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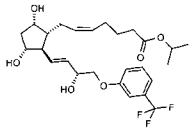
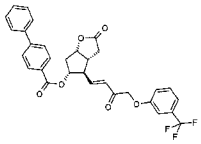
(54) Title: PROCESS FOR THE PREPARATION OF TRAVOPROST


(I)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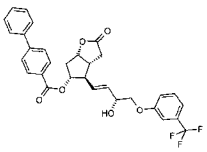
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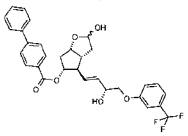
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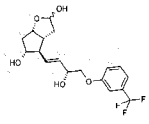
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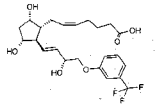
(VI)

(57) Abstract: The invention relates to a process for the preparation of travoprost of formula(I), comprising that, the compound of formula (II), is stereoselectively reduced, the resulting compound of formula (III), is if desired crystallized, the lactone group of the the compound of formula (III) is reduced, the p-phenyl-benzoyl protecting group of the thus obtained compound of formula *(TV)*, is removed, the resulting triol of formula (V), is, if desired after crystallization, transformed by Wittig reaction into the acid of formula (VI), which is then esterified.

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Published:

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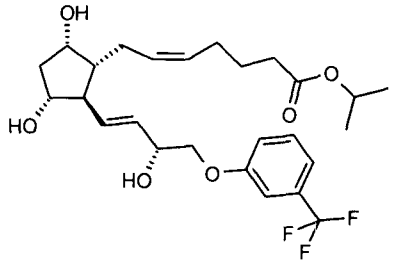
PROCESS FOR THE PREPARATION OF TRAVOPROST

The subject of our invention is a novel process for the preparation of travoprost.

Travoprost of formula (I)



is a known prostaglandin derivative used for the treatment of glaucoma and high eye pressure (US 5510383).

Processes for the preparation of travoprost are disclosed for example in EP 2143712, WO 201 1/046569, WO 201 1/055377.

The process according to EP 2143 712 is shown on Figure 1.

Stereoselectivity of the enone→enol reduction is 88.7 % (Example 10.).

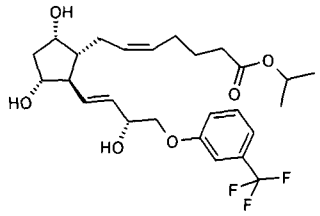
According to the process disclosed in WO 201 1/046569 the 15-epi impurity is removed by protection of the OH-groups of the diol with tert-butyl-dimethylsilyl group (TBDMS) and crystallization of the thus obtained protected diol.

In the process according to WO 201 1/055377 the enone→enol transformation is carried out with *N,N*-diethylaniline - borane complex as reducing agent, in the presence of Corey catalyst (CBS-oxazaborolidine). The product is purified by preparative HPLC.

The overall yield is 7%.

We aimed to work out a process with higher stereoselectivity and better yield.

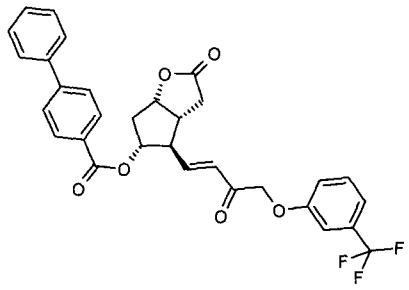
The subject of our invention is the preparation of travoprost of formula (I)



(I)

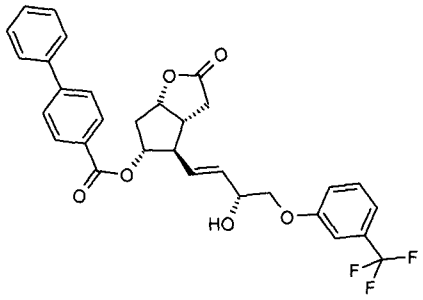
by

stereoselective reduction of the compound of formula (II),



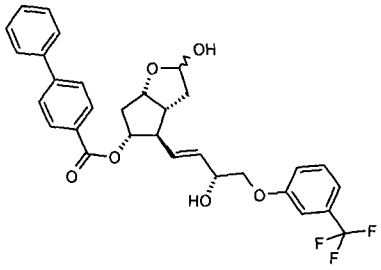
(II)

reduction of the lactone group of the resulting compound of formula (III),



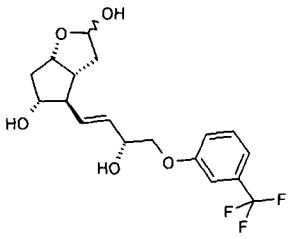
(III)

removal of the /?-phenylbenzoyl protecting group of the thus obtained compound of formula (IV),



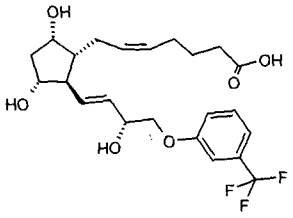
(IV)

transformation of the resulting triol of formula (V) by Wittig reaction



(V)

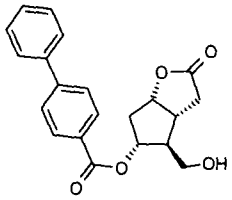
into the acid of formula (V



(VI)

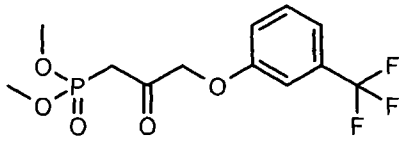
which is then esterified.

The starting compound of formula (II) can be prepared for example by oxidation of the PPB-Corey-lactone of formula (XII)



(XII)

into the aldehyde, which is then transformed with the phosphonate of formula (XIII)



(XIII)

in HWE reaction, in water free medium, in the presence of solid potassium hydroxide into the compound of formula (II).

According to one embodiment of the process based on the invention, the PPB-Corey-lactone is oxidized under Pfitzner-Moffatt reaction conditions into the aldehyde (Pfitzner, K.E., Moffatt J.G.; *J.Am.Chem.Soc.* **1963,** *85,* 3027), then the lower chain is built up with the help of Horner-Wadsworth-Emmons (HWE) reaction (Wadsworth, W.; *Org. React.,* **1977,** *25,* 73) - by use of the appropriate phosphonate - under water-free conditions, in the presence of solid potassium hydroxide. For the deprotonation of the phosphonate - instead of using the widely described sodium hydride, potassium tert-butylate, lithium carbonate, DBU, lithium- or magnesium halogenides, triethylamine, potassium hexamethyl disilazide (KHMDS) or crown ether bases - we applied solid potassium hydroxide which is economical and can be safely used in industrial scale.

The HWE reaction is carried out in an aprotic organic solvent in a temperature range of 40-(-50)°C, preferably at (-10)°C, by using as solvent an aromatic hydrocarbon, such as toluene or

an ether, like tetrahydrofuran, methyltetrahydrofuran, cyclopentyl methyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, diethyl ether or their mixtures.

According to another embodiment of the invention, the selective reduction of the compound of formula (II) is accomplished with a borane-type reducing agent.

As the borane-type reducing agent borane-dimethyl sulfide, (-)-B-chlorodiisopinocampheylborane (DIP-CI), catecholborane, especially catecholborane may be applied. According to a further embodiment of the process the reduction of the compound of formula (II) is carried out in the presence of a chiral catalyst. As chiral catalyst CBS-oxazaborolidine can be used. The reaction is carried out in the presence of an organic solvent, at a temperature between (10°C) and (-80°C), preferably between (-10°C) and (-20°C). As for solvent toluene, hexane, heptane, pentane, tetrahydrofuran, methyltetrahydrofuran, cyclopentyl methyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, diethyl ether or their mixtures may be applied, among others toluene - tetrahydrofuran mixtures are used.

The resulting compound of formula (III) is purified by crystallization, while the amount of the undesired isomer is lowered in a significant manner. The crystalline form of the compound of formula (III) has not been known before, it is a novel form. Crystallization is carried out in polar or apolar solvents or in the mixture of them.

In an embodiment of the process according to the invention the crystallization is performed between (-20)-70°C, in such a way that the material is dissolved in alcohol at reflux temperature and crystallized by cooling gradually. The crystals are then filtered off, washed and dried.

Reduction of the compound of formula (III) may be carried out with diisobutyl-aluminum hydride (DIBAL-H). As for solvent, inert aprotic solvents such as THF, toluene, hexane, and heptane may be applied. The reaction is performed at a temperature between (-80°C) and (-50°C), especially between (-80°C) and (-70°C).

The product of the DIBAL-H reduction, the intermediate of formula (IV), is a novel compound.

The PPB-protecting group may be removed in a known way by methanolysis, under basic conditions, especially in the presence of potassium carbonate.

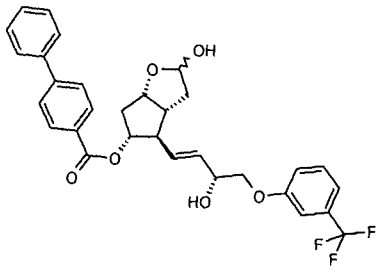
In a further embodiment of the process, the resulting intermediate of formula (V) is purified by crystallization, while the amount of the undesired isomer is decreased under a strickt limit

value. The crystalline form of the compound of formula (V) has not been described before, it is a novel form. Crystallization is carried out in the mixture of polar and apolar solvents. As for the mixture of polar and apolar solvents, an ethyl acetate - hexane mixture may be used.

Transformation of the compound of formula (V) into the compound of formula (VI) is accomplished by Wittig reaction, while esterification of the compound of formula (VI) is carried out with isopropyl iodide.

In the esterification reaction cyclic tertiary amides, such as N-methylpyrrolidone and/or 1,3-dimethylimidazolidinone are used as solvents. The esterification is performed at a temperature between 20-90°C, especially between 40-50°C.

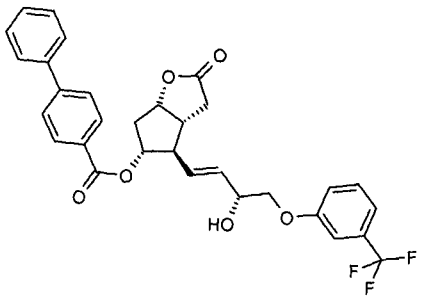
A further subject of the invention is the novel compound of formula (IV)



(IV)

and its use for the preparation of Travoprost.

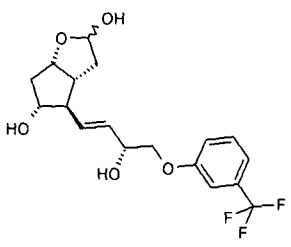
Furthermore, the subject of the invention is the crystallinecompound of formula (III),



(III)

having the melting point of 129.5-134.5°C, and its use for the preparation of Travoprost.

