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NOTICE OF ENTITLEMENT

We, **KABI PHARMACIA AB & CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA** of, 7 Raps Gatan, S-751 82 Uppsala, Sweden and H-1045 Budapest, Tó u. 1-5, being the applicants in respect of Application No. **22629/92** state the following:-

The Persons nominated for the grant of the patent has entitlement from the actual inventors by assignment.

The persons nominated for the grant of the patent are the applicants of the application listed in the declaration under Article 8 of the PCT.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

KABI PHARMACIA AB & CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

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Louis C. Gebhardt
Registered Patent Attorney

8 December 1994

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 656994

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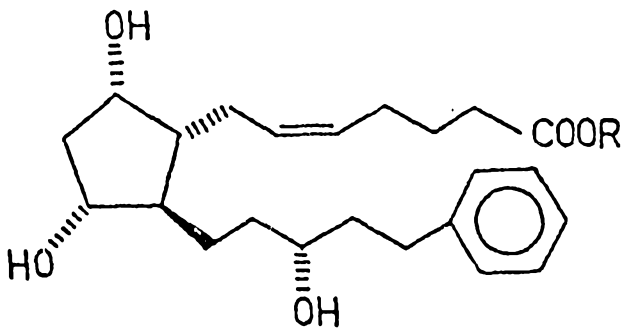
(56) Prior Art Documents
AU 470384 43940/72 09.16 09.17 9.18

(57) Claim

1. Process for the preparation of 13,14-dihydro-15(R)--17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ esters of the general formula (I), wherein R stands for saturated or unsaturated straight, branched or cyclic C_{1-7}alkyl or phenyl or benzyl group



(I)

which comprises reducing the oxo group on the side chain of the compound of formula (VII),

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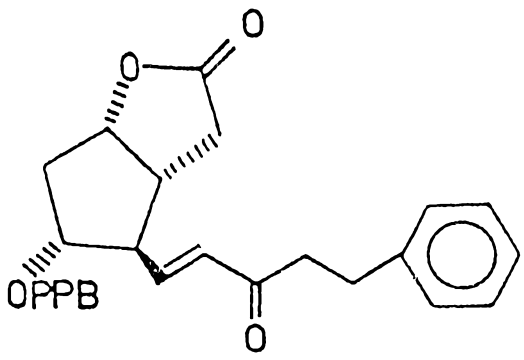
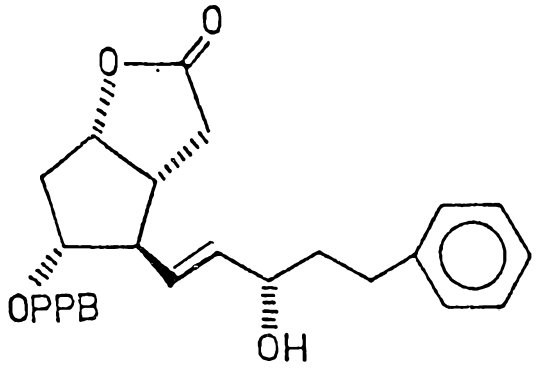


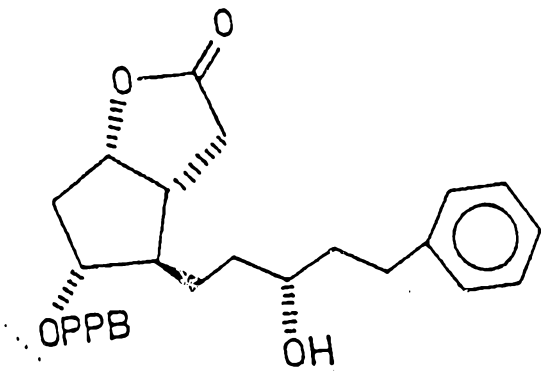
(VII)

transforming the obtained 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxypent-1'-enil]-5-(4'-phenylbenzoxyloxy)-2H-cyclopenta[b]furan of the formula (VI)



(VI)

by hydrogenation to 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (V)



(V)

reducing the compound of formula (V) to 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (IV),

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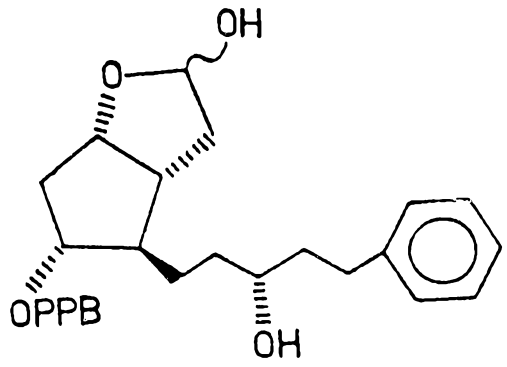
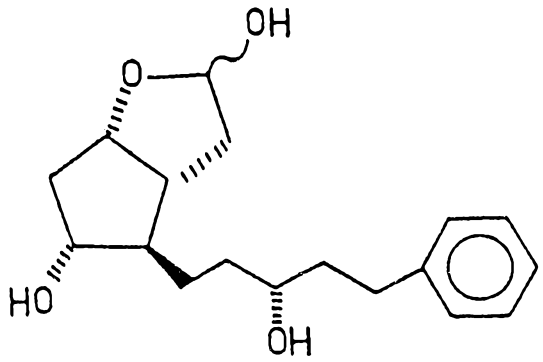


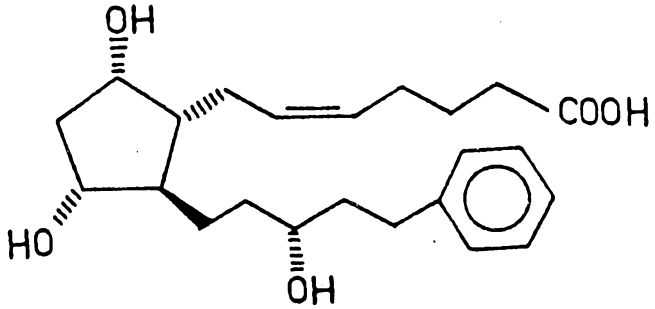
(IV)

removing the protective group from the compound of formula (IV) to obtain 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan of the formula (III)



(III)

then transforming the compound of formula (III) obtained to 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ of the formula (II)



(II)

by using 4-carboxybutyl-triphenylphosphonium halide and finally, transforming the compound of formula (II) with a com-

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pound of the general formula R-X, wherein R has the same meaning as stated above, X is halogen, sulphate, mesyl, tosyl or any suitable group, to 13,14-dihydro-15(R)-17-phenyl--18,19,20-trinor-$PGF_{2\alpha}$ esters of the general formula (I).

11.13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ of the formula (II).

12.3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4-[5'-phenyl--3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan of the formula (III).

13. 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4-[5'-phenyl--3'(R)-hydroxy-1'-pentyl]-5-(4-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (IV).

14. 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl--3'(R)-hydroxy-1'-pentyl]-5-(4-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (V).

