Supplementary material

Preparation and Chiral HPLC Separation of the Enantiomeric Forms of Natural Prostaglandins

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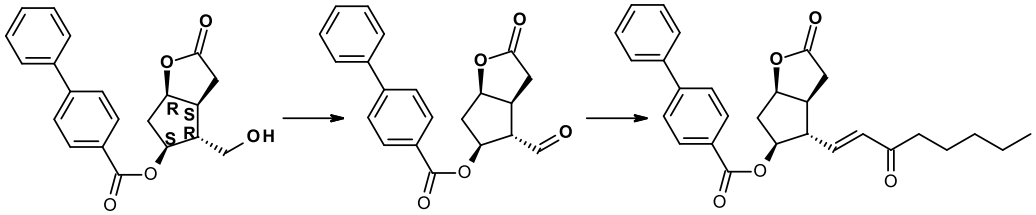
[(3a*S*,4*S*,5*S*,6a*R*)-2-oxo-4-[(E)-3-oxooct-1-enyl]-3,3a,4,5,6,6a-hexahydrocyclopenta[b]furan-5-yl] 4-phenylbenzoate (**8**)



$C_{21}H_{20}O_5$	$C_{21}H_{18}O_5$	$C_{28}H_{30}O_5$
Mw: 352.38	Mw: 350.36	Mw: 446.53
ent-Corey-Lactone		
(+)**-5**	**6**	**8**

Oxidation

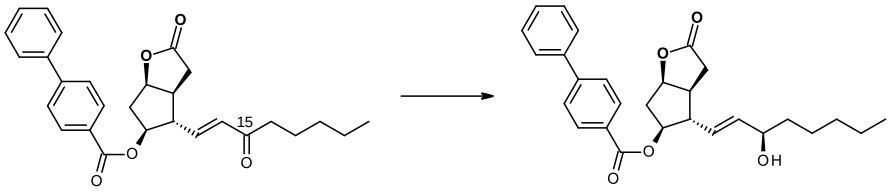
Lactone (**5**) (20 g, 56.76 mmol) was dissolved in dichloromethane (DCM) (200 ml), potassium bromide (0.675g, 5.68 mmol) and 2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical **(**TEMPO catalyst) (0.089g, 0.57 mmol) were added. The reaction mixture was cooled and a pre-prepared NaOCl solution was added at 0-10 °C (31 ml of 2.07 mol/l NaOCl, 62 ml of water and 1.926 g of $NaHCO_3$ to adjust the pH to pH=9.2). After completion of the reaction, stirring was continued for 25 minutes, then the reaction was quenched by addition of 10 % $Na_2S_2O_3$ solution (85 ml). After stirring, the phases were separated. The aqueous layer was extracted with DCM (28 ml), the combined organic layers containing crude aldehyde (**6**) were poured into a dropping funnel and used in the next reaction step without purification.

HWE reaction

Dimethyl (2-oxoheptyl)phosphonate (**7**) (15.135 g, 86.11 mmol) was dissolved in DCM (96 ml), NaOH (2.724 g, 68.11 mmol) dissolved in water (5 ml) was added to the DCM solution. The reaction mixture was cooled to 0-5 °C and the solution of aldehyde **6** was added dropwise. The reaction mixture was stirred at 5-10 °C. When the required conversion was complete, the reaction mixture was quenched by

the addition of 1 mol/l $NaHSO_4$ solution (68 ml). After stirring, the phases were separated. The aqueous layer was extracted with DCM (28 ml), and the combined organic layers were washed 15 % NaCl solution (3 x 11 ml), water (114 ml) then dried over sodium sulfate (20 g). The drying agent was filtered off and the filtrate was evaporated. The residue crystallized spontaneously. The crystalline residue was recrystallized from diisopropyl ether-hexane.
Yield: 16.55 g (65.3%).

[(3a*S*,4*S*,5*S*,6a*R*)-4-[(E,3*R*)-3-hydroxyoct-1-enyl]-2-oxo-3,3a,4,5,6,6a-hexahydrocyclopenta[b]furan-5-yl] 4-phenylbenzoate (**9**)

