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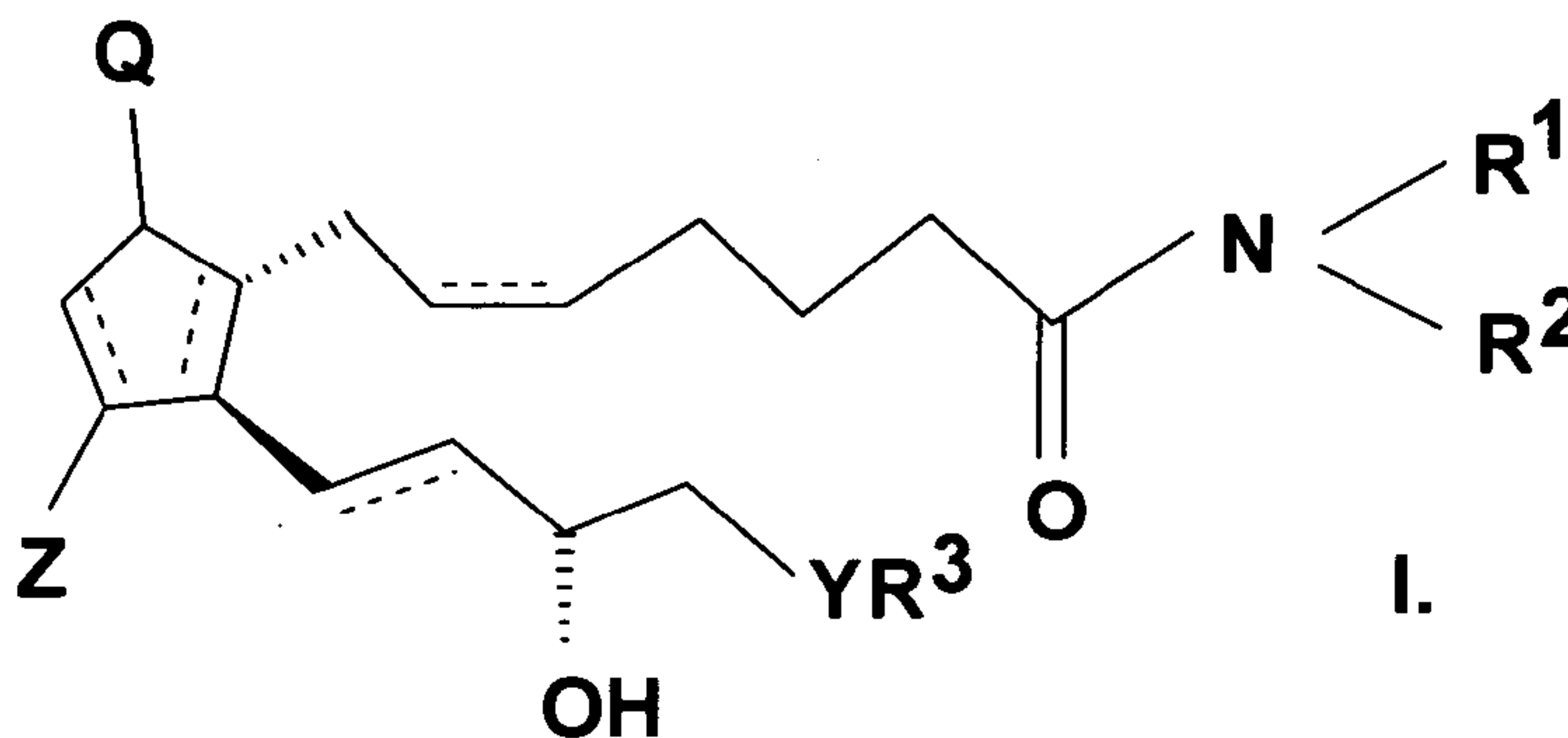
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(54) Titre : NOUVEAU PROCEDE POUR LA PREPARATION D'AMIDES DE PROSTAGLANDINES

(54) Title: NOVEL PROCESSES FOR THE PREPARATION OF PROSTAGLANDIN AMIDES



(57) **Abrégé/Abstract:**

The subject of the invention is process for the preparation of the prostaglandin amides of the general formula I, - where in the formula the bonds marked with dotted lines may be single or double bonds, in the case of double bounds at positions 5,6 and 13,14 they may be in cis or in trans orientation, Q stands for a hydroxyl-group and Z stands for a hydroxyl- or oxo-group, R¹ and R² independently represent hydrogen atom or a straight or branched C₁₋₁₀ alkyl- or aralkyl- group, optionally substituted with -ONO₂ group, or an aralkyl- or aryl- group, which contains heteroatom, R³ represents a straight or branched, saturated or unsaturated C₄₋₆ hydrocarbon group, or a C₄₋₁₀ alkylcycloalkyl- or cycloalkyl- group, or an optionally with alkyl group or halogen atom substituted phenyl-, C₇₋₁₀ alkylaryl- or hetaryl- group, Y represents (CH₂)_n group or O atom or S atom, and where n=0-3.



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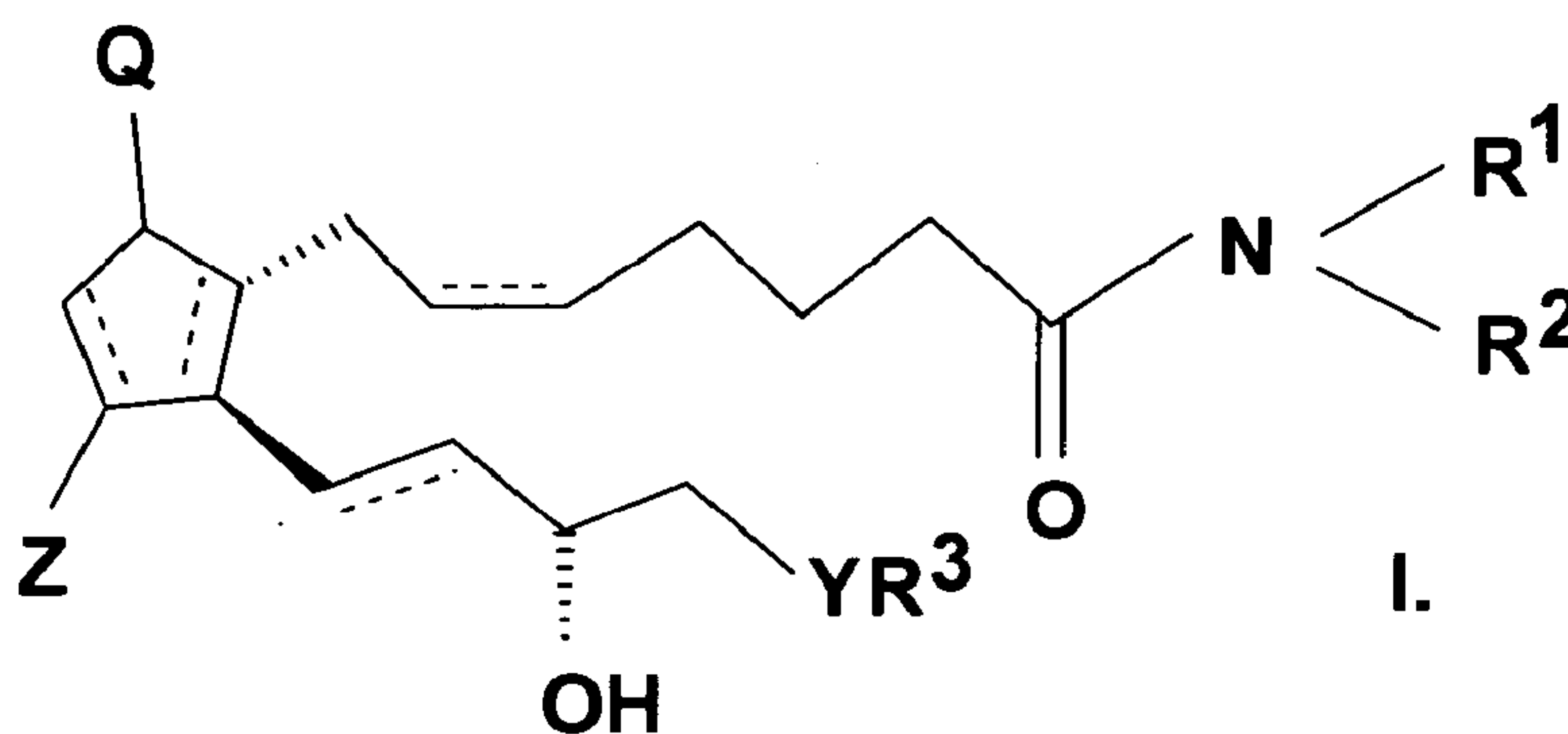
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(54) Title: NOVEL PROCESSES FOR THE PREPARATION OF PROSTAGLANDIN AMIDES



(57) Abstract: The subject of the invention is process for the preparation of the prostaglandin amides of the general formula I, - where in the formula the bonds marked with dotted lines may be single or double bonds, in the case of double bounds at positions 5,6 and 13,14 they may be in cis or in trans orientation, Q stands for a hydroxyl-group and Z stands for a hydroxyl- or oxo-group, R¹ and R² independently represent hydrogen atom or a straight or branched C₁₋₁₀ alkyl- or aralkyl- group, optionally substituted with -ONO₂ group, or an aralkyl- or aryl- group, which contains heteroatom, R³ represents a straight or branched, saturated or unsaturated C₄₋₆ hydrocarbon group, or a C₄₋₁₀ alkylcycloalkyl- or cycloalkyl- group, or an optionally with alkyl group or halogen atom substituted phenyl-, C₇₋₁₀ alkylaryl- or hetaryl- group, Y represents (CH₂)_n group or O atom or S atom, and where n=0-3.

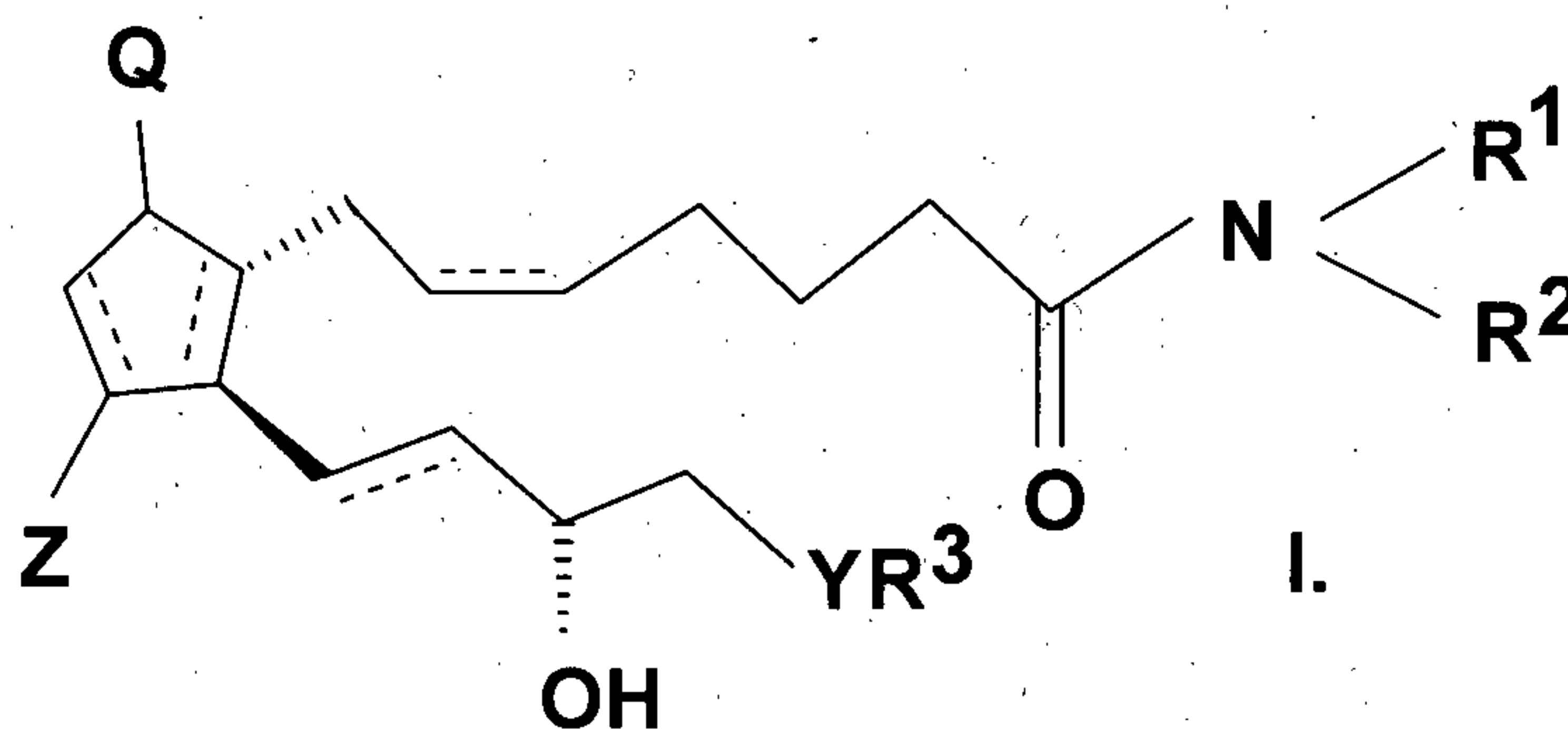
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Novel processes for the preparation of prostaglandin amides

The subject of the invention is a process for the preparation of prostaglandin amides of the general formula (I).

