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Prostanoids: LXXXIII.* Synthesis of (±)-19-Carboxy-20-norprostaglandin $F_{2\alpha}$ and Its 15β-Epimer**

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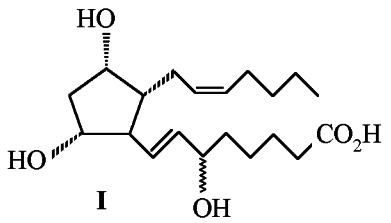
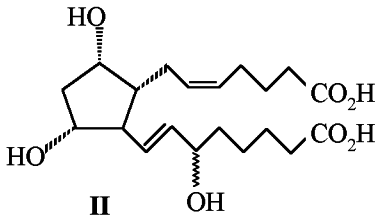
Abstract—Starting with (±)-7α-hydroxy-6β-hydroxymethyl-2-oxa-cis-bicyclo[3.3.0]octan-3-one 15α,β-19-carboxy-20-norprostaglandins F_{α} were synthesized.

We reported earlier on the synthesis [2] and pharmacological characteristics of compound **I** isomeric to a natural prostaglandin $F_{2\alpha}$. The standard biotests demonstrated a high prostaglandin-like activity of individual 15α- and 15β-epimers of compound **I**, and the substances were considered promising for further investigation. In this connection arose a necessity to prepare the probable metabolites of **I** that might form in vivo, specifically, the oxidation product at the C^{1} atom of the alkene side chain, namely, a dicarboxylic acid **II**.



I



II

In the synthesis of acid **II** we used fairly available racemic lactonediol **III** [4]. Under standard conditions diol **III** was converted into monotrityl derivative **IV** that was reduced by *i*-Bu_2AlH into lactol **V**. The latter was brought into olefination reaction with an ylide generated from the triphenylphosphonium 5-bromopentanoate by hexamethyldisilazide in THF. The overall yield of olefin **VI** with respect to diol **III** was over 50%. The reaction of acid **VI** with diazomethane provided methyl ester **VII** in a quantitative yield.

Then the free hydroxy functions of ester **VII** were protected with benzoate groups, the trityl rest of compound **VIII** thus obtained was removed by acid hydrolysis to afford a primary alcohol **IX** that was subjected by oxidation with Collins reagent followed by condensation of aldehyde **X** with phosphonate **XI** [2] along Emmons–Horner procedure. As a result enone **XII** was obtained in an overall yield of 46%.

The final stages of compound **II** synthesis were performed virtually without losses and consisted of the standard procedures of reduction with $NaBH_4$ of the keto function in enone **XII** with subsequent alkaline hydrolysis of the ester and benzoate groups in compound **XIII**. We failed to separate 15α- and 15β-epimers of compound **II** by chromatography on SiO_2.

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord M-80 from films or mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered on Bruker AM-300 instrument at operating frequencies 300 and 75.47 MHz respectively from solutions in $CDCl_3$ and $(CD_3)_2CO$, internal reference TMS.

* For communication LXXXII see [1].