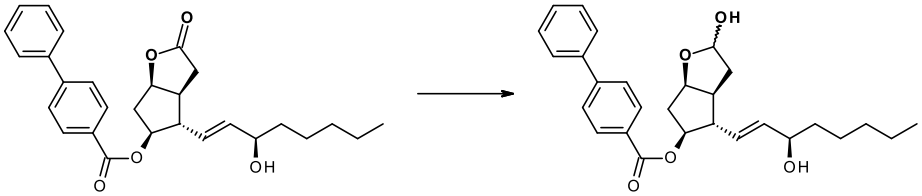


$C_{28}H_{30}O_5$
Mw: 446.53
8

$C_{28}H_{32}O_5$
Mw: 448.55
9

9.9 mol/l borane-dimethylsulfide complex solution (5.6 ml, 55.76 mmol) was dissolved in a mixture of dry toluene (31 ml) and dry tetrahydrofuran (THF) (31 ml) under an inert atmosphere. Pyrocatechol (6.140 g, 55.76 mol) dissolved in dry THF (47 ml) was added at room temperature. After stirring for 30 minutes, *S*-2-methyl-CBS-oxazaborolidine (0.773 g, 2.79 mol) was added and the reaction mixture was cooled to (-15)-(-10) °C and the PPB-protected enone (**8**) (12.450 g, 27.88 mmol) dissolved in dry toluene (37 ml) was added dropwise over about 60 minutes. After stirring for 30 minutes, another portion of the reducing agent, 9.9 mol/l BH_3-DMS complex solution (4.2 ml, 41.82 mmol) was added. When the required conversion was complete, the reaction mixture was quenched by methanol (10.2 ml, 250 mmol). The reaction mixture was stirred for 30 minutes, then poured into a mixture of toluene (105 ml) and 1 mol/l sodium hydroxide solution (125 ml). After stirring, the phases were separated. The aqueous layer was extracted with toluene (70 ml), and the combined organic layers were washed with brine (2 x 100 ml) and dried over sodium sulfate (20 g). The drying agent was filtered off, the filtrate was evaporated. The residue was dried giving another portion of dry toluene (50 ml) and distilling off about 25 ml. The dry solution of the residue, PPB-protected lactone (**9**) was used in the next reaction step without purification.

[(3a*S*,4*S*,5*S*,6a*R*)-2-hydroxy-4-[(E,3*R*)-3-hydroxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydro-2H-cyclopenta[b]furan-5-yl] 4-phenylbenzoate (**10**)

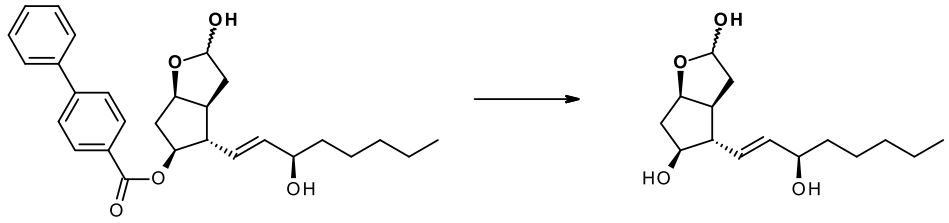


$C_{28}H_{32}O_5$
Mw: 448.55
9

$C_{28}H_{34}O_5$
Mw: 450.57
10

A toluene solution of the PPB-protected lactone (**9**) was diluted with dry THF (31 ml) under an inert atmosphere. Reaction mixture was cooled to (-78)-(-70) °C and a 1.5 mol/l solution of DIBAL-H (46.5 ml, 69.75 mmol in toluene) was added dropwise. When the required conversion was complete, the reaction mixture was quenched with 1 mol/l $NaHSO_4$ solution (250 ml). The reaction mixture was stirred for 45-60 minutes and then the phases were separated. The aqueous layer was extracted with toluene (37 ml) and the combined organic layers were washed with 1 mol/l $NaHCO_3$ solution (pH > 8) and dried over sodium sulfate (20 g). The drying agent was filtered off and triethylamine (0.06 ml) was added to the filtrate and the filtrate was evaporated. The residue was purified chromatography using toluene:ethyl acetate=3:1 as eluent. The main fraction of chromatography was evaporated and crystallized with toluene:hexane.
Yield: 4.79 g (38.1%).

(3a*S*,4*S*,5*S*,6a*R*)-4-[(E,3*R*)-3-hydroxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydro-2H-cyclopenta[b]furan-2,5-diol (**11**)

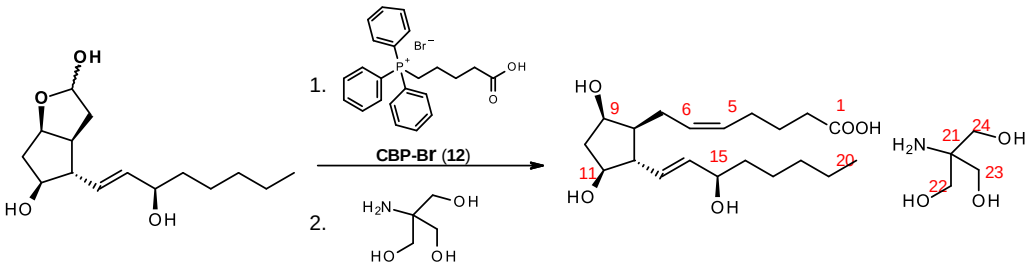


$C_{28}H_{34}O_5$
Mw: 450.57
10

$C_{15}H_{26}O_4$
Mw: 270.36
11

PPB-protected lactol (**10**) (9.217 g, 2.46 mmol) was dissolved in methanol (28 ml) under an inert atmosphere. Potassium carbonate (1.498 g, 10.84 mmol) was added and the reaction mixture was stirred at 35-40 °C. When the required conversion was complete, the reaction mixture was cooled to 0 °C and quenched by the addition of 0.5 mol/l H_3PO_4 solution (21 ml). After stirring for 30 minutes the white solid was filtered off, the filtrate was concentrated. Water and brine were added to the concentrate, that was extracted with ethyl acetate (3 x 26 ml), the phases were separated, the combined organic phases were concentrated, clarified by charcoal. The charcoal was filtered off, the filtrate was evaporated and crystallized from ethyl acetate-diisopropyl ether.
Yield: 4.485 g (81.1%)