Furthermore, the subject of the invention is the crystalline compound of formula (V),

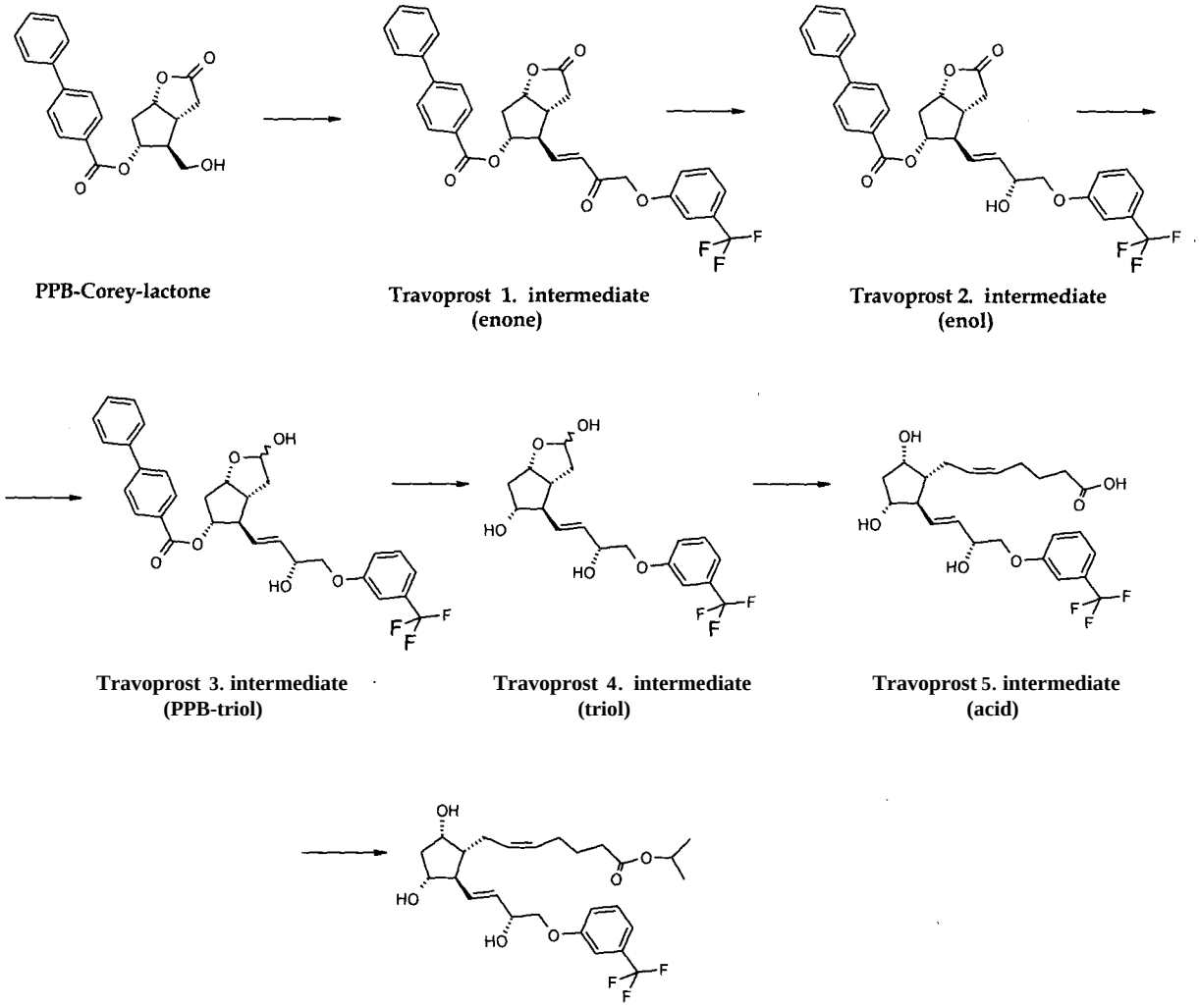


(V)

having the melting point of 85.4-86.6°C, and its use for the preparation of Travoprost.

One embodiment of the full synthesis of Travoprost according to the invention is demonstrated on Scheme 1 below:

Scheme 1



In one embodiment of the invention, which starts from the PPB-Corey-lactone, the lower chain is constructed with the help of the appropriate phosphonate, by Horner-Wadsworth-Emmons reaction. For the deprotonation of the phosphonate the inexpensive and in industrial scale safely applicable solid potassium hydroxide is used. Reduction of the resulting Travoprost 1. intermediate (enone -compound of Formula (II)) is carried out in the presence of a 2-methyl-CBS-oxazaborolidine catalyst, with a borane-type reducing agent, like catecholborane, resulting in a stereoselectivity of 90%. The thus obtained Travoprost 2. intermediate (enol - compound of Formula (III)) is purified by crystallization and reduced with diisobutylaluminum hydride (DIBAL-H). From the resulting Travoprost 3. intermediate (PPB-triol - compound of Formula (IV)) the PPB-protecting group is removed and the thus obtained Travoprost 4. intermediate (triol - compound of Formula (V)) is purified by

crystallization. Travoprost 5. intermediate (acid - compound of Formula VI) is prepared by Wittig reaction. Finally, the esterification is carried out with isopropyl iodide in DMI (1,3-dimethylimidazolidin-2-one) solvent to obtain the ester (Travoprost - Formula (I)).

Advantages of the process introduced by the invention:

- In the HWE reaction, to prepare the starting compound of formula (II), the deprotonation of the phosphonate is carried out with the inexpensive and in industrial scale safely applicable solid potassium hydroxide - instead of the expensive and flammable sodium hydride which is commonly and widely used in the present practice.

- The use of CBS-oxazaborolidine and catecholborane for the reduction of the 15-oxo group in the synthesis of travoprost is a new solution, not applied before, by which a diastereomeric excess even higher than 90-92% may be reached. In the method described in EP 2 143712 the selectivity is de(S)=88.7 %, using DIP-Cl. In the process disclosed in WO 201 1/055377 Al, beside the CBS catalyst *N.N*-diethylaniline-borane complex is applied, but the extent of stereoselectivity is not given.

- The purification strategy is fully novel, since removal of the 15-epi-impurity is accomplished by crystallization, without chromatography, in a high yield, contrary to the MPLC (medium pressure chromatography purification method) (WO 201 1/046569 Al) or preparative HPLC (WO 201 1/055377 Al) methods known in the literature.

- The crystalline form of the compound of formula (III) and that of the compound of formula (V) have not been described in the literature before. In the present process the crystalline form is also utilized for the purification of the intermediates and removal of the undesired isomer.

- In the esterification step, as a novel solvent, 1,3-dimethylimidazolidinone (DMI) is used, which is not strongly toxic, in contrast to the generally used dimethylformamide (EP 2 143 712 Al, WO 201 1/046569 Al). DMI is a solvent used in the beauty industry. As a further advantage, the formyl-impurities which generate from the

widely used dimethylformamide solvent, are not formed from DMI. The esterification reaction can be carried out with very high conversion, without forming new impurities (-100%).

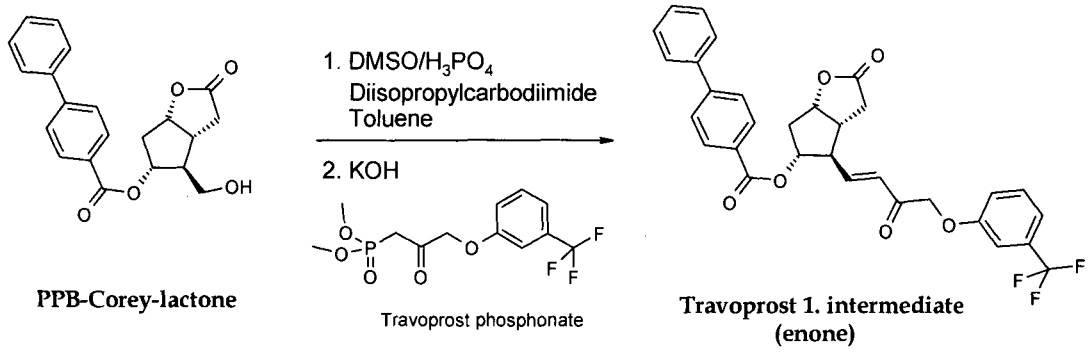
- The overall yield of the new process is very high, 16%, which is more than double of the yield described in WO 201 1/055377 A1 (7%).

- Further details of the invention are included, but not limited to the examples below.

Examples

1. Construction of the lower chain (Oxidation and HWE reaction)

Preparation of the [l,l'-Biphenyl]-4-carboxylic acid, (3aR,4R,5R,6aS)-hexahydro-2-oxo-4-[(1E)-3-oxo-4-[3-(trifluoromethyl)phenoxy]-1-buten-1-yl]-2H-cyclopenta[b]furan-5-yl ester /compound of formula (II)/



PPB-Corey-lactone

Travoprost phosphonate

Travoprost 1. intermediate (enone)

$C_{21}H_{20}O_5$
Mr: 352.39

$C_{31}H_{25}F_3O_6$
Mr: 550.54

1069 g of PPB-Corey-lactone is suspended in an inert atmosphere in 11.1 L of water-free toluene. To this suspension are added 1.4 L of diisopropylcarbodiimide and then 0.855 L of dimethyl sulfoxide in phosphoric acid. The reaction mixture is heated to 50°C and a further 0.34 L of dimethyl sulfoxide in phosphoric acid is added in portions. After the accomplishment of the oxidation reaction, the mixture is

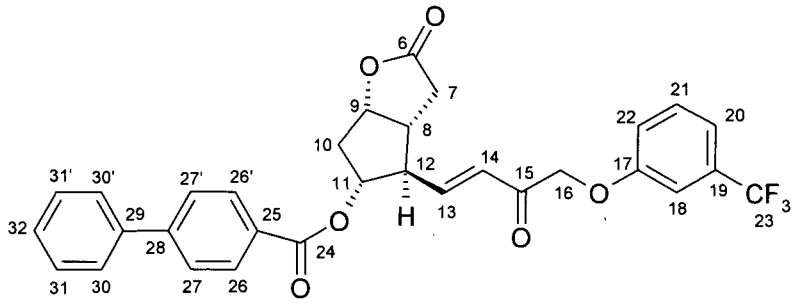
cooled to-10°C and while that temperature is maintained, 316 g of potassium hydroxide followed by 1.45 kg of Travoprost phosphonate in toluene solution are added. When the HWE reaction has completed, the reaction mixture is poured onto 1 M hydrochloric acid solution and the mixture is stirred. The precipitated crystals are filtered off and washed. The phases of the filtrate are separated, the organic phase is washed with 1M sodium hydrogen carbonate solution and then with diluted hydrochloric acid solution. The organic phase is evaporated and purified by chromatography on a silica gel column (eluent: toluene - ethyl acetate mixture). The main fraction is evaporated and crystallized from ethyl acetate - hexane mixture.

Yield: 915 g, 55 %.

Melting point: 112.5-1 14.5°C

IR spectrum of Travoprost 1. intermediate is shown on Figure 2.