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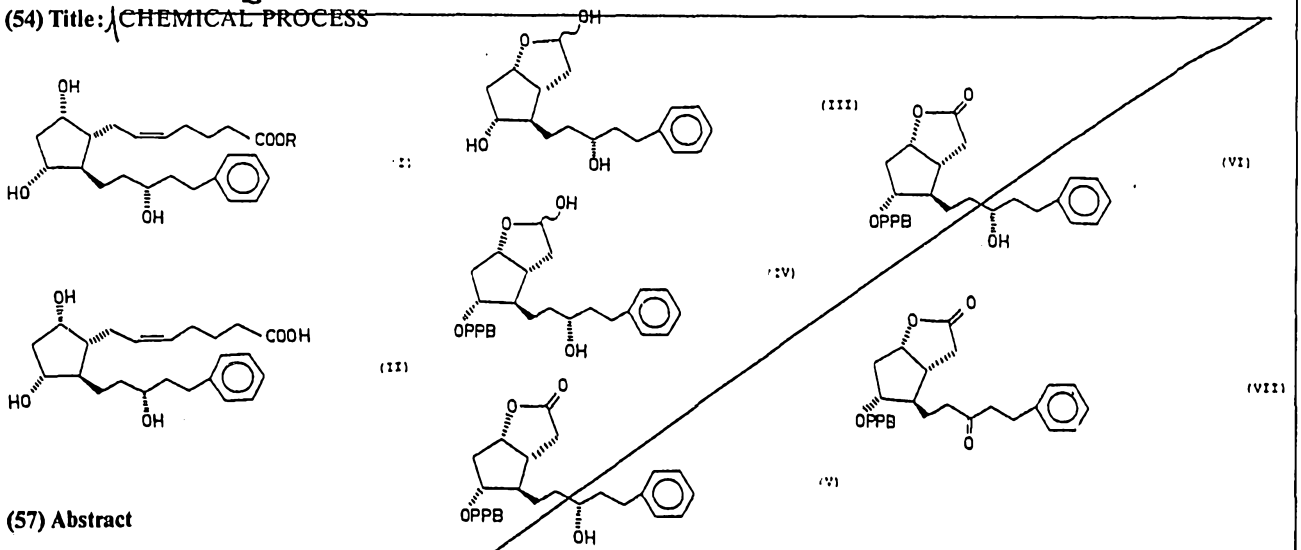
Prostaglandins

(54) Title: ~~CHEMICAL PROCESS~~



(57) Abstract

The invention relates to a novel process for the preparation of 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ isopropyl ester of formula (I), wherein R stands for saturated or unsaturated straight, branched or cyclic C_{1-7} alkyl or phenyl or benzyl group. The process of the invention comprises reducing the oxo group on the side chain of the compound of formula (VII), transforming the obtained 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxypent-1'-enil]-5-(4'-phenylbenzoxyloxy)-2H-cyclopenta[b]furan of formula (VI) by hydrogenation to 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of formula (V) reducing the compound of formula (V) to 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of formula (IV), removing the protective group from the compound of formula (IV) to obtain 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan of formula (III) then transforming the compound of formula (III) obtained to 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ of formula (II) by using 4-carboxybutyl-triphenylphosphonium halide and finally, transforming the compound of formula (II) with a compound of the general formula R-X wherein R has the same meaning as stated above, X is halogen sulphate, mesyl, tosyl or any suitable group to 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ esters of general formula (I).

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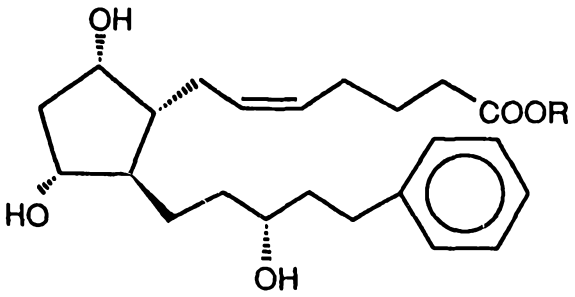
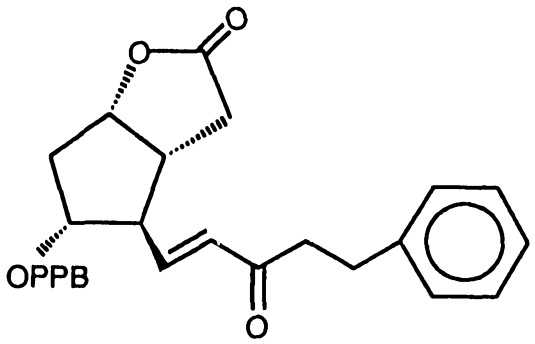
ABSTRACT

The invention relates to a novel process for the preparation of 13, 14-dihydro-15(R)-17-phenyl-18, 19, 20-trinor-PGF_{2a} isopropyl ester of the formula (I) - wherein R stands for saturated or unsaturated straight, branched or cyclic C_{1-7} alkyl or phenyl or benzyl group -



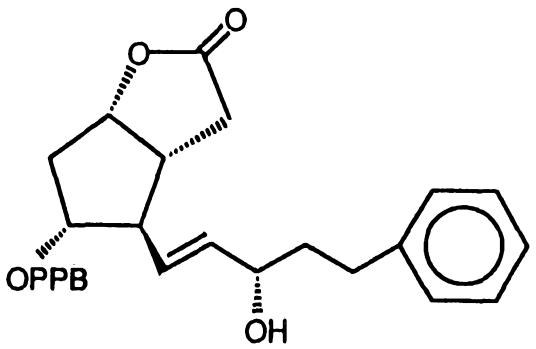
(I)

The process of the invention comprises reducing the oxo group on the side chain of the compound of formula (VII),



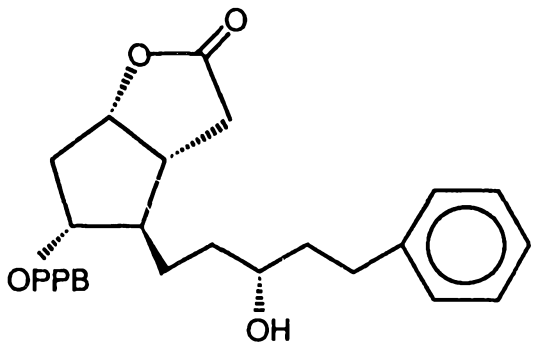
(VII)

transforming the obtained 3, 3a, 4, 5, 6, 6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxypent-1'-enil]-5-(4'-phenylbenzoxyloxy)-2H-cyclopenta[b]furan of the formula (VI)



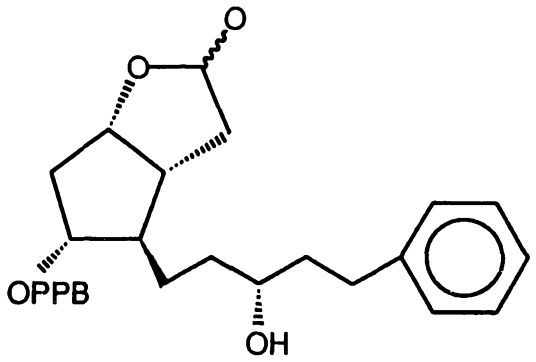
(VI)

by hydrogenation to 3, 3a, 4, 5, 6, 6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (V)



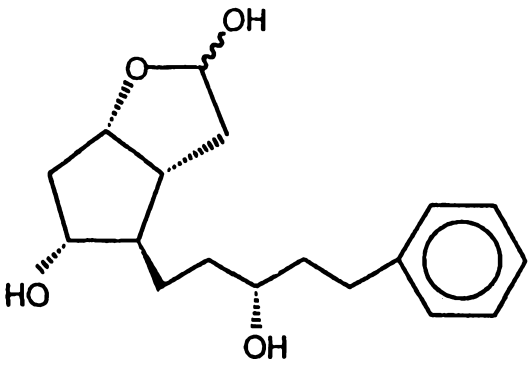
(V)

reducing the compound of formula (V) to 3, 3a, 4, 5, 6, 6a-hexahydro-2-hydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (IV),



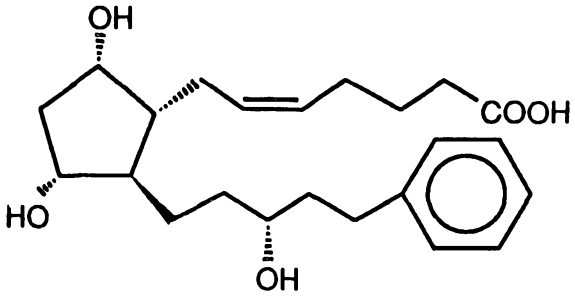
(IV)

removing the protective group from the compound of formula (IV) to obtain 3, 3a, 4, 5, 6, 6a-hexahydro-2, 5-dihydroxy-4-(5'-phenyl-3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan of the formula (III)