Ent-PGF_{2a} tromethamine salt ((-)-**1**.TAM)



$C_{15}H_{26}O_4$
Mw: 270.36
11

$C_{20}H_{34}O_5.C_4H_{11}NO_3$
Mw: 354.49 . 121.14
(-)-1.TAM

Wittig reaction

CBP-Br (**12**) (1.820 g, 4.10 mmol) was suspended in dry THF (12 ml) under an inert atmosphere. A solution of potassium *tert*-butoxide (1.631 g, 14.53 mmol) in dry THF (12 ml) was added and the reaction mixture was cooled to (-10)-(-5)°C. After stirring for 30 minutes, a solution of unprotected lactol (**11**) (0.560 g, 2.07 mmol) in dry THF (3 ml) was added dropwise while maintaining the temperature at (-10)-(-5)°C. After stirring for 2 hours, the reaction temperature was gradually increased to 10-15 °C. When the required conversion was complete, the reaction mixture was quenched by adding the solution of 2 mol/l $NaHSO_4$ (4 ml) and water (8 ml). After stirring for 20 minutes, THF was distilled off, the precipitated white solid was filtered off and washed with 1 mol/l $NaHCO_3$ solution (3 x 2 ml). The *ent*-PGF_{2a} containing filtrate was acidified with 2 mol/ $NaHSO_4$ (10 ml) then extracted with ethyl acetate (3 x 10 ml). The combined organic phases were washed with 15 % NaCl (2 x 4 ml) and then concentrated. The residue was crystallized from acetone-diisopropyl ether, the crystals were filtered off. The filtrate was evaporated and purified by column chromatography using diisopropyl ether-acetone-water = 40:25:1 mixture as eluent. The main fraction was extracted with brine containing 0.5 mol/l K_2CO_3 solution (3 x 6 ml), and concentrated. The residue was extracted with DCM (3 ml), the aqueous phase was acidified with 2 mol/l $NaHSO_4$ solution to pH=2 and it was extracted with ethyl acetate (3 x 4 ml). The combined organic layers were washed with 15% NaCl (3 x 2 ml), dried over Na_2SO_4. The drying agent was filtered off, and the filtrate was evaporated. The residue was converted to the tromethamine salt.

Salt formation

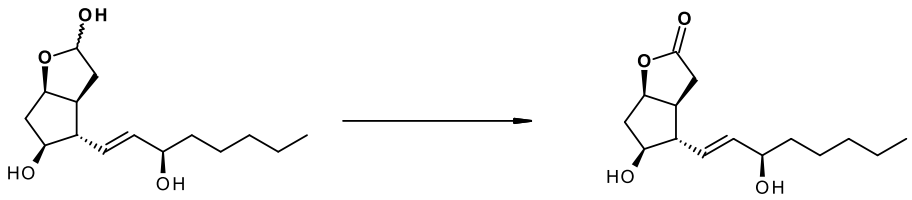
Tromethamine base (0.252 g, 2.08 mmol) was added to the evaporated residue, and the mixture was dissolved in methanol (4 ml) at 45 °C. The solution was clarified by charcoal (0.02 g). The charcoal was filtered off, and was washed with methanol (3 x 2 ml), and the filtrate was concentrated to a residue of 4 ml. The solution was stirred at 25-28 ° C until intense crystallization began. Crystallization was completed by adding acetone (14 ml) and then hexane (14 ml) at 0-5 °C. After stirring for 1 hour, crystals were filtered off and washed with cooled acetone:hexane=2:1 mixture.
Yield: 0.824 g (83.7%), enantiomeric excess (ee): 0.982 (by chiral HPLC), purity: approximately 96% (by NMR spectra)

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 5.475-5.21 (m – in: 5.415 (dt, ^3J~10.2 Hz and ~7.4 Hz, 1H, C6-H), 5.37 (dd, ^3J=15.3 Hz and 6.0 Hz, 1H, C14-H), 5.315 (dd, ^3J=15.3 Hz and 7.5 Hz, C13-H) and 5.26 (dt, ^3J=10.6 Hz and 7.4 Hz, 1H, C5-H)– 4H), 5.21-4.71 (br, 9H, C9-OH, C11-OH, C15-OH, C22-OH, C23-OH, C24-OH, NH_3), 3.94-3.81 (m – in: 3.90 (td, ^3J=5.1 Hz and 2.1 Hz, 1H, C9-H) and 3.855 (q, ^3J=5.9 Hz, 1H, C15-H) – 2H), 3.65 (td, ^3J=7.8 Hz and 6.0 Hz, 1H, C11-H), 3.31* (s, 6H, C22-CH_2, C23-CH_2, C24-CH_2), 2.24-1.995 (m – in: 2.175 (ddd, ^3J=14.2 Hz, 8.2 Hz and 6.1 Hz, 1H, C10-H_α), 2.115 (dt, ^3J=11.5 Hz and 7.6 Hz, 1H, C12-H), 2.07 (m, 1H, C7-Ha), 2.025 (t, ^3J=7.5 Hz, 2H, C2-CH_2) – 5H), 1.995-1.885 (m – in: 1.965 (m, 1H, C7-Hb) and 1.96 (q, ^3J=7.3 Hz, 2H, C4-CH_2) – 3H), 1.535-1.365 (m – in: 1.48 (qui, ^3J=7.4 Hz, 2H, C3-CH_2), 1.425 (ddd, ^3J=14.2 Hz, 5.6 Hz and 2.0 Hz, 1H, C10-H_β) and 1.41 (m, 1H, C16-Ha) – 4H), 1.365-1.17 (m, 8H, C8-H, C16-Hb, C17-CH_2, C18-CH_2, C19-CH_2), 0.845 (t, ^3J=7.0 Hz, 3H, C20-CH_3).