Travoprost 1. intermediate ^{1}H, ^{13}C and ^{19}F NMR data:



Travoprost 1. intermediate (enone - Formula (II)):

Numbering	$^{13}C/^{19}F$ (ppm)	^{1}H (ppm)	Number of ^{1}H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
6	176.56	-	-		
7	34.46	β: 2.96* α: 2.55	1 1	m (dd) d	J_{gem}=17.3; $J_{7\beta,8}$=10.2
8	42.17	3.00*	1	m (dddd)	
9	83.32	5.13	1	td	$J_{8,9}$=$J_{9,10\beta}$=6.4; $J_{9,10\alpha}$=1.3
10	37.50	β: 2.63 α: 2.14	1 1	dt dd	J_{gem}=15.2; $J_{10\beta,11}$=6.4; $J_{10\alpha,11}$=3.6
11	78.95	5.35	1	dt	$J_{11,12}$=5.6
12	53.66	3.10	1	m (ddd)	$J_{8,12}$=5.0
13	146.19	6.99	1	dd	$J_{13,14}$=16.0; $J_{12,13}$=8.1
14	127.24	6.44	1	d	
15	194.08	-	-	-	
16	71.12	5.17	2	s	
17	158.14	-	-	-	
18	111.16 (q)	7.22**	1	broad	$^{3}J_{C\text{-}18,F}$ =3.8; $J_{18,20}$=1.5; $J_{18,22}$=2.5
19	130.24 (q)	-	-	-	$^{2}J_{C\text{-}19,F}$ =31.7
20	117.50 (q)	7.285	1	m (d)	$^{3}J_{C\text{-}20,F}$ =3.8; $J_{20,21}$=7.8; $J_{20,22}$=0.8;
21	130.63	7.495***	1	m (dd)	$J_{21,22}$=8.2

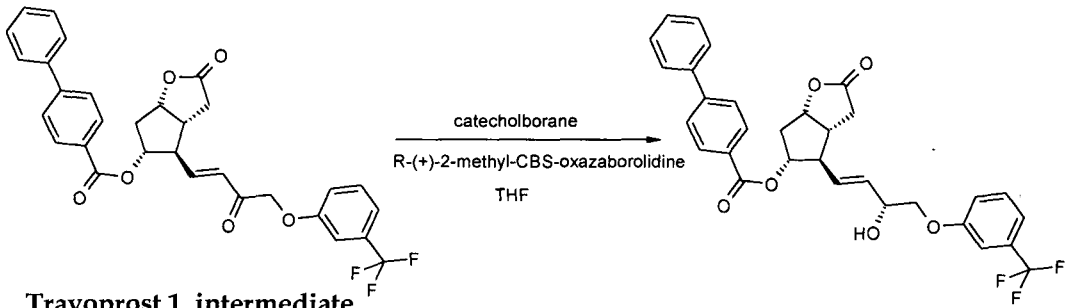
22	118.75	7.20**	1	m (dd)	
23	123.95 (q)	-	-	-	$^{1}J_{C-23,F}$ = 272.5
23-F	-61.10 (s, 3)	-	-	-	
24	164.94	-	-	-	
25	128.16	-	-	-	
26, 26'	129.95	8.015	2	m	$J_{26,27}$ = 8.5;
27, 27'	126.87	7.81	2	m	
28	144.93	-	-	-	
29	138.77	-	-	-	
30, 30'	127.01	7.74	2	m (dd)	$J_{30,31}$=7.4
31, 31'	129.10	7.51***	2	m (t)	$J_{31,32}$=7.4
32	128.46	7.43	1	m (tt)	$J_{31,32}$ ~1·6

*, **, ***: Overlapping ^{1}H NMR signals

2. 15-oxo-reduction (Stereoselective reduction)

Preparation of [l,l'-Biphenyl]-4-carboxylic acid, (3aR,4R,5R,6aS)-hexahydro-4-[(lE,3R)-3-hydroxy-4- [3-(trifluoromethyl)phenoxy] -1-buten- 1-yl]-2-oxo-2H-cyclopenta[b]furan-5 -yl ester

/compound of formula (III) /



Travoprost 1. intermediate (enone)

$C_{31}H_{25}F_3O_6$

Mr: 550.54

Travoprost 2. intermediate (enol)

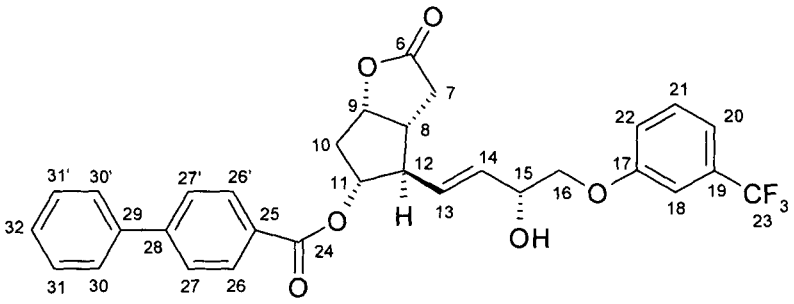
$C_{31}H_{27}F_3O_6$

Mr: 552.55

279 ml of catecholborane is dissolved in 4.6 L of tetrahydrofuran (THF) and the 1M toluene solution of 549 ml of R-(+)-2-methyl-CBS-oxazaborolidine is added to it. The mixture is cooled to -10°C and while that temperature is maintained, the solution of 915 g of

Travoprost 1. intermediate (enone - compound of Formula (II)) in 6.9 L of THF is added. When the reaction has completed, the mixture is decomposed by stirring with 13 L of 1 M $NaHS0_4$ solution. Ethyl acetate is then added and the phases are separated. The organic phase is washed with NaOH solution and then with hydrochloric acid solution. The organic phase is dried over sodium sulfate, filtered, evaporated and crystallized first from hexane: acetone mixture, then from methanol for removing the undesired isomer de(S)92% - >de(S)98%.
(de means: diastereomeric excess)

Yield: 701 g, 55% de(S): 98%
M.p.: 129.5-134.5°C
IR spectrum of Travoprost 2. intermediate is shown on Figure 3.
Travoprost 2. intermediate ^1H, ^{13}C and ^{19}F NMR data:



Numbering	$^{13}C/^{19}F$ (ppm)	^1H (ppm)	Number of ^1H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
6	176.76	-	-	-	
7	34.53	β: 2.93 α: 2.46	1 1	dd dd	J_{gem}=17.8; $J_{7\beta,8}$=10.0 $J_{7\alpha,8}$=0.9
8	42.14	2.85*	1	m (dddd)	
9	83.28	5.09	1	td	$J_{8,9}$=$J_{9,10\beta}$=6.5; $J_{9,10\alpha}$=1.4
10	37.20	β: 2.55 α: 2.05	1 1	dt m (dd)	J_{gem}=15.2; $J_{10\beta,11}$=6.4; $J_{10\alpha,11}$=4.6
11	79.58	5.20	1	m (ddd/dt)	$J_{11,12}$~5.5
12	53.49	2.83*	1	m (ddd)	
13	129.87$	5.76**	1	m	

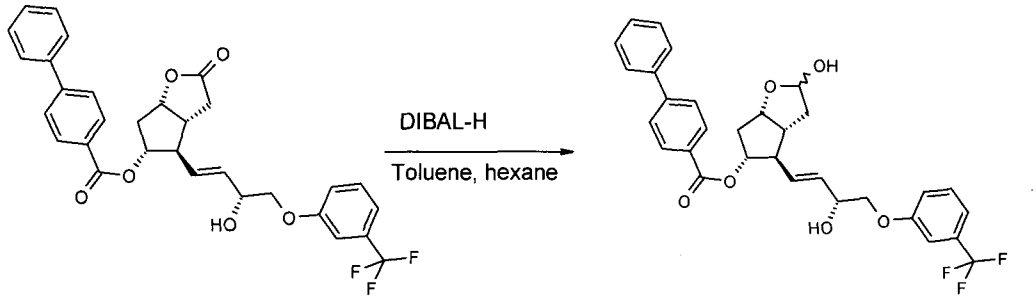
14	132.18	5.76**	1	m	
15	68.83	4.34	1	m (broad)	
15-OH		5.26	1	d	$J_{15,OH}$=4.9
16	72.18	a: 3.95 b: 3.90	1 1	dd dd	J_{gem}=9.8; $J_{15,16a}$=4.6; $J_{15,16b}$=6.7
17	158.88	-	-	-	
18	111.08 (q)	7.195***	1	m	$^{3}J_{C-18,F}$ =3.7
19	130.25 (q)	-	-	-	$^{2}J_{C-19,F}$ =31.5
20	117.04 (q)	7.25	1	d	$^{3}J_{C-20,F}$ =3.7; $J_{20,21}$=7.7; $J_{18,20}$=1.4; $J_{20,22}$=1.0
21	130.63	7.47#	1	m (t/dd)	$J_{21,22}$=8.2
22	118.80	7.20***	1	m	$J_{18,22}$=2.5;
23	123.98 (q)	-	-	-	$^{1}J_{C-23,F}$ = 272.4
23-F	-61.16 (s, 3)	-	-	-	
24	165.02	-	-	-	
25	128.33	-	-	-	
26, 26'	129.87$	7.99	2	d	$J_{26,27}$=8.4
27, 27'	126.80	7.77	2	d	
28	144.81	-	-	-	
29	138.77	-	-	-	
30, 30'	126.97	7.72	2	d	$J_{30,31}$=7.4
31, 31'	129.07	7.50#	2	m (t)	$J_{31,32}$=7.4
32	128.42	7.43#	1	m (tt)	

*, **, ***, #, ##: Overlapping ^{1}H NMR signals. $: Overlapping ^{13}C NMR signals.

3. Lactone reduction (Preparation of the Lactol)

Preparation of [l,l'-Biphenyl]-4-carboxylic acid, (3aR,4R,5R,6aS)-hexahydro-4-[(lE,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-l-buten-l-yl]-2-hydroxy-cyclopenta[b]furan-5-yl ester

/ compound of formula (IV) /



Travoprost 2. intermediate (enol)

$C_{31}H_{27}F_3O_6$

Mr: 552.55

Travoprost 3. intermediate (PPB-triol)

$C_{31}H_{29}F_3O_6$

Mr: 554.57

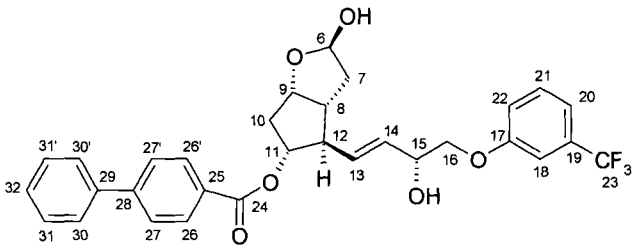
A multi-neck flask is charged under nitrogen atmosphere with 701 g of enol which is then dissolved in 6.8 L of room temperature THF. The clear solution is cooled to -75°C and in approximately 30 minutes the pre-cooled (-75°C) 1 M hexane solution of 2921 ml diisobutylaluminum hydride (DIBAL-H) is added to it. The reaction mixture is stirred at -75°C until the reaction is completed. After reaching the suitable conversion, the reaction mixture is poured onto the mixture of $NaHS0_4$ solution and ethyl acetate. The phases are separated, the aqueous phase is extracted with ethyl acetate, the united organic phase is washed with $NaHC0_3$ solution and with diluted hydrochloric acid solution, and then evaporated while adding triethylamine (TEA) to it. 639.5 g oil is obtained.