(III)

then transforming the compound of formula (III) obtained to 13, 14-dihydro-15 (R)-17-phenyl-18, 19, 20-trinor-PGF_{2a} of the formula (II)

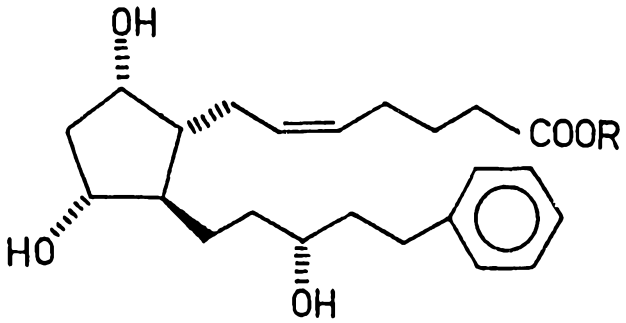


(II)

by using 4-carboxybutyl-triphenylphosphonium halide and finally, transforming the compound of formula (II) with a compound of the general formula R-X, wherein R has the same meaning as stated above, X is halogen, sulphate, mesyl, tosyl or any suitable group, to 13, 14-dihydro-15(R)-17-phenyl-18, 19, 20-trinor-PGF_{2a} esters of the general formula (I).

CHEMICAL PROCESS

This invention relates to a novel process for the preparation of 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ esters of the general formula (I)



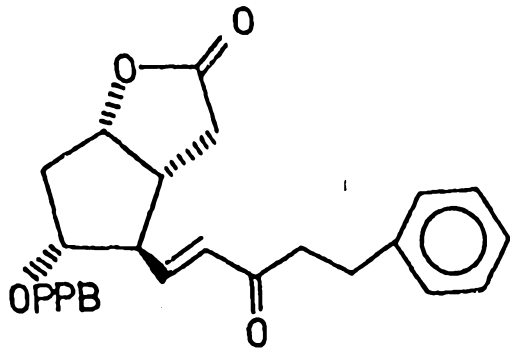
(I)

wherein R stands for saturated or unsaturated straight, branched or cyclic C_{1-7} alkyl or phenyl or benzyl group.

It is known that many prostaglandin derivatives are capable to decrease intraocular tension when used topically, i.e. they are useful for the treatment of glaucoma (published European patent applications Nos. 0,170,258 and 0,253,094). Prostaglandin derivatives possessing particularly advantageous effect have been described in the published PCT patent application No. WO 90/02553. From these, the compound of formula (I) proved to be particularly favourable. A method for synthesis of the compound of formula (I) has been disclosed in the PCT application cited above.

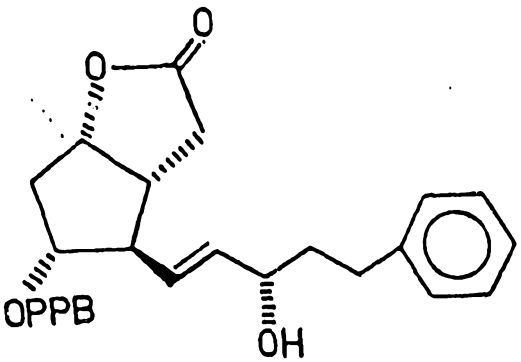
The aim of this invention is to present an improved method for a synthesis, which is useful for the production of the compound of formula (I) in a good yield, in large amounts, with the desired purity.

It has been found that the compound of formula (I) is obtained in a high purity and in high yield by reducing the oxo group on the side chain of the compound of formula (VII),



(VII)

transforming the obtained 3,3a,4,5,6,6a-hexahydro-2-oxo-4--[5'-phenyl-3'(R)-hydroxypent-1'-enil]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (VI)



(VI)

by hydrogenation to 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (V)

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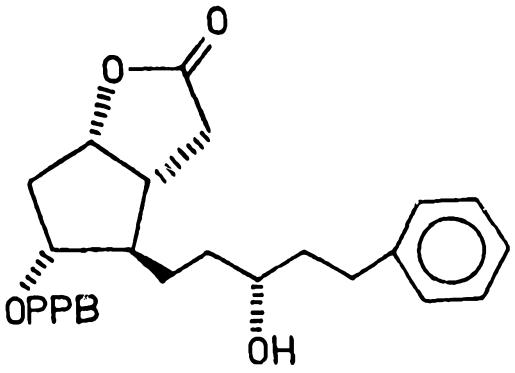
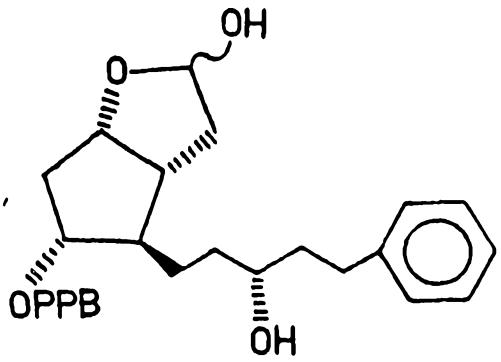


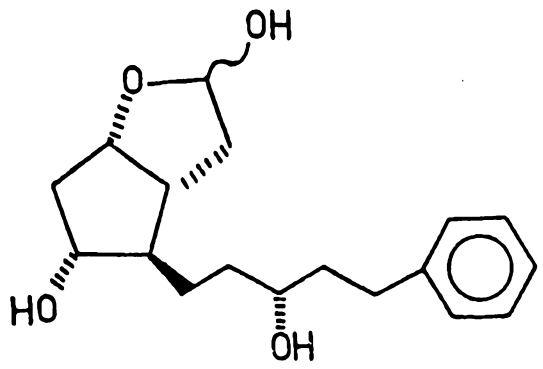
(V)

reducing the compound of formula (V) to 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (IV),



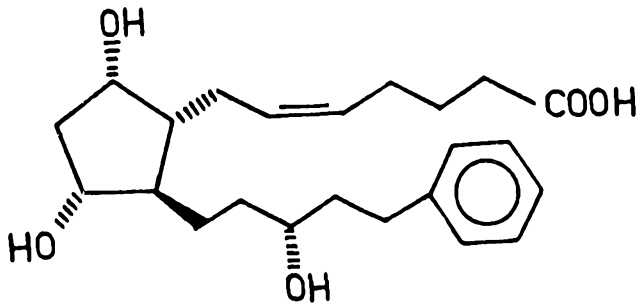
(IV)

removing the protective group from the compound of formula (IV) to obtain 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan of the formula (III)



(III)

then transforming the compound of formula (III) to give 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ of the formula (II)



(II)

by using 4-carboxybutyl-triphenylphosphonium halide and finally, transforming the compound of formula (II) with a compound of the general formula R-X, wherein R has the same meaning as stated above, X is halogen, sulphate, mesyl, tosyl or any other suitable group, to 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ ester of the general formula (I).