^{13}C NMR (500 MHz, DMSO-d_6): δ [ppm] = 176.23 (C1), 135.48 (C14), 131.79 (C13), 129.26 (C6), 129.10 (C5), 75.77 (C11), 71.31 (C15), 69.52 (C9), 61.85 (3C, C22, C23 and C24), 58.34 (C21), 54.27 (C12), 49.00 (C8), 43.94 (C10), 37.58 (C16), 35.45 (C2), 31.35 (18), 26.55 (C4), 25.51 (C3), 24.80 (C17), 24.73 (C7), 22.17 (C19), 13.94 (C20).

*Partly overlapped by the ^{1}H NMR signal of the water content in the sample.

(3a*S*,4*S*,5*S*,6a*R*)-5-hydroxy-4-[(E,3*R*)-3-hydroxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydrocyclopenta[b]furan-2-one (**13**)

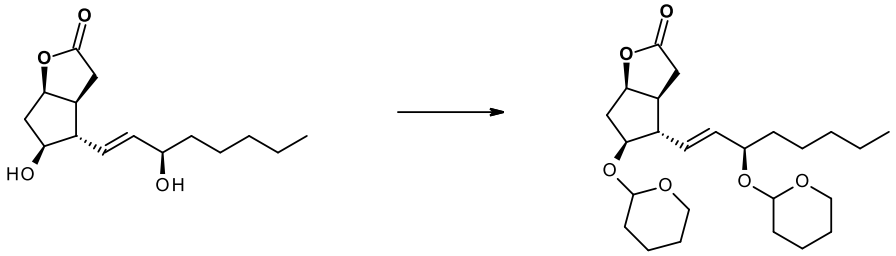


$C_{15}H_{26}O_4$
Mw: 270.36
11

$C_{15}H_{24}O_4$
Mw: 268.35
13

KI (7.176 g, 43.23 mmol) and $KHCO_3$ (4.306 g, 43.02 mmol) were dissolved in water (30 ml). Lactol (**11**) (3.925 g, 14.52 mmol) was added to the solution at 30-35 °C. The mixture was stirred for 15 minutes and then iodine (5.4448 g, 20.97 mmol) was added, while maintaining the temperature at 40-60 ° C. When the reaction was completed, the excess of iodine was quenched with $Na_2S_2O_4$ (3.401g, 21.51 mmol) at 20-25 °C. Ethyl acetate (28 ml) was added to the solution. After stirring, the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 28 ml). The combined organic layers were evaporated, the residue was dissolved in toluene (10ml) and was evaporated again. The residue was dissolved in dry THF (3ml) and the weight of the residue was adjusted to 13.45 g by addition of dry toluene. The intermediate was used in the next reaction step without further purification.
Yield: 100 %

(3a*S*,4*S*,5*S*,6a*R*)-5-tetrahydropyran-2-yloxy-4-[(E,3*R*)-3-tetrahydropyran-2-yloxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydrocyclopenta[b]furan-2-one (**14**)

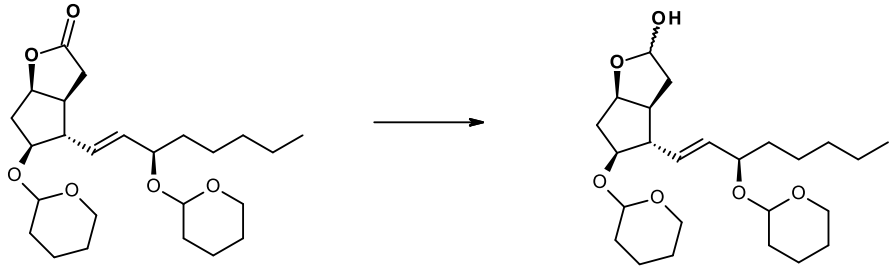


$C_{15}H_{24}O_4$
Mw: 268.35
13

$C_{25}H_{40}O_6$
Mw: 436.58
14

To the solution of **13** lactone intermediate (14.52 mmol) 3,4-dihydropyran (4.0 ml, 43.56 mmol) and *p*TsOH.3H_2O (0.055 g, 0.29 mmol) dissolved in THF (0.3 ml) were added and the reaction mixture was stirred at 35-45 °C. When the reaction was completed, triethylamine (0.162 ml, 1.16 mmol) was added, and the reaction mixture was poured into 15% NaCl solution (10 ml). After stirring the phases were separated, the organic phase was washed with 15% NaCl solution (10 ml), dried over sodium sulfate and evaporated. The intermediate was used in the next reaction step without further purification.
Yield: 100 %