Yield: 639.5 g, 91%

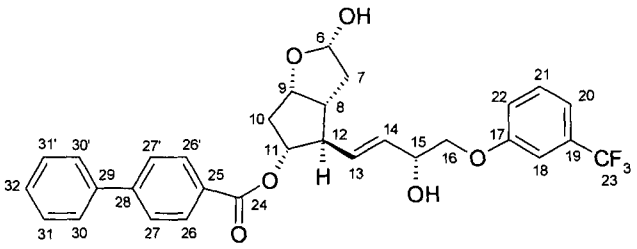
IR spectrum of Travoprost 3. intermediate is shown on Figure 4.

Travoprost 3. intermediate ^1H, ^{13}C and ^{19}F NMR data:

A)



B)



Travoprost 3. intermediate, diastereomer A

Numbering	$^{13}C/^{19}F$ (ppm)	^{1}H (ppm)	Number of ^{1}H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
6	98.78	5.53	1	td	$J_{6,OH}$=4.6; $J_{6,7}$=2.2 and 4.6
6-OH		6.02	1	d	
7	39.31$^{\$}$	a: 1.93* b: 1.89*	1 1	m m	
8	45.28	2.565**	1	m	
9	79.43	4.565	1	td	$J_{8,9}$=6.2; $J_{9,10}$=2.7 and 6.2
10	37.21	β: 2.51 α: 1.74***	1 1	m m (ddd)	J_{gem}~14.0 $J_{10\alpha,11}$=6.9
11	79.72	5.08	1	m (q/dt)	$J_{10\beta,11}$=$J_{11,12}$=6.9
12	53.23	2.575**	1	m	
13	130.60	5.75^{+}	1	dd	$J_{13,14}$=15.6; $J_{12,13}$=6.5
14	131.71	5.70^{+}	1	dd	$J_{14,15}$=4.5
15	68.79	4.32^{++}	1	m (dddd)	
15-OH		5.23^{+++}	1	m (d)	$J_{15,OH}$=5.0
16	72.23$^{\$\$}$	a: 3.91$^{\#}$ b: 3.87$^{\#}$	1 1	m (dd) m (dd)	J_{gem}=9.7; $J_{15,16a}$=4.8; $J_{15,16b}$=6.7

17	158.88[$$]	-	-	-	
18	111.09 (q)	7.16[##]	1	m	$^3J_{C\text{-}18,F}$=3.6; $J_{18,20}$~$J_{18,22}$~1.3
19	130.24[$$] (q)	-	-	-	$^2J_{C\text{-}19,F}$ =31.7
20	117.01[$$] (q)	7.22[###]	1	m	$^3J_{C\text{-}20,F}$=3.8; $J_{20,21}$=7.8
21	130.56	7.44[&]	1	m (t/dd)	$J_{21,22}$=7.8
22	118.73	7.15[##]	1	m	
23	123.97[$$] (q)	-	-	-	$^1J_{C\text{-}23,F}$=272.4
23-F	-61.19 (s, 3)	-	-	-	
24	165.16	-	-	-	
25	128.61	-	-	-	
26, 26'	129.75[$$]	7.985[&&]	2	d	$J_{26,27}$=8.4
27, 27'	126.90[$$]	7.77	2	d	
28	144.71[$$]	-	-	-	
29	138.84[$$]	-	-	-	
30, 30'	126.96[$$]	7.70[&&&]	2	m (d)	$J_{30,31}$=7.5
31, 31'	129.07[$$]	7.50[€]	2	m (t/dd)	$J_{31,32}$=7.4
32	128.40[$$]	7.43[&]	1	m (tt)	

*, **, ***, +, ++, +++, #, ##, ###, &, &&, &&&, €: Overlapping ^{1}H NMR signals. [$]: Overlapping ^{13}C NMR signals with the DMSO signal.

[$$]: Overlapping ^{13}C NMR signals.

Travoprost 3. intermediate, diastereomer B

Numbering	$^{13}C/^{19}F$ (ppm)	^{1}H (ppm)	Number of ^{1}H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
6	99.70	5.45	1	m (td/ddd)	$J_{6,7}$= 0.9 and 4.5
6-OH		6.25	1	d	$J_{6,OH}$=3.4
7	37.51	β: 1.99$^{€€}$ α: 1.73***	1 1	m m	$J_{7,8β}$=5.7 J_{gem}~11.8; $J_{6,7α}$=1.9
8	44.64	2.41	1	m (q/ddd)	$J_{8,12}$=10.1
9	80.04	4.46	1	td	$J_{8,9}$=$J_{9,10β}$=7.3; $J_{9,10α}$=5.2
10	39.45$^{$}$	β: 2.65 α: 1.90*	1 1	dt m	J_{gem}=13.0; $J_{10β,11}$=7.3
11	78.11	5.00	1	td	$J_{10α,11}$=$J_{11,12}$=9.8
12	52.34	3.10	1	td	$J_{12,13}$=7.1
13	130.74				
14	131.85				
15	68.68				
15-OH		5.21^{+++}	1	m (d)	$J_{15,OH}$=5.1
16	72.25$^{$$}$	a: 3.88$^{#}$ b: 3.84$^{#}$	1 1	m m (dd)	J_{gem}=9.7 $J_{15,16b}$=6.6
17	158.86$^{$$}$	-	-	-	
19	130.22$^{$$}$ (q)	-	-	-	$^{2}J_{C-19,F}$ =31.7
20	116.97$^{$$}$ (q)	7.205$^{###}$	1	m	$^{3}J_{C-20,F}$=3.8; $J_{20,21}$=7.8
21		7.41$^{&}$	1	m (dd)	$J_{21,22}$=8.1
22	118.64	7.11$^{##}$	1	m (dd)	2.3; 0.8
23	123.95$^{$$}$ (q)	-	-	-	$^{1}J_{C-23,F}$=272.4
23-F	-61.21 (s,3$^{%}$)	-		-	

24	165.28	-	-	-	
25	128.57	-	-	-	
26, 26'	129.76[$$]	7.995[&&]	2	d	$J_{26,27}$=8.4
27, 27'	126.85[$$]	7.73	2	d	
28	144.68[$$]	-	-	-	
30, 30'	126.94[$$]	7.68[&&&]	2	m (d)	$J_{30,31}$=7.5
31, 31'	129.065[$$]				

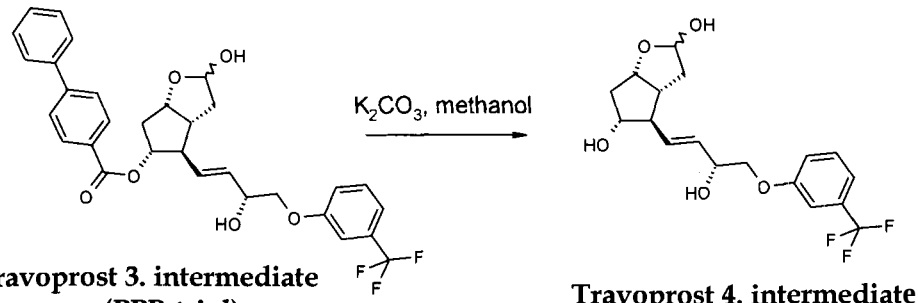
*, ***, +++, #, ##, ###, &, &&, &&&: Overlapping ^{1}H NMR signals. $: Overlapping ^{13}C NMR signals with the signal of DMSO. €€: Overlapping ^{1}H NMR signals with the signal of ethyl acetate. $$: Overlapping ^{13}C NMR signals. %The presence of the 3 fluoro atoms is shown by the ^{19}F and ^{13}C NMR spectra.

4. Removal of the protecting group (Preparation of the triol)

4a.

Preparation of 2H-cyclopenta[b]furan-2,5-diol, hexahydro-4-[(lE,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-l-buten-l-yl]-, (3aR,4R,5R,6aS)-

/ Compound of formula (V) /



Travoprost 3. intermediate (PPB-triol)

$C_{3i}H_{29}F_30_6$

Mr: 554.57

Travoprost 4. intermediate (triol)

$C_{18}H_{21}F_30_5$

Mr: 374.36

639.5 g of PPB-triol is dissolved in 6.4 L of methanol and the solution is heated to 40°C. 95 g of K_2C0_3 is added and the mixture is stirred at 40°C until the reaction is completed. After reaching the suitable conversion, the reaction mixture is cooled to 2°C and phosphoric acid solution is added in portions. The precipitated PPB-methyl ester crystals are filtered off and washed. The filtrate is concentrated, water and ethyl acetate are added and the phases are separated. The aqueous phase is extracted with ethyl acetate, dried over Na_2S0_4 and the

solution is evaporated. The crude oil is crystallized from ethyl acetate : hexane mixture. The precipitated crystals are filtered off, washed with hexane: ethyl acetate mixture and dried.

Yield: 367 g, 85%

Melting point: 85.4-86.6 °C

4b.

Recrystallyzation of 2H-cyclopenta[b] furan-2,5-diol, hexahydro-4- [(1E,3R)-3-hydroxy-4- [3-(trifluoromethyl)phenoxy]-l-buten-l-yl]-, (3aR,4R,5R,6aS)-

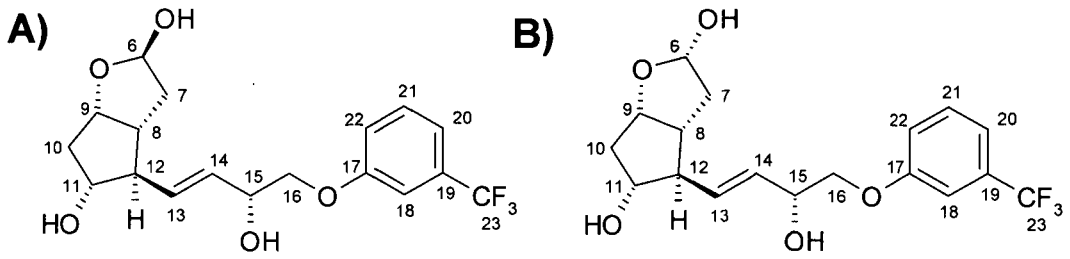
/ Compound of formula (V) - the triol /

The precipitated crystals are solved in 10 folds ethyl-acetate, thereafter 10 folds n-hexane is added and the solution is mixed at room temperature. To the crystal-suspension obtained 20 folds n-hexane is added and mixed at room temperature. The precipitated crystals are filtered, washed with a mixture of hexane: ethyl-acetate and dried. With repetition of the above process at any time the amount of the undesired isomer may be lowered to any amount, also decreasing of the amount of the undesired isomer under the disregard limit (<0,05%) is possible.