The compound of formula (VII) is prepared from phenylphosphonium salts and 3,3a,4,5,6,6a-hexahydro-2-oxo-4-(5'--phenyl-3-oxopent-1'-enyl)-5-(4'-phenylbenzoyloxy)-2H-

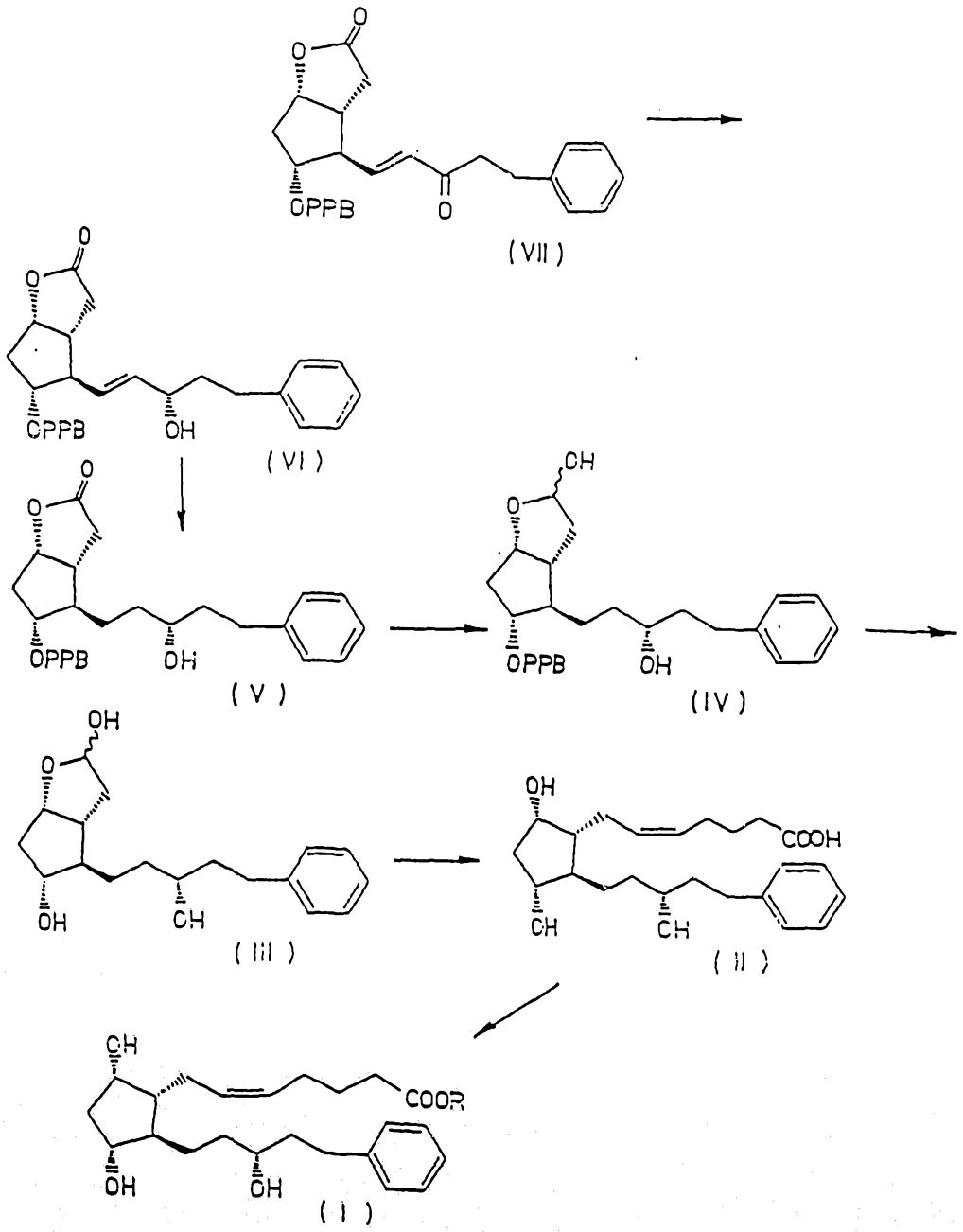
-cyclopenta[b]furan, which is a known prostaglandin intermediate and can be obtained e.g. according to the United States patent specification No. 3,778,450. Other reagents used are commercially available.

The reduction of the compound of formula (VII) to the compound of formula (VI) is carried out by using any reagent known suitable for the reduction of enones especially from the chemical literature of prostaglandins, e.g. by using lithium tri(sec-butyl)borohydride or sodium borohydride [J. Am. Chem. Soc. 94, 8616 (1972); J. Am. Chem. Soc. 106, 6717 (1984)]. The transformation of the compound of formula (VI) to the substances of formula (V) may be realized in the presence of a catalyst commonly used for hydrogenation, for example palladium on carbon or rhodium on carbon but preferably palladium on carbon, preferably in the presence of a base or sodium salts like sodium hydroxide or sodium nitrite.

The transformation of the compound of formula (III) to a compound of formula (II) may be carried out by using any combination of conditions (base, solvent and the like) commonly used in the Wittig reaction. Preferably sodium amid, potassium terc.butylate, sodium hydride or buthyl lithium as a base and diglyme, DMSO, DMF or tetrahydrofurane as a solvent can be used. The transformation of the compound of formula (V) to the compound of formula (IV) and subsequently, the transformation of the compound of formula (IV) to the product of formula (III) can be achieved without isolating the compound of formula (IV), too, under suitably selected conditions. It is obvious to a man skilled in the art that

the compounds of the formula (II-VII) and the general formula (I) may contain further substituents and the claimed process still takes place. Such reactions are therefore clearly within the scope of this patent application.

We summarize our process on the following Scheme I.



The process of the invention is illustrated in detail by the following non-limiting Examples.

Example 1

Preparation of 3,3a,4,5,6,6a-hexahydro-2-oxo-4-(5'--phenyl-3-oxo-pent-1'-enyl)-5-(4'-phenylbenzoyloxy)--2H-cyclopenta[b]furan [compound of the formula (VII)]

A solution containing 3,3a,4,5,6,6a-hexahydro-2-oxo-4--hydroxymethyl-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan (18 g, 51 mmol) in dry toluene (110 ml) is cooled to 18 °C, then the solution of dicyclohexylcarbodiimide (18 g, 83 mmol) and 1 Molar phosphoric acid solution (8 ml, 8 mmol) in dry dimethylsulfoxide is added. The reaction mixture is maintained below a temperature of 25 °C under continuous cooling. After 30 minutes, the following reagents are added to the reaction mixture in intervals of 30 minutes:

1 M phosphoric acid solution (4 ml) in dimethylsulfoxide; dicyclohexylcarbodiimide (9 g, 41 mmol) and 1 M phosphoric acid solution (5 ml) in dimethylsulfoxide.

Subsequently, the reaction mixture is stirred at 20-22 °C for 2 hours. Meanwhile triphenyl-(4-phenyl-3-oxobutyl)-phosphonium iodide (27.3 g, 50 mmol) and 5 M calcium hydroxide solution (10 ml) in toluene (250 ml) are stirred at 45 °C for 90 minutes; then the solution obtained is washed 3 times with 100 ml of water each of 45-50 °C temperature, until neutral, then toluene (45 ml) are removed from the solution under reduced pressure. The residual solution is added to the other reaction mixture at a rate that its temperature does not exceed 30 °C. After 2 hours the solution is

heated to 35 °C, after additional 1 hour concentrated hydrochloric acid (4 ml) dissolved in water (30 ml) are added and then stirred for 1 additional hour. The precipitate is removed by filtration, the filtrate is washed with toluene and after combination, the toluene solution is washed with water (150 ml), 4 times with saline (30 ml), dried over anhydrous sodium sulfate and then evaporated to 350 ml.

The above solution is transferred to a column containing silica gel (135 g) and toluene and eluted by using an 5:1 mixture of toluene and ethyl acetate. After evaporating the solution, dark brown solid (21 g) are obtained which is dissolved in boiling methanol (840 ml). After cooling the solution to 0 °C, filtering the precipitate and washing with cold methanol (30 ml), the product is dried at room temperature to give the title product of formula (VII) as a white substance in a yield of 12.0 g (48.7 %), m.p.: 129-130 °C, $[\alpha]_D$ = -145° (c = 1, ethyl acetate).

Example 2

Preparation of 3,3a,4,5,6,6a-hexahydro-2-oxo-4-(5'--phenyl-3-oxo-pent-1'-enyl)-5-(4'-phenylbenzoyloxy)--2H-cyclopenta[b]furan [compound of the formula (VII)]

a) To a solution of 3,3a,4,5,6,6a-hexahydro-2-oxo-4-hydroxymethyl-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[a]furan (27 kg) in toluene (165 L), cooled to 17 °C, dicyclohexylcarbodiimide (DCC) (27 kg), phosphoric acid in dimethylsulfoxid (DMSO) 1M (12L) was added. The temperature of the reaction mixture was kept below 25 °C after 60 min. The following reagents in the following orders were added to the

reaction mixture in 60 min. intervals; phosphoric acid in DMSO 1M (6L), DCC (13.5 kg), phosphoric acid in DMSO 1M (6L). The reaction mixture was stirred at 20-25 °C for additional 7 hours (TLC monitoring).