(3a*S*,4*S*,5*S*,6a*R*)-5-tetrahydropyran-2-yloxy-4-[(E,3*R*)-3-tetrahydropyran-2-yloxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydro-2H-cyclopenta[b]furan-2-ol (**15**)

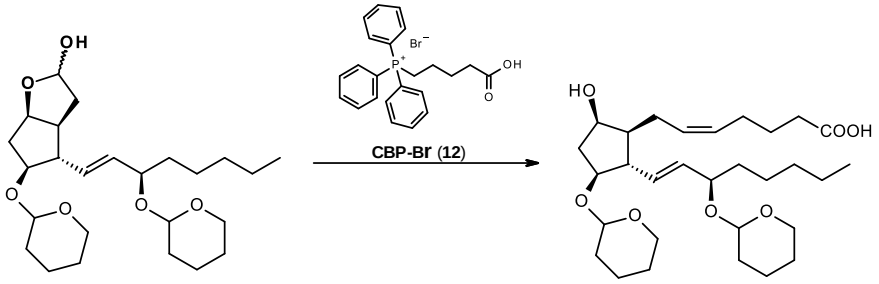


$C_{25}H_{40}O_6$
Mw: 436.58
14

$C_{25}H_{42}O_6$
Mw: 438.60
15

Protected lactone (**14**) (14.52 mmol) was dissolved in dry toluene (60 ml). 1.5 mol/l DIBAL-H solution (17.5 ml, 26.25 mmol in toluene) was added dropwise to the solution at (-75)-(-70)°C under an inert atmosphere. When the required conversion was complete, the reaction mixture was quenched with 1 mol/l $NaHSO_4$ solution (170 ml). The reaction mixture was stirred for 45-60 minutes, and then the phases were separated. The aqueous layer was extracted with toluene (25 ml) and the combined organic layers were washed with 1 mol/l $NaHCO_3$ solution (pH > 8) and dried over sodium sulfate. The drying agent was filtered off, and triethylamine (0.07 ml) was added to the filtrate and the filtrate was evaporated. The intermediate was used in the next reaction step without further purification.
Yield: 6.212 g (97.6%).

ent-THP_2-$PGF_{2\alpha}$ (**16**)



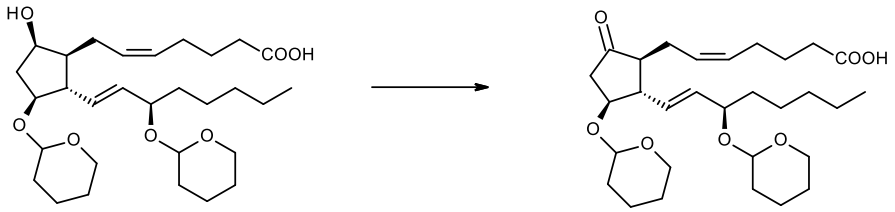
$C_{25}H_{42}O_6$
Mw: 438.60
15

$C_{30}H_{50}O_7$
Mw: 522.71
16

CBP-Br (**12**) (12.942 g, 29.19 mmol) was suspended in dry THF (75 ml) under an inert atmosphere. Potassium *tert*-butoxide (9.836 g, 87.65 mmol) was added and the reaction mixture was cooled to (-10)-(-5)°C. After stirring for 30 minutes, a solution of the protected lactol (**15**) (6.212 g, 14.16 mmol) in dry toluene (6 ml) was added dropwise while maintaining the temperature at (-5)-0°C. After completion of the reaction, the reaction mixture was quenched by adding 1 mol/l $NaHSO_4$ solution (30 ml). After stirring for 20 minutes, THF was distilled off, the precipitated white solid was filtered off and washed with 1 mol/l $NaHCO_3$ solution (2 x 14 ml) and water (14 ml). To the *ent*-PGF_{2a} containing filtrate diisopropyl ether (55 ml) was added, and it was neutralized with 2 mol/l $NaHSO_4$ solution, then extracted with diisopropyl ether (2 x 27 ml). The combined organic phases were washed with 15 % NaCl

(2 x 15 ml), dried over sodium sulfate, the drying agent was filtered off, and the filtrate was diluted with toluene (20 ml) and evaporated.
Yield: 7.101 g (95.9%)

ent-THP$_2$-PGE$_2$ (**17**)