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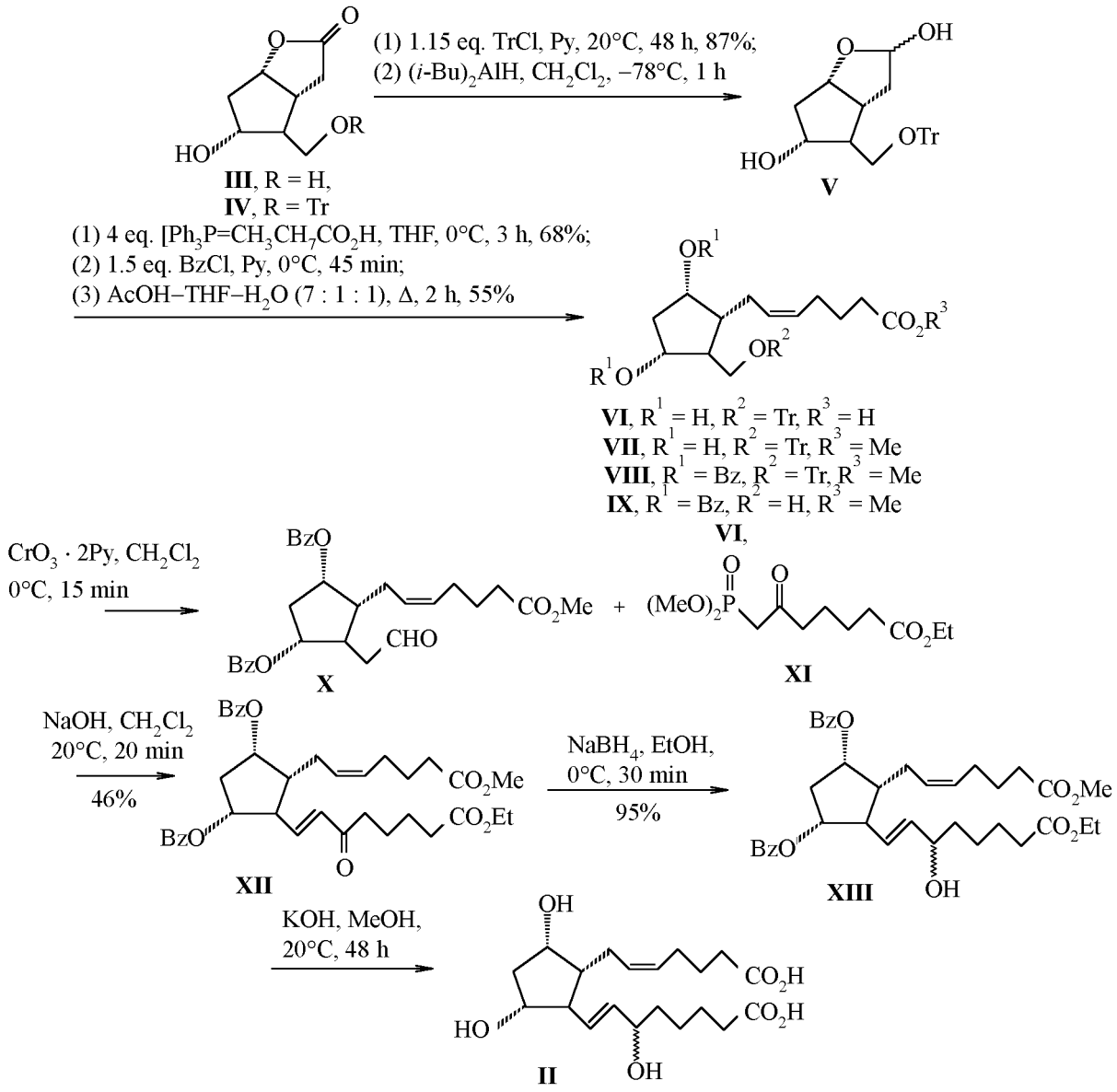

For TLC were used Silufol UV 254 : 366 plates, development in iodine vapor, by calcining, or by wetting the plates with a mixture anisaldehyde–sulfuric acid–ethanol (1 : 0.5 : 10) with subsequent heating to 120–150°C.

(±)-19-Carboxy-20-nor-15α,β-prostaglandins F$_{2\alpha}$ (II). A solution of 0.61 g of alcohols **XIII** and 0.3 g of KOH in 7 ml of 50% aqueous methanol was stirred for 2 days at room temperature. Then the reaction mixture was acidified with 0.5 N water solution of HCl till pH 6, the reaction products were extracted into chloroform (4×25 ml), the organic layer was washed with saturated water solution of NaCl (2 × 10 ml), dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent benzene–acetone, 1 : 1) to afford 0.14 g (38%) of a mixture of α- and β-isomers of compound **II** (R_f 0.28). IR spectrum (ν, cm^{-1}): 1720, 3400. ^{1}H NMR spectrum [$CDCl_3$ + $(CD_3)_2CO$, δ, ppm]: 1.1–2.25 m (20H, 9CH$_2$, 2CH), 3.50–3.65 m (1H, C^{15}H), 3.84–3.94 m (2H, C^{9}H, OH), 4.04–4.14 m (3H, C^{11}H, 2OH), 5.30–5.40 m (2H, C^{5}H=C^{6}H), 5.25–5.5 m (4H, CH=CH, 2CO$_2$H). ^{13}C NMR spectrum [$CDCl_3$ + + $(CD_3)_2CO$, δ, ppm]: 24.36 (C^3), 24.55 (C^{17}), 24.71 (C^{18}), 25.99 (C^7), 26.31 (C^4), 32.41 and 32.53 (C^{19}), 33.12 (C^{19}), 33.12 (C^2), 36.72 (C^{16}), 43.07 (C^{10}), 50.11 (C^8), 55.02 (C^{12}), 70.45 and 70.77 (C^{15}), 71.51 (C^9),

76.28 (C^{11}), 128.48 (C^{6}), 129.31 and 129.49 (C^{14}), 131.88 (C^{5}), 134.46 (C^{13}), 173.91 (CO_2), 173.97 (CO_2).