TLC Rf = 0.32 (silicagel, AcOEt:toluene)

(silicagel, toluene-AcOEt-AcOH: 30:15:2)

b) Triphenyl-2-oxo-4-phenylbutylphosphonium iodide (38.4 kg), potassium hydroxide (5 kg) in water (105L), toluene (210L) and dichloromethane (90L) was stirred vigorously for 3 hours followed by addition of sodium chloride (5 kg). The organic layer was separated and washed with brine (3x113L), dried on sodium sulphate, concentrated in vacuo to 70L, this solution was added to the solution prepared by the method described in part a) of this example at a rate that the temperature of the reaction mixture not exceed 25 °C. After 7 hours the solution was cooled to 18 °C (TLC monitoring). A solution of concentrated HCL (6L) in water (45L) was added and the mixture was stirred for an hour. The precipitate was removed by filtration, washed with toluene (2x45L + 2x23L). The organic layer was washed with water (225L) and brine (4x45L), the water solution was extracted with toluene (2x23 + 1x30L), the organic layers were collected and dried on sodium sulphate (15 kg), filtered, washed with toluene (2x15L), and evaporated in vacuo to 85L and added methanol (240L), cooled to 0 °C, filtered, washed with methanol:toluene 9:1 (49L) and methanol (98+60L) to give a white crystalline product, mp: 129-130 °C, (yield 19.4 kg, 52.7 %) $[\alpha]_D^{20}$ = -116° (c = 1.26, CH_3CN).

Example 3

Preparation of 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'--phenyl-3'(R)-hydroxypent-1'-enyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan [compound of the formula (VI)]

A mixture containing 1.04 M lithium-tri(sec-butyl)-borohydride (418 ml, 0.434 mol) in tetrahydrofuran solution and dry diethyl ether (420 ml) is cooled to -130 °C. The compound of formula (VII) (200 g) are dissolved in tetrahydrofuran (1000 ml) and diethyl ether (900 ml), cooled to -130 °C and added to the above borohydride solution during 1 minute. After 5 minutes the reaction mixture is poured into a mixture containing water (5.5 l), 2 M sodium sulfate solution (250 ml) and saline (500 ml) and stirred at room temperature for 15 minutes. The solution is successively washed with water (2 L), ethyl acetate (1 L) and twice with saline (200 ml) each, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The liquid residue obtained is transferred to a column containing silica gel (5 kg). After eluting with a 7:1 mixture containing methylene chloride and ethyl acetate and recrystallizing the product obtained from the mixture of ethyl acetate (80 ml), diisopropyl ether (160 ml) and hexane (80 ml), white, crystalline title compound of formula (VI) (69.7 g) are obtained, m.p.: 129-130 °C, $[\alpha]_D$ = -108° (c = 1, ethyl acetate).

Example 4

Preparation of 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'--phenyl-3'(R)-hydroxypent-1'-enyl]-5-(4'-phenyl-benzoyloxy)-2H-cyclopenta[b]furan [compound of the formula (VI)]

To a stirred suspension of enone of the formula (VII) (19.3 kg) in methanol (4.5L) and chloroform (200L), cooled to -3-5 °C sodium borohydride (2.38 kg) was added (TLC monitoring). The reaction mixture was poured into water (20L) followed by addition of conc. HCl (12.6L). The mixture was dried on Silicagel (30 kg), filtered, washed with chloroform (60+30L). The organic layer was concentrated to 60L and chromatographed on two columns. Both columns were packed with silicagel (135 kg) and toluene (300L). Toluene: AcOEt 666L:133L + (250L:150L) and AcOEt 250L were used successively as eluent, for both columns. Fraction V (410L) was concentrated in vacuo to 35L. To the residue diisopropyl ether (90L) was added, cooled to 0 °C/-5 °C, stirred for an hour. The white crystalline product was filered and washed with DIPE- AcOEt 3:1 (16L). Yield 7.38 kg (38%). TLC:Rf = = 0.5 (silicagel; AcOEt) (0.36 (AcOEt:hexane 1:1) [α] = = -101.59 (c = 0.69 CH_3CN).

Example 5

Preparation of 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'--phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenyl-benzoyloxy)-2H-cyclopenta[b]furan [compound of the formula (V)]

To a solution containing -3,3a,4,5,6,6a-hexahydro-2-

-oxo-4-[5'-phenyl-3'(R)-hydroxypent-1'-enyl]-5-(4'-phenyl--benzoyloxy)-2H-cyclopenta[b]furan (70 g, 144 mmol) in ethanol (2 L) at 18-20 °C, palladium-on-carbon catalyst (7.0 g) and sodium nitrite (3.5 g, 50 mmol) as a suspension in water (100 ml) are added. The mixture is stirred under hydrogen of 5 bar pressure for 90 minutes, then the catalyst is filtered off, 1 M hydrochloric acid solution (100 ml) are added and the mixture is stirred at room temperature for 1 hour. After removing the solvent under reduced pressure the oily residue obtained is dissolved in ethyl acetate (700 ml). The aqueous phase is twice extracted with ethyl acetate (200 ml) each and the combined ethyl acetate solution is twice washed with saline (100 ml) each. After drying over anhydrous sodium sulfate and evaporating the solvent, the title compound of formula (V) is obtained as an oily residue in a yield of 95 % with an R_f value of 0.23 (developing system hexan/ethyl acetate 1:1), $[\alpha]_D$ = -66° (c = 1, ethyl acetate). IR spectrum (taken on a Zeiss Specord M-80 type spectrometer) (KBr, cm^{-1}): 3500 (OH), 3080, 3020 (CH aromatic), 2940, 2860 (CH aliphatic), 1770, 1710 (C=O), 1610, 1500 (aromatic ring vibration), 1290, 1190, 1100 (C-O-C), 850 (p-subst. aromatic), 750, 700 (monosubst. aromatic).

Example 6

Preparation of 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'--phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenyl-benzoyloxy)-2H-cyclopenta[b]furan [compound of the formula (V)]

To a solution of the compound of the formula (VI) (7.2

kg) in ethanol abs. (200L) at 15-20 °C a suspension of 10 % Pd/C (1.4 kg) and sodium nitrite (0.72 kg) in water (36L) was added. The solution was stirred under hydrogen atmosphere (1200 kbL) for 3 hrs (TLC monitoring). 2M HCl (105L) was added and stirred at room temperature for 1 hour. The catalyst was removed by filtration, washed with ethanol abs. (20 L). The solvent was removed in vacuo to 50L. The resulting oil was dissolved in toluene (140L), washed with brine 15% (3x30L). The water phase was washed with toluene (20L). The combined organic extracts were dried on sodium sulphate (10 kg) and sodium hydrogen carbonate (0.5 kg), respectively, filtered. The precipitate was washed with toluene (30L). The solvent was removed in vacuo to have a residue (90L) which was used directly for the next step. The residue contains the compound of the formula (V) (7.03 kg, 96.7 %).

Example 7

Preparation of 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan [compound of the formula (IV)]

After dissolving 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan (65.7 g, 135 mmol) in dry tetrahydrofuran (330 ml), diisobutyl aluminium hydride (150 ml, 297 mmol) in dry hexane solution (150ml) are dropwise added at a temperature between -65 °C and -75 °C. After stirring the reaction mixture for 10 minutes, the solution is poured into the mixture of water (1 L) and 2 M sodium hydrogen sulfate solution

(500 ml) and stirred for 30 minutes. The solution is washed with ethyl acetate (1 liter and than twice with 500 ml) each, then the combined organic phase is twice washed with saline (200 ml) each. After evaporating the organic phase under reduced pressure, the title product of formula (IV) is obtained as a colourless oily residue which is used without purification in the next step, R_f = 0.25 (benzene/ethyl acetate 1:1).