Yield: 52-85% (depending of the number of recrystallizations)

IR spectrum of Travoprost 4. intermediate is shown on Figure 5.

Travoprost 4. intermediate ^{1}H, ^{13}C and ^{19}F NMR data:



Travoprost 4. intermediate, diastereomer A ^{1}H, ^{13}C and ^{19}F NMR data:

Numbering	^{13}C / ^{19}F (ppm)	^{1}H (ppm)	Number of ^{1}H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
6	98.73	5.42	1	td	$J_{6,7}$~4.6 and 2.6
6-OH		5.90	1	d	$J_{6,OH}$ =4.6

7	39.04[$]	1.75	2	m	
8	44.65	2.27**	1	m	
9	78.29	4.345***	1	td	$J_{8,9}=J_{9,10\beta}=7.1$; $J_{9,10\alpha}=4.3$
10	40.58	β: 2.24** α: 1.44	1 1	m m (ddd)	$J_{gem}=14.0$; $J_{10\alpha,11}=9.1$
11	76.60	3.67	1	m (dddd)	$J_{10\beta,11}=7.2$; $J_{11,12}=9.2$
11-OH		4.80	1	d	$J_{6,OH}=5.9$
12	55.97	1.95[+]	1	m (td)	$J_{8,12}=9.2$; $J_{12,13}=7.4$
13	132.44	5.69	1	dd	$J_{13,14}=15.6$
14	130.30	5.55	1	dd	$J_{14,15}=5.6$
15	69.24	4.32***	1	m	
15-OH		5.16[++]	1	d	$J_{15,OH}=4.9$
16	72.48[$$]	a: 3.97[+++] b: 3.92[#]	1 1	m (dd) m (dd)	$J_{gem}=9.9$; $J_{15,16a}=4.4$; $J_{15,16b}=7.0$
17	158.99[$$]	-	-	-	
18	111.17 (q)	7.22	1	m (dd)	$^3J_{C\text{-}18,F}=3.7$; $J_{18,20}=1.6$; $J_{18,22}=3.6$
19	130.28 (q)	-	-	-	$^2J_{C\text{-}19,F}=31.7$
20	117.04 (q)	7.27[##]	1	m (dd)	$^3J_{C\text{-}20,F}=3.8$; $J_{20,21}=8.0$
21	130.70	7.51	1	m (t)	$J_{21,22}=8.0$
22	118.93	7.25[##]	1	m (dd)	$J_{20,22}=1.0$
23	124.03 (q)	-	-	-	$^1J_{C\text{-}23,F}=272.5$
23-F	-61.14 (s, 3)	-	-	-	

*, **, ***, +, ++, +++, #, ##: Overlapping ^{1}H NMR signals. [$]: Overlapping ^{13}C NMR signals with the signal ofDMSO.

**: Overlapping ^{13}C NMR signal.

Travoprost 4. intermediate, diastereomer B ^{1}H, ^{13}C and ^{19}F NMR data:

Numbering	^{13}C (ppm)	^{1}H (ppm)	Number of ^{1}H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
6	99.55	5.36	1	m (t/ddd)	$J_{6,7\beta}$=5.1
6-OH		6.10	1	d	$J_{6,OH}$=3.8
7	37.86	β: 1.92^{+} α: 1.61	1 1	m m	$J_{7,8\beta}$=5.7 J_{gem}=12.9; $J_{6,7\alpha}$~1.5
8	44.85	2.18**	1	m (dt/dddd)	$J_{7\alpha,8}$~1.5; $J_{8,12}$=9.9
9	80.07	4.28***	1	td	$J_{8,9}$=$J_{9,10\beta}$=7.8; $J_{9,10\alpha}$=5.7
10	42.88	β: 2.26** α: 1.72*	1 1	m m (ddd)	J_{gem}=12.7; $J_{10\alpha,11}$=9.9
11	76.02	3.59	1	m (dddd)	$J_{10\alpha,11}$=6.5; $J_{11,12}$=9.9
11-OH		4.75	1	d	$J_{6,OH}$=5.9
12	55.03	2.52$^{\#\#\#}$	1	m (td)	$J_{12,13}$~7.3,
13	133.10				
14	130.08				
15	69.32				
15-OH		5.15^{++}	1	m (d)	$J_{15,OH}$=4.9
16	72.53$^{\$\$}$	a: 3.98$^{\#}$ b: 3.92$^{\#}$	1 1	m (dd) m (dd)	J_{gem}=9.9; $J_{15,16a}$=4.4 $J_{15,16b}$=6.9
17	159.01$^{\$\$}$	-	-	-	

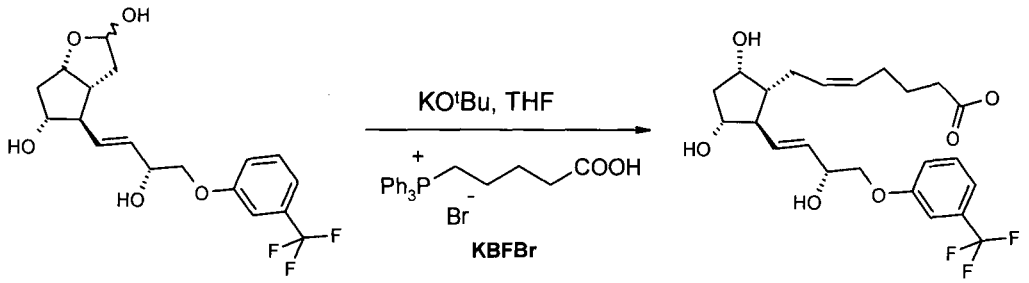
*, ***, $^{+++}$, $^{\#}$, $^{\#\#}$: Overlapping ^{1}H NMR signals. $^{\#\#\#}$: Overlapping ^{1}H NMR signals with the signal of DMSO. $^{\$\$}$: Overlapping ^{13}C NMR signals.

5

5. Construction of the upper chain (Preparation of Travoprost acid)

Preparation of 5-heptanoic acid, 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]- 1-buten- 1-yljcyclopentyl]-, (5Z)-

/ Compound of formula (VI) /



Travoprost 4. intermediate (triol)

$C_{23}H_{32}F_3O_5$

Mr: 374.36

Travoprost 5. intermediate (acid)

$C_{23}H_{29}F_3O_6$

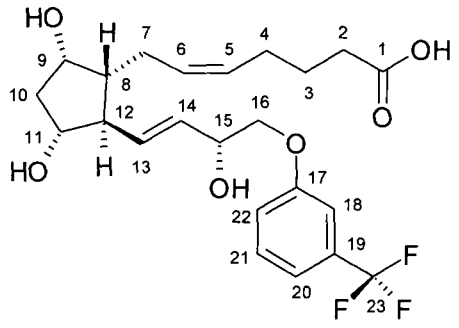
Mr: 458.48

Under nitrogen atmosphere 1509 g of 4-carboxybutyl-phosphonium bromide (KBFBr) is dissolved in 12.8 L of THF, the solution is cooled to 0°C, and by maintaining that temperature, 1.12 kg of potassium tert-butylate is added to it in portions. After 15 minutes of stirring the reaction mixture is cooled to (-)10°C, then 367 g of triol dissolved in 2.24 L of THF is added and the mixture is stirred at (-10)°C. When the reaction has completed, the reaction mixture is decomposed with water and toluene is added. The aqueous phase is extracted with dichloromethane (DKM) and acidified with a solution of $NaHSO_4$. Ethyl acetate is then added, the phases are separated and the aqueous phase is extracted with ethyl acetate. The united organic phase is washed with a diluted sodium chloride solution, dried over Na_2SO_4, the drying material is filtered off, the filtrate is washed and the filtrate solution is evaporated. The residue is crystallized from acetone : diisopropyl ether mixture. The crystals are filtered off, washed with diisopropyl ether : acetone mixture. The mother liquor is evaporated.

Yield: 463 g, 103%

IR spectrum of Travoprost 5. intermediate is shown on Figure 6.

Travoprost 5. intermediate ^1H, ^{13}C and ^{19}F NMR data:

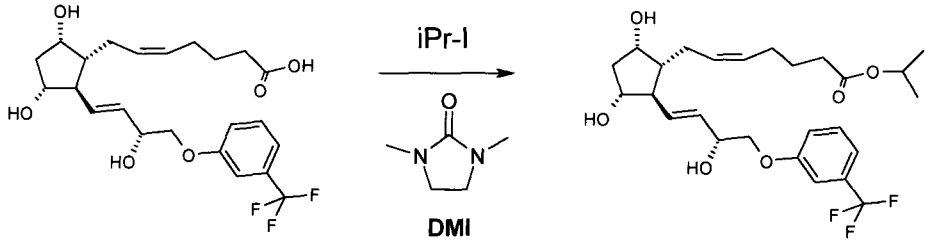


Numbering	$^{13}C/^{19}F$ (ppm)	^{1}H (ppm)	Number of ^{1}H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
1	174.37	-	-	-	
1-COOH		11.95	1	broad (s)	
2	33.09	2.13*	2	t	$J_{2,3}$=7.4
3	24.46	1.49**	2	m (tt)	$J_{3,4}$=7.4
4	26.06	1.96***	2	m	
5	128.56	5.23	1	dt	$J_{5,6}$=10.7; $J_{4,5}$=7.2
6	129.73	5.43	1	dt	$J_{6,7}$=7.4
7	24.78	b: 2.10* a: 1.96***	1 1	m m	
8	48.78	1.32	1	m (dddd / tt)	11.1; 10.0; 5.0; 5.0
9	69.58	3.90^{+}	1	m	
9-OH		4.36^{++}	1	broad (s)	
10	43.96	b: 2.20* a: 1.44**	1 1	ddd ddd	J_{gem}=14.1; $J_{10b,11}$=8.4; $J_{9,10b}$=5.8; $J_{10a,11}$=5.6; $J_{9,10a}$=2.3;
11	75.64	3.69	1	m	
11-OH		4.53	1	broad (s)	
12	54.30	2.18*	1	m (td)	
13	133.97	5.57	1	dd	$J_{13,14}$=15.5; $J_{12,13}$=8.0
14	131.01	5.51	1	dd	$J_{14,15}$=5.7
15	69.51	4.32^{++}	1	q (ddd)	5.6
15-OH		5.125	1	broad (s)	
16	72.55	b: 3.96^{+} a: 3.93^{+}	1 1	dd dd	J_{gem}=9.9; $J_{15,16b}$=4.9 $J_{15,16a}$=6.6
17	158.97	-	-	-	
18	111.13 (q)	7.20^{+}	1	m (t/dd)	$^{3}J_{C\text{-}18,F}$ =3.7; $J_{18,20}$=1.5; $J_{18,22}$=2.5
19	130.29 (q)	-	-	-	$^{2}J_{C\text{-}19,F}$ = 31.7

20	117.01 (q)	7.26^{+++}	1	m (ddd)	$^3J_{C\text{-}20,F} = 3.8$; $J_{20,21}=7.8$; $J_{20,22}=0.7$
21	130.68	7.50	1	t (dd)	$J_{21,22}=8.2$
22	118.75	7.24^{+++}	1	m (ddd)	
23	124.01 (q)	-	-	-	$^1J_{C\text{-}23,F} = 272.4$
23-F	-61.19 (s, 3)	-	-	-	

*, **, ***, $^+$, $^{++}$, $^{+++}$: Overlapping ^{1}H NMR signals.