5

In the compounds of the general formula (I)



the meanings of the substituents are as follows:

10 the bonds marked with dotted lines may be single or double bonds, in the case of double bonds in positions 5,6 and 13,14 they may be in cis or in trans orientation,

Q represents hydroxy-group and Z represents hydroxy- or oxo-group,

R^1 and R^2 independently represent hydrogen atom or a straight or branched C_{1-10} alkyl- or aralkyl- group, optionally substituted with $-ONO_2$ group, or an aralkyl- or aryl- group,

15 which contains heteroatom,

R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

Y represents $(CH_2)_n$ group or O atom or S atom, and

20 $n=0-3$.

To prepare the prostaglandin amide derivatives economically, the appropriately substituted prostan acid has to be activated.

According to the present state of the art, carboxylic acids may be activated by transformation into their

5 mixed anhydrides

activated esters or

activated amides,

and these compounds may then be further transformed into the desired prostaglandin amide derivatives by reaction with the appropriate amines.

10

Of the above possibilities, activation of the chemically very sensitive prostaglandin acids through ester formation is described for example in EP 0 660 716.

According to the process, the starting ester is formed with the help of alkyl halogenides and the ester is then reacted with the appropriate amine to give the amide function.

15 Disadvantage of the method is that the use of alkyl halogenides at the end of a synthesis – in the last step – is to avoid, since alkyl halogenides are proved to be genotoxic agents.

In addition, the resulting ester has to be treated with the appropriate amine at a high temperature for a long time and conversion rarely exceeds 50% (EP0660716 page 42.

Example12.). Considering the known temperature-sensitivity of prostaglandins, their

20 treatment at high temperature unfavourably influences the impurity profile and the yield of the prostaglandin derivatives obtained in this way.

Preparation of the mixed anhydride and its reaction with the appropriately substituted amine is demonstrated in WO9153206.

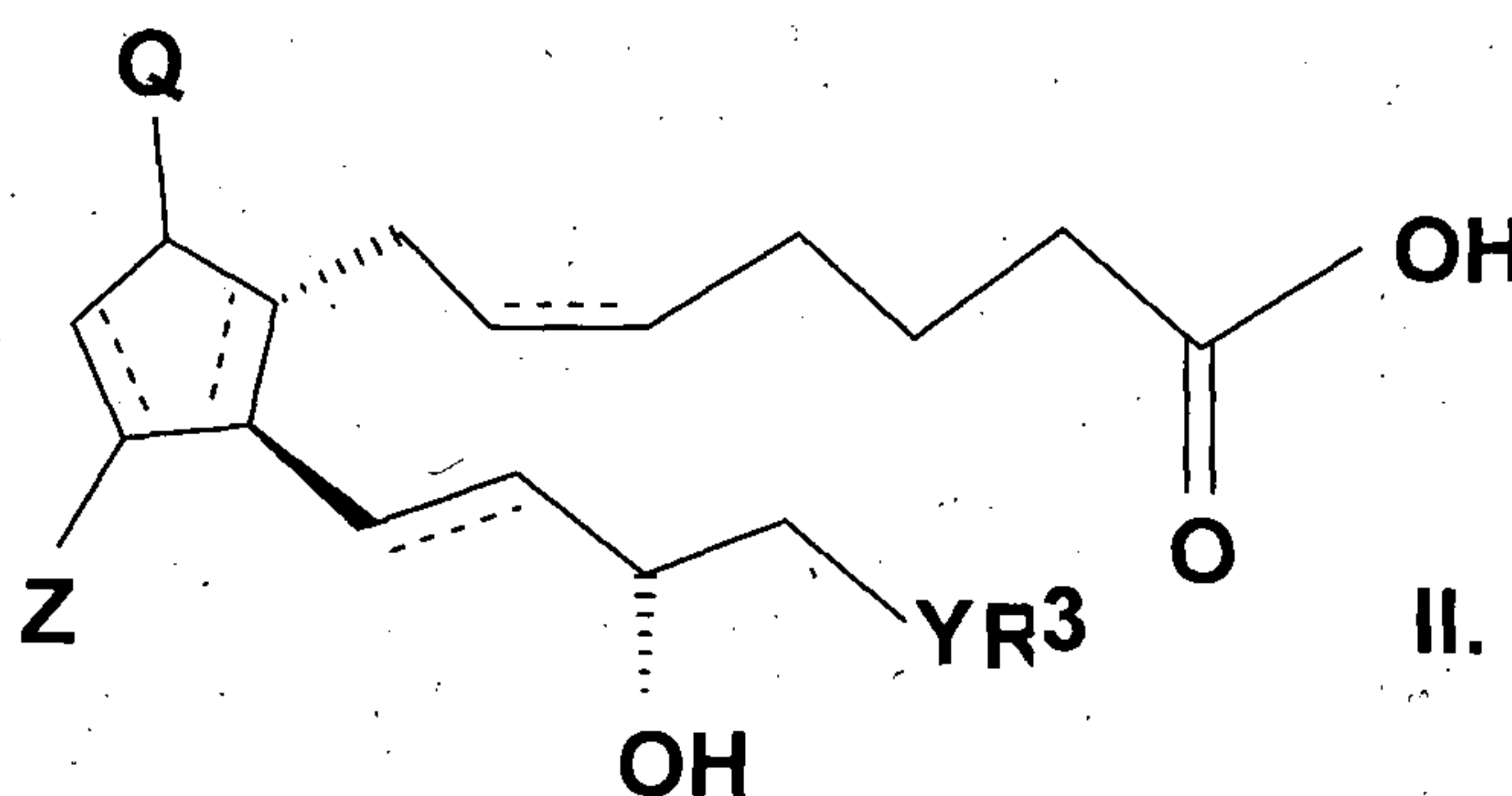
Disadvantage of the method is that the active alkylating agents used for the preparation of the mixed anhydrides - halogenated formic acid esters, pivaloyl chlorides and others - are proved to be genotoxic compounds.

- 5 In the method descibed in WO2005058812 (page 23.) the starting carboxylic acid is directly transformed into the ethyl amide by use of the activating agent 1-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC HCl) and ethylamine. During the amidation reaction the hydroxyl groups at positions 11 and 15 are protected with tetrahydropyran (THP) protecting group, which is then removed.

10

We have found that via the novel activated esters and novel activated amides according to the invention, the compounds of the general formula (I) can be prepared under mild reaction conditions in high yield and purity.

- 15 The compounds of the general formula (I) according to the invention can be prepared by reacting an acid of the general formula (II),



where in the formula

the bonds marked with dotted lines may be single or double bonds, in the case of double

- 20 bounds at positions 5,6 and 13,14 they may be in cis or in trans orientation,

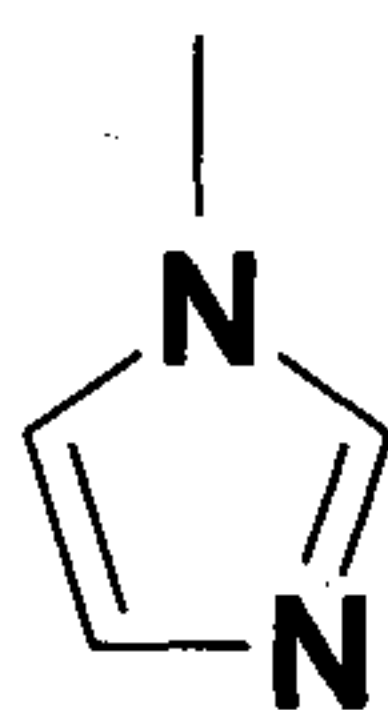
Q represents hydroxy-group and Z represents hydroxy- or oxo-group,

R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

Y represents $(CH_2)_n$ group or O atom or S atom, and

5 $n=0-3$,

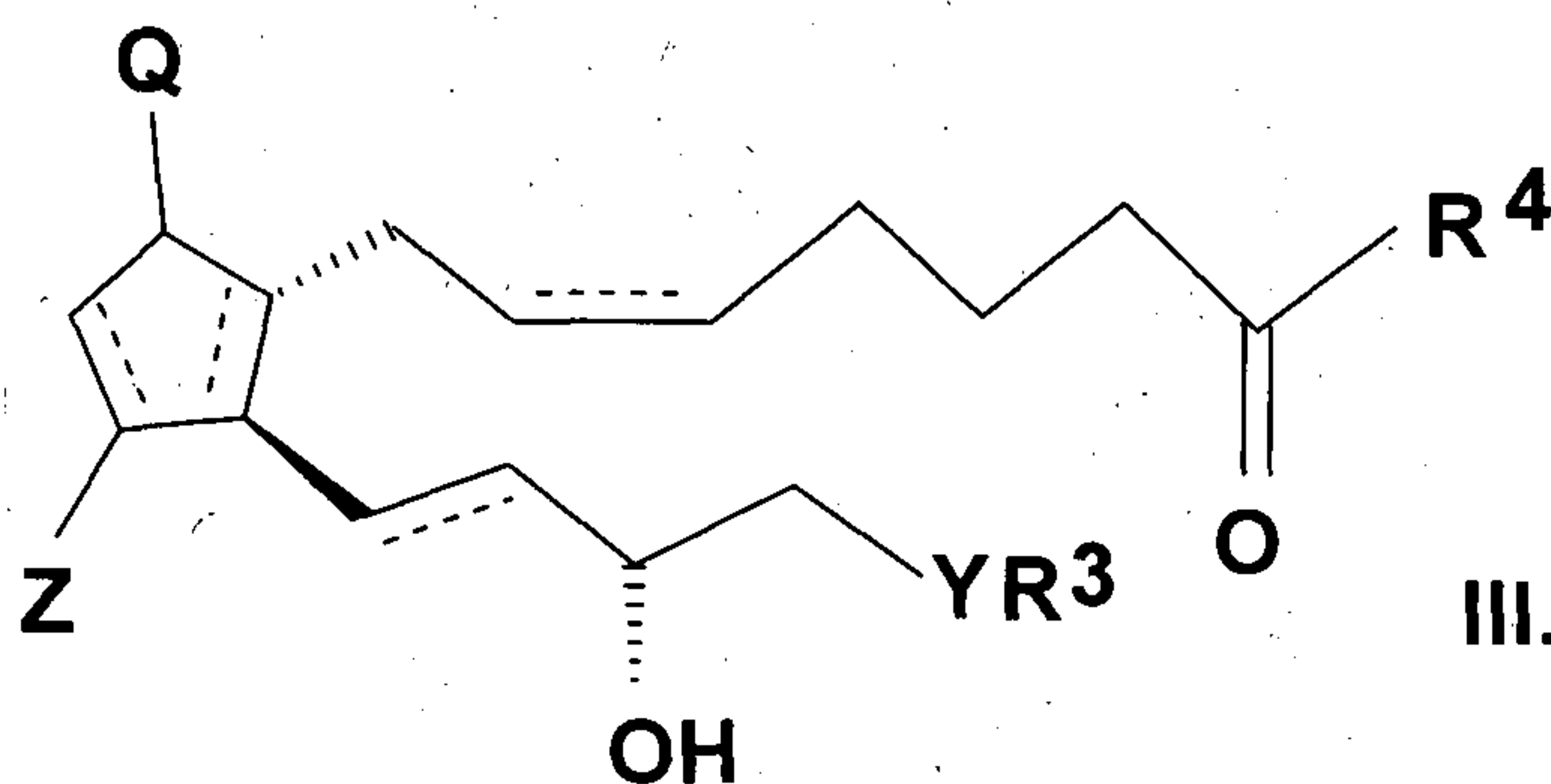
i.) with a compound suitable for the introduction of group R^4 , where R^4 represents



a.)