Example 8

Preparation of 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4--[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenyl-benzoyloxy)-2H-cyclopenta[b]furan [compound of the formula (IV)]

A solution of diisobutylaluminium hydride (DIBAL) (9.1 kg) in dry toluene (31 L) was added to a stirred solution of the compound of formula (V) (6.8 kg) in toluene (70L) at -72/-80 °C, after 1 hour (TLC monitoring) ethyl acetate (5L) was added, followed by addition of sodium hydrogen sulphate 1M (240L). The organic layer was separated and dried on sodium sulphate (9 kg), filtered, washed with toluene; AcOEt (5L:5L). The water layer was washed with AcOEt (3x35L). The organic layers were collected and dried with sodium sulphate (9 kg), filtered, washed with toluene: AcOEt 1:1 (40L). The organic layers were collected and toluene (100L), triethyl-amine (0.5L) were added to stabilise the triol. The solution of the triol was chromatographed on silicagel (34 kg) packed on toluene (60L), using toluene:AcOEt (1:1) (400L) and AcOEt (560L) respectively as eluent,the following fractions in the

following order were collected; fraction I (50 L), fractions II and III (400L) each, fraction IV (230L). Fraction III was rich of the desired product. The solvent was removed in vacuo. To the residue (20 L) diisopropyl ether (DIPE) (65L) was added, cooled to 0 °C. A solid substance was formed, filtered and washed with DIPE:AcOEt 3:1 (2x10L) to give a white crystalline product yield (2.8 kg, 63.1 %). Excess of DIBAL have been used to remove the PPB while the compound of the formula (V) was reduced to compound of the formula (IV).

Example 9

Preparation of 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy--4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan [compound of the formula (III)]

A mixture containing 3,3a,4,5,6,6a-hexahydro-2-hydroxy-15-4-[5'-phenyl-3'(R)-hydroxy--1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan (65.2 g, 133.4 mmol), potassium carbonate (19.0 g, 133.4 mmol) and methanol (330 ml) is stirred at 40-45 °C for 5 hours, then cooled to 0 °C and the pH value is adjusted to 7-8 by the slow addition of 1 N phosphoric acid solution. After filtering off the precipitate, the filtrate is washed twice with water (70 ml) each and then twice with a 2:1 mixture of methanol (30 ml) and water each.

After adding saline to the filtrate and extracting four times with ethyl acetate (250 ml) each, the combined organic phase is washed with saline, dried and evaporated under reduced pressure. The solid obtained is dissolved in ethyl acetate (100 ml) at 60 °C, diisopropyl ether (100 ml) are

added to the solution, cooled to room temperature and then hexane (200 ml) are slowly added. After stirring the mixture at 0 °C, the crystalline precipitate is filtered, washed twice with a 2:1 mixture of diisopropyl ether (30 ml) and ethyl acetate each and dried to give white crystalline title compound (35.93 g, 87.90 %) of formula (III), m.p.: 103-106 °C, $[\alpha]_D$ = -47° (c = 1, ethyl acetate).

IR spectrum (taken on a Zeiss Specord M-80 type spectrometer) (KBr, cm^{-1}): 3380 (OH), 3030 (CH aromatic), 2980, 2960, 2920, 2860 (CH aliphatic), 1600, 1590, 1570, 1500 (aromatic ring vibration), 1090 (C-O-C), 1000 [C-O-(H)], 750, 700 (monosubst. aromatic).

^{1}H-NMR spectrum (taken on a Bruker WP 80 device, $CDCl_3$, TMS standard, δ ppm): 7.23 (s, 5H, aromatic H), 5.64, 5.51 (d, 1H, 3-H),4.63 (m, 1H, 1-H),3.90 (1H, 7-H), 3.60 (1H, 3'-H).

The product is an 1:1 mixture of the exo and endo isomers.

Example 10

Preparation of 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ [compound of the formula (II)]

4-carboxybutyl-triphenylphosphonium bromide (147.2 g, 3.32 mmol) and potassium tert-butoxide (186g, 1.66 mmol) are added to a solution of 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan (33.9 g, 110.7 mmol) [compound of the formula (III)] in tetrahydrofuran (500 ml) and the solution is cooled to -25 °C. The mixture is stirred first at -20 °C, then at 0 °C altogether 6 hours, then the pH is adjusted to 8-9 by adding

2 M aqueous sodium hydrogen sulfate solution and tetrahydrofuran is distilled off under reduced pressure. After adding water (200 ml) to the residue, the mixture is cooled to room temperature, the precipitate is filtered, washed twice with saturated sodium hydrogen carboate solution (200 ml) each and then twice with water (100ml) each. The combined aqueous phase is washed twice with methylene chloride (150 ml) each, the pH value is adjusted to 3-4 by using sodium hydrogen sulfate solution and then extracted twice with ethyl acetate (500 ml) each. The combined ethyl acetate phase is twice washed with saline (100 ml) each and evaporated. The thick, liquid suspension is shaken with acetone (100 ml) for 10 minutes, the precipitate is filtered, washed 6 times with 100 ml of 40:25 (by volume) mixture of diisopropyl ether and aceton each and the filtrate is evaporated under reduced pressure to obtain the title compound of the formula (II) as an oily residue in a yield of 85 %, which can be transformed to the compound of formula (I) without purification.

Example 11

Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor-1-$PGF_{2\alpha}$ [compound of the formula (II)]

To a stirred suspension of 4-carboxybutyl triphenyl phosphonium bromide (5.32 kg) in THF (40L) under nitrogen at 0-5 °C potassium butoxide (4.49 kg) was added, and stirred for 20 min. at room temperature. To the resultant red orange solution of ilyde at -15/-10 °C the compound of the formula (III) was added (1.23 kg) in THF (8L), the mixture was stirred for 4-7 hours (TLC monitoring). The reaction mixture

was diluted with water (25L), washed with toluene (25L), the organic phase was separated. The water layer was washed with chloroform (3x6L), acidified with sodium hydrogen sulfate 2M (15L), extracted with AcOEt (18L and 22x6L) successively. The organic layer was washed with 15 % sodium chloride solution (2x6L), dried on sodium sulphate (0.4 kg), filtered. The precipitate was washed twice with AcOEt (4L). The solvent was removed in vacuo, the slurry was shaken with DIPE: :acetone 2:1 (18L) to crystallize the byproduct triphenylphosphoxide which was removed by filtration, washed with DIPE:acetone 1:1 (4x3L). The organic layer was concentrated in vacuo to give the compound of the formula (II) which is used directly without isolation for the next step.

Example 12

Preparation of 13,14-dihydro-15(R)-17-phenyl-18,19,20--trinor-$PGF_{2\alpha}$ isopropyl ester [compound of the formula (I)]

After adding anhydrous potassium carbonate (22.95 g) and isopropyl iodide (37.55 g, 221.4 mmol) to the solution of crude 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ in 200 ml of dry dimethylformamide (50.64 g, 110.7 mol) obtained in Example 6, the mixture is stirred at 50 °C for 5 hours, then the reaction mixture is poured to a mixture of water (900 ml), 2M sodium hydrogen sulfate solution (120 ml) and ethyl acetate (500ml).The aqueous phase is extracted with additional ethyl acetate (500ml).The combined ethyl acetate phase is successively washed twice with 2% lithium chloride solution (500 ml) each, saturated sodium hydrogen carbonate

solution (100 ml) and twice with saline (200 ml) each, dried and ethyl acetate is evaporated under reduced pressure. The oily residue is purified by chromatography on silica gel (1 kg) containing silicon gel by using a 20:1 mixture of methylene chloride and isopropanol as eluent, then on silica gel (900 g) by using an 1:1 mixture of ethyl acetate and hexane as eluent to obtain after evaporation colourless oily title compound (16 g) of the formula (I), R_f = 0.42 (diisopropyl ether/acetone/water 40:25:1), $[\alpha]_D$ = +34° (c = 1, acetonitrile).