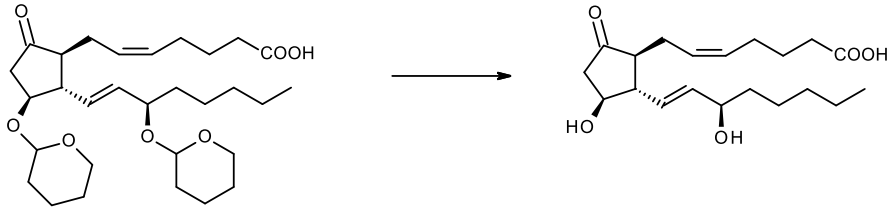


$C_{30}H_{50}O_7$
Mw: 522.71
16

$C_{30}H_{48}O_7$
Mw: 520.70
17

To a suspension of pyridinium chlorochromate (2,615 g, 12.13 mmol) in ethyl acetate (25 ml) NaOAc (0.995 g, 12.13 mmol), acetic acid (0.55 ml, 9.70 mmol) and silica gel (4.0 g) were added. The reaction mixture was heated to 40 °C and a solution of *ent*-THP$_2$-PGF$_{2\alpha}$ (**16**) (2.536 g, 4.85 mmol) in ethyl acetate (7 ml) was added dropwise. After completion of the reaction, silica gel was filtered off, the precipitate was washed with ethyl acetate (3 x 3 ml), the filtrate was diluted with diisopropyl ether (12 ml) and purified by column chromatography using ethyl acetate-diisopropyl ether as eluent. The main fraction was evaporated.
Yield: 1.706 g (67.5%)

ent-PGE$_2$ (+)-(**2**)



$C_{30}H_{48}O_7$
Mw: 520.70
17

$C_{20}H_{32}O_5$
Mw: 352.46
(+)-2

To a solution of *ent*-THP$_2$-PGE$_2$ (**17**) (1.706 g, 3.28 mmol) in isopropanol (9 ml) 1 mol/l HCl solution (8 ml, 8 mmol) than a solution of 1 mol/l HCl (3 ml, 3 mmol) in water (1.5 ml) was added dropwise at 15-20 °C. After completion of the reaction, brine (7.5 ml) and diisopropyl ether (25 ml) were added to the reaction mixture. After stirring, phases were separated, the organic layer was washed with brine (3 x 20 ml) and purified by column chromatography using hexane-ethyl acetate mixtures as eluents. The main fraction was evaporated and crystallized from diethyl ether-diisopropyl ether.
Yield: 0.193 g (16.7%), ee: 0.999 (by chiral HPLC), purity: approximately 98% (by NMR spectra)

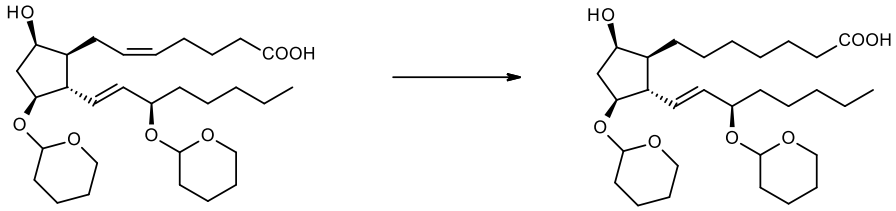
^{1}H NMR (500 MHz, DMSO-d$_6$): δ [ppm] = 11.99 (br, 1H, C1-H), 5.545-5.40 (m – in: 5.495 (dd, ^3J=15.4 Hz and 7.5 Hz, 1H, C13-H) and 5.44 (dd, ^3J=15.4 Hz and 6.1 Hz, C14-H) – 2H), 5.355 (dt, ^3J=10.9 Hz and 7.2

Hz, 1H, C5-H), 5.26 (dt (ddd), ^3J=10.6 Hz and 7.2 Hz, 1H, C6-H), 5.02 (br, 1H, C11-OH), 4.55 (br, 1H, C15-OH), 4.00-3.84 (m – in: 3.94 (q, ^3J=8.1 Hz, 1H, C11-H) and 3.885 (q, ^3J=6.1 Hz, 1H, C15-H) – 2H), 2.565* (dd, ^3J=18.1 Hz and 7.3 Hz, 1H, C10-H$_\alpha$), 2.31-2.07 (m – in: 2.255 (dt, ^3J=11.4 Hz and 7.9 Hz, 1H, C12-H), 2.215 (m, 1H, C7-Ha), 2.175 (m, 1H, C7-Hb), 2.175 (t, ^3J=7.5 Hz, 2H, C2-CH$_2$), 2.115 (dt, ^3J=11.3 Hz and 5.0 Hz, 1H, C8-H) – 6H), 2.04-1.92 (m – in: 1.99 (dd, ^3J=18.0 Hz and 9.1 Hz, 1H, C10-H$_\beta$) and 1.98 (q, ^3J=7.0 Hz, 2H, C4-CH$_2$) – 3H), 1.52 (qui, ^3J=7.4 Hz, 2H, C3-CH$_2$), 1.47-1.17 (m, 8H, C16-CH$_2$, C17-CH$_2$, C18-CH$_2$, C19-CH$_2$), 0.855 (t, ^3J=6.9 Hz, 3H, C20-CH$_3$).

^{13}C NMR (500 MHz, DMSO-d$_6$): δ [ppm] = 215.12 (C9), 174.27 (C1), 136.38 (C14), 130.34 (C5), 129.73 (C13), 126.81 (C6), 71.00** (C15), 70.95** (C11), 53.50 (C8), 52.33 (C12), 46.79 (C10), 37.47 (C16), 33.15 (C2), 31.33 (18), 26.18 (C4), 24.76 (C17), 24.41 (2C, C3 and C7), 22.17 (C19), 13.92 (C20).