6. Preparation of Travoprost /Compound of formula (I)/



Travoprost 5. intermediate (acid) **Travoprost**

$C_{23}H_{29}F_3O_6$ $C_{26}H_{35}F_3O_6$

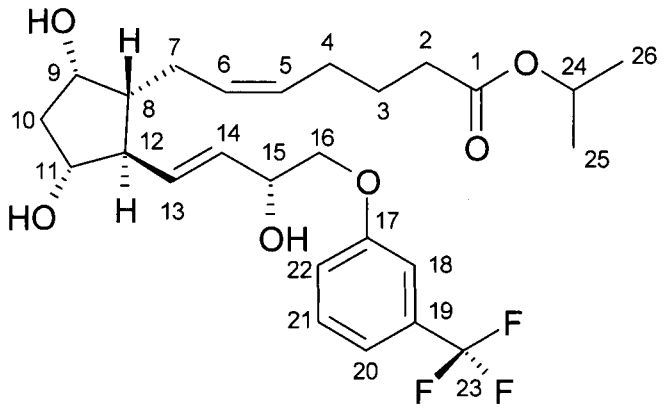
Mr: 458,48 Mr: 500,56

463 g of Travoprost acid is dissolved in 2.3 L of 1,3-dimethylimidazolidinone (DMI), and 420 g of K_2CO_3 and 300 ml of isopropyl iodide are added. The reaction mixture is stirred at 45°C. After the completion of the reaction $NaHSO_4$ solution, water, hexane and ethyl acetate are added. The mixture is shaken, then the phases are separated and the lower, aqueous phase is extracted with hexane : ethyl acetate mixture. The united organic phase is washed with water, dried over Na_2SO_4, the drying material is filtered off and the solution is evaporated. The product is purified by chromatography on silica gel, using diisopropyl ether, acetone, dichloromethane, isopropanol mixture as eluent.

Yield: 338.7 g, 67%

IR spectrum of Travoprost is shown on Figure 7.

Travoprost ^{1}H, ^{13}C and ^{19}F NMR data:



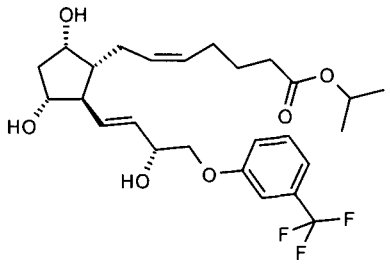
Numbering	^{13}C (ppm)	^{1}H (ppm)	Number of ^{1}H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
1	172.23	-	-	-	
2	33.19	2.16*	2	t	$J_{2,3}$=7.3
3	24.42	1.49**	2	tt	$J_{3,4}$=7.3
4	25.93	1.96***	2	m (q)	$J_{4,5}$=7.3
5	128.36	5.23	1	dt	$J_{5,6}$=10.7
6	129.85	5.44	1	dt	$J_{6,7}$=7.4
7	24.75	b: 2.09 a: 1.96***	1 1	m (dt) m	
8	48.76	1.31	1	m (dddd / tt)	11.2; 10.0; 4.8; 4.8
9	69.54$	3.90	1	m (dddd)	2.0; 5.3; 5.3, 5.3
9-OH		4.36	1	d	$J_{9,OH}$=4.9
10	43.96	b: 2.20* a: 1.44**	1 1	m (ddd) ddd	J_{gem}=14.1; $J_{10b,11}$=8.7; $J_{9,10b}$=5.9; $J_{10a,11}$=5.7; $J_{9,10a}$=2.3;
11	75.63	3.69	1	m (dddd / tt)	7.9; 7.9; 5.9; 5.9
11-OH		4.54	1	d	$J_{11,OH}$=5.8
12	54.30	2.175*	1	m	
13	134.01	5.57	1	dd	$J_{13,14}$=15.5; $J_{12,13}$=8.0
14	131.03	5.51	1	dd	$J_{14,15}$=6.0

15	69.54[$]	4.315	1	qui (tt)	5.5
15-OH		5.12	1	d	$J_{15,OH}$=4.8
16	72.55	a: 3.94 b: 3.95	1 1	m m	
17	158.96	-	-	-	
18	111.07 (q)	7.20	1	m	$^{3}J_{C\text{-}18,F}$ = 3.7; $J_{18,20}$=$J_{18,22}$=2.0
19	130.28 (q)	-	-	-	$^{2}J_{C\text{-}19,F}$ = 31.8
20	117.02 (q)	7.27[+]	1	t	$^{3}J_{C\text{-}20,F}$ = 3.9; $J_{20,21}$=8.0; $J_{20,22}$=0.7
21	130.67	7.51	1	t	$J_{21,22}$=8.0;
22	118.77	7.24[+]	1	dd	
23	124.01 (q)	-	-	-	$^{1}J_{C\text{-}23,F}$ = 272.2
23-F	-61.28 (s, 3)	-	-	-	
24	66.80	4.84	1	sep	$J_{24,25}$=6.3
25; 26	21.55	1.13	6	d	

[$]: Overlapping ^{13}C NMR signals. *, **, ***, [+]: Overlapping ^{1}H NMR signals.

Claims

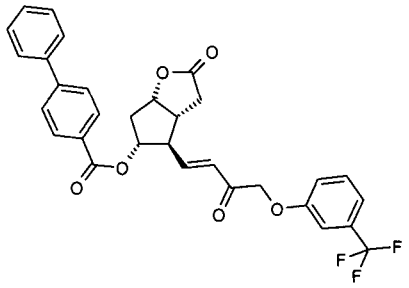
1. A process for the preparation of travoprost of formula (I).



(I)

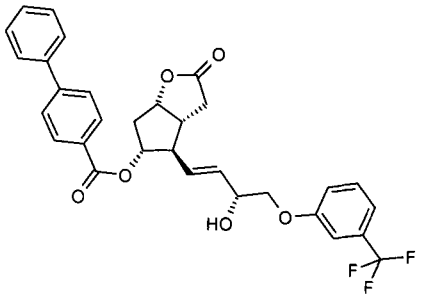
comprising that,

the compound of formula (II).



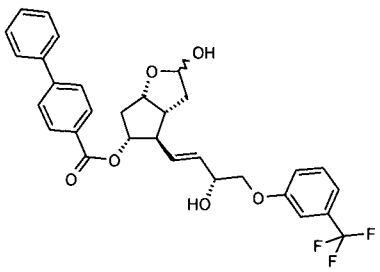
(II)

is stereoselectively reduced, the resulting compound of formula (III)



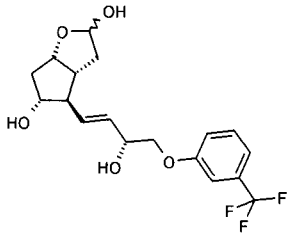
(III)

is if desired crystallized, the lactone group of the compound of formula (III) is reduced, the *p*-phenyl-benzoyl protecting group of the thus obtained compound of formula (IV)



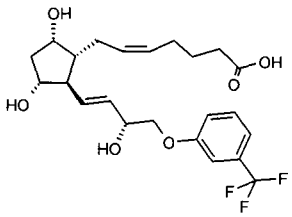
(IV)

is removed, the resulting triol of formula (V)



(V)

is if desired after crystallization transformed by Wittig reaction into the acid of formula (VI),



(VI)

which is then esterified.

2. The process as defined in claim 1., comprising that the selective reduction of the compound of formula (II) is carried out with a borane-type reducing agent.

3. The process as defined in claim 2., comprising that as borane-type reducing agent catecholborane is applied.

4. The process as defined in claim 2., comprising that the reduction of the compound of formula (II) is carried out in the presence of a chiral catalyst.

5. The process as defined in claim 4., comprising that CBS-oxazaborolidine is used as catalyst.

6. The process as defined in claims 2.-5., comprising that the reduction is performed in hydrocarbon- or ether-type solvents.

7. The process as defined in claim 6., comprising that the reduction is performed in toluene, hexane, heptane, pentane, tetrahydrofuran, methyltetrahydrofuran, cyclopentyl methyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, diethyl ether or in the mixture of them.

8. The process as defined in claim 7., comprising that the reduction is performed in a toluene - tetrahydrofuran mixture.

9. The process as defined in claims 2.-7., comprising that the reduction is carried out at a temperature between (-)10 and (-)90 °C.

10. The process as defined in claim 9., comprising that the reduction is carried out at a temperature between (-)10 and (-)20 °C.

11. The process as defined in claims 2-10., comprising that the resulting compound of formula (III) is purified by crystallization.

12. The crystallization as defined in claim 11., comprising that the crystallization is carried out in hydrocarbon, chlorinated hydrocarbon, ether, ester, ketone or alcohol-type solvents or in the mixture of them.

13. The crystallization as defined in claim 12., comprising that the crystallization is carried out repeatedly, in different solvents or in the mixture of them.

14. The crystallization as defined in claim 13., comprising that the crystallization is carried out in hexane : acetone mixture and/or in methanol.

15. The crystallization as defined in claims 11-14., comprising that the crystallization is carried out at a temperature between (-20) - 70°C in such a way that the material is dissolved in alcohol at reflux temperature, crystallized by cooling gradually, and then filtered off, washed and dried.

16. The process as defined in claim 1., comprising that the reduction of the compound of formula (III) is carried out with diisobutylaluminum hydride.

17. The process as defined in claim 1., comprising that the /?-phenylbenzoyl protecting group of the compound of formula (IV) is removed by methanolysis, under basic conditions.

18. The process as defined in claim 17., comprising that the protecting group is removed in the presence of potassium carbonate.

19. The process as defined in claim 1., comprising that the intermediate of formula (V) is purified by crystallization.

20. The process as defined in claim 19., comprising that the crystallization is carried out in the mixture of polar and apolar solvents.

21. The process as defined in claim 20., comprising that the crystallization is carried out in ethyl acetate - hexane mixture.

22. The process as defined in claims 20 and 21, comprising that the amount of the undesired isomer is decreased under the disregarding limit (0,05%) with adequate repetition of the crystallization process

23. The process as defined in claim 1., comprising that esterification of the compound of formula (VI) is carried out with isopropyl iodide.