IR spectrum (taken on a Zeiss Specord M-80 type spectrometer, by using the liquid film method between NaCl sheets) (cm^{-1}): 3400 (OH), 3060 (CH aromatic), 2990, 2930, 2860 (CH aliphatic), 1730 (C=O), 1600, 150 (aromatic ring vibration), 1110 (C-O-C), 750, 700 (monosubst. aromatic).

^{1}H-NMR spectrum (taken on a Bruker AC 400 device, $CDCl_3$, TMS inner standard, δ ppm):

7.24 (s, 5H, aromatic H), 5.44 (dd, 1H, 6-H), 5.41 (dd, 1H, 5-H), 4.99 (m, 1H, -CH- isopropanol), 4.17 (s, 1H, 9-H), 3.94 (s, 1H, 11-H), 3.66 (m, 1H, 15-H).

Example 13

Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ isopropyl ester

[Compound of the general formula (I), wherein R is isopropyl group]

To the crude product of the formula (II) dissolved in DMF (6L), potassium carbonate (1.24 kg) and isopropyl iodide (1.15 L) were added, and the mixture was warmed to 45-50 °C

over a period of 5-7 hours at which time the reaction was completed (TLC monitoring). The mixture was diluted with water (2.8L), acidified to pH 2-3 with sodium hydrogen sulphate 1M (13L). The water layer was extracted with AcOEt:hexane 3:2 (3x9L), wherupon the organic layer was washed with water (2x4L) and dried over sodium sulphate (1.5 kg) filtered. The precipitate was washed with AcOEt (2x1.5L), concentrated in vacuo, furnishing the target compound as a light brown oil. The crude oil (2.7 kg) was subjected to a column chromatography twice on silicagel.

The crude oil was dissolved in DIP:acetone 3:1 (6L) and chromatographed on silicagel (70 kg) using DIPE:acetone 3:1 (1200L), as eluent, and five fractions were collected in the following order; I (280), II (50), III (10), IV (270) and V (70L) respectively. Fraction IV was containing the major amount of the product (TLC monitoring) which was concentrated in vacuo. The resulting oil was dissolved in dichloromethane (6L) and chromatographed on silicagel (20 kg) using a gradient elution with dichloromethane (20L) and dichloromethane:isopropanol 40:1 (61.5L), 30:1 (20.7L) and 5:1 (60L) successively. Five fractions were collected in the following order; I (127L), II (0.5L), III (0.5L), IV (12L) and V (5L) respectively. The purity of the fractions were investigated with TLC and HPLC. Fraction IV was found to be pure. The solvent was removed in vacuo, the yellowish oil was treated with active carbon (0.11kg) in isopropanol (6.2L), filtered, washed with isopropanol (2x0.56L).The solvent was removed in vacuo (0.2 bar) at 40-50 °C to give the target compound as

pure colourless to slightly yellowish oil yield (0.96 kg, 55.5 %).

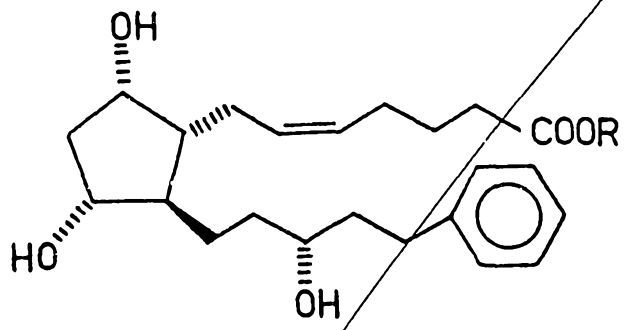
Example 14

Preparation of 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4--[5'-phenyl-3'-(R)-hydroxy-1'-pentyl)-2H-cyclopenta[b]-furan [compound of the formula (III)]

A solution containing 3,3a,4,5,6,6a-hexahydro-2-oxo-4--[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy--2H-cyclopenta[b]furan (6.8 g, 14 mmol) in anhydrous toluol (82 ml) is cooled to -80 °C and diisobutyl aluminum hydride (9.1 g, 64 mmol) dissolved in of anhydrous toluene (31 ml) are dropwise added under cooling. The reaction mixture is stirred at a temperature between -70 °C and -80 °C until the reaction becomes complete (about 1 hour). Then, the reaction mixture is poured into 1M sodium hydrogen sulfate solution (204 ml), stirred for 45 minutes and after separating the phases the product remained in the aqueous phase is extracted into ethyl acetate. After combining, the organic phase is dried over anhydrous sodium sulfate and then transferred to a column prepared from silica gel (34 g) and toluene (60 ml). The aimed product is eluted with a mixture of toluene and ethyl acetate. The fraction containing the pure product is evaporated to a volume of 20-25 ml and the product is crystallized by using diisopropyl ether (65 ml). The product obtained is washed by a mixture of diisopropyl ether and ethyl acetate to give the title product (2.8 g) of formula (III), m.p.: 103-106 °C.

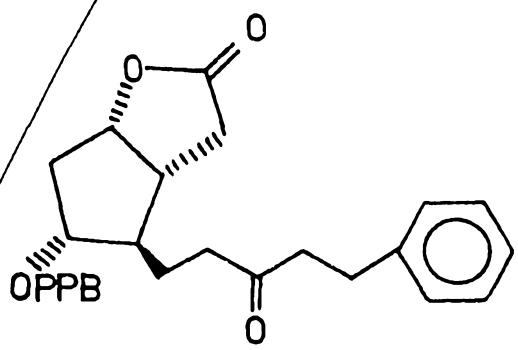
Claims

1. Process for the preparation of 13,14-dihydro-15(R)--17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ esters of the general formula (I), wherein R stands for saturated or unsaturated straight, branched or cyclic C_{1-7}alkyl or phenyl or benzyl group



(I)

which comprises reducing the oxo group on the side chain of the compound of formula (VII),



(VII)

transforming the obtained 3,3a,4,5,6,6a-hexahydro-2-oxo-4--[5'-phenyl-3'(R)-hydroxypent-1'-enil]-5-(4'-phenylbenzoxyl-oxy)-2H-cyclopenta[b]furan of the formula (VI)

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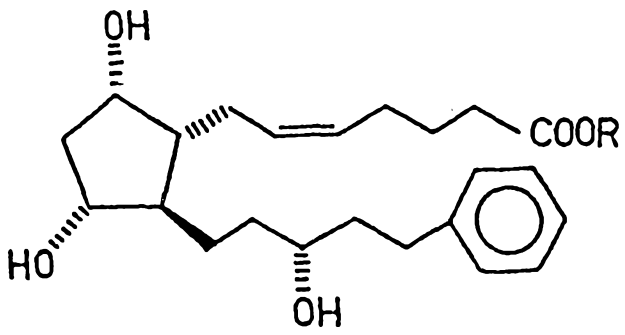
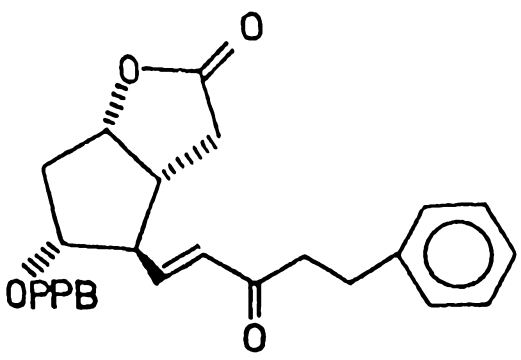
Claims