*Partly overlapped by the ^{1}H NMR signal of the DMSO-d$_6$ solvent. **: Partly overlapped ^{13}C NMR signals.

ent-THP$_2$-PGF$_{1\alpha}$ (**18**)

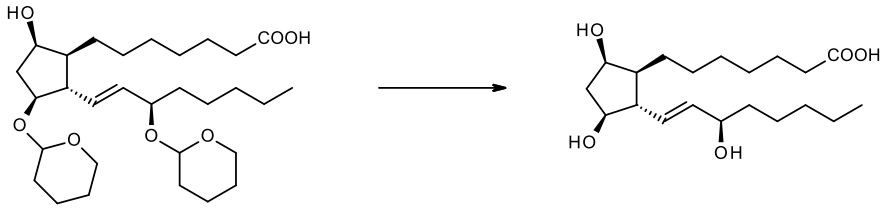


$C_{30}H_{50}O_7$
Mw: 522.71
16

$C_{30}H_{52}O_7$
Mw: 524.73
18

Prior to catalytic hydrogenation, *ent*-THP$_2$-PGF$_{2\alpha}$ (**16**) (4.565 g) was purified by column chromatography using hexane:acetone=4.1 as eluent. The evaporated main fraction of chromatography (3.407 g, 6.52 mmol) was dissolved in DCM (30 ml), diisopropyl ethylamine (0.25 ml) and 10% Pd/C catalyst (0.7 g) were added to the solution. After careful inerting, the hydrogenation reaction was carried out at pressure of 0.9 bar. After completion of the reaction, the catalyst was filtered off, washed with DCM (3 x 3 ml), the filtrate was acidified to pH 2with 1 mol/l NaHSO$_4$ solution. The phases were separated, the organic layer was washed with water (2 x 10 ml), dried over sodium sulfate (4 g), the drying agent was filtered off, and the filtrate was evaporated.
Yield: 3.247 g (94.9%)

ent-$PGF_{1\alpha}$ ((-)-**3**)



$C_{30}H_{52}O_7$
Mw: 524.73
18

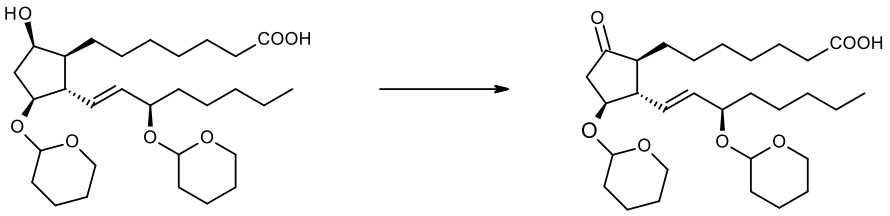
$C_{20}H_{36}O_5$
Mw: 356.60
(-)-3

To a solution of *ent*-THP_2-$PGF_{1\alpha}$ (**18**) (1.443 g, 2.75 mmol) in isopropanol (8 ml) 1 mol/l HCl solution (7ml) then a solution of 1 mol/l HCl solution (2.5 ml) in water (1 ml) were added dropwise at 15-20 °C. After completion of the reaction, brine (7 ml) and diisopropyl ether (20 ml) were added to the reaction mixture. After stirring, the layers were separated, the organic layer was washed with brine (3 x 10 ml), dried over sodium sulfate (5 g). The drying agent was filtered off and the filtrate was evaporated. The residue was first crystallized from ethyl acetate, then from ethyl acetate-hexane.
Yield: 0.116 g (11.8 %), ee: 0.993 (by chiral HPLC), purity: approximately 97% (by NMR spectra)

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 11.94 (br, 1H, C1-H), 5.38-5.215 (m – in: 5.315 (dd, ^3J=15.4 Hz and 6.3 Hz, 1H, C14-H) and 5.275 (dd, ^3J=15.4 Hz and 7.6 Hz, C13-H) – 2H), 4.57-4.34 (m – in: 4.47 (br, 1H, C15-OH) and 4.435 (br, 1H, C11-OH) – 2H), 4.255 (br, 1H, C9-OH), 3.97-3.78 (m – in: 3.905 (tbr (ddd), ^3J=4.8 Hz, 1H, C9-H) and 3.84 (q (td), ^3J=5.9 Hz, 1H, C15-H) – 2H), 3.635 (td, ^3J=7.1 Hz and 6.1 Hz, 1H, C11-H), 2.24-2.11 (m – in: 2.185 (ddd, ^3J=14.3 Hz, 8.4 Hz and 6.1 Hz, 1H, C10-H_α) and 2.16 (t, ^3J=7.3 Hz, 2H, C2-CH_2 – 3H), 2.06 (dt, ^3J=11.3 Hz and 7.6 Hz, 1H, C12-H), 1.525-1.04 (m, 20H, C3-CH_2, C4-CH_2, C5-CH_2, C6-CH_2, C7-CH_2, C8-H, C10-H_β, C16-CH_2, C17-CH_2, C18-CH_2, C19-CH_2), 0.845 (t, ^3J=6.7 Hz, 3H, C20-CH_3).