24. The process as defined in claim 23., comprising that the esterification is carried out in cyclic tertiary-amide type solvents.

25. The process as defined in claim 24., comprising that as cyclic tertiary-amide type solvent *N*-methylpyrrolidone or 1,3-dimethylimidazolidinone is applied.

26. The process as defined in claims 23-25., comprising that the esterification is carried out within a temperature range of 20 - 90°C.

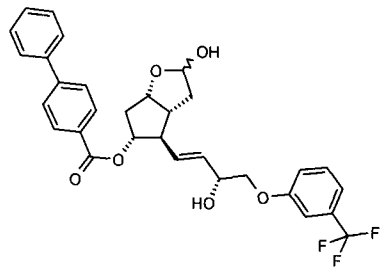
27. The process as defined in claim 26., comprising that the esterification is carried out within a temperature range of 40 - 50°C.

28. The process as defined in claim 1., comprising that the product of formula (I) is purified by chromatography.

29. The process as defined in claim 28., comprising that the product is purified by gravimetric silica gel chromatography.

30. The process as defined in claim 29., comprising that the chromatographic purification is performed using hydrocarbon, chlorinated hydrocarbon, ether, ester, alcohol, ketone and acid-type solvents or their mixtures, as eluents.

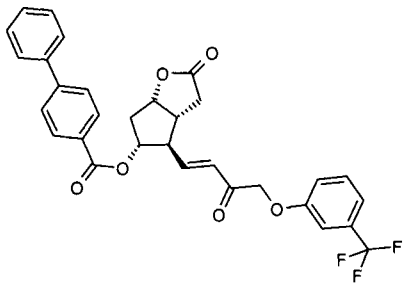
31. The compound of formula (IV)



(IV)

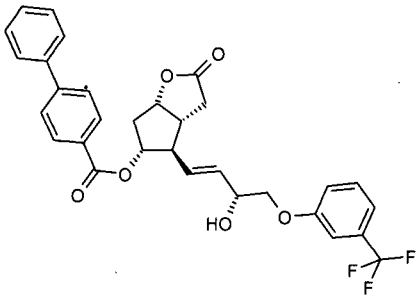
32. Use of the compound of formula (IV) as defined in claim 30., for the preparation of travoprost of formula (I).

33. The process for the preparation of the compound of formula (IV), comprising that the compound of formula (II)



(II)

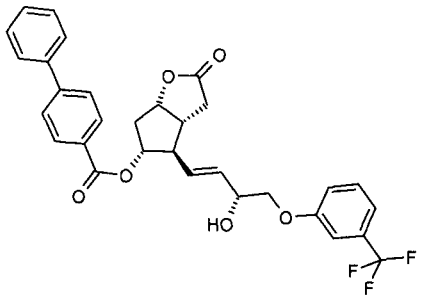
is stereoselectively reduced, and the lactone group of the resulting compound of formula (III)



(III)

is reduced.

34. The crystalline compound of formula (III)

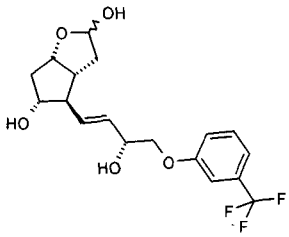


(III)

having the melting point of 129.5-134.5°C.

35. Use of the crystalline compound of formula (III) as defined in claim 33., for the preparation of Travoprost of formula (I).

35. The crystalline compound of formula (V).,



(V)

having the melting point of 85.4-86.6°C.

36. The crystalline compound of formula (V) as defined in claim 35., having an amount of the undesired isomer less than 0,05%

37. Use of the crystalline compound of formula (V) as defined in claim 35., for the preparation of Travoprost of formula (I).

Figure 1.

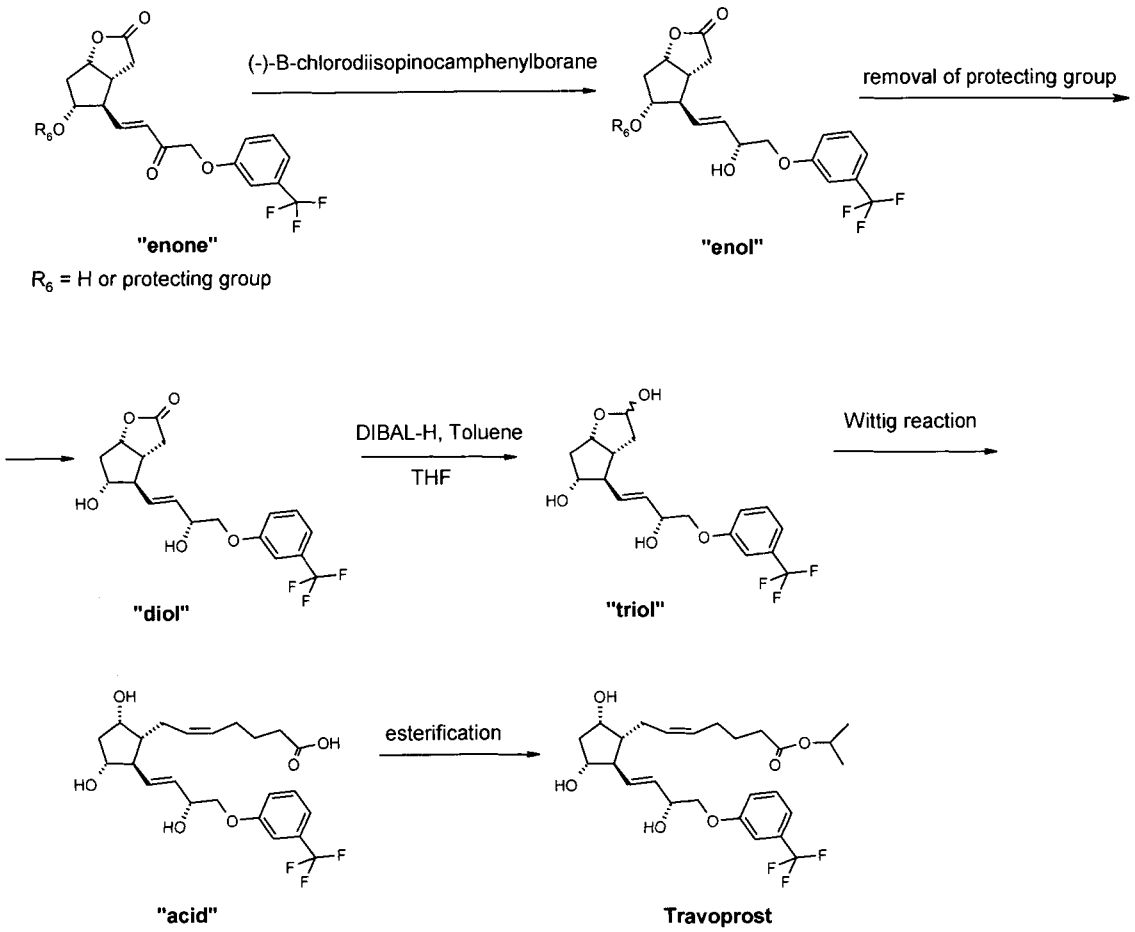

(-)-B-chlorodiisopinocamphenylborane
removal of protecting group
"enone"
"enol"
R6 = H or protecting group
DIBAL-H, Toluene
THF
Wittig reaction
"diol"
"triol"
esterification
"acid"
Travoprost

Figure 2.

Travoprost 1. intermediate IR spectrum:

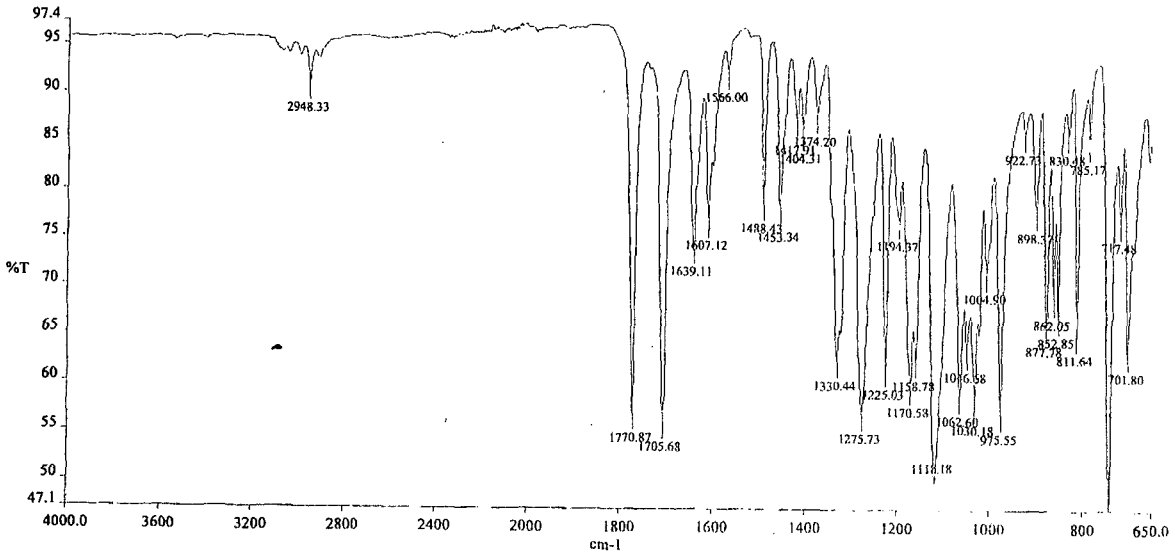


Figure 3.