1. Process for the preparation of 13,14-dihydro-15(R)--17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ esters of the general formula (I), wherein R stands for saturated or unsaturated straight, branched or cyclic C_{1-7}alkyl or phenyl or benzyl group



(I)

which comprises reducing the oxo group on the side chain of the compound of formula (VII),



(VII)

transforming the obtained 3,3a,4,5,6,6a-hexahydro-2-oxo-4--[5'-phenyl-3'(R)-hydroxypent-1'-enil]-5-(4'-phenylbenzoxyl-oxy)-2H-cyclopenta[b]furan of the formula (VI)

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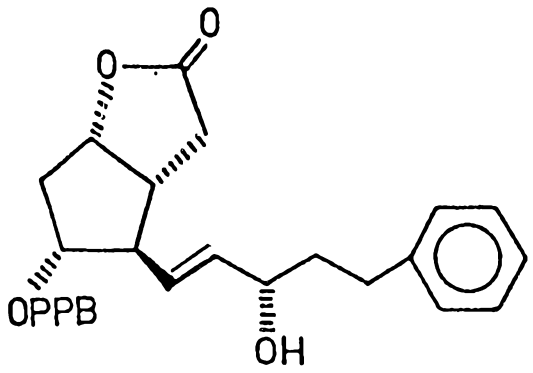
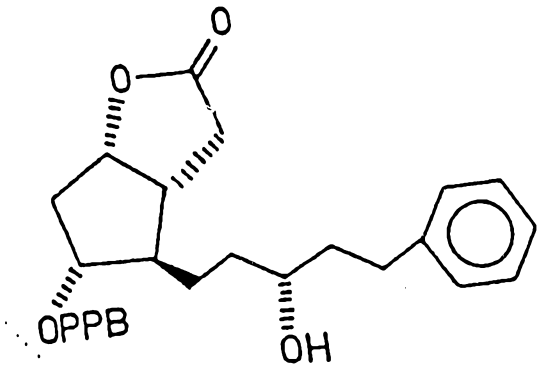


(VI)

by hydrogenation to 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (V)



(V)

reducing the compound of formula (V) to 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-5-(4'-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (IV),

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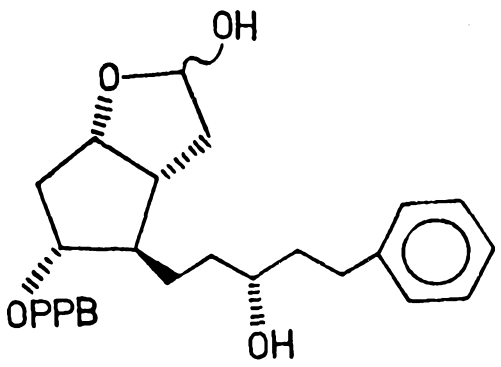
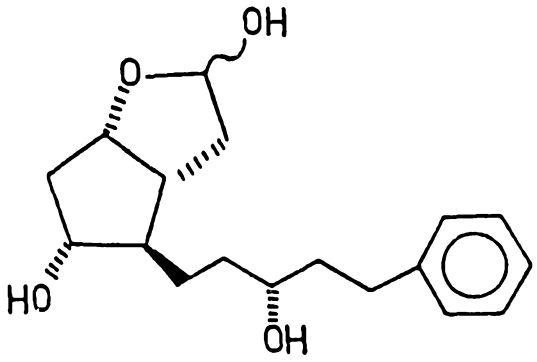


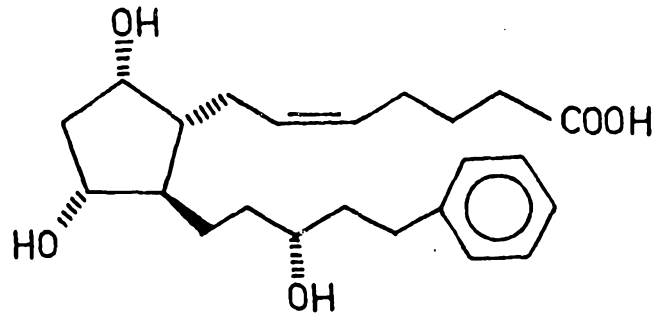
(IV)

removing the protective group from the compound of formula (IV) to obtain 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4-[5'-phenyl-3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan of the formula (III)



(III)

then transforming the compound of formula (III) obtained to 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ of the formula (II)



(II)

by using 4-carboxybutyl-triphenylphosphonium halide and finally, transforming the compound of formula (II) with a compound of the general formula R-X, wherein R has the same meaning as stated above, X is halogen, sulphate, mesyl, tosyl or any suitable group, to 13,14-dihydro-15(R)-17-phenyl--18,19,20-trinor-$PGF_{2\alpha}$ esters of the general formula (I).

2. A process as claimed in claim 1, which comprises reducing the compound of formula (VII) by using lithium tri(sec-butyl)borohydride or sodium borohydride.

3. A process as claimed in claim 1, which comprises hydrogenating the compound of formula (VI) in the presence of a palladium-on-carbon catalyst.

4. Process as claimed in claim 1, which comprises hydrogenating the compound of formula (VI) in the presence of sodium salts.

5. A process as claimed in claim 1, which comprises reducing the enone compound of the formula (V) to the enol compound of formula (IV) by using diisobutylaluminum hydride.

6. A process as claimed in claim 1, which comprises removing the 4-phenylbenzoyloxy protective group from the

compound of formula (IV) by using a mixture of potassium carbonate and methanol.

7. A process as claimed in claim 1, which comprises reacting the compound of formula (III) with 4-carboxybutyl-triphenylphosphonium bromide in the presence of potassium tert-butoxide in an ether-type solvent.

8. A process as claimed in claim 1, which comprises alkylating the $PGF_{2\alpha}$ derivative of formula (II) with isopropyl iodide in the presence of potassium carbonate in an organic solvent.

9. A process as claimed in claim 1, which comprises isolating (separating) the compounds of formulae (VI), (V) and (III) in the course of the synthesis starting from the compound of formula (VII) and, if desired, purifying them by recrystallization.

10. A process as claimed in claim 1, which comprises carrying out the reduction of the compound of formula (V) and the removal of the 4-phenylbenzoyloxy protective group from the obtained enol compound of formula (IV) by using diisobutylaluminum hydride in toluene.

11. 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ of the formula (II).

12. 3,3a,4,5,6,6a-hexahydro-2,5-dihydroxy-4-[5'-phenyl--3'(R)-hydroxy-1'-pentyl]-2H-cyclopenta[b]furan of the formula (III).

13. 3,3a,4,5,6,6a-hexahydro-2-hydroxy-4-[5'-phenyl--3'(R)-hydroxy-1'-pentyl]-5-(4-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (IV).

14. 3,3a,4,5,6,6a-hexahydro-2-oxo-4-[5'-phenyl--3'(R)-hydroxy-1'-pentyl]-5-(4-phenylbenzoyloxy)-2H-cyclopenta[b]furan of the formula (V).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 92/00025

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.[5]: C 07 C 405/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.[5]: C 07 C 405/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

G-DARC u. CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 90/2 553 (PHARMACIA AB) 22 March 1990 (22.03.90), examples.	1
X	DE, A, 2 234 709 (ICI) 01 February 1973 (01.02.73), page 29, nr. 1,	11
A	examples	1
X	Chemical Abstracts, Volume 85, no. 3, issued 1976, July 19 (Columbus, Ohio, USA), E.Granstrom et al. "Effect of chemical modifications on the metabolic transformation of prostaglandins" page 76, column 2, the abstract No. 14249e, Adv. Prostaglandin Thromboxane Res. 1976, 1, 215-19 (Eng).	11

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 1992 (18.09.92)	25 September 1992 (15.09.92)

Name and mailing address of the ISA/AT	Authorized officer
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Facsimile No. 0222/53424/535	Telephone No. 0222/5337066/30

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 92/00025

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO 902553		keine - none - rien	
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