(±)-7α-Hydroxy-2-oxa-6β-triphenylmethoxymethyl-*cis*-bicyclo[3.3.0]octan-3-one (IV). To a solution of 4 g of diol **III** in 25 ml of anhydrous pyridine was added 8.4 g of triphenylchloromethane (TrCl), and the reaction mixture was stirred at 20°C for 2 days. On completion of the reaction the mixture was diluted with 120 ml of ethyl ether, washed with saturated water solution of NaCl (25 ml), dried with $MgSO_4$, the solvent was evaporated, and the residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–hexane, 1:4) to afford 8.2 g (87%) of crystalline alcohol **IV**, mp 115–117°C.

(±)-3α-(6-Methoxycarbonyl-2Z-hexenyl)-2β-triphenylmethoxymethyl-1α,4α-cyclopentanediol (VII). To a solution of 4 g of lactone **IV** in 35 ml of CH_2Cl_2 while stirring at −78°C under argon atmosphere was added dropwise 5.12 ml of 73% hexane solution of *i*-Bu_2AlH diluted by 32 ml of CH_2Cl_2. The reaction mixture was stirred for 1 h, then 40 ml of moist ether was added followed by 16 ml of 10% aqueous KOH. The reaction products were extracted into ether (3×10 ml). The combined organic solutions were washed with saturated water solution of NaCl, dried with $MgSO_4$, the solvent was evaporated at room temperature. We obtained 4g of lactol **V**. IR spectrum (ν, cm^{-1}): 1072, 1600, 1640, 3080, 3110, 3370. Under argon atmosphere to a heated to 75°C suspension of 23.84 g of 4-carboxybutyltriphenylphosphonium bromide in 48 ml of benzene was added at stirring 57.6 ml of 0.55 N benzene solution of sodium hexamethyldisilazide. The stirring continued at the same temperature for 30 min, and the reaction mixture was cooled to room temperature. Then to the ylide formed was added a solution of 4 g of lactone **V** in 16 ml of benzene. The mixture was stirred for 3 h, then it was acidified with 0.5 N aqueous HCl till pH 7, the unsaturated acid was extracted with ethyl ether (4×70 ml). The combined organic extracts were washed with saturated water solution of NaCl (30 ml), dried with $MgSO_4$, and evaporated under reduced pressure at room temperature. The residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–hexane, 3:7; R_f 0.32) to obtain 2.5 g (52%) of oily compound **VI**. To a stirred solution of 2.5 g of acid VI in 15 ml of ether was added 10 ml of 1 N solution of diazomethane prepared from 10 mmol of nitrosomethylurea and 3.5 ml of 40% aqueous KOH. After the gas evolution finished the reaction mixture was evaporated, and ether **VII** was isolated in a quantitative yield. IR spectrum (ν, cm^{-1}): 704, 748, 764, 1507, 1740, 3020, 3045, 3056, 3450. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.60–1.72 m (2H, $2CH_2$), 1.80–2.30 (10H, $4CH_2$, 2CH), 2.50–3.20 br.m (2H, 2HO), 3.03 d.d (1H, $0.5CH_2$, J_{gem} 9.0, 6.6 Hz), 3.30 d.d (1H, $0.5CH_2$, J_{gem} 9.0, 4.6 Hz), 3.63 s (3H, OMe), 4.15–4.20 m (2H, C^1H, C^4H), 5.25–5.40 m (2H, CH=CH), 7.18–7.32 m (9H, $6H^o$, $3H^p$), 7.35–7.50 m (6H, $6H^m$). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 24.79 ($C^{5'}$), 26.56 ($C^{1'}$), 26.87 ($C^{4'}$), 33.37 ($C^{6'}$), 42.64 (C^5), 47.26 (C^3), 51.43 (OMe), 53.30 (C^2), 64.50 (CH_2O), 74.61 (C^4), 77.53 (C^1), 86.57 (CPh_3), 126.95 (C^p arom), 127.74 (C° arom), 128.66 (C^m), 129.26 ($C^{2'}$), 129.35 ($C^{3'}$), 144.05 (C arom), 174.18 (CO_2).

(±)-2β-Hydroxymethyl-1α,4α-dibenzoyloxy-3α-(6-methoxycarbonyl-2Z-hexenyl)cyclopentane (IX). To a stirred solution of 2.5 g of ester **VII** in 15 ml of anhydrous pyridine at 0°c was gradually added 1.72 ml of benzoyl chloride, the reaction mixture was stirred for 45 min. On completion of reaction the mixture was diluted with 50 ml of ethyl ether, acidified with 2 N aqueous HCl till pH 6, the organic layer was washed with saturated water solution of NaCl (3 × 30 ml), dried with $MgSO_4$, and the solvent was evaporated. The residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–benzene, 1:8, R_f 0.46) to isolate 1.82 g (78%) of oily alcohol **IX**. IR spectrum (ν, cm^{-1}): 738, 1508, 1595, 1615, 1720, 1750, 3080, 3470. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.50–1.63 m (2H, CH_2), 1.85–2.50 m (12H, $5CH_2$, 2CH), 3.60 s (3H, OMe), 3.50–3.90 m (1H, OH), 3.75 d.d (1H, $0.5CH_2O$, J_{gem} 11, ^3J 6.2 Hz), 4.00 d.d (1H, $0.5CH_2O$, J_{gem} 11, ^3J 3.6 Hz), 5.35–5.55 m (4H, C^4H, CH=CH, C^1H), 7.20–7.30 m and 7.38–7.52 m (4H, $2H^m$, $2H^p$), 7.55–7.65 m (2H, $2H^m$), 7.86 m (2H, $2H^\circ$ arom, J 7.5 Hz), 8.10 m (2H, $2H^o$ arom, J 7.5 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 24.48 ($C^{5'}$), 26.09 ($C^{1'}$), 26.44 ($C^{4'}$), 33.05 ($C^{6'}$), 38.57 (C^5), 45.34 (C^2), 51.22 (OMe), 53.69 (C^3), 65.64 (CH_2O), 76.64 (C^4), 78.01 (C^1), 127.81 ($C^{2'}$), 130.07 ($C^{3'}$), 128.02 and 128.23 ($4C^m$ arom), 129.41 and 129.46 ($4C^\circ$ arom), 129.75 and 130.30 (2C arom), 132.85 (C^p arom), 165.71 ($2CO_2$), 166.64 (CO_2).

(±)-1α,4α-Dibenzoyloxy-3α-(6-methoxycarbonyl-2Z-hexenyl)-2β-(3-oxo-6-ethoxycarbonyl-2Z-heptenyl)cyclopentane (XII). Under argon atmosphere to Collins reagent prepared from 2.56 g of CrO_3 and 4.4 ml of pyridine in 30 ml of CH_2Cl_2 at vigorous stirring and cooling to 0°C was added 0.82 g of

alcohol **IX** in 4,5 ml of CH_2Cl_2. After 15 min (TLC monitoring) the reaction mixture was filtered through a thin bed of silica gel, acidified with 2 N water solution of HCl till pH 6, the organic layer was washed with saturated water solution of NaCl (3 × 30 ml), dried on $MgSO_4$, the solvent was removed under reduced pressure. We obtained 0.82 g of aldehyde **X** (R_f 0.47, eluent ethyl acetate–pentane, 1:1). IR spectrum (ν, cm^{-1}): 1500, 1590, 1610, 1720, 2740, 3020, 3040. To a solution of 0.82 g of the obtained aldehyde **X**, 0.54 g of phosphonate **XI**, and 2.3 mg of triethylbenzylammonium chloride in 9.2 ml of CH_2Cl_2 at room temperature and vigorous stirring was added 0.2 ml of 50% water solution of NaOH, and the mixture was stirred for 15–20 min. On completion of reaction (TLC monitoring) the reaction mixture was diluted with 23 ml of CH_2Cl_2, acidified with 1 N HCl water solution till pH 5, washed with saturated water solution of NaCl (3 × 15 ml), dried with $MgSO_4$. The solvent was evaporated under reduced pressure at room temperature, and the residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–pentane, 1:1; R_f 0.35) to afford 0.67 g (62%) of enone **XII**. IR spectrum (ν, cm^{-1}): 712, 1584, 1600, 1628, 1676, 1720, 1732, 1736, 3048, 3064. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.18 t (3H, Me, *J* 7 Hz), 1.40–2.70 m (19H, $9CH_2$, C^2H), 2.90–3.04 m (1H, C^3H), 3.54 s (3H, OMe), 4.04 q (2H, OCH_2, *J* 7.0 Hz), 5.25–5.50 m (4H, C^4H, CH=CH, C^1H), 6.23 d (1H, C^2H, *J* 15.9 Hz), 5.85 d (1H, C^1H, *J* 15.0, 8.9 Hz), 7.20–7.30 m (2H, $2H^m$ arom), 7.34–7.60 m (4H, $2H^p$ arom, $2H^m$ arom), 7.86 mm(2H, H^o arom, *J* 7.5), 8.05 m (2H, $2H^o$ arom, *J* 7.5). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.10 (Me), 23.25 ($C^{5'}$), 24.36 ($C^{6'}$), 24.44 ($C^{5''}$), 25.40 ($C^{1'''}$), 26.52 ($C^{4''}$), 33.06 ($C^{6''}$), 33.92 ($C^{7'}$), 39.14 (C^5), 39.73 ($C^{4'}$), 48.50 (C^3), 51.25 (OMe), 53.16 (C^2), 60.20 (OCH_2), 75.23 (C^4), 78.26 (C^1), 127.07 ($C^{2''}$), 128.17 and 128.34 (C^m arom), 129.44 (C^o arom), 129.64 and 130.11 (C arom), 130.56 ($C^{3''}$), 131.58 ($C^{2'}$), 132.96 and 133.05 (C^m arom), 145.33 ($C^{1'}$), 165.51 (CO_2), 165.83 (CO_2), 173.62 (CO_2), 173.25 (CO_2), 199.42 (C=O).

(±)-1α,4α-Dibenzoyloxy-2β-(3α,β-hydroxy-7-ethoxycarbonyl-2Z-heptenyl)-3α-(2Z-6-methoxycarbonyl-2-hexen-1-yl)cyclopentane (XIII). To a stirred solution of 0.67 g of enone **XII** in 7 ml of EtOH at 0°C was added freshly prepared solution of 0.18 g of $NaBH_4$ in 3 ml of NaOH. The mixture was stirred for 30 min, then 1.8 ml of MeOH was added, the reaction mixture was acidified with 3% water solution of HCl till pH 5, the reaction product was extracted into ethyl acetate (3 × 30 ml), the extract was washed with saturated water solution of NaCl (2 × 15 ml), dried with $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–pentane, 1:1; R_f 0.23) to afford 0.61 g (91%) of alcohol **XIII**. IR spectrum (ν, cm^{-1}): 1584, 1600, 1702, 1716, 1720, 1732, 1736, 3048, 3064, 3120, 3512. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.16 t (3H, Me, *J* 7 Hz), 1.18 t (3H, Me, *J* 7 Hz), 1.20–2.50 m (18H, $9CH_2$), 2.50–2.70 m (1H, C^2H), 2.75–2.90 m (1H, C^3H), 3.00–3.50 m (1H, OH), 3.54 s and 3.56 s (3H, OMe), 3.95– 4.10 m (H, $C^{3''}H$), 4.05 q (2H, CH_2O, *J* 7 Hz), 5.15–5.54 m (4H, 2CH=CH,), 5.55–5.70 m (2H, C^4H, C^1H), 7.20–7.30 m (2H, $2H^m$ arom), 7.30–7.48 m (3H, H^p arom, $2H^m$ arom), 7.48– 7.55 m (1H, H^p arom), 7.8–7.93 m (2H, $2H^o$ arom), 7.93–8.12 m (2H, $2H^o$ arom). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.34 (Me), 24.73 ($C^{5'}$), 25.05 ($C^{5''}$), 25.43 ($C^{1'''}$), 26.72 ($C^{4''}$), 33.22 and 33.32 ($C^{7'}$), 34.29 ($C^{6''}$), 36.84 ($C^{4'}$), 39.21 (C^5), 48.67 and 48.77 (C^3), 51.55 (OMe), 53.13 and 53.18 (C^2), 60.27 (CH_2O), 72.18 ($C^{3'}$), 75.31 and 75.45 (C^4), 79.00 and 79.24 (C^1), 127.92 ($C^{2''}$), 128.02 ($C^{3''}$), 128.36 and 128.53 (C^m arom), 129.62 and 129.66 (C^o arom), 130.28 and 130.51 ($C^{2'}$), 130.14 and 130.61 (C arom), 133.05 and 133.18 (C^p arom), 136.22 and 136.53 ($C^{1''}$), 165.86 (CO_2), 166.21 and 166.29 (CO_2), 173.78 (CO_2), 174.06 and 174.19 (CO_2).

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