Travoprost 2. intermediate IR spectrum:

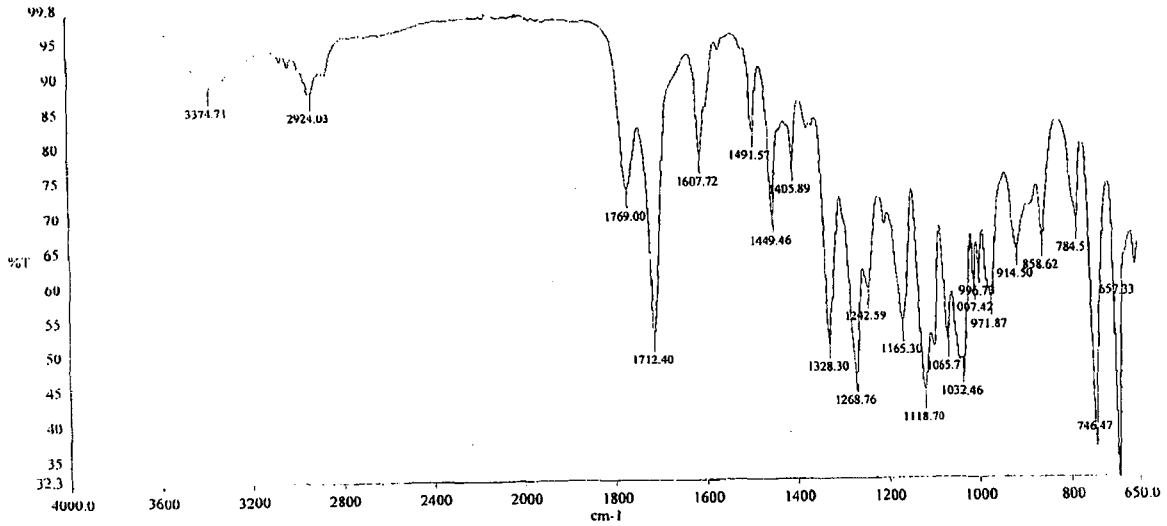


Figure 4

Travoprost 3. intermediate IR spectrum:

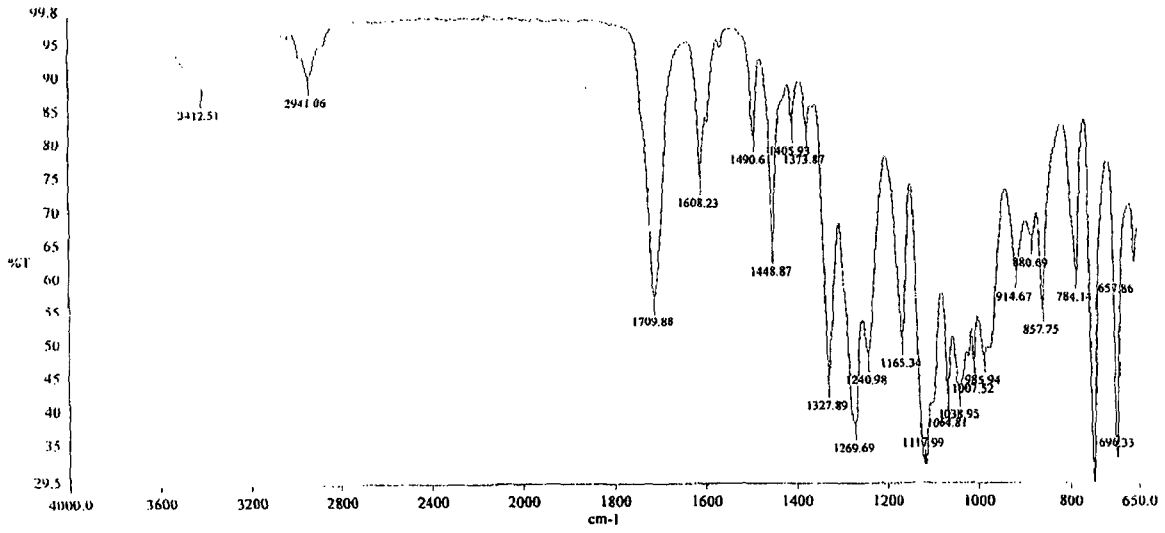


Figure 5.

Travoprost 4. intermediate IR spectrum:

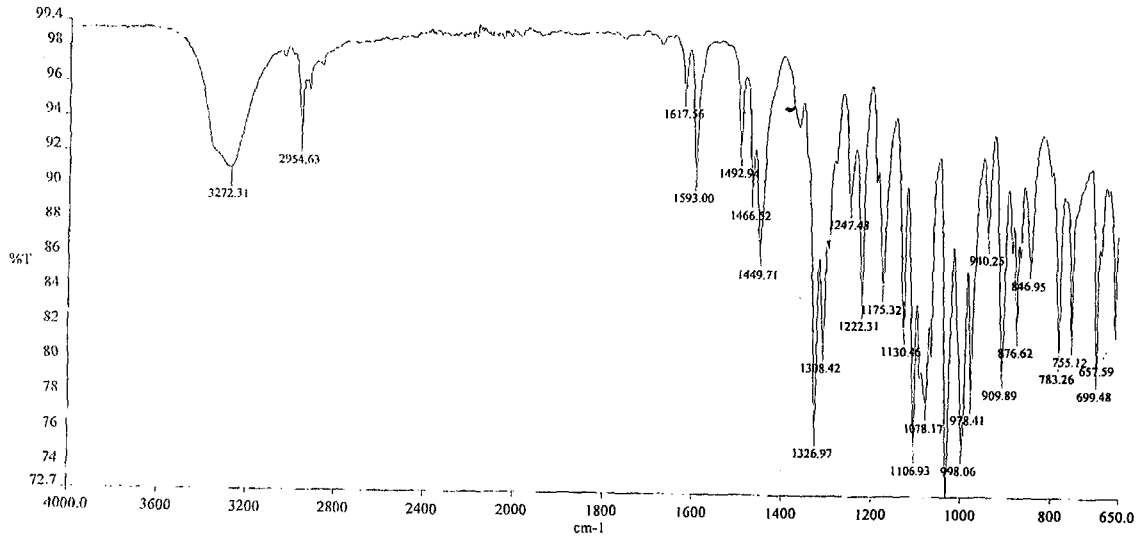


Figure 6.

Travoprost 5. intermediate IR spectrum:

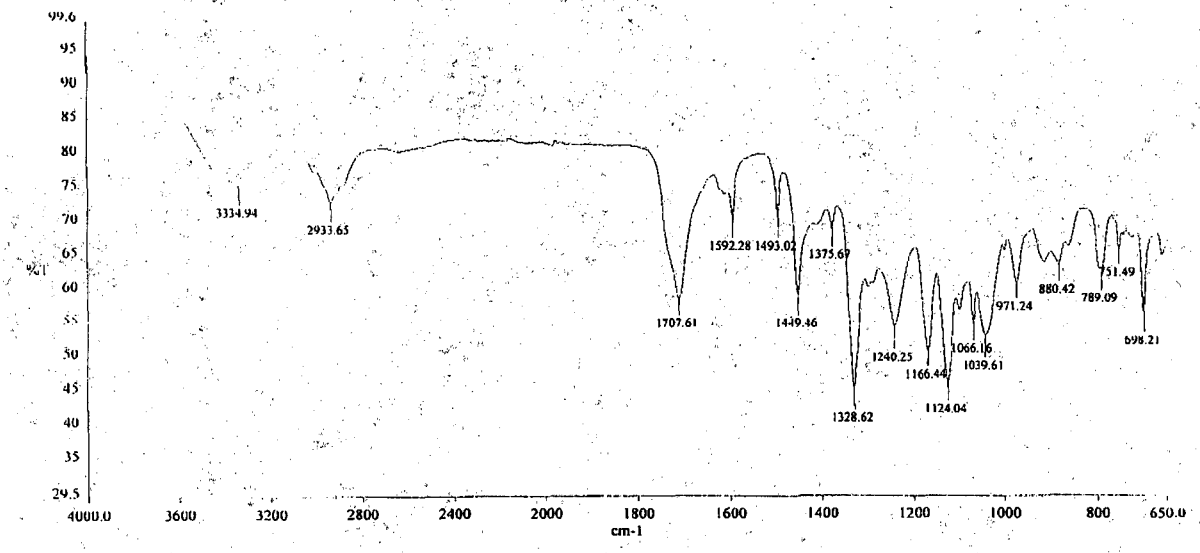


Figure 7.

Travoprost IR spectrum:

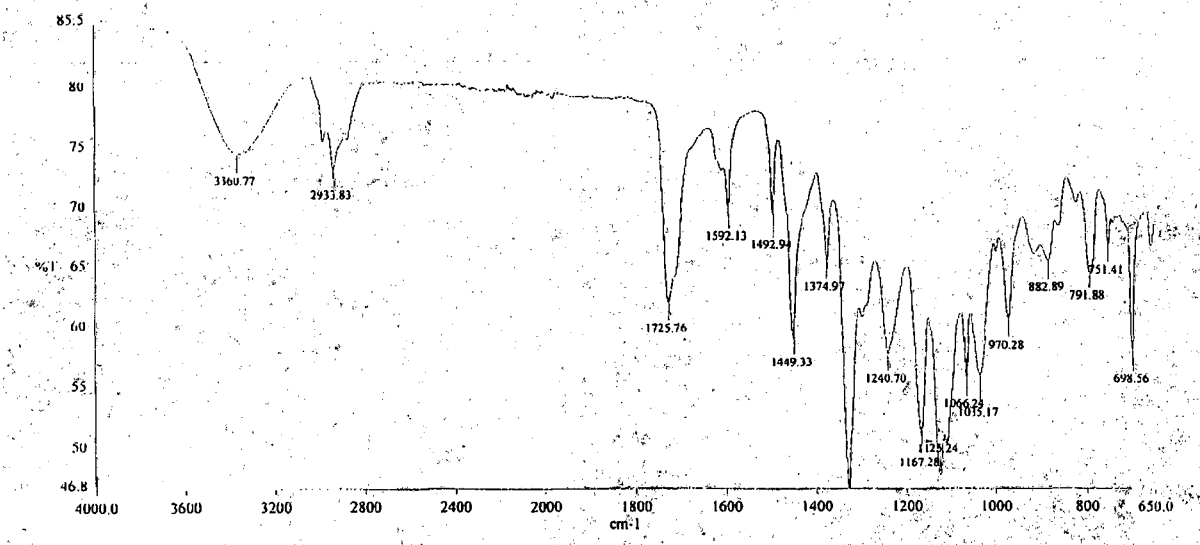


Fig. 6.

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2012/000132

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C405/00 C07D307/935
ADD.

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)
C07C C07D

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)
EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 143 712 Al (SANDOZ AG [CH]) 13 January 2010 (2010-01-13) cited in the application	36-38
Y	examples 9-12 page 59, line 19: "described in example 4" example 4 on page 55, line 15: "crystals" claims 14, 15	1-38

X	ASWATHANARAYANAPPA, C. ET AL: "Diastereoselective reduction of the enone intermediate of Travoprost" , ORGANIC PROCESS RESEARCH & DEVELOPMENT , 15(5) , 1085-1087 CODEN: 0PRDFK; ISSN: 1083-6160, 15 August 2011 (2011-08-15) , XP002693410,	34,35
Y	page 1086, schemes 1-3 page 1087, column 2, line 9: mp 130-133 oC	1-38

	-/- .	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"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
11 March 2013	20/03/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fitz, Wolfgang

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2012/000132

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1988, HAJEK, JIRI ET AL: "Separation of 15S- and 15R-isomers of 4-[4-(substituted X-phenoxy) 3-hydroxy-1-butenyl]hexahydro-5-hydroxy-2H-cyclopenta[b]furan-2-one as intermediates for prostaglandin analogs.", XP002693411, retrieved from STN Database accession no. 1988:406306	34
Y	abstract -& CS 239 696 B1 (CZECH.) 16 January 1986 (1986-01-16) page 3, penultimate paragraph -----	1-38

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/HU2012/000132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2143712 A1	13-01-2010	EP 2143712 A1	13-01-2010
		US 2010010239 A1	14-01-2010
CS 239696 B1	16-01-1986	NONE	