a group of formula a.),

10 and reacting the amide of the general formula (III), thus obtained



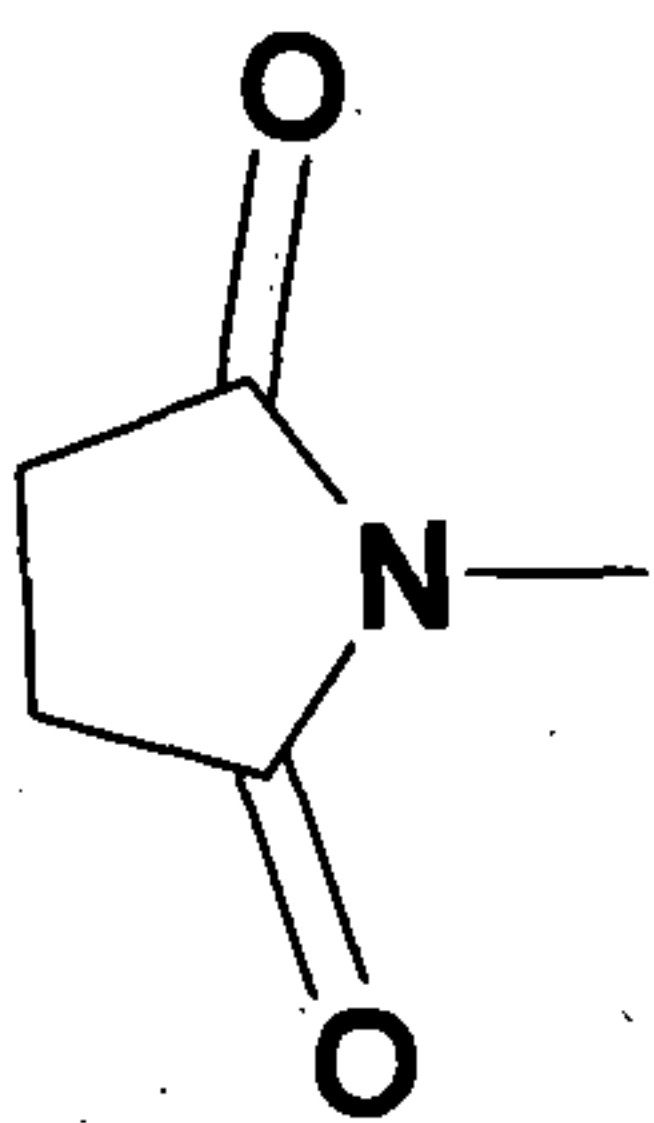
where the meanings of Q, Z, R^3 , R^4 , Y and n are as defined above, with an amine of the general formula (IV),



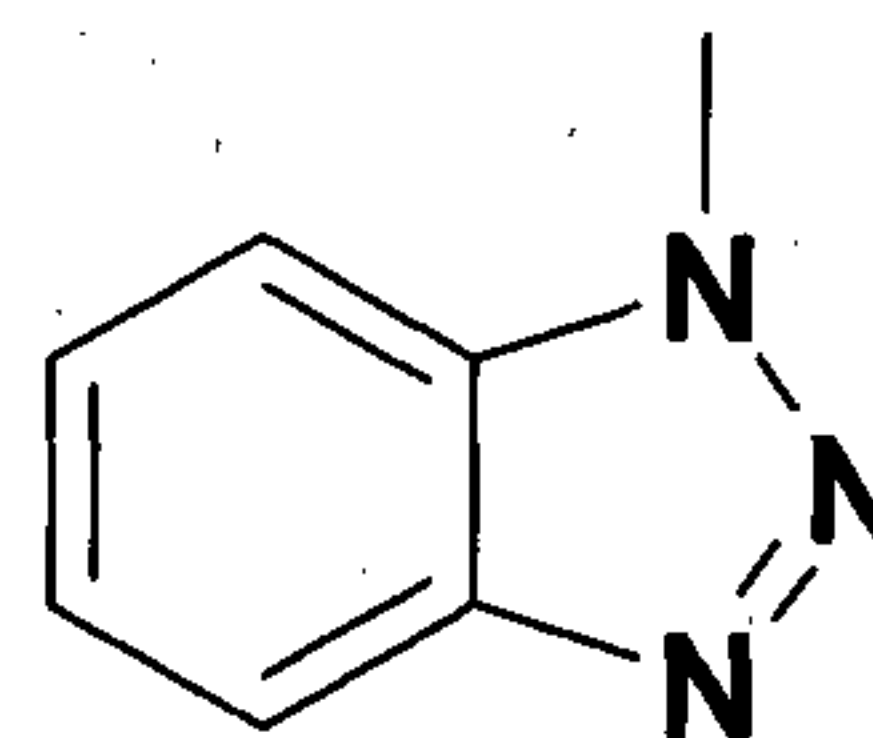
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where the meanings of R^1 and R^2 are as defined above, or

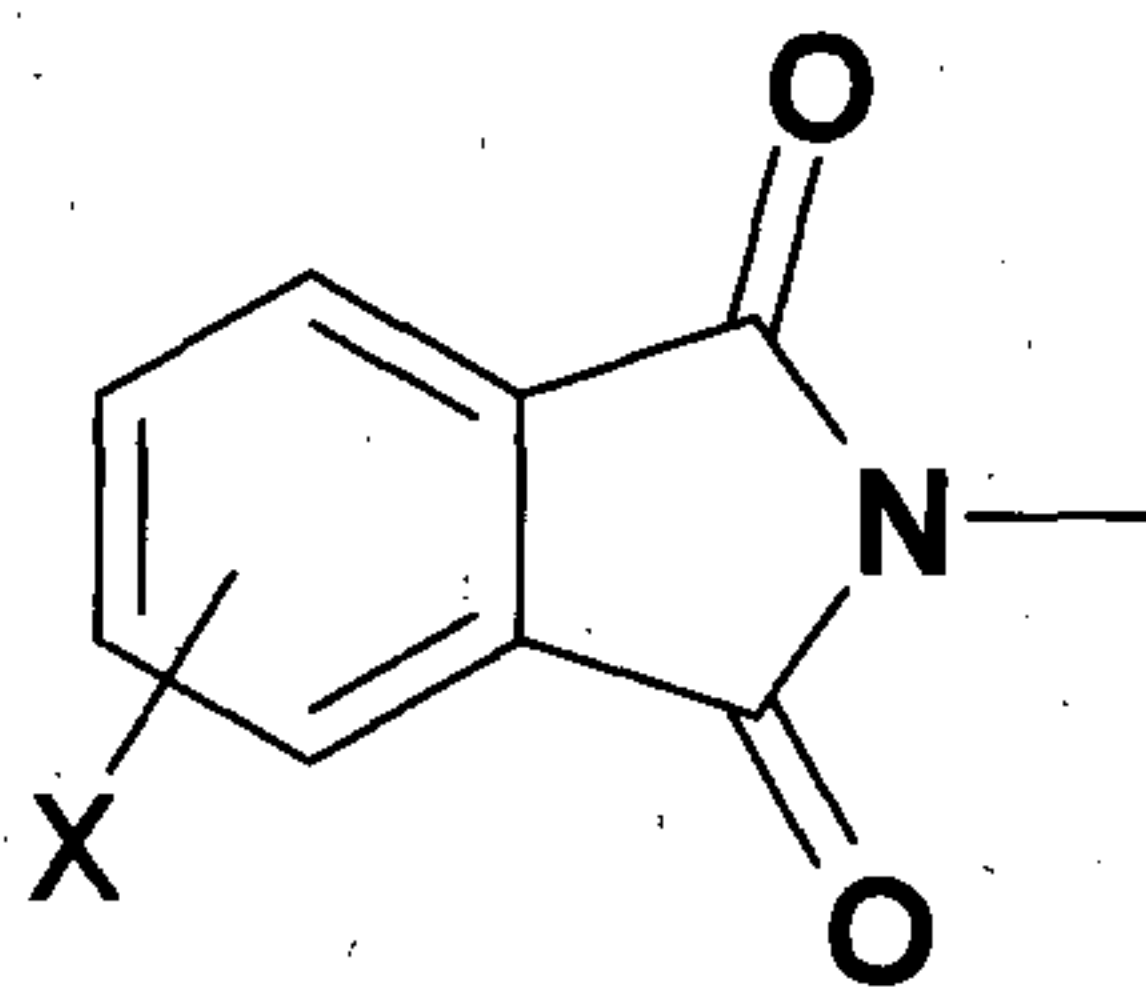
ii.) with a compound suitable for the introduction of group R^5 , where R^5 represents



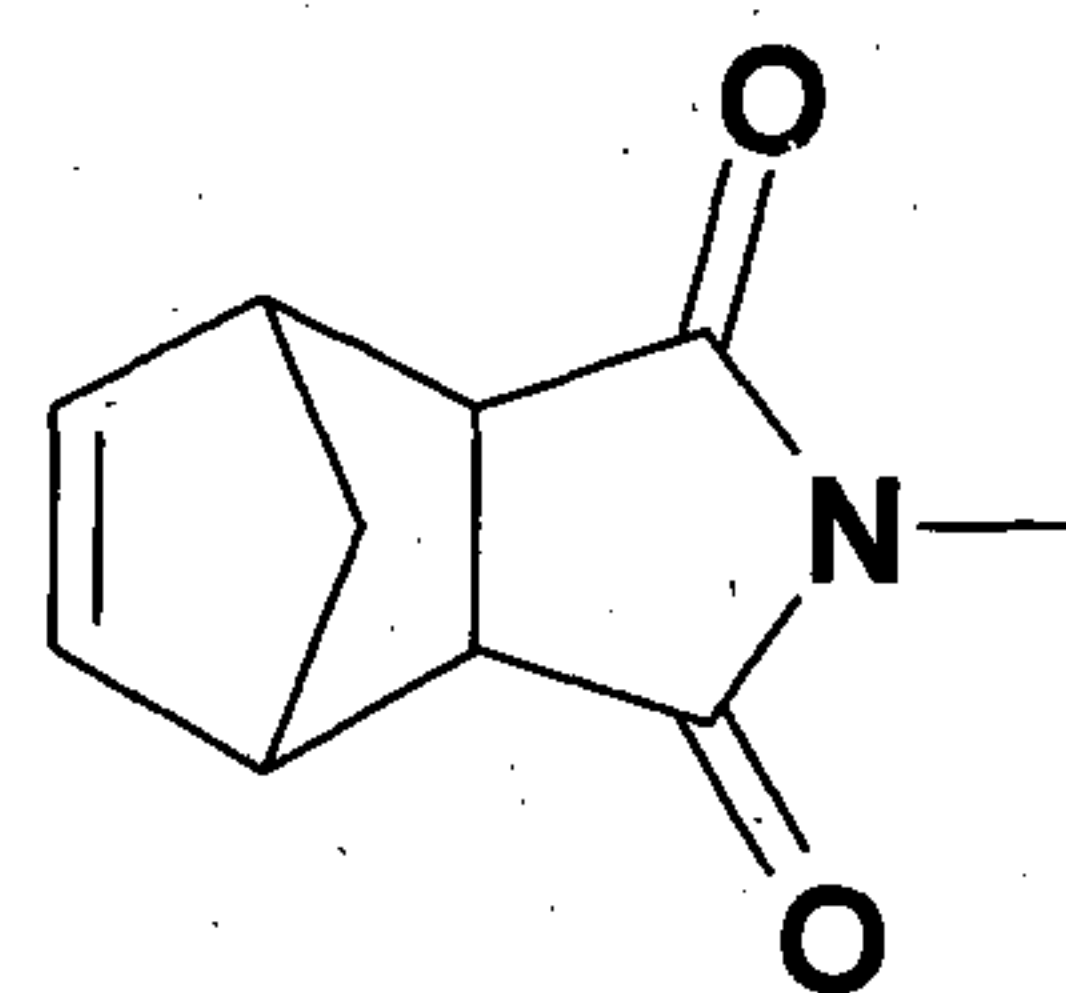
b.)



c.)

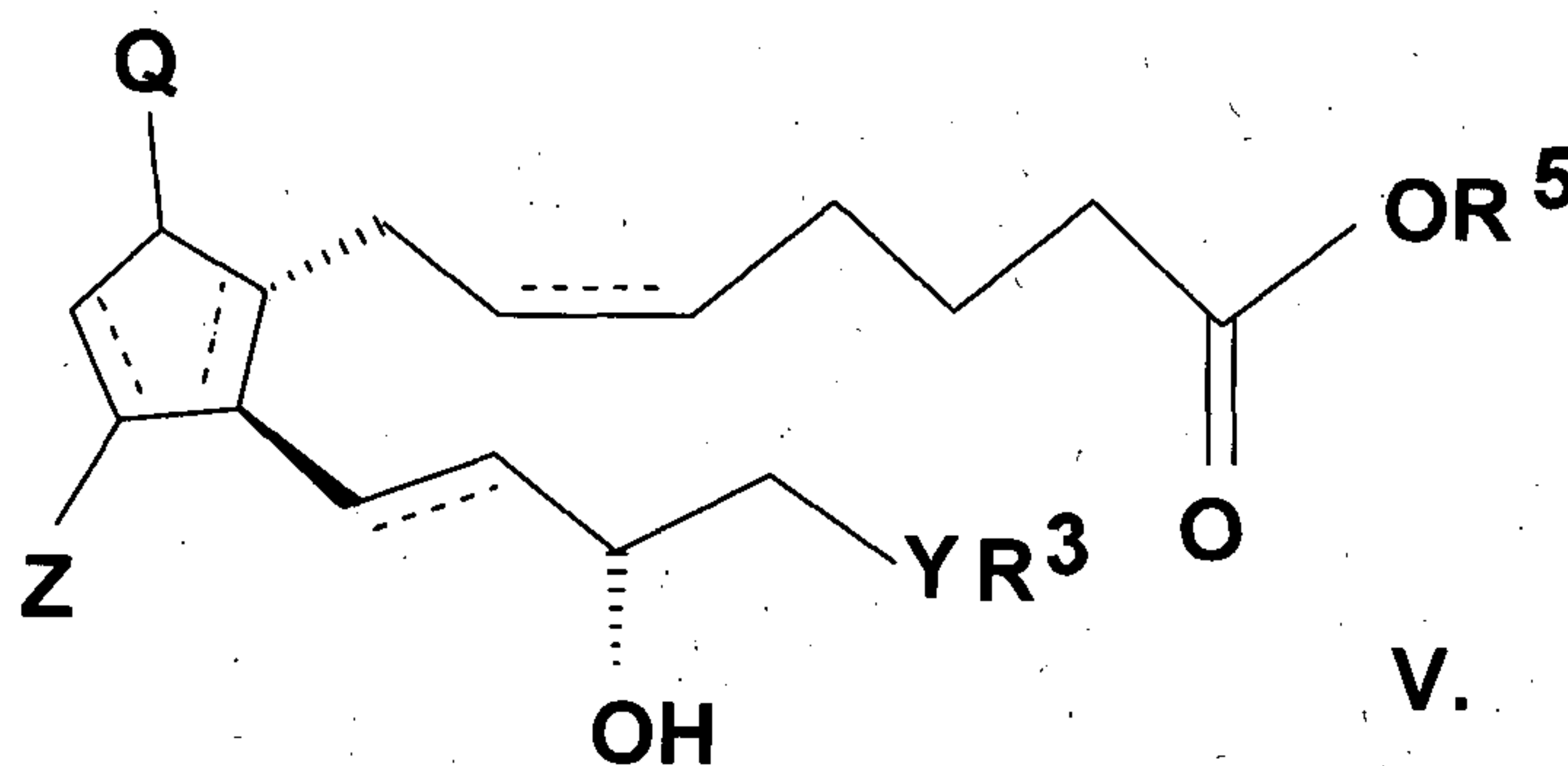


d.)



e.)

a group of formula b.), c.), d.) or e.), where X stands for halogen or hydrogen atom, and reacting the activated ester of the general formula (V), thus obtained



5

where the meanings of Q, Z, R³, R⁵, Y and n are as defined above, with an amine of the general formula (IV), where the meanings of R¹ and R² are as defined above.

We have further found that the compounds of the general formula (I) according to the invention can also be prepared by reacting a compound of the general formula (II) with a compound of the general formula (IV) - where in the formulae the meanings of the substituents are as defined above - in the presence of 2-chloro-1,3-dimethylimidazolinium chloride and a base (method iii.).

10

The intermediates of the general formula (III) and (V) are novel compounds.

As for a compound suitable to introduce group R^4 , preferably 1,1'-carbonyldiimidazole(DCI) or 1,1'-thiocarbonyldiimidazole, to introduce group R^5 , in a
5 given case in the presence of an activating agent, N-hydroxysuccinimide, N-hydroxyphthalimide, N-hydroxy-5-norben-endo-2,3-dicarboxamide, 1-hydroxybenzotriazole, (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate, N,N'-disuccinimidyl carbonate (DSC) or N,N'-disuccinimidyl oxalate, especially N,N'-disuccinimidyl carbonate may be applied.

10 As for activating agent N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide or 2-chloro-1,3-dimethylimidazolinium chloride, preferably N,N'-diisopropylcarbodiimide may be applied.

In the course of method i.) according to the invention, group R^4 can be introduced in an
15 ether-type solvent or aromatic solvent or polar aprotic solvent or in their mixtures, using for example diisopropyl ether, tert-butyl methyl ether, 2-methyltetrahydrofuran, toluene, anisole, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, especially tetrahydrofuran. The resulting activated amide of the general formula (III) is reacted with the amine of the general formula (IV) after or without isolation.

20 The reaction temperature during the introduction of group R^4 is between 20-80°C, preferably 70°C, while the reaction of the compounds of formula (III) and (IV) is carried out between 20-80°C, preferably at room temperature.

In the course of method ii.) according to the invention, the introduction of group R^5 is
25 carried out in an ether-type solvent or in an aromatic or polar aprotic solvent or in their mixtures, using for example diisopropyl ether, tert-butyl methyl ether, 2-

methyldihydrofuran, toluene, anisole, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, especially tetrahydrofuran. The resulting activated ester of the general formula (V) is reacted with the amine of the general formula (IV) after or without isolation. The reaction temperature during the introduction of group R⁵ is between 0-80°C, preferably at room temperature, while the reaction of the compounds of formula (V) and (IV) is carried out between 20-80°C, preferably at room temperature.

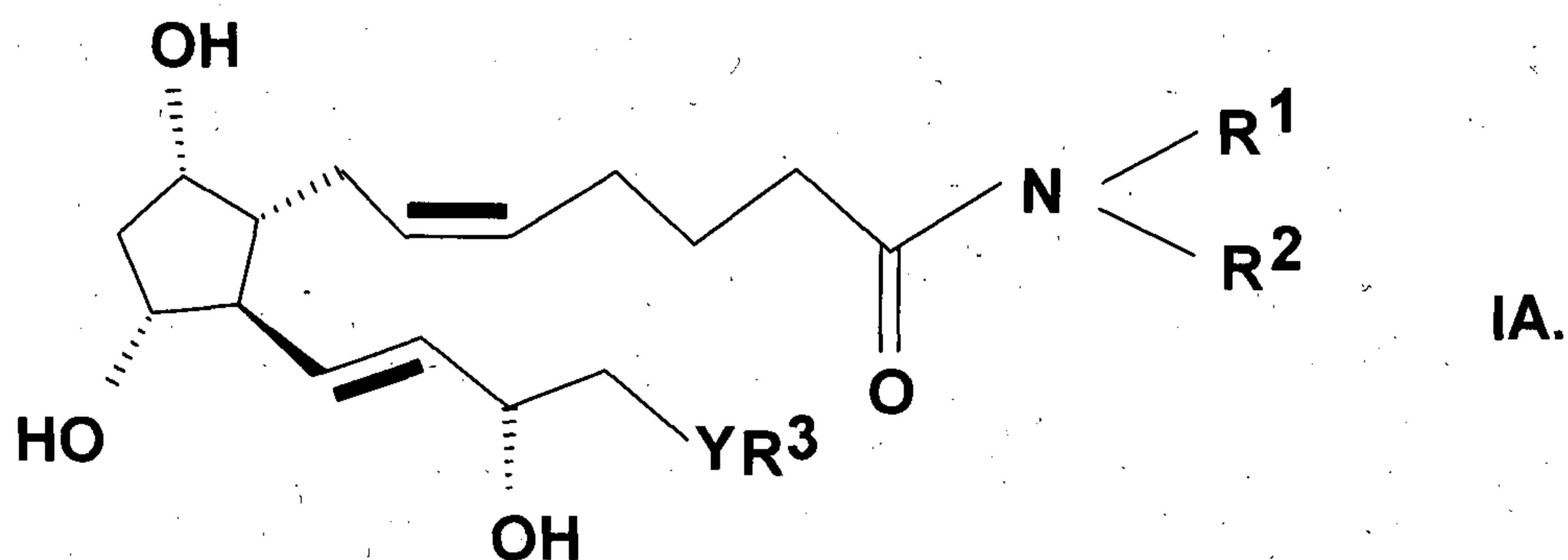
In the course of method iii.) according to the invention, the reaction is performed in an ether-type solvent or in an aromatic or polar aprotic solvent or in their mixtures, using for example diisopropyl ether, tert-butyl methyl ether, 2-methyldihydrofuran, toluene, anisole, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone or tetrahydrofuran. As for base, the usually applied bases, like pyridine, N-methylmorpholine, diisopropylethylamine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,8-diazabicyclo[5,4,0]undec-7-ene or triethylamine may be employed.

The reaction is carried out at a temperature between 0-70°C, in such a way that to the solution of the compound of the general formula (II) in an organic solvent are added at 0-70°C, preferably at 30°C, the compound of the general formula (IV), the 2-chloro-1,3-dimethylimidazolinium chloride and 2 molar equivalent amount of the base. The mixture is first stirred at that temperature and then gradually heated until the starting material disappears. The reaction is followed by TLC.

Methods i., ii or iii may be carried out also under „one pot” conditions.

As for the amine of the general formula (IV) the amine appropriate for the final compound, in the case of bimatoprost ethylamine may be used.

For the preparation of the compounds of the general formula (IA)

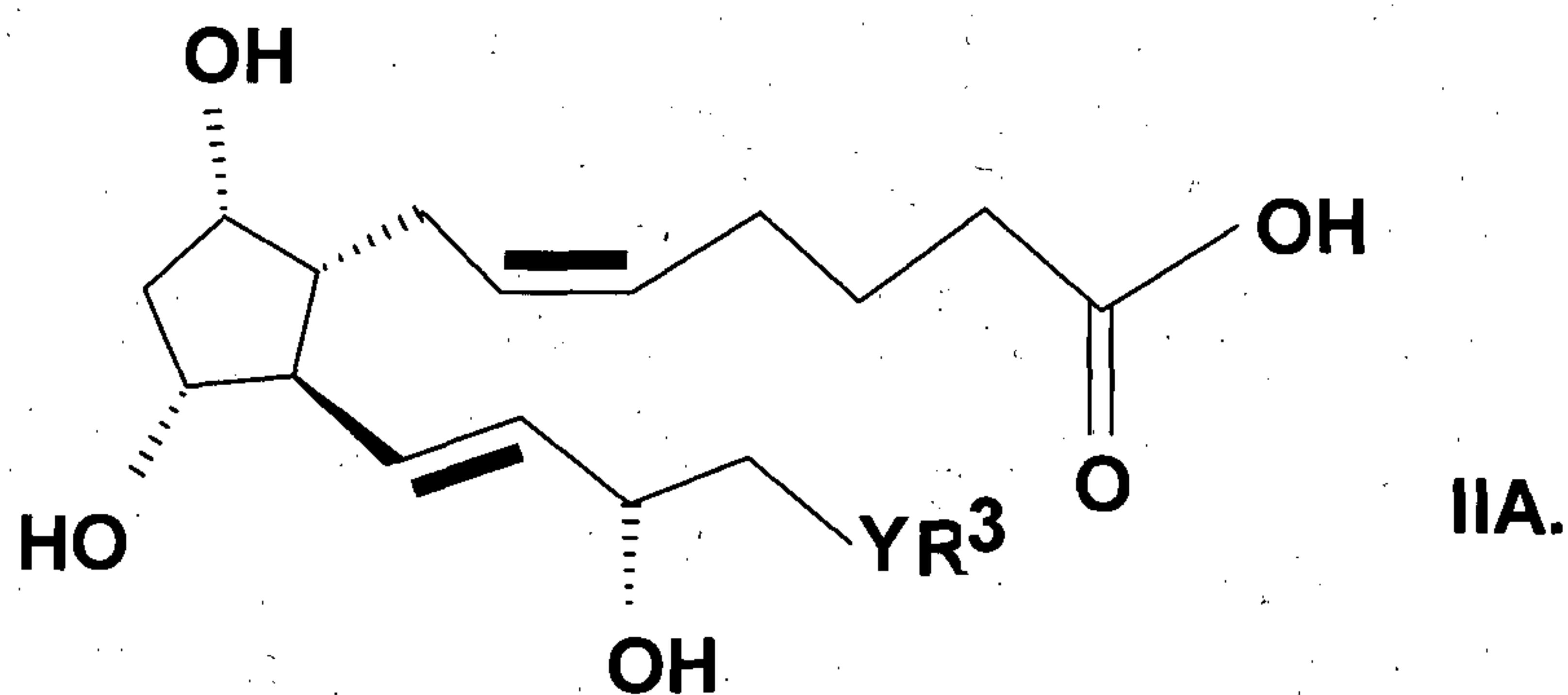


where in the formula the meanings of R^1 , R^2 , R^3 , Y and n are as defined above,

the compounds of the general formula (IIA) according to the invention are used as starting materials.

5

The compounds of the general formula (IIA)



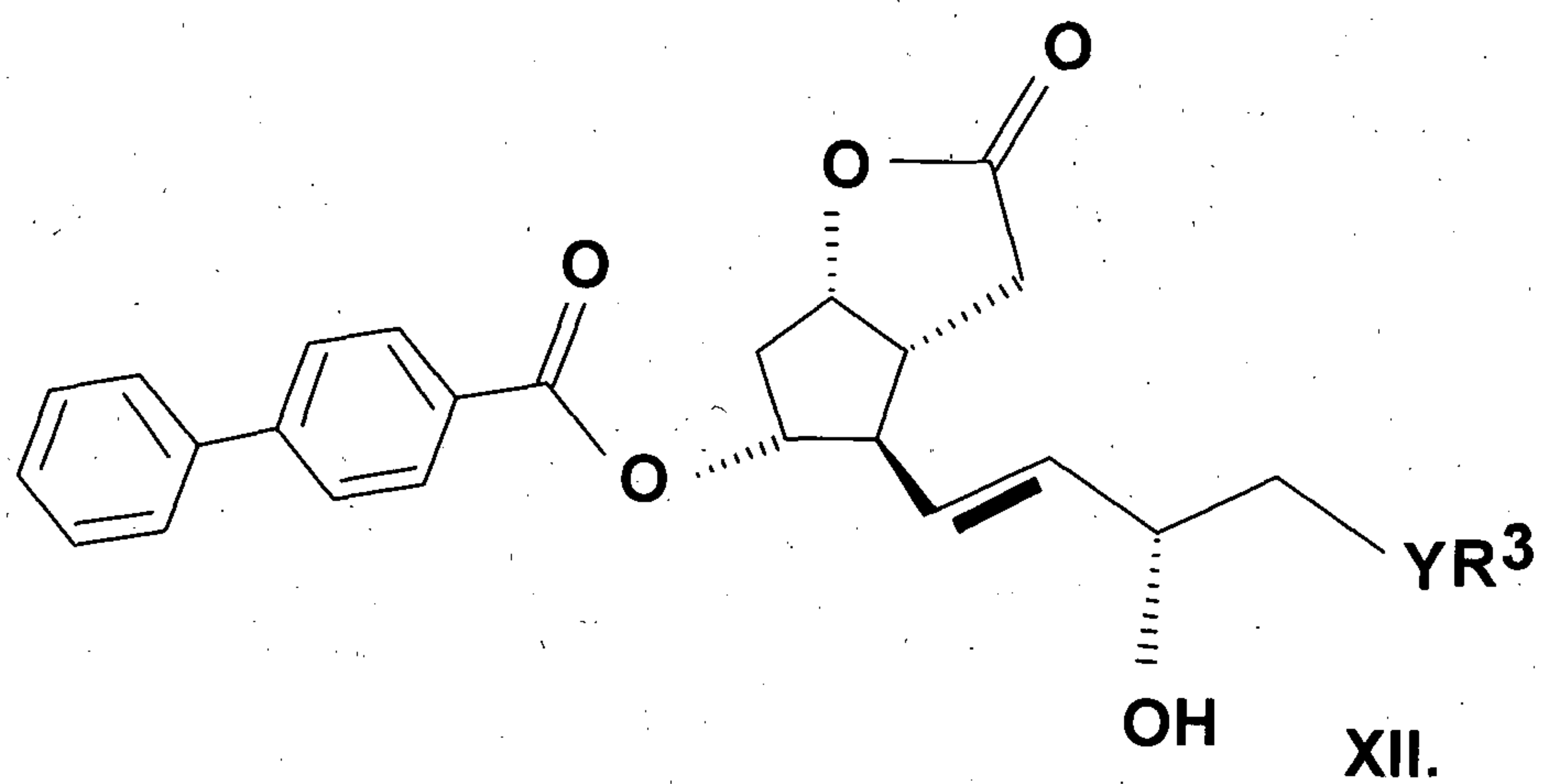
where in the formula

R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a
 10 C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

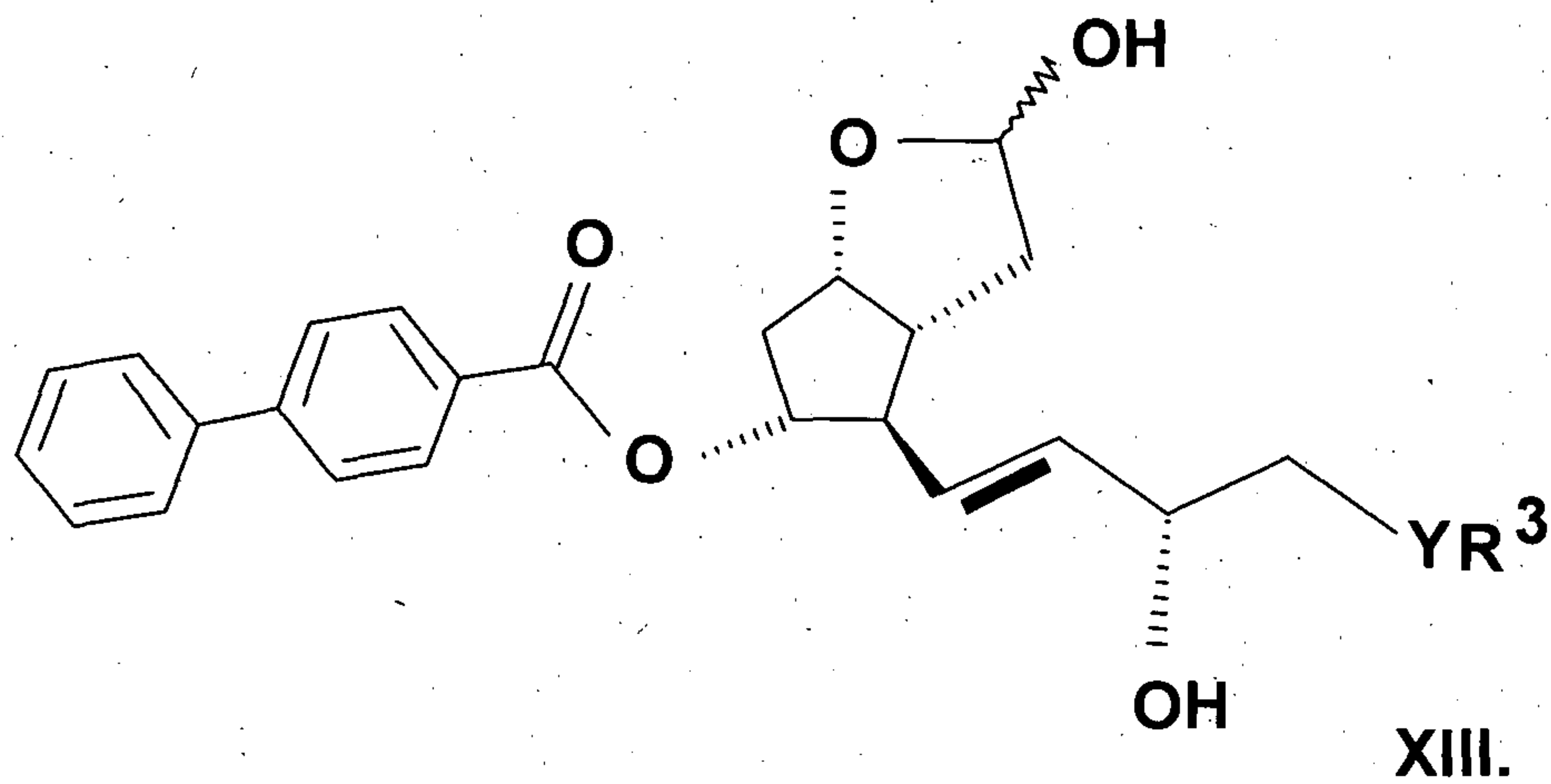
Y represents $(CH_2)_n$ group or O atom or S atom, and

$n=0-3$,

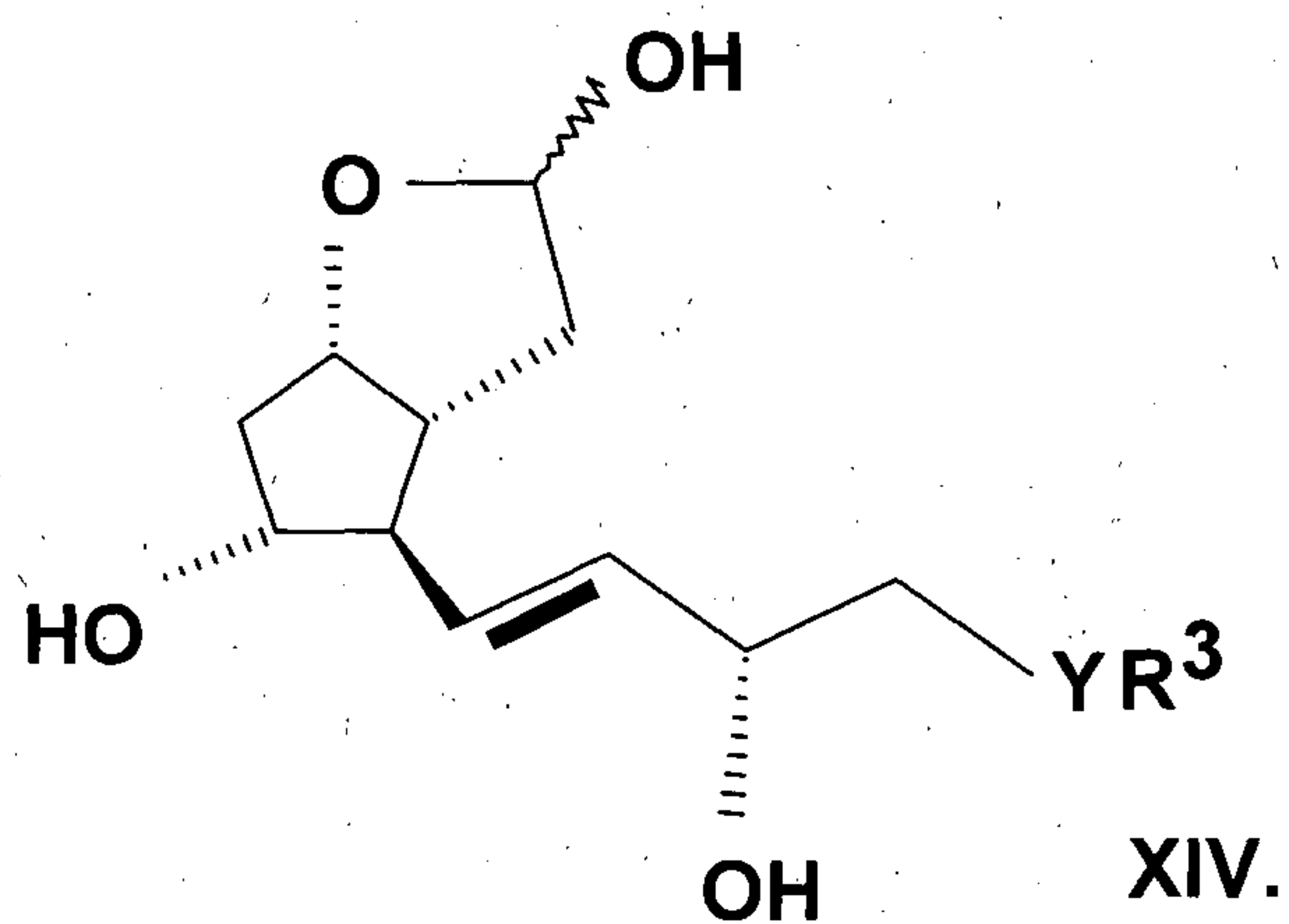
may be prepared according to the invention by reducing the lactondiol of the general
 15 formula (XII),



where in the meanings of R³, Y and n are defined above, to the lactontriol of the general formula (XIII),



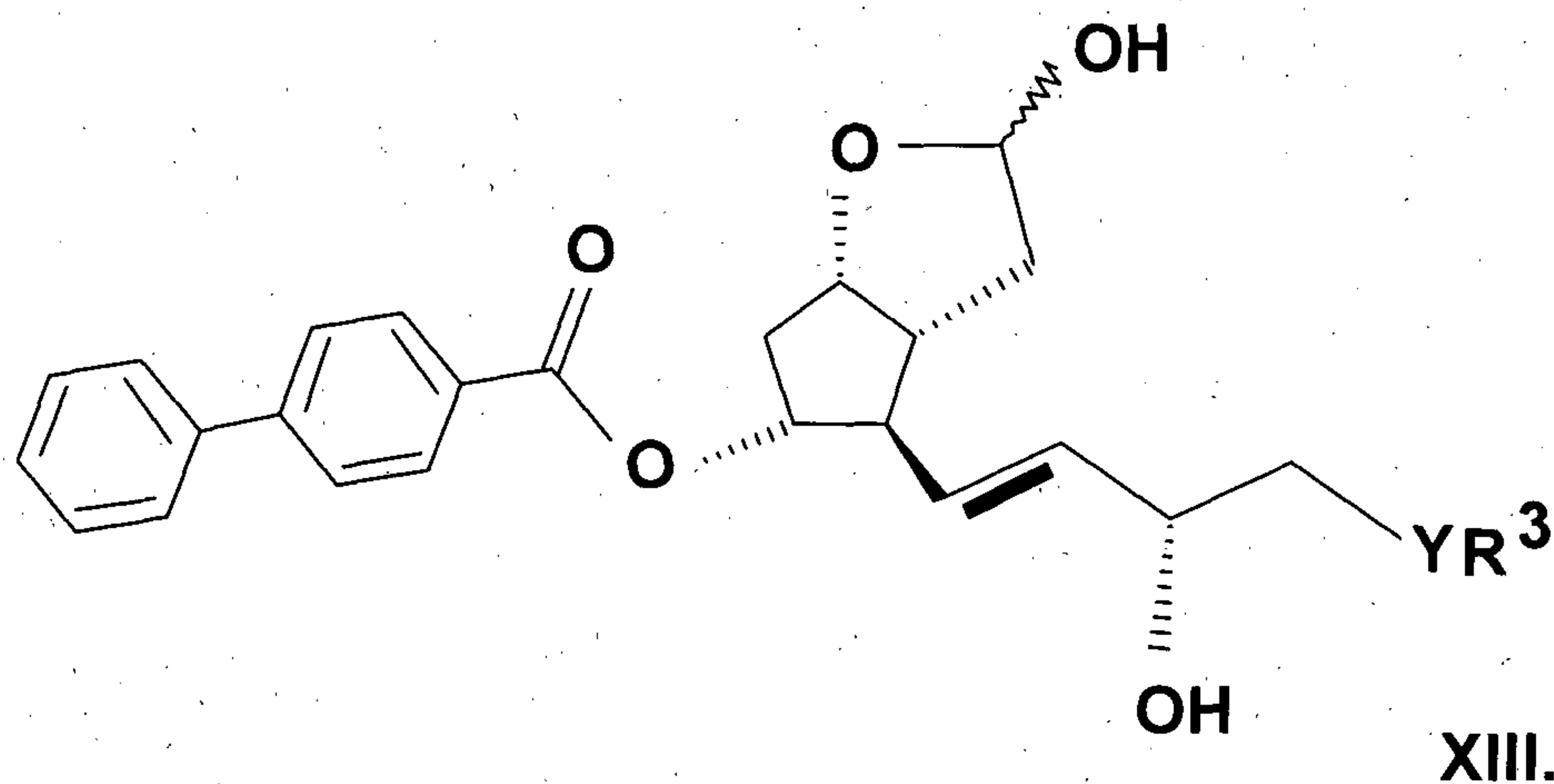
- 5 where the meanings of R³, Y and n are defined above, the protecting group of the compound of formula (XIII) is then removed, and the compound of the general formula (XIV), thus obtained,



where the meanings of R^3 , Y and n are defined above, is transformed by Wittig reaction into the compound of the general formula (IIA).

Reduction of the compounds of the general formula (XII) may be carried out by known methods, for example with diisobutylaluminium hydride in tetrahydrofuran medium. The protecting group can be removed by known methods in acidic or alkaline medium, preferably in alkaline medium.

The lactoltriol derivatives of the general formula (XIII),



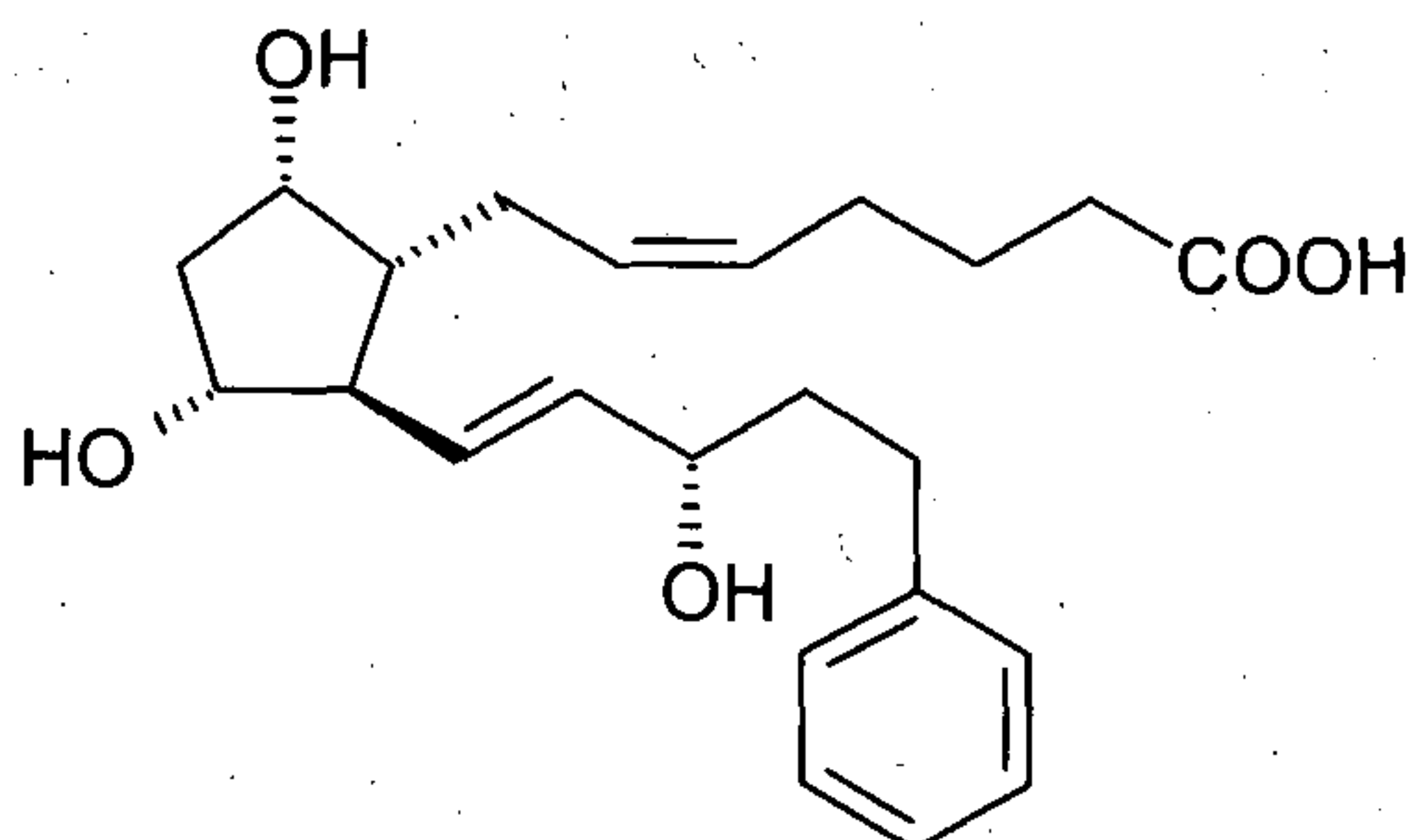
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where R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

Y represents $(CH_2)_n$ group or O atom or S atom, and $n=0-3$,

15 are novel compounds.

According to a further embodiment of the invention, the special compound of the general formula IIA, where R^3 stands for a phenyl group and Y stands for a $-(CH_2)_n$ -group, compound of the formula (IIB) can be prepared also in crystalline form.



(IIB)

The crystalline form of the compound of the formula (IIB) is new.

The compound of the formula (IIB) can be prepared in crystalline form, in such a way that
 5 to a mixture containing the compound of the formula (IIB) a mixture of ester type and ether type solvents is added.

According to the process dimethyl ether, diethyl ether, diisopropyl ether, preferably diethyl-ether and diisopropyl ether are used as ether-type solvents, and ethyl-acetate, methyl-acetate, isopropyl-acetate, preferably isopropyl-acetate as ester-type solvents.

10 The crystallisation is performed between (-)30°C and 30°C, preferably between 0-25°C.

The suspension of crystals, thus obtained is stirred 1-24 hours, preferably 8 hours, then filtered and washed with ether type solvent, preferably with diisopropyl ether.

The filtered crystals are dried under vacuum between 25-50°C, preferably at 35-40°C.

15 The compounds of the general formulae (II) and (XII) may be prepared by known methods, for example as described in US 5359095, WO 93/00329.

The advantage of the method according to the invention is that the desired bimatoprost final product – if desired - may be synthesized through a crystalline bimatoprost acid.

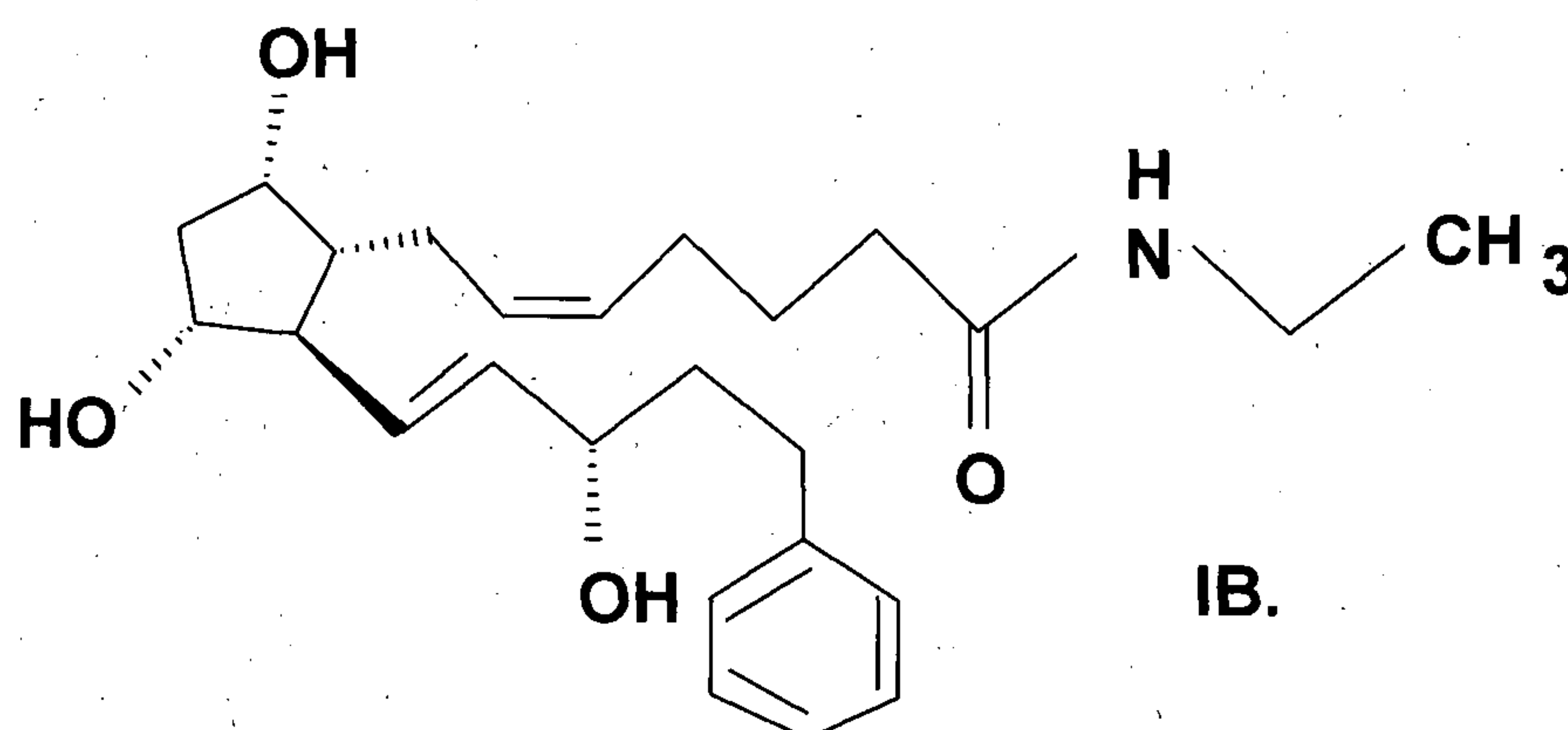
20 Further advantage of the method according to the invention is that the desired final product is synthesized through a novel intermediate, a crystalline, activated ester or amide, which - if desired- can be isolated and -if desired- can be purified by crystallisation or

chromatography. Due to the applied carboxylic acid activating agents (e.g. DSC, DCI), the protection of the secondary hydroxyl groups in positions 9, 11 and 15 is not necessary, parallel reactions, for example dimer formation was not observed, either in the case of the activated ester or activated amide, or under the conditions of the final amide formation, and the activated carboxylic acid derivatives according to the invention were easily isolated with high yield and purity.

Surprisingly it was found that the crystalline activated carboxylic acid derivatives of the invention can be easily purified by crystallisation processes for eliminating the impurities and can also be transformed into the desired amide final product simply, under mild reaction conditions and in high yield.

It is well known that in case of an active pharmaceutical ingredient (API) the level of the impurities is a key issue, in case of bimatoprost the amount of every unknown impurity must be reduced under 0,1 %. According to the process of the invention - to keep this very strict limitation – the crystallisation of bimatoprost acid and the crystallisation of the active carboxylic acid derivatives were used instead of the expensive preparative HPLC resolution described in WO09153206.

Further embodiment of our invention is a process for the preparation of a high melting crystal form II of bimatoprost of the formula (IB).



By the process according to the invention a chemically and thermodynamically stable and from other crystal forms free, high melting crystal form II. of bimatoprost can be prepared.

The following patent applications deal with the crystallisation of bimatoprost product:

5 US 2005/0209337 A1, WO 2009/153206 A2, US 2009/0163596 A1.

In Example 30 of US 2005/0209337 A1, the high melting point crystal form of bimatoprost (DSC peak read value 79°C) (further on: crystal form II.) is characterized by its X-ray diffraction, by its IR spectrum in KBr pellet and by its DSC and TGA curves.

WO 2009/153206 describes the purification of bimatoprost product by preparative HPLC,
10 followed by crystallisation. Crystallisation is carried out from acetonitrile solvent or from acetonitrile as dissolution and TBME (tert-butyl methyl ether) as precipitating solvent. According to the description, by that method the high melting point crystal form of bimatoprost (DSC peak read value 79°C) can be prepared. By reproducing the method we did not succeed to obtain the high melting point crystal form of bimatoprost.

15 US 2009/0163596 discloses crystal form I. of bimatoprost and its preparation. Crystal form I. of bimatoprost is characterized by its melting point (62-64°C), by DSC, X-ray diffraction and IR investigation. It describes in details the crystallisation process, such as the dissolution process (in an organic solvent or in the mixture of an organic dissolution- and precipitation- solvent at a temperature near the boiling point), the cooling process, the
20 separation of the precipitated crystals from the mother liquor and the drying process (in vacuum at low temperature). The high melting point crystal form (DSC peak read value 79°C) of bimatoprost cannot be prepared by the methods described in US 2009/0163596.

By the process of the invention the chemically and thermodynamically stable, high melting
25 point crystal form II. of bimatoprost (=high melting point crystal form (DSC peak read value 79°C)) can be prepared which is free of crystal form I. Form II. is characterized by

its melting point (72-78°C), by DSC investigation and by IR and X-ray powder diffraction studies.

The essence of the process is, that from a bimatoprost-containing reaction mixture after work-up and evaporation, or from any crystalline or non-crystalline form of bimatoprost or from their mixtures of any ratio, through crystallisation from a protic or ether-type solvent the thermodynamically stable, pure form II. is prepared. The crystallisation process is the following: to the oily or crystalline crude bimatoprost calculated amount of the solvent is added, then it is dried and periodically exposed to mechanical effect.

In accordance with the above, our invention relates to a process for the preparation of form II. of bimatoprost of formula (IB), characterized in that to a bimatoprost-containing reaction mixture after work-up and evaporation, or to any crystalline or non-crystalline form of bimatoprost or to their mixtures of any ratio, calculated amount of an ether-type or protic solvent is added, if desired the resulting mixture is exposed to mechanical effect, then it is dried and homogenized.

The melting point of crystal form II. obtained in the above process is between 72-78°C, the endothermic peak, based on DSC investigation, is between 73-79°C and the melting heat is higher than 75 J/g.

Figures VI., VIII. and IV. respectively, present the DSC curve, the X-ray powder diffraction curve and the IR spectrum of crystal form II. obtained in the process according to the invention.

Figures V., VII. and III respectively, present the DSC curve, the X-ray powder diffraction curve and the IR spectrum of crystal form I.

In the process according to the invention we use calculated amount, favourably 20-60 mass %, preferably 35 mass % amount of protic solvent, especially alcohols like methanol, ethanol and/or water. Preferably water is used as protic solvent.

- 5 As mechanical effect we apply stirring or scratching, or both. The added solvent is removed by drying. Drying is performed at a temperature between (-) 60°C and 70°C, especially at 35°C, in vacuum.

As ether-type solvent we apply calculated amount, preferably 2000-8000 mass% amount of dimethyl ether, diethyl ether, diisopropyl ether, preferably diethyl ether. The added solvent
10 is removed by drying. Drying is performed at low temperature, preferably between 0-(-)50°C by passing through nitrogen gas.

Identification of the products was carried out with the help of the following analytical instruments:

- 15 NMR spectra were recorded by Bruker-Avance III-500 MHz instrument, DSC curves by Mettler-Toledo DSC 1/700 instrument, IR spectra by Perkin-Elmer Spektrum 400 FT-IR spectrophotometer, MS spectra by Shimadzu LC-MS-IT-TOF instrument. Melting points were determined by Büchi Melting Point B-545 apparatus.

- 20 Further details of the invention are described in the examples, without to limit the invention to the examples.

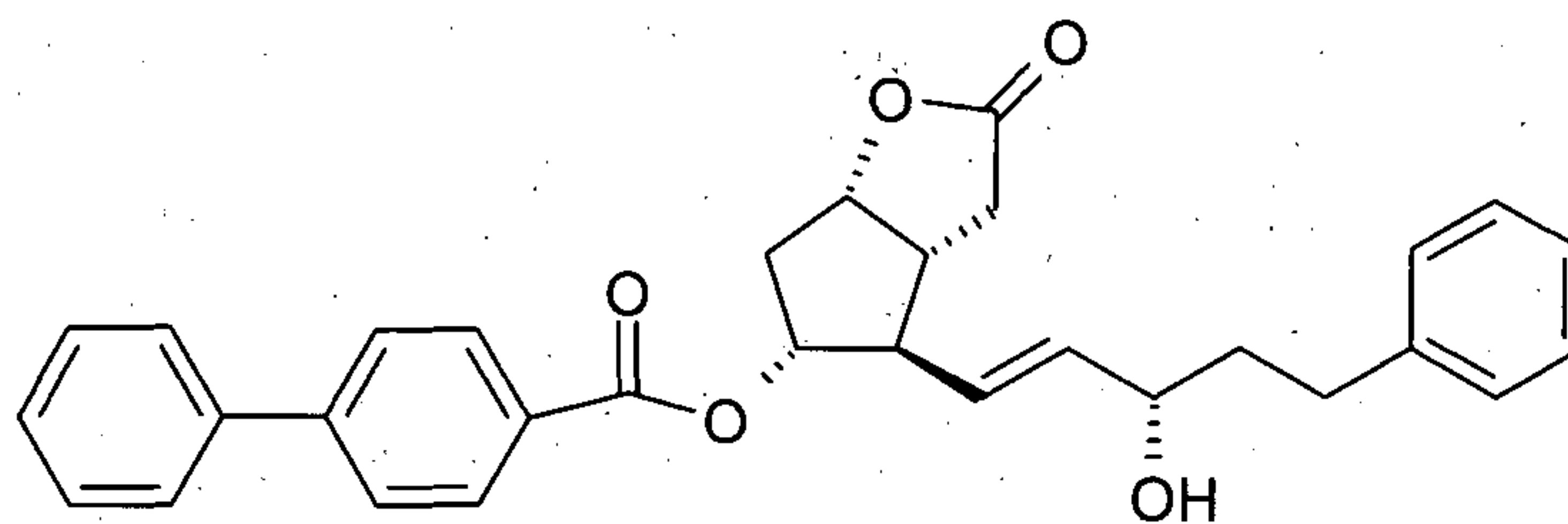
Examples

- 25 **1. Preparation of the starting material**

a.) Preparation of the [1,1'-Biphenyl]-4-carboxylic acid ((3aR,4R,5R,6aS)-hexahydro-4-[(1E,3S)-3-hydroxy-5-phenyl-1-penten-1-yl]-2-hydroxy-2H-cyclopenta[b]furan-5-yl) ester (PPB-lactoltriol)

5

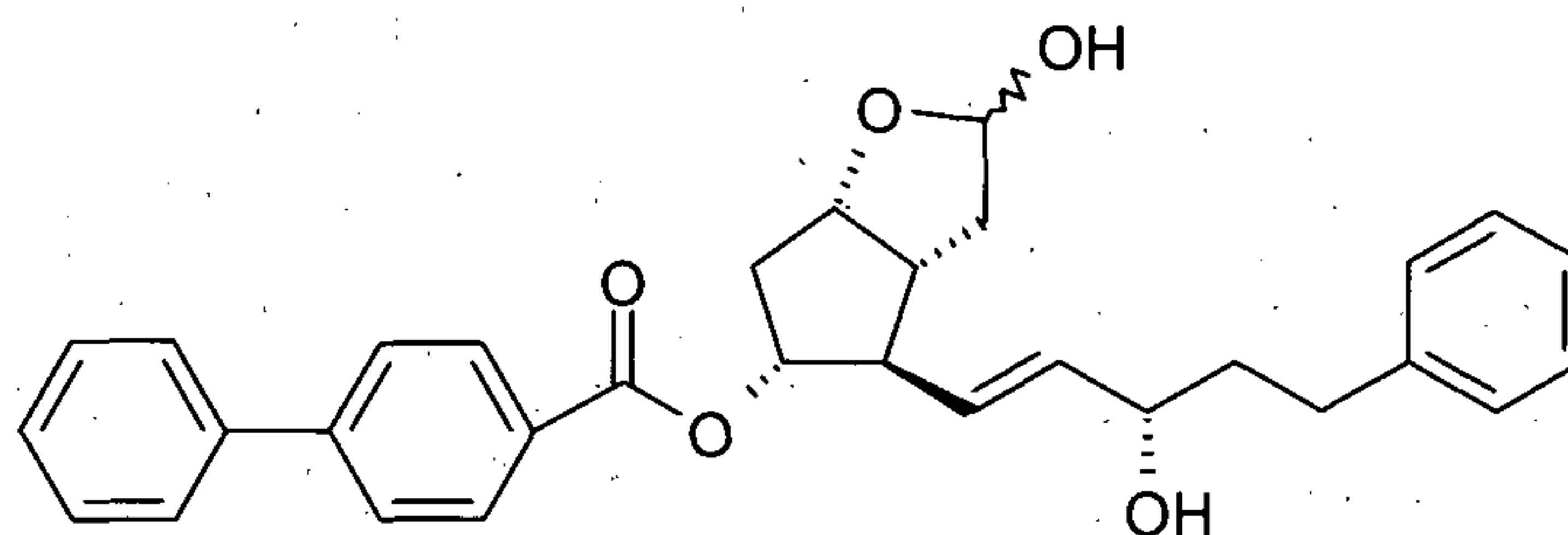
The lacton group of 55 g of [1,1'-Biphenyl]-4-carboxylic acid ((3aR,4R,5R,6aS)-hexahydro-4-[(1E,3S)-3-hydroxy-5-phenyl-1-penten-1-yl]-2-oxo-2H-cyclopenta[b]furan-5-yl) ester (PPB-lactondiol)



M: 482,58
C₃₁H₃₀O₅

10 is reduced in 1000 ml of tetrahydrofuran (THF) solvent at (-)65 - (-)85°C with the hexane solution of 422 ml diisobutyl aluminium hydride (DIBAL-H). The reaction mixture is destroyed with NaHSO₄ solution, the aqueous phase is extracted with ethyl acetate, the organic phase is washed with NaHCO₃ solution and the solvent is removed at 40-50 °C. The crude material is evaporated to obtain 46.2 g oil.

15 Structural formula of the obtained PPB-lactoltriol:



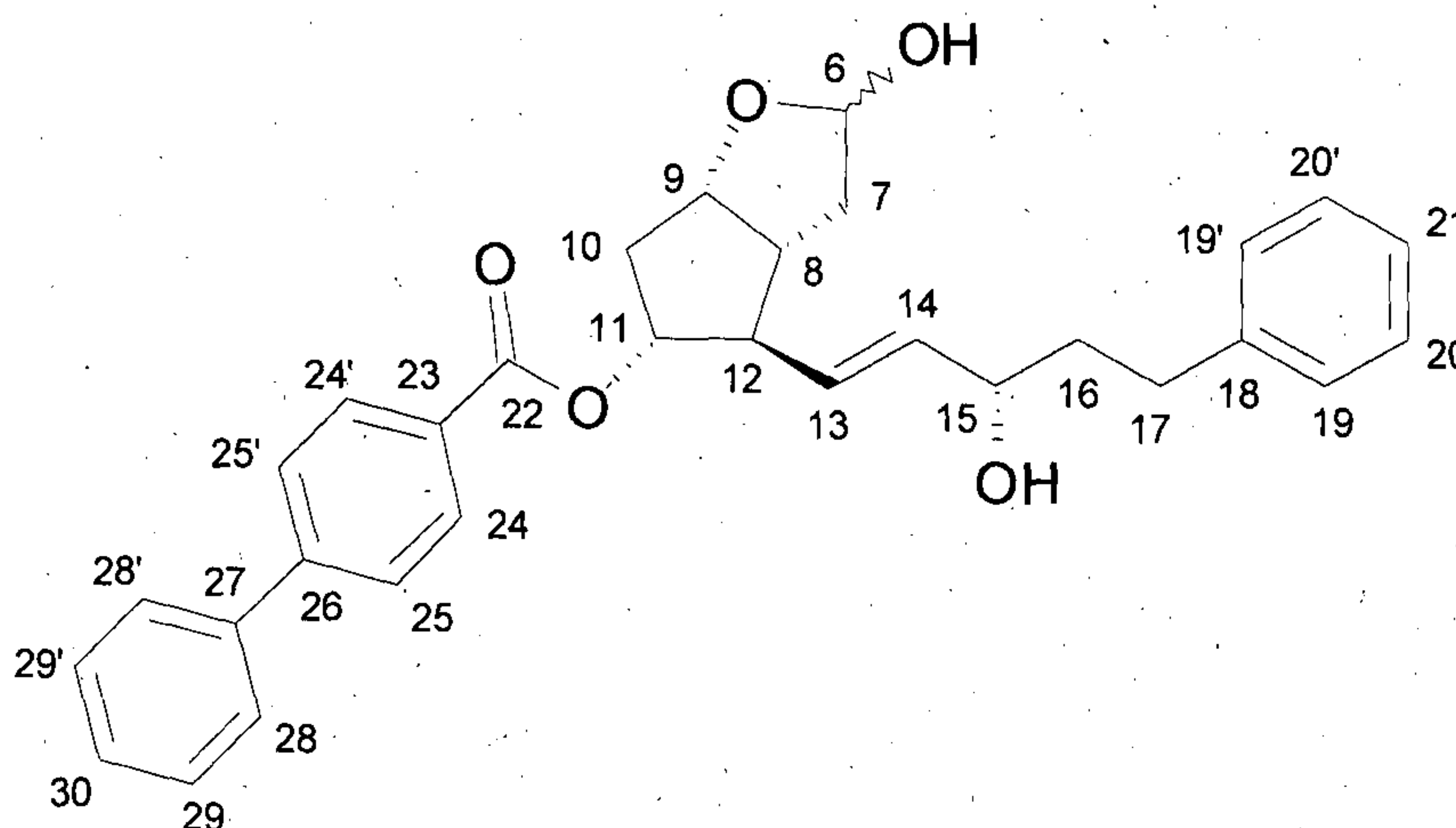
M: 484,60
C₃₁H₃₂O₅

From the crude oil after crystallization in tert-butyl methyl ether (TBME): hexane mixture, 41.6 g white crystals are obtained.

Melting point: 91.1-91.7 °C

5 IR spectrum of the lactoltriol of example 1a. is shown in Figure I

^{13}C and ^1H NMR data:



Position	^{13}C (ppm)	^1H (ppm)	Number of the protons	Multiplicity	Coupling (Hz)
6; OH	99.72; 100.64	5.57* (20H); 5.49 OH: 6.05; 6.28	1 1	m d	$J_{6,\text{OH}}=4.65; 3.6$
7	38.14; 38.44	2.57* (32H); 1.77 (39H) 1.78* (39H)	1;1	m; m	2.3-2.9; 7.0; $J_{7\alpha,7\beta}=14.0$
8	46.26; 45.69	2.57* (32H); 2.43	1	m	-; $J_{8,9}=8.85-9.1$
9	80.19; 80.92	4.60; 4.50	1	m	$J_{8,9}=9.1; 2.7-3.3;$ $7.3-7.4; J_{9,10}=5.25$
10	40.12**; 40.37**	1.98; 1.93; 2.69;	1; 1	m; m	$J_{9,10}=5.5;$ $J_{10\alpha,10\beta}=13.6-13.65$
11; OR	80.54; 79.03	5.12; 5.05	1	m	7.1-7.3 7.4-7.55; 9.8
12	54.12; 53.22	2.55* (33H); 3.11	1	m	-; 9.85-10.1; 7.55
13	129.38; 129.62	5.59* (19-20H); 5.59* (19-20H)	1	m	6.3; $J_{13,14}=15.3$
14	136.66; 136.69	5.65* (17-18H); 5.65* (17-18H)	1	m	$J_{14,15}=5.15;$ $J_{13,14}=15.45$
15; OH	70.47; 70.39	3.98* (28H); 3.98* (28H) OH: 4.80* (24H); 4.79* (25H)	1 1	m d	$J_{14,15}=5.2-5.5$ $J_{15,\text{OH}}=4.7; 4.8$
16	40.09**	1.71-1.61* (40H)	1; 1	m; m	
17	31.86; 31.80	2.57* (32H); 2.55* (33H)	2	m	
18	143.14	-	-	-	
19, 19'	129.06	7.10; 7.06	1	d	$J_{19,20}=7.3; 7.2$
20, 20'	129.09	7.23* (9H); 7.20* (10H)	1	t	$J_{19,20}=J_{20,21}=7.4; 7.5$
21	126.41; 126.37	7.14* (11H); 7.13* (12H)	1	t	$J_{20,21}=7.3-7.45$
22	166.07; 166.16	-	-	-	

23	129.52; 129.48	-	-	-	-
24, 24'	130.71	8.04* (2H); 8.06* (1H)	1	d	J _{24,25} =8.3; 8.4
25, 25'	127.86	7.83* (3H); 7.81* (4H)	1	d	J _{24,25} =8.5; 8.4
26	145.64	-	-	-	-
27	139.77	-	-	-	-
28, 28'	127.90	7.75* (5H); 7.73* (6H)	1	d	J _{28,29} =7.6; 7.95
29, 29'	130.01	7.55	1	t	J _{28,29} =J _{29,30} =7.4-7.8
30	129.33	7.47	1	t	J _{29,30} =7.3-7.35

*Overlapping ¹H NMR signals (The number in brackets signifies the position number of the signal group in the PMR spectrum, direction: towards decreasing shifts)

**¹³C NMR signals overlapping with the multiplett of the DMSO solvent.

5