^{13}C NMR (500 MHz, DMSO-d_6): δ [ppm] = 174.46 (C1), 135.27 (C14), 132.16 (C13), 75.88 (C11), 71.39 (C15), 69.55 (C9), 54.52 (C12), 48.37 (C8), 43.99 (C10), 37.59 (C16), 33.68 (C2), 31.34 (18), 29.30 (C5), 28.65 (C4), 27.27 (C6), 26.79 (C7), 24.81 (C17), 24.57 (C3), 22.22 (C19), 13.89 (C20).

ent-THP$_2$-PGE$_1$ (**19**)

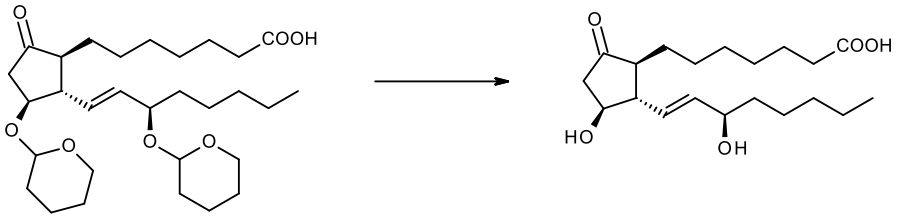


$C_{30}H_{52}O_7$
Mw: 524.73
18

$C_{30}H_{50}O_7$
Mw: 522.71
19

To a suspension of pyridinium chlorochromate (1,860 g, 8.63 mmol) in ethyl acetate (20 ml) NaOAc (0.708 g, 8.63 mmol), acetic acid (0.4 ml, 6.90 mmol) and silica gel (3.0 g) were added. The reaction mixture was heated to 40 °C and a solution of *ent*-THP$_2$-PGF$_{1\alpha}$ (**18**) (1.804 g, 3.44 mmol) in ethyl acetate (7 ml) was added dropwise. After completion of the reaction, silica gel was filtered off, the precipitate was washed with ethyl acetate (3 x 2 ml), the filtrate was diluted with diisopropyl ether (8 ml) and purified by column chromatography using ethyl acetate-diisopropyl ether as eluent. The main fraction was evaporated.
Yield: 1.258 g (70.0 %)

ent-PGE$_1$ ((+)-**4**)



$C_{30}H_{50}O_7$
Mw: 522.71
19

$C_{20}H_{34}O_5$
Mw: 354.48
(+)-**4**

To a solution of *ent*-THP$_2$-PGE$_1$ (**19**) (1.258 g, 2.41 mmol) in isopropanol (7 ml) 1 mol/l HCl solution (6 ml) then a solution of 1 mol/l HCl solution (2 ml) in water (1 ml) were added dropwise at 15-20 °C. After completion of the reaction, brine (6 ml) and diisopropyl ether (20 ml) were added to the reaction mixture. After stirring, the layers were separated, the organic layer was washed with brine (3 x 10 ml), dried over sodium sulfate (5 g). The drying agent was filtered off and the filtrate was evaporated. The residue was crystallized from diisopropyl ether-hexane.
Yield: 0.350 g (41.0 %), ee: 0.999 (by chiral HPLC), purity: approximately 98% (by NMR spectra)

^{1}H NMR (500 MHz, DMSO-d$_6$): δ [ppm] = 11.95 (br, 1H, C1-H), 5.535-5.405 (m – in: 5.495 (dd, ^3J=15.4 Hz and 7.1 Hz, 1H, C13-H) and 5.455 (dd, ^3J=15.4 Hz and 6.0 Hz, C14-H) – 2H), 4.99 (d (br), ^3J~4.0, 1H, C11-OH), 4.55 (br, 1H, C15-OH), 3.985-3.835 (m – in: 3.925 (qd, ^3J=8.1 Hz and 2.3 Hz, 1H, C11-H) and 3.89 (q, ^3J=6.0 Hz, 1H, C15-H) – 2H), 2.545* (m (dd), ^3J=18.1 Hz and 7.3 Hz, 1H, C10-H$_\alpha$), 2.235 (dt, ^3J=11.4 Hz and

7.4 Hz, 1H, C12-H), 2.165 (t, ^{3}J=7.4 Hz, 2H, C2-CH_2), 2.065-1.935 (m – in: 2.02 (dd, ^{3}J=18.1 Hz and 8.8 Hz, 1H, C10-H_β) and 1.98 (dt, ^{3}J=11.3 Hz and 5.6 Hz, 1H, C8-H) – 2H), 1.54-1.11 (m, 18H, C3-CH_2, C4-CH_2, C5-CH_2, C6-CH_2, C7-CH_2, C16-CH_2, C17-CH_2, C18-CH_2, C19-CH_2), 0.85 (t, ^{3}J=6.8 Hz, 3H, C20-CH_3).

^{13}C NMR (500 MHz, DMSO-d_6): δ [ppm] = 215.69 (C9), 174.42 (C1), 136.25 (C14), 130.16 (C13), 71.03 (C15), 70.92 (C11), 53.42 (C12), 53.29 (C8), 46.58 (C10), 37.46 (C16), 33.62 (C2), 31.33 (18), 28.97 (C5), 28.38 (C4), 27.22 (C7), 26.17 (C6), 24.70 (C17), 24.44 (C3), 22.17 (C19), 13.90 (C20).

*Partly overlapped by the ^{1}H NMR signal of the DMSO-d_6 solvent.