (4 H, m, aromatic H), 5.92–5.65 (2 H, m, trans olefinic H), 5.65–5.20 (2 H, m, cis olefinic H), 5.17–4.98 (1 H, m, $C_{15}$ H), 4.29–3.83 (2 H, m, $C_9$ and $C_{11}$ H), 3.65 (3 H, m, $COOCH_3$); $[\alpha]^{25}_D$ (*c* 1.7, $CHCl_3$) +15.0°. High-resolution MS for $C_{24}H_{27}ClO_4$ (dehydration peak from molecular ion): calcd, *m/e* 414.15977; found, 414.15754.

**16,16,17,17-Tetradehydro-17-phenoxy-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (19).** Column chromatography gave **19** ($R_f$ 0.32; 22%), the $C_{15}$ epimer [$R_f$ 0.40 (AcOEt); 26%], and their mixture (27%). **19**: IR (film) 3400 (OH), 2275 (C≡C), 1740 (ester), 1590 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.50–6.94 (5 H, m, aromatic H), 5.90–5.63 (2 H, m, trans olefinic H), 5.60–5.20 (2 H, m, cis olefinic H), 5.16–4.90 (1 H, m, $C_{15}$ H), 4.26–3.80 (2 H, m, $C_9$ and $C_{11}$ H), 3.64 (3 H, s, $COOCH_3$). High resolution MS for $C_{24}H_{30}O_6$ (molecular ion peak): calcd, *m/e* 414.20422; found, 212.20370.

**15-(2-Benzo[*b*]thienyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ 9,11-Diacetate Methyl Ester (3b; R = 2-**

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**Benzo[*b*]thienyl).** To a stirred solution of the aldehyde **1b** (1.70 g, 4.47 mmol) in dry THF (45 mL) at −78 °C was added dropwise a solution of 2-benzo[*b*]thienyllithium[10] (1.5 equiv) in dry THF. The mixture was stirred at −78 °C for 30 min, then −40 °C for 30 min, and poured into saturated aqueous $NH_4Cl$ (50 mL). The aqueous layer was extracted with AcOEt (50 mL × 3), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to yield a mixture of $C_{15\alpha}$- and $C_{15\beta}$-hydroxy compounds. Column chromatography on silica gel (Merck, 200 g) with 20% AcOEt in benzene afforded **3b** [R = 2-benzo[*b*]thienyl; $R_f$ 0.43 (benzene–AcOEt, 2:1); 740 mg, 32%], the $C_{15\beta}$ isomer [$R_f$ 0.51 (benzene–AcOEt, 2:1); 637 mg, 28%], and their mixture (467 mg, 20%). **3b** (R = 2-benzo[*b*]thienyl): IR (film) 3450 (OH), 1740 (ester) $cm^{-1}$; NMR ($CDCl_3$) δ 8.00–7.05 (5 H, m, benzothiophene ring H), 5.95–5.65 (2 H, m, trans olefinic H), 5.60–5.20 (2 H, m, cis olefinic H), 5.20–4.70 (3 H, m, $C_9$, $C_{11}$, and $C_{15}$ H), 3.63 (3 H, s, $COOCH_3$), 2.05 (3 H, s, $CH_3COO$), 2.02 (3 H, s, $CH_3COO$).

**15-(2-Benzofuranyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ 9,11-Diacetate Methyl Ester (3b; R = 2-Benzofuranyl).** By the same method as described previously, **3b** (R = 2-benzofuranyl) was obtained from the aldehyde **1b** and 2-benzofuranyllithium.[10] Column chromatography gave **3b** (R = 2-benzofuranyl; 28%), the $C_{15}$ epimer (29%), and their mixture (23%): TLC $R_f$ ($C_{15\alpha}$ isomer) 0.40, $R_f$ ($C_{15\beta}$ isomer) 0.48 (benzene–AcOEt, 2:1); **3b**: IR (film) 3440 (OH), 1735 (ester) $cm^{-1}$; NMR ($CDCl_3$) δ 7.80–7.20 (4 H, m, aromatic H), 6.69 (1 H, s, furan ring H), 6.10–5.80 (2 H, m, trans olefinic H), 5.70–4.75 (5 H, m, $C_9$, $C_{11}$, $C_{15}$ H, and cis olefinic H), 3.68 (3 H, s, $COOCH_3$), 2.10 (3 H, s, $CH_3COO$), 2.05 (3 H, s, MeCOO).

**15-(2-Benzo[*b*]thienyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ Methyl Ester (10).** A mixture of the compound **3b** (R = 2-benzo[*b*]thienyl; 130 mg, 0.25 mmol), anhydrous $K_2CO_3$ (70 mg, 0.55 mmol), and absolute MeOH (2.5 mL) was stirred at 50 °C for 30 min and then neutralized by the addition of AcOH at 5 °C. Water (2 mL) was added and the mixture was extracted with AcOEt (10 mL × 3). The combined 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 (Mallinckrodt, 5 g) with 40% AcOEt in cyclohexane to yield **10** (96 mg, 80%): TLC $R_f$ 0.28 (AcOEt); IR (film) 3370 (OH), 1730 (ester) $cm^{-1}$; NMR ($CDCl_3$) δ 7.60–7.10 (5 H, m, benzothiophene ring H), 6.10–4.90 (5 H, m, olefinic and $C_{15}$ H), 4.28–3.78 (2 H, m, $C_9$ and $C_{11}$ H), 3.62 (3 H, s, $COOCH_3$). High-resolution MS for $C_{24}H_{30}O_5S$ (molecular ion peak): calcd, *m/e* 430.18138; found, 430.18144.

**15-(2-Benzofuranyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ Methyl Ester (11).** By the same method as applied for the preparation of **10**, the analogue **11** was obtained in 85% yield using the compound **3b** (R = 2-benzofuranyl). **11**: TLC $R_f$ 0.29 (AcOEt); IR (film) 3360 (OH), 1735 (ester) $cm^{-1}$; NMR ($CDCl_3$) δ 7.70–7.08 (4 H, m, benzofuranyl $C_4$, $C_5$, $C_6$, and $C_7$ H), 6.63 (1 H, s, benzofuranyl $C_3$ H), 5.95–5.58 (2 H, m, trans olefinic H), 5.53–5.10 (3 H, m, cis olefinic and $C_{15}$ H), 4.28–3.80 (2 H, m, $C_9$ and $C_{11}$ H), 3.64 (3 H, s, $COOCH_3$). High-resolution MS for $C_{24}H_{28}O_5$ (dehydration peak from molecular ion) calcd, *m/e* 396.19366; found, 396.19278.

**15-(1-Indenyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ Methyl Ester (12).** To a stirred solution of indene (174 mg, 1.5 mmol) in dry THF (7.8 mL) at −78 °C was added 1.2 M *n*-butyllithium in hexane (1.25 mL, 1.5 mmol). After stirring at −78 °C for 30 min, to this anion solution[11] was added at −78 °C a solution of the aldehyde **1a** (100 mg, 0.34 mmol) in dry THF (3 mL). The mixture was stirred at −78 °C for 1 h, poured into saturated aqueous $NH_4Cl$ (10 mL), and extracted with AcOEt (10 mL × 3). The extracts were washed with water and then brine, dried over $MgSO_4$, and concentrated in vacuo to provide a mixture of $C_{15\alpha}$- and $C_{15\beta}$-hydroxy isomers. Chromatography on silica gel (Mallinckrodt, 10 g) with 30% AcOEt in benzene afforded **12** [$R_f$ 0.25 (AcOEt); 43 mg, 32%], the $C_{15\beta}$ isomer [$R_f$ 0.40 (AcOEt); 40 mg, 30%], and their mixture (17 mg, 13%). **12**: IR ($CHCl_3$) 3400 (OH), 1740 (ester) $cm^{-1}$; NMR ($CDCl_3$) δ 7.70–6.40 (6 H, m, indenyl H), 5.70–5.10 (4 H, m, olefinic H), 4.75–4.28 (1 H, m, $C_{15}$ H), 4.28–3.50 (3 H, m, $C_9$, $C_{11}$, and indenyl $C_1$ H), 3.67 (3 H, s, $COOCH_3$). High-resolution MS for $C_{25}H_{30}O_4$ (dehydration peak from molecular ion): calcd, *m/e* 394.21440; found, 394.21272.

**17-Methyl-17-phenyl-17-sila-19,20-dinorprostaglandin $F_{2\alpha}$ Methyl Ester (13).** The Grignard reaction was started by the addition of a small amount of dimethylchloromethylphenylsilane and a catalytic amount of methyl iodide to a stirred mixture of magnesium (236 mg, 9.85 mmol) and dry ether (10 mL). To this mixture was added a solution of dimethylchloromethylphenylsilane (1.812 g, 9.85 mmol) in dry ether (10 mL) at such a rate that a moderated reflux was maintained. After the addition had been completed, the solution was refluxed for 30 min. The Grignard solution was then cooled to room temperature and was added to a stirred solution of **1a** (585 mg, 1.97 mmol) in dry THF (40 mL) cooled in an ice–water bath. The mixture was stirred at about 5 °C for 1 h, poured into cold aqueous $NH_4Cl$ (50 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 (Mallinckrodt, 60 g) with 30% AcOEt in cyclohexane to give **13** [350 mg, 40%; $R_f$ 0.32 (AcOEt)], the $C_{15\beta}$ hydroxy isomer [233 mg, 26%; $R_f$ 0.42 (AcOEt)], and their mixture (114 mg, 13%) **13**: IR (film) 3350 (OH), 1740 (ester) $cm^{-1}$; NMR ($CDCl_3$) δ 7.63–7.15 (5 H, m, aromatic H), 5.65–5.18 (4 H, m, olefinic H), 4.40–3.70 (3 H, m, $C_9$, $C_{11}$, and $C_{15}$ H), 3.63 (3 H, s, $COOCH_3$), 0.20 (6 H, s, Si-$CH_3$). High-resolution MS for $C_{25}H_{36}O_4Si$ (dehydration peak from molecular ion): calcd, *m/e* 428.23826; found, 428.23931.

**16ξ-Carbomethoxy-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Methyl Ester (14).** To a stirred solution of phenoxyacetic acid methyl ester (1.455 g, 9.45 mmol) in dry THF (20 mL) at −78 °C was added dropwise a solution of lithium diisopropylamide (9.45 mmol) in dry THF. The mixture was stirred at −78 °C for 30 min and then a solution of **1a** (800 mg, 2.7 mmol) in dry THF (30 mL) was added. The mixture was stirred at −78 °C for 1 h, poured into cold aqueous $NH_4Cl$ (100 mL), and extracted with AcOEt (50 mL × 3). The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography on silica gel (Mallinckrodt, 70 g) with 30% AcOEt in benzene afforded **14** [400 mg, 32%; $R_f$ 0.25 (AcOEt)], the $C_{15\beta}$-hydroxy isomer [362 mg, 29%; $R_f$ 0.34 (AcOEt)], and their mixture (312 mg, 25%). **14**: IR (film) 3380 (OH), 1735 (ester), 1590 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) δ 7.40–6.78 (5 H, m, aromatic H), 5.88–5.60 (2 H, m, trans olefinic H), 5.60–5.17 (2 H, m, cis olefinic H), 4.83–4.40 (2 H, m, $C_{15}$ and $C_{16}$ H), 4.30–3.82 (2 H, m, $C_9$ and $C_{11}$ H), 3.75 (3 H, s, $C_{16}$ $COOCH_3$), 3.66 (3 H, s, $C_1$ $OOCH_3$). High-resolution MS for $C_{25}H_{32}O_7$ (dehydration peak from molecular ion): calcd, *m/e* 444.21828; found, 444.21800.

**15-(2-Methoxyphenyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ Methyl Ester (15).** To a solution of **1a** (540 mg, 1.83 mmol) in dry THF (35 mL) at 5 °C was added dropwise a solution of 2-methoxyphenylmagnesium bromide (3.5 equiv) in THF which had been prepared by the Grignard reaction of *o*-bromoanisole. The mixture was stirred at 5 °C for 50 min. The reaction was worked up as described above to yield the crude **15**, which was purified by column chromatography on silica gel (Mallinckrodt, 30 g) with 40% AcOEt in cyclohexane to give **15** (604 mg, 82%). The $C_{15\beta}$-hydroxy isomer could not be separated by chromatography. **15**: $R_f$ 0.28 (AcOEt); IR (film) 3380 (OH), 1738 (ester), 1595 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) δ 7.50–6.78 (4 H, m, aromatic H), 6.06–5.17 (4 H, m, olefinic H), 4.87 (3 H, s, $CH_3OC_6H_4$), 4.30–3.93 (2 H, m, $C_9$ and $C_{11}$ H), 3.67 (3 H, s, $COOCH_3$). High-resolution MS for $C_{23}H_{30}O_5$ (dehydration peak from molecular ion): calcd, *m/e* 386.20931; found, 386.21085.

**16,16-Ethylene-16-(phenylthio)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester [3c; R = 1-(Phenylthio)cyclopropyl].** To a stirred solution of **1c** (1.1 g, 3.3 mmol) in dry THF (40 mL) at −78 °C was added dropwise a solution of 1-(phenylthio)cyclopropyllithium[14] (2.5 equiv) in dry

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THF. The mixture was stirred at −78 °C for 2 h. The reaction was quenched by the addition of acetic acid (1 mL) and worked up as described above to yield a mixture of $C_{15\alpha}$- and $C_{15\beta}$-hydroxy isomers. Column chromatography on silica gel (Merck, 60 g) with 50% AcOEt in benzene provided the desired **3c** [R = 1-(phenylthio)cyclopropyl; 585 mg, 37% $R_f$ 0.50 (AcOEt)], the $C_{15\beta}$-hydroxy isomer [490 mg, 31%; $R_f$ 0.62 (AcOEt)], and their mixture (238 mg, 15%). **3c**: IR (film) 3450 (OH), 1740 (ester), 1585 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) δ 7.70–7.00 (5 H, m, aromatic H), 6.00–4.90 (5 H, olefinic and $C_9$ H), 3.65 (3 H, s, $COOCH_3$), 2.05 (3 H, s, $CH_3COO$), 1.30–0.80 (4 H, m, cyclopropyl H).

**16,16-Ethylene-16-(phenylthio)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Methyl Ester (16).** **16**: $R_f$ 0.29 (AcOEt); IR ($CHCl_3$) 3400 (OH), 1730 (ester), 1585 (phenyl) $cm^{-1}$; NMR ($CDCl_3$) δ 7.60–7.05 (5 H, m, aromatic H), 5.80–5.15 (4 H, m, olefinic H), 4.30–3.76 (3 H, m, $C_9$, $C_{11}$, and $C_{15}$ H), 3.64 (3 H, s, $COOCH_3$), 1.18–0.85 (4 H, m, cyclopropyl H). High-resolution MS for $C_{25}H_{32}O_4S$ (dehydration peak from molecular ion): calcd, $m/e$ 428.20212; found, 428.20375.

**16-(Cyclohex-1-enylthio)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester 11-(Tetrahydropyran-2-yl ether) [3e, R = (Cyclohex-1-enylthio)methyl].** To a solution of 1-(methylthio)cyclohexene[15] (141 mg, 1.1 mmol) in dry THF (2 mL) at −78 °C was added dropwise *n*-butyllithium (1.1 equiv) in hexane. After the solution was stirred at −78 °C for 10 min, the temperature was raised gradually up to 5 °C. The mixture was stirred at 5 °C for 3 h, then warmed to 20 °C, and was added to a solution of the aldehyde **1e** (422 mg, 1.0 mmol) in dry THF (10 mL) cooled at −78 °C. After stirring at −78 °C for 1 h, the reaction was quenched by the addition of AcOH (0.1 mL). The mixture was poured into cold water (50 mL) and extracted with AcOEt. 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, 50 g) with 30% AcOEt in benzene to give **3e** [R = (cyclohex-1-enylthio)methyl; 216 mg, 39%; $R_f$ 0.50 (AcOEt–benzene, 1:2)], the $C_{15\beta}$-hydroxy isomer [200 mg, 36%; $R_f$ 0.55 (AcOEt–benzene, 1:2)], and their mixture (108 mg, 20%). **3e** [R = (cyclohex-1-enylthio)methyl]: IR (film) 3430 (OH), 1737 (ester) $cm^{-1}$; NMR ($CCl_4$) δ 5.78–5.45 (3 H, m, olefinic H in cyclohexene ring and trans olefinic H), 5.45–5.15 (2 H, m, cis olefinic H), 5.01 (1 H, m, $C_9$ H), 4.69–4.47 (1 H, m, –OCHO–), 3.62 (3 H, s, $COOCH_3$), 2.01 (3 H, s, $CH_3COO$).

**16-(Cyclohex-1-enylthio)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 9-Acetate Methyl Ester [3c, R = (Cyclohex-1-enylthio)methyl].** A mixture of the corresponding **3e** (550 mg, 1 mmol), 65% aqueous AcOH (10 mL), and THF (1 mL) was stirred at 40 °C for 1 h and then diluted with AcOEt (50 mL). The mixture 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 (Merck, 20 g) with 10% benzene in AcOEt to give **3c** [R = (cyclohex-1-enylthio)methyl; 326 mg, 70% yield): $R_f$ 0.28 (AcOEt–benzene, 2:1); IR (film) 3390 (OH), 1736 (ester) $cm^{-1}$; NMR ($CCl_4$) δ 5.82–5.17 (5 H, m, olefinic H), 5.01 (1 H, m, $C_9$ H), 3.64 (3 H, s, $COOCH_3$), 2.01 (3 H, s, $CH_3COO$).

**16-(Cyclohex-1-enylthio)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Methyl Ester (17).** **17** (361 mg, 85% yield) was obtained from the corresponding **3c** (466 mg, 1.0 mmol), anhydrous $K_2CO_3$ (500 mg, 3.62 mmol), and MeOH (12 mL) by the same method as applied for the preparation of **7**. **17**: $R_f$ 0.26 (AcOEt); IR (film) 3340 (OH), 1735 (ester), 975 (trans olefin) $cm^{-1}$; NMR ($CDCl_3$) δ 5.79 (1 H, m, olefinic H in cyclohexene ring), 5.52–5.20 (4 H, m, olefinic H), 4.27–3.80 (3 H, m, $C_9$, $C_{11}$, and $C_{15}$ H), 3.68 (3 H, s, $COOCH_3$). High-resolution MS for $C_{23}H_{34}O_4S$ (dehydration peak from molecular ion): calcd, $m/e$ 406.21777; found, 406.21483.

**16-Carbomethoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Methyl Ester (18).** To a stirred solution of **1d** (1.1 g, 2.9 mmol) in dry THF (30 mL) at −78 °C was added dropwise a solution of carbo-*tert*-butoxymethyllithium[13] (2.5 equiv) in dry THF. The mixture was stirred at −78 °C for 1 h, then poured into saturated aqueous $NH_4Cl$ (50 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, 60 g) with 25% AcOEt in benzene to give **20** [474 mg, 39%; $R_f$ 0.59 (AcOEt–benzene, 2:1)], the $C_{15}$-hydroxy isomer [437 mg, 35%; $R_f$ 0.63 (AcOEt–benzene, 2:1)], and their mixture (270 mg, 22%). **20**: IR (film) 3430 (OH), 1725 (ester) $cm^{-1}$; NMR ($CDCl_3$) δ 5.75–5.20 (4 H, m, olefinic H), 4.75–4.50 (1 H, m, OCHO), 3.65 (3 H, s, $COOCH_3$), 1.50 (9 H, s, COOBu-*t*).

A mixture of **20** (400 mg, 0.8 mmol), trifluoroacetic acid (7 mL), and THF (3 mL) was stirred at 25 °C for 15 min and then concentrated in vacuo. The residue was column chromatographed on silica gel (Merck, 15 g) with 30% benzene in AcOEt to give **21** (187 mg, 65% yield): $R_f$ 0.18 (AcOEt–HCOOH, 80:1); IR ($CHCl_3$) 3370 (OH), 1725 (ester and acid) $cm^{-1}$; NMR ($CDCl_3$ + acetone-$d_6$) δ 6.10–5.00 (8 H, m, olefinic H, OH and COOH), 4.70–4.30 (1 H, m, $C_{15}$ H), 3.65 (3 H, s, $COOCH_3$).

A mixture of **21** (100 mg, 0.28 mmol), phenol (52 mg, 5.6 mmol), dicyclohexylcarbodiimide (174 mg, 0.84 mmol), and $CH_2Cl_2$ (9 mL) was stirred at about 5 °C for 2 h and concentrated in vacuo. The residue was column chromatographed on silica gel (Mallinckrodt, 7 g) with 30% AcOEt in cyclohexane to provide **18** (36 mg, 30% yield): $R_f$ 0.25 (AcOEt); IR ($CCl_4$) 3360 (OH), 1738 (ester) $cm^{-1}$; NMR ($CCl_4$) δ 7.50–6.90 (5 H, m, aromatic H), 5.78–5.10 (4 H, m, olefinic H), 4.80–4.40 (1 H, m, $C_{15}$ H), 4.25–3.73 (2 H, m, $C_9$ and $C_{11}$ H), 3.64 (3 H, s, $COOCH_3$), 2.87–2.63 (2 H, d, $J$ = 7 Hz, $C_{16}$ H). High-resolution MS for $C_{24}H_{28}O_5$ (didehydration peak from molecular ion): calcd, $m/e$ 396.19366; found, 396.19234.

**Biological Procedure. Antinidatory Effect.** Wistar female rats (9 weeks old, body weight 180–200 g) were cohabited with males overnight, and every morning mating was determined microscopically by the presence of sperm in the vagina. These rats were used for the experiments. A stock solution of prostaglandin analogues was prepared as follows: they were dissolved in 10% EtOH–0.4% Tween 80 in physiological saline solution to a concentration of 1 mg/mL. The stock solution itself or the dilute solution with physiological saline solution (prepared at use) was used for administration.

The day sperms were observed in the vaginal smear was deemed day 0 of pregnancy, and three to eight doses of each prostaglandin analogue were subcutaneously injected twice daily (10:00 and 16:00 h) for 3 days on days 3, 4, and 5. Antinidatory effect was evaluated on day 11. All animals (5–20 cases/1 dose) were killed by exsanguination on day 11, and the numbers of implantation sites were recorded. The case of no implantation site was evaluated to be effective, and the case of partial antinidation was ineffective. The antinidation rate was expressed as the percentage of effective cases against the treated cases. A dose–response curve of each prostaglandin analogue was drawn in order to estimate the 50% antinidation value. The relative activity to that of prostaglandin $F_{2\alpha}$ was exhibited by comparison of the dose showing 50% antinidation.

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