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15,15-Ketals of Natural Prostaglandins and Prostaglandin Analogues. Synthesis and Biological Activities[1]

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The synthesis is described of new 15,15-ethylene ketals of natural prostaglandins and prostaglandin analogues. Especially the crystalline trisamine salt of the 15,15-ethylene ketal of 15-dehydro-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ is a very active inducer of luteolysis in laboratory animals and cattle.

For the biological activity of natural prostaglandins, the presence of a 15α-hydroxy group is essential, whereas the corresponding 15β-hydroxy compounds, e.g., 15β-hydroxyprostaglandin E_1, show drastically diminished biological activities.[2]

However, in certain analogues, e.g., 15-methyl- or 16-phenoxy-ω-tetranorprostaglandins, the 15β-hydroxy epimers are themselves often biologically active.[3,4]

Since the 15-methyl ether of $PFG_{2\alpha}$ methyl ester shows a two to three times stronger abortifacient activity in the pregnant hamster than $PGF_{2\alpha}$ methyl ester,[5] the presence of a free 15-hydroxy group is apparently not essential for the biological activity in vivo.

It seemed therefore logical to us that the combination of (a) the sometimes considerable biological activity of 15β-hydroxy compounds with (b) the biological activity of 15-methyl ethers would lead to the conclusion that the prostaglandin 15-ketals, e.g., 15,15-ethylenedioxy- or 15,15-dimethoxyprostaglandins, might also possess interesting biological properties. In all conformations of these new analogues, at least one ketal oxygen would always be available for the interaction with the receptor molecules.

It should be noted here that the active form of 15-keto prostaglandins like 15-keto prostaglandin $F_{2\alpha}$, which is formed during metabolism, might act in the hydrated form (15,15-dihydroxyprostaglandins) since they still cause pronounced contractions of the smooth muscles of the guinea-pig ileum as well as of the gerbil colon.[6]

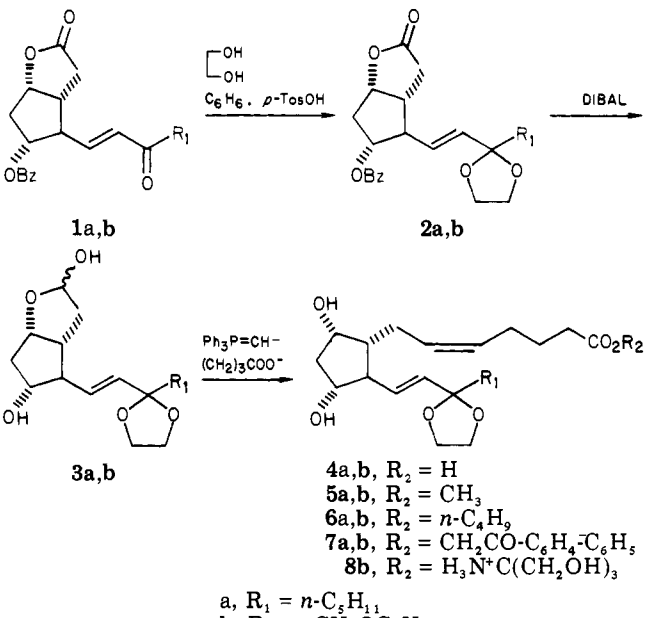
We have therefore synthesized a series of 15-ketals of natural prostaglandins and prostaglandin analogues which are readily available by ketalization of the unsaturated keto lactones (compare Scheme I). The chiral center at C-15 in natural PG's is thereby eliminated, resulting in a simplification of the Corey synthetic scheme[7] (Scheme I).

Chemistry. Starting from unsaturated ketones 1[8,9] (Scheme I) standard ketalization with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid gave the ketals **2** in good yields. Reduction of the lactones and simultaneous removal of the benzoate with diisobutylaluminum hydride (DIBAL) afforded the lactols **3** which were transformed by Wittig reaction to the 15-deoxy-15,15-ethylenedioxyprostaglandins **4**. Esterification with diazomethane and butyl bromide–silver oxide yielded the methyl esters **5** and the butyl esters **6**. Treatment of **4** with *p*-phenylphenacyl bromide in the presence of triethylamine afforded the esters **7**.[10]

The free acid **4b** afforded on neutralization with tris(hydroxymethyl)aminomethane the crystalline tris salt **8b**.

In an analogous way, starting from known 15-ketones, other new 15,15-ethylene ketals in Table II, e.g., substituted 16-phenoxy- and 15- or 17-arylprostaglandin analogues, were synthesized, and the structure of the inter-

Scheme I

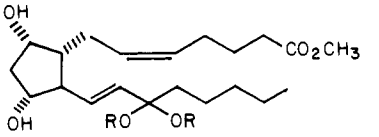


1a,b **2a,b** **3a,b**

4a,b, R_2 = H
5a,b, R_2 = CH_3
6a,b, R_2 = n-C_4H_9
7a,b, R_2 = CH_2CO-C_6H_4-C_6H_5
8b, R_2 = $H_3N^+C(CH_2OH)_3$

a, R_1 = n-C_5H_{11}
b, R_1 = $-CH_2OC_6H_5$

Chart I



9, R,R = $-CH_2CH_2CH_2-$
10, R,R = $-CH_2C(CH_3)_2CH_2-$
11, R = $-CH_3$

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Table I. Relative Activities of 15-Ketals of Natural Prostaglandins

Compd	Isolated rat uterus[a]	Isolated guinea-pig ileum[a]	Abortion rat
4a	5-10 × $F_{2\alpha}$		1 × $F_{2\alpha}$[b]
5a	5 × $F_{2\alpha}$	0.1 × $F_{2\alpha}$	1 × $F_{2\alpha}$
9	<0.1[c] × $F_{2\alpha}$		<0.3 × $F_{2\alpha}$
10	<<0.1[d] × $F_{2\alpha}$		<0.3 × $F_{2\alpha}$
11	0.1 × $F_{2\alpha}$	<<0.1 × $F_{2\alpha}$	<0.1 × $F_{2\alpha}$
17a	1 × $F_{2\alpha}$		<0.3 × $F_{2\alpha}$

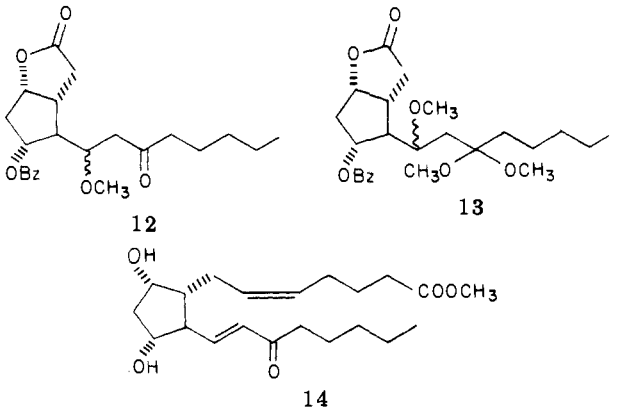
[a] Compared with a standard solution of $PGF_{2\alpha}$. [b] $PGF_{2\alpha}$ was active in this standard test at about 0.3-1 mg/rat/day. [c] Slightly less active than one-tenth of $PGF_{2\alpha}$. [d] Inactive at more than ten times the threshold dose of $PGF_{2\alpha}$.

mediates and the final PG analogues were characterized by physical methods and analysis.

In order to evaluate the influence of different ketal moieties in natural prostaglandins on the biological activity, we prepared the ketals **9** and **10** in an analogous way (Chart I).

To synthesize the dimethyl ketal **11** (Chart II) we first attempted to prepare the 15,15-dimethyl ketal of **1a** by heating **1a** with methanol in the presence of *p*-toluenesulfonic acid but obtained only a mixture of the 1,4-addition products **12** and **13**. Since dimethyl ketals are usually less stable than the corresponding ethylene or propylene ketals and may not survive the DIBAL reduction and Wittig reaction, we converted the corresponding 15-dehydroprostaglandin $F_{2\alpha}$ methyl ester **14**, which is readily available by hydrolysis of **5a**, into **11** in 24% yield at room temperature by treatment with methanol–trimethyl orthoformate in the presence of traces of hydrochloric acid.

Chart II



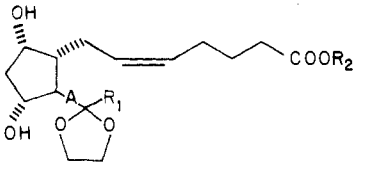
The 13,14-dihydro-15-ethylene ketal 1-methyl esters **17** were prepared according to Scheme II starting from **15** which are readily available by hydrogenation of **1**.

Results and Discussion

a. Variation of the Ketal Moiety. The antifertility data of Table I show that the 15,15-ethylene ketals of the $F_{2\alpha}$ series (**4a** and **5a**) have the highest biological (luteolytic) activities. Variation of this ketal moiety leads to a decrease in luteolytic activity. The lower biological efficacy of **9** and **10** might be due to steric hindrance by the bulky ketal groups. Saturating the 13,14 double bond as in **17a** and **17b** leads to a decrease in abortive activity without diminishing the uterotropic activity.

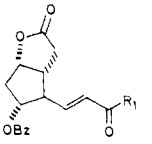
b. Variation of the Lower Side Chain. From all the new prostaglandin analogues described in Table II, the 16-phenoxy-ω-tetranorprostaglandin 15,15-ethylene ketals have the highest abortive activity in rats.

Table II. Relative Activities of 15,15-Ethylene Ketals of PGF Analogues with Modified Lower Side Chain

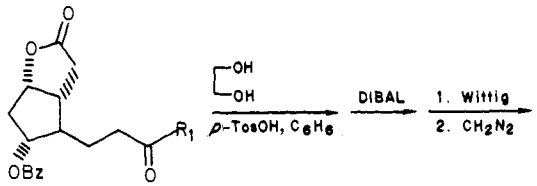


Compd	R_1	R_2	A	Isolated rat uterus[a]	Isolated guinea-pig ileum[a]	Abortion rat	Ref[b]
4b	$-CH_2O-C_6H_5$	H	$-C(H)=C(H)-$	10 × $F_{2\alpha}$	0.1 × $F_{2\alpha}$	10-30 × $F_{2\alpha}$	9
5b	$-CH_2O-C_6H_5$	CH_3	$-C(H)=C(H)-$	≥10 × $F_{2\alpha}$	<0.1 × $F_{2\alpha}$	100 × $F_{2\alpha}$	9
6b	$-CH_2O-C_6H_5$	n-C_4H_9	$-C(H)=C(H)-$	10 × $F_{2\alpha}$		30 × $F_{2\alpha}$	9
8b	$-CH_2O-C_6H_5$	$\overset{+}{N}H_3C(CH_2OH)_3$	$-C(H)=C(H)-$	>10 × $F_{2\alpha}$			9
17b	$-CH_2O-C_6H_5$	CH_3	$-CH_2CH_2-$	≥10 × $F_{2\alpha}$		10 × $F_{2\alpha}$	9
18	$-CH_2O-C_6H_4$-4-F	CH_3	$-C(H)=C(H)-$	10 × $F_{2\alpha}$		10 × $F_{2\alpha}$	9
19	$-CH_2O-C_6H_4$-3-CF_3	CH_3	$-C(H)=C(H)-$	≥10 × $F_{2\alpha}$	<0.1 × $F_{2\alpha}$	10 × $F_{2\alpha}$	9
20	$-CH_2CH_2-C_6H_5$	CH_3	$-C(H)=C(H)-$	>10 × $F_{2\alpha}$		30 × $F_{2\alpha}$	12
21	$-C_6H_4$-4-Cl	CH_3	$-C(H)=C(H)-$	~10 × $F_{2\alpha}$		10 × $F_{2\alpha}$	13

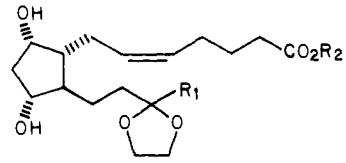
[a] See footnote *a* in Table I. [b] The references refer to the origin of the starting keto lactone



Scheme II



15a,b



16a,b, $R_2 = H$
17a,b, $R_2 = CH_3$

a, $R_1 = n\text{-}C_5H_{11}$
b, $R_1 = -CH_2OC_6H_5$

The esters **5b** and **6b** showed a higher activity (in vivo) in the pregnant rat than the free carboxylic acid **4b**. **5b** exhibited a 100 times stronger abortifacient activity than $PGF_{2\alpha}$ and a diminished activity on other smooth muscles like guinea-pig ileum in vitro. However, from a practical point of view the water-soluble sodium salt of the free acid **4b** and especially the water-soluble and crystalline tris salt **8b** seem to be the most interesting compounds. They show excellent efficacy to induce luteolysis and have been used in aqueous (saline) solution to synchronize estrus in cattle and heifers efficiently.[11]

Experimental Section

Chemistry. The IR spectra were measured in $CHCl_3$ with a Perkin-Elmer G 157 instrument, if not indicated otherwise, and the NMR spectra with a Varian HA-100 instrument. The melting points were determined with a Kofler melting point microscope and are not corrected. Column chromatography was carried out on E. Merck silica gel 60, particle size 0.063–0.2 mm.

(3a*R*,4*R*,5*R*,6a*S*)-5-Benzoyloxy-4-[(*E*)-3,3-ethylenedioxy-1-octenyl]perhydrocyclopenta[*b*]furan-2-one (2a). 1a[8] (15.38 g, 41.52 mmol), 44.5 mL of ethylene glycol, 237 mg of *p*-toluenesulfonic acid hydrate, and 1080 mL of benzene were heated for 7 h in a Dean-Stark apparatus. After cooling and extracting with saturated $NaHCO_3$ and finally saturated NaCl solution, the benzene solution was dried ($MgSO_4$) and evaporated in vacuo to give 15.26 g (97%) of crystalline **2a**. Recrystallization from CH_2Cl_2–hexane afforded the analytical sample: mp 91–93 °C; $[\alpha]^{22}_D$ −80.2° (*c* 1.0, $CHCl_3$); IR 1770, 1715, 1602 cm^{-1}; NMR (Me_2SO-d_6) δ 3.71 (4 H, m, $-OCH_2CH_2O-$). Anal. Calcd for $C_{24}H_{30}O_6$ (414.48): C, 69.55; H, 7.30. Found: C, 69.5; H, 7.46.

(2*RS*,3a*R*,4*R*,5*R*,6a*S*)-4-[(*E*)-3,3-Ethylenedioxy-1-octenyl]perhydrocyclopenta[*b*]furan-2,5-diol (3a). To a solution of 7.54 g (18.19 mmol) of **2a** in 200 mL of absolute toluene, 74 mL of a 20% solution of diisobutylaluminum hydride (DIBAL) in toluene was added dropwise at −70 °C under argon. After stirring 30 min at −70 °C, the excess reagent was destroyed by addition of a few drops of 2-propanol and the reaction mixture warmed up to 0 °C. Water (37 mL) was added and the mixture stirred at room temperature until the gel-like mass had turned crystalline (ca. 30 min). The mixture was then filtered and washed with CH_2Cl_2, and the combined organic phase was evaporated in vacuo. Chromatography on 100 g of silica gel and elution with hexane–ethyl acetate gave **3a** (5.20 g, 91%) as a colorless oil: $[\alpha]_D^{22}$ −6.0° (*c* 1.0, $CHCl_3$); IR 3600, 3410, 2955, 2875, 978, 948, 915 cm^{-1}.

15-Deoxy-15,15-ethylenedioxyprostaglandin $F_{2\alpha}$ (4a). A solution of dimsylsodium was prepared from 6.0 g (125 mmol) of a 50% dispersion of NaH in paraffin oil and 120 mL of Me_2SO at 70–75 °C (under argon) and added dropwise to a solution of 28.37 g (64 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in 125 mL of Me_2SO. After 30 min of stirring at 24 °C, a solution of 5 g (16 mmol) of **3a** in 60 mL of Me_2SO was added, and the reaction mixture was stirred 16 h at 24 °C. After dilution with ice-cold NaCl solution and extraction with ether, the aqueous phase was acidified with a 10% aqueous solution of citric acid to pH 5. After extraction with hexane–ether (1:1), washing with saturated NaCl solution, drying ($MgSO_4$), and evaporation in vacuo the residue (4.66 g) was chromatographed on a column of 200 g of SiO_2. Elution with mixtures of ether–dioxane gave 1.62 g (26%) of **4a** as a yellowish oil: IR 1710 cm^{-1}; NMR (Me_2SO-d_6) δ 0.85 (3 H, t, *J* = 7 Hz, CH_3CH_2), 3.65–4.00 (6 H, m, $-OCH_2CH_2O-$, 2CHO), 5.2–5.8 [4 H, m, 2(−CH=CH−)]. Anal. Calcd for $C_{22}H_{36}O_6$ (396.53): C, 66.64; H, 9.15. Found: C, 66.21; H, 9.10.

15-Deoxy-15,15-ethylenedioxyprostaglandin $F_{2\alpha}$ Methyl Ester (5a). To a solution of 1.62 g (4.06 mmol) of **4a** in 20 mL of CH_3OH a slight excess of an ethereal diazomethane solution was added dropwise at 0 °C. After evaporation in vacuo the residue was filtered with ether–dioxane (9:1) over 25 g of SiO_2 to give 1.52 g (91%) of oily **5a**: IR 1730 cm^{-1}; NMR δ 3.58 (3 H, s, CH_3O), 3.83 (4 H, m, $-OCH_2CH_2O-$).

15-Deoxy-15,15-ethylenedioxyprostaglandin $F_{2\alpha}$ 4-Phenylphenacyl Ester (7a). To a solution of 200 mg (0.50 mmol) of **4a** and 56 mg (0.55 mmol) of triethylamine in 4 mL of acetone, 152 mg (0.55 mmol) of *p*-phenylphenacyl bromide was added and the mixture stirred 18 h at 24 °C. After dilution with H_2O, extraction with ether, and drying ($MgSO_4$), evaporation gave the crude ester which was chromatographed on 30 g of SiO_2 with ether–dioxane (1–5%) to give 140 mg (47%) of crude **7a**. Recrystallization from hexane–CH_2Cl_2 afforded 105 mg of pure **7a**: mp 77–79 °C; IR 1730, 1680 cm^{-1}; NMR (Me_2SO-d_6) δ 3.5–4.1 (6 H, m, $-OCH_2CH_2O-$, 2CHO), 7.35–8.12 (9 H, m, aromatic H); UV λ_{max} 284 nm (ε 23 600). Anal. Calcd for $C_{36}H_{46}O_7$ (590.76): C, 73.19; H, 7.85. Found: C, 73.75; H, 8.22.

15-Deoxy-15,15-(propylene-1,3-dioxy)prostaglandin $F_{2\alpha}$ Methyl Ester (9). (3a*R*,4*R*,5*R*,6a*S*)-5-(4-Phenylbenzoyloxy)-4-[(*E*)-3-oxooctenyl]perhydrocyclopenta[*b*]furan-2-one[7] (1 g, 2.24 mmol) was ketalized with 1,3-propylenediol in analogy to the preparation of **2a** to give 770 mg (68%) of the 15,15-propylene ketal lactone: mp 84–85 °C. Anal. Calcd for $C_{31}H_{36}O_6$ (504.63): C, 73.78; H, 7.19. Found: C, 73.88; H, 6.97. After DIBAL reduction, Wittig reaction, and esterification with CH_2N_2 (as described during the preparation of **4a** and **5a**), **9** was obtained as an oil: IR (neat) 1738, 1625 cm^{-1}; NMR ($CDCl_3$) δ 3.64 (3 H, s, CH_3OCO), 3.72–4.30 (6 H, m, $-OCH_2CH_2CH_2O-$, 2CHO).

15-Deoxy-15,15-[(2,2-dimethyl)trimethylene-1,3-dioxy]prostaglandin $F_{2\alpha}$ Methyl Ester (10). (3a*R*,4*R*,5*R*,6a*S*)-5-(4-Phenylbenzoyloxy)-4-[(*E*)-3-oxooctenyl]perhydrocyclopenta[*b*]furan-2-one[7] (1.6 g, 3.58 mmol) was ketalized with 1 g of 2,2-dimethylpropane-1,3-diol and 30 mg of *p*-toluenesulfonic acid in 70 mL of C_6H_6 in a Dean-Stark apparatus to furnish 1.35 g (71%) of crystalline ketal, mp 104–105 °C, which was converted by DIBAL reduction, Wittig reaction, and esterification with CH_2N_2 into oily **10**: IR (neat) 1735 cm^{-1}; NMR (Me_2SO-d_6) δ 0.62 (3 H, s, CH_3C), 0.82 (3 H, t, *J* = 7 Hz, CH_3CH_2), 1.05 (3 H, s, CH_3C-), 3.54 (3 H, s, CH_3OCO), 3.40–4.05 (6 H, m, OCH_2CCH_2O-, 2CHO−).

15-Deoxy-15,15-dimethoxyprostaglandin $F_{2\alpha}$ Methyl Ester (11). 15-Dehydroprostaglandin $F_{2\alpha}$ methyl ester (14) (220 mg, 0.60 mmol) in 4 mL of $CHCl_3$ and 4 mL of CH_3OH was reacted for 18 h with 2 mL of methyl orthoformate and 0.2 μL of concentrated HCl. After addition of 0.1 mL of triethylamine and evaporation, the residue was chromatographed on a column of 10 g of SiO_2. On elution with hexane–ether mixtures and finally with ether–1% dioxane, **11** (58 mg) followed by a mixture of **11** and **14** (65 mg) was obtained. **11** gave IR 1730 cm^{-1}.

15-Dehydroprostaglandin $F_{2\alpha}$ Methyl Ester (14). A solution of 800 mg (1.95 mmol) of **5a** in 30 mL of methanol was stirred for 1 h with 0.5 mL of 10% H_2SO_4, poured on ice, and extracted with CH_2Cl_2. After washing with $NaHCO_3$ and NaCl solutions, drying ($MgSO_4$), and evaporation, the residue was chromatographed with hexane–ethyl acetate (1:1) on SiO_2 to give 560 mg (78%) of **14** as yellowish oil: $[\alpha]^{22}_D$ +50.7° (*c* 0.75, $CHCl_3$); UV λ_{max}^{MeOH} 233 nm (ε 12 600); IR 1730, 1690, 1668, 1625 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (3 H, s, CH_3OCO), 6.14 (1 H, d, *J* = 15.5 Hz, trans −CH=CHCO), 6.68 (1 H, dd, *J* = 15.5, 9 Hz, trans −CH=CHCO).

(3a*R*,4*S*,5*R*,6a*S*)-5-Benzoyloxy-4-(3-oxo-1-octyl)perhydrocyclopenta[*b*]furan-2-one (15a). A solution of 5 g (13.5 mmol) of **1a** in 75 mL of ethyl acetate was shaken with H_2 in the

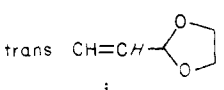
presence of 500 mg of Pd/C (10%). After uptake of 340 mL of H_2, the catalyst was filtered off and the filtrate evaporated in vacuo. The crystals were triturated with hexane and filtered to give 4.80 g (95%) of colorless crystals: mp 42–43 °C; $[\alpha]^{22}_D$ −79.4° (*c* 1.00, $CHCl_3$); IR 1770, 1718 (sh), 1710, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (3 H, t, *J* = 7 Hz, $-CH_3$), 4.85–5.28 (2 H, m, CHO).

13,14-Dihydro-15-deoxy-15,15-ethylenedioxyprostaglandin $F_{2\alpha}$ Methyl Ester (17a). **15a** (2.80 g, 7.52 mmol) was ketalized with ethylene glycol analogous to the preparation of **2a** to give the oily ketal (2.90 g, 93%): IR 1770, 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.94 (4 H, s, $-OCH_2CH_2O-$). The ketal (2.88 g, 6.92 mmol) was reduced with DIBAL at −70 °C (compare preparation of **3a**) to give 1.45 g (67%) of an oily lactol which was transformed by standard Wittig reaction (compare preparation of **4a**) and treatment with diazomethane into **17a** (215 mg, 22% of pure material, + 163 mg of slightly impure **17a**): IR 3600 (sh), 3405, 2995, 2950, 2875, 1710, 948 cm^{-1}.

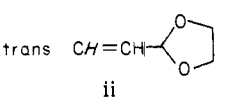
(3a*R*,4*R*,5*R*,6a*S*)-5-Benzoyloxy-4-[(*E*)-3,3-ethylenedioxy-4-phenoxy-1-butenyl]perhydrocyclopenta[*b*]furan-2-one (2b). **1b**[9] (9.6 g, 23.6 mmol), 22.5 mL of ethylene glycol, and 140 mg of *p*-toluenesulfonic acid hydrate in 225 mL of benzene were heated for 14 h in a Dean-Stark apparatus. After cooling and dilution with ether, the solution was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was dissolved in ether and filtered over a column of 220 g of SiO_2 to give 10.4 g (98.5%) of **2b** as a homogeneous colorless oil. On trituration with 2-propanol–ethyl acetate **2b** crystallized to give colorless crystals: mp 69–71 °C; IR 1772, 1715, 1600 cm^{-1}; NMR δ 3.82–4.06 (6 H, m, $-OCH_2CH_2O-$, $-CH_2O-$). Anal. Calcd for $C_{26}H_{26}O_7$ (450.47): C, 69.32; H, 5.82. Found: C, 68.92; H, 6.14.

(2*RS*,3a*R*,4*R*,5*R*,6a*S*)-4-[(*E*)-3,3-Ethylenedioxy-4-phenoxy-1-butenyl]perhydrocyclopenta[*b*]furan-2,5-diol (3b). To a solution of 9.5 g (22.1 mmol) of **2b** in 450 mL of absolute toluene, 95 mL of a 20% solution of DIBAL in toluene was added at −70 °C under an atmosphere of argon. After 30 min of stirring at −70 °C, the excess reagent was destroyed by addition of 2-propanol and finally of 48 mL of H_2O. After warming to 24 °C and stirring for 1.5 h at 24 °C, the precipitate was filtered and washed with CH_2Cl_2, and the filtrate was evaporated in vacuo. The residue was dissolved in ether and filtered over a column of 150 g of SiO_2 to give 6.3 g (86%) of crude **3b**.

15-Deoxy-15,15-ethylenedioxy-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ (4b). A mixture of 4.90 g (102 mmol) of a 50% dispersion of NaH in paraffin oil and 90 mL of absolute Me_2SO was stirred for 1 h at 70 °C under argon. This solution was added dropwise to a solution of 23.4 g (53 mmol) of 4-(carboxybutyl)triphenylphosphonium bromide in 94 mL of Me_2SO and stirred for 30 min at 24 °C. To the Wittig reagent a solution of 5.60 g (16 mmol) of **3b** in 56 mL of Me_2SO was added dropwise with stirring and the reaction mixture heated for 3 h at 50 °C under argon. After dilution with an ice-cold saturated aqueous solution of NaCl, the reaction mixture was extracted three times with ether and finally with ether–ethyl acetate (1:1). After acidification of the aqueous phase with citric acid to pH 5 and extraction with ethyl acetate, the extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed with CH_2Cl_2–2-propanol on a column of 100 g of SiO_2 to give 2.50 g (36%) of **4b** as a colorless oil and a further quantity of 0.96 g of slightly impure **4b**: IR 1705, 1600, 1588 cm^{-1}; NMR δ 3.85–4.03 (6 H, m, $-OCH_2CH_2O-$, $-CH_2O-$), 5.23–5.40 (2 H, m, cis CH=CH), 5.50 (1 H, d, *J* = 16 Hz, structure i), 5.79 (1 H, dd, *J* = 8, 16 Hz, structure ii), 6.80–7.40 (5 H, m, aromatic H). Anal. Calcd for $C_{24}H_{32}O_7$ (432.50); C, 66.65; H, 7.46. Found: C, 66.78; H, 7.09.



i



ii

15-Deoxy-15,15-ethylenedioxy-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Methyl Ester (5b). To a solution of 2.20 g (5.08 mmol) of **4b** in 50 mL of CH_2Cl_2, a slight excess of ethereal CH_2N_2 solution was added dropwise at 0 °C. After evaporation in vacuo the residue was dissolved in ether–dioxane (9:1) and filtered over a column of 50 g of SiO_2 to give 2.05 g (90%) of **5b** as a colorless oil: IR 1728 cm^{-1}; NMR δ 3.60 (3 H, s, CH_3O-). Anal. Calcd for $C_{25}H_{34}O_7$ (446.52): C, 67.27; H, 7.68. Found: C, 66.63; H, 8.30.

15-Deoxy-15,15-ethylenedioxy-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ *n*-Butyl Ester (6b). A mixture of 85 mg (0.197 mmol) of **4b**, 23 mg of Ag_2O, and 0.15 mL of *n*-butyl bromide was stirred for 56 h in 1.5 mL of *N,N*-dimethylacetamide at 24 °C under argon. After dilution with ether, the organic phase was extracted twice with H_2O, dried ($MgSO_4$), and evaporated in vacuo. On preparative TLC with ether–dioxane (8:2), 35 mg (37%) of **6b** was isolated as a colorless oil: IR 1730 cm^{-1}.

15-Deoxy-15,15-ethylenedioxy-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Tris(hydroxymethyl)methylamine Salt (8b). To a boiling solution of 2.14 g (4.95 mmol) of **4b** in 300 mL of acetonitrile, 1.10 mL of an aqueous solution of 82.25 g of tris(hydroxymethyl)methylamine in 150 mL of H_2O was added. On slowly cooling to 55 °C and scratching of the reaction flask, the mixture started to crystallize. After stirring for 16 h at 24 °C, the crystals of **8b** were filtered and dried at 60 °C (0.1 mm) to give 1.81 g (66%) of **8b** as colorless crystals: mp 105–106 °C; IR (KBr) 1596 cm^{-1}; NMR δ 3.31 [6 H, s, $H_3N^+C(CH_2OH)_3$], 3.55–4.05 (8 H, m, $-OCH_2CH_2O-$, CH_2O, 2CHO–), 5.1–5.45 (2 H, m, cis −HC=CH–), 5.47 (1 H, d, *J* = 16 Hz, see structure i), 5.77 (1 H, dd, *J* = 8, 16 Hz, see structure ii), 6.8–7.35 (5 H, m, aromatic H). Anal. Calcd for $C_{28}H_{43}NO_{10}$ (555.63): C, 60.74; H, 7.83; N, 2.53. Found: C, 60.45; H, 8.30; N, 2.52.

(3a*R*,4*R*,5*R*,6a*S*)-5-Benzoyloxy-4-(3-oxo-4-phenoxybutyl)perhydrocyclopenta[*b*]furan-2-one (15b). A solution of 1.60 g (3.95 mmol) of **1b**[9] in 25 mL of ethyl acetate was treated with 200 mg of Pd/C (10%) and shaken with H_2 until 90 mL of H_2 had been taken up. After filtration of the catalyst and evaporation, 1.60 g (99%) of **15b** was obtained as a colorless oil: IR 1770, 1718, 1598 cm^{-1}.

15-Deoxy-15,15-ethylenedioxy-13,14-dihydro-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ Methyl Ester (17b). **15b** (1.60 g, 3.92 mmol) was ketalized with ethylene glycol as described for **2** to give 0.80 g (45%) of 15-ethylene ketal as a colorless oil: IR 1770, 1713, 1598 cm^{-1}; NMR δ 3.85–4.05 (6 H, m, $-OCH_2CH_2O$, $-CH_2O$), 5.0–5.25 (2 H, m, >CHO).

To a solution of 780 mg (1.75 mmol) of this ketal in 40 mL of absolute toluene, 8 mL of a 20% solution of DIBAL in toluene was added at −70 °C under argon. After 30 min 2-propanol was added, followed by 5 mL of H_2O, and the reaction mixture was warmed and stirred 30 min at 24 °C. CH_2Cl_2 was added and the precipitate filtered. After evaporation of the filtrate the residue was dissolved in ether and filtered over a column of 15 g of silica gel to give 390 mg (70%) of the corresponding lactol as a colorless oil: IR 1598, 1588 cm^{-1}.

The Wittig reagent was prepared from 576 mg (12 mmol) of NaH (50%) and 2.66 g (6.02 mmol) of 4-(carboxybutyl)triphenylphosphonium bromide and reacted with 390 mg (1.21 mmol) of lactol (as described for **4b**). The crude product (400 mg) was dissolved in 10 mL of CH_2Cl_2 and treated at 0 °C with an excess ethereal CH_2N_2 solution. After evaporation the crude ester was purified by preparative TLC (ether–dioxane 9:1) to give 120 mg (22%) of **17b** as a colorless oil: IR 1728, 1598, 1586 cm^{-1}; NMR δ 3.62 (3 H, s, CH_3O), 3.81–4.05 (6 H, m, $-OCH_2CH_2O$, CH_2O), 5.17–5.6 (2 H, m, cis CH=CH), 6.82–7.40 (5 H, m, aromatic H).

15-Deoxy-15,15-ethylenedioxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester (20). (3a*R*,4*R*,5*R*,6a*S*)-5-Benzoyloxy-4-[(*E*)-3-oxo-5-phenyl-1-pentenyl]perhydrocyclopenta[*b*]furan-2-one[12] (3.45 g, 8.52 mmol) was ketalized with ethylene glycol as described for **2** to give, after crystallization from isopropyl alcohol, 2.94 g (77%) of the 15-ethylene ketal, mp 134.5–135 °C. This material (2.91 g, 6.52 mmol) was reduced with DIBAL as described for **3** to give 2.05 g (92%) of the lactol as a colorless oil: IR 3600, 3400, 2954, 1603, 1450, 978, 948 cm^{-1}. This lactol (2.0 g, 5.78 mmol) was converted into **20** by Wittig reaction and treatment with ethereal CH_2N_2 solution to give 1.15 g (45%) of **20**: mp 62–64 °C (from diisopropyl ether–methylene chloride); NMR (Me_2SO-d_6) δ 1.50 [2 H, t, *J* = 7 Hz, $-CH_2C(=O)O-$], 3.56 (3 H, s, CH_3O), 3.78–4.02 (4 H, m, $-OCH_2CH_2O$), 5.25–5.75 (4 H, m, cis CH=CH and trans CH=CH), 7.10–7.30 (5 H, m, aromatic H). Anal. Calcd for $C_{26}H_{36}O_6$ (444.57): C, 70.24; H, 8.16. Found: C, 69.70; H, 8.19.

15-Deoxy-15,15-ethylenedioxy-15-(4-chlorophenyl)-16,-17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ Methyl Ester (21). (3a*R*,4*R*,5*R*,6a*S*)-5-Benzoyloxy-4-[(*E*)-3-oxo-3-(4-chlorophenyl)-1-propenyl]perhydrocyclopenta[*b*]furan-2-one[13] (7 g, 15.1 mmol) was ketalized for 48 h with ethylene glycol as described for **2** to give 6.01 g (77%) of the ethylene ketal: mp 83–84 °C (from diisopropyl ether–methylene chloride); IR 2955, 2890, 1770, 1714, 1600, 1270, 970, 947, 832 cm^{-1}. This ketal (2.0 g, 4.40 mmol) was reduced with DIBAL as described for **3** to give 1.20 g (77%) of the lactol as a colorless oil: IR 3600, 3400, 2945, 1600, 972, 947, 832 cm^{-1}. This lactol (1.20 g, 3.40 mmol) was converted into **21** by Wittig reaction and treatment with ethereal CH_2N_2 solution to give 900 mg (59%) **21** as a colorless oil: NMR δ 3.60 (3 H, s, CH_3O), 5.25–5.88 (4 H, m, cis CH=CH, trans CH=CH), 7.28–7.52 (4 H, m, aromatic H); IR 3600, 3520, 2923, 1732, 1600, 976, 947, 835 cm^{-1}.

Assay Methods. (a) In Vitro. Isolated Rat Uterus. When incubated in salt solutions whose composition corresponds to the medium of extracellular fluid and stimulated with prostaglandins, isolated horns of the rat uterus respond with contractions. Under isotonic conditions these contractions can be recorded and analyzed as changes in length. Uteri of estrous rats (wt 150 g) were used for the tests.

The investigations were carried out using an apparatus for tests on isolated organs developed by Braun, Melsungen, West Germany. A modified Tyrode's solution was used as the bath fluid. The isotonic contractions of the uterine musculature were transferred via a potentiometer to a Servogor S compensatory recorder of Metrawatt and could be traced as waves.

The response obtained with the test preparation was assessed in a paired comparison with the reference preparation, four replicates (n = 4) being performed in each case. Both uterine horns of each animal were used, contraction being stimulated by adding the test preparation to the organ bath containing one horn and the reference preparation to that containing the other horn. The test data (height of contraction in millimeters) were analyzed statistically by means of an analysis of variance.

Isolated Guinea-Pig Ileum. The contractions of isolated guinea-pig ileum segments were recorded isotonically as changes in length.

Female guinea pigs weighing about 300 g were used for the investigations. The guinea pigs were sacrificed by decapitation, after which the ileum was immediately removed. After removal of the mesentery, the intestinal portions were bisected and the portions, each of which was about 4 cm long, immediately suspended in the bath fluid (modified Tyrode's solution).

Tests were carried out with the same apparatus as was used for the investigations performed on isolated rat uteri.

Four replicates (n = 4) were carried out to permit paired comparisons of the responses obtained with the test and reference preparations. The test data (height of contraction in millimeters) were analyzed statistically by means of an analysis of variance.

(b) In Vivo. Assay for Luteolytic and Abortifacient Effects in Rats. PG's exert their abortifacient activity in rats by functional disintegration of the corpora lutea of pregnancy (luteolysis). The luteolytic activities of test compounds were estimated from their ability to depress serum progesterone levels and induce abortion in early pregnant rats.

Female Wistar rats were mated at proestrus. If sperm were found in the vaginal smear the next day, this day was defined as day 1 of gestation. The test compounds were administered in 0.2 mL of oil sc (benzyl benzoate + castor oil, 1:3) on days 4–7 of gestation. Four animals per group were used. Blood for serum progesterone determinations by RIA was collected from the orbital venous plexus on days 3, 5, 7, and 9 of gestation. On day 9 the animals were killed and the number in which abortion had been induced was determined by inspection of the uteri.

The lowest dose of a PG inducing abortion in 50% of the animals was determined (0.3–1.0 mg per animal per day sc for $PGF_{2\alpha}$) by this assay. Analogues which did not show any activity with 10 mg/animal were considered inactive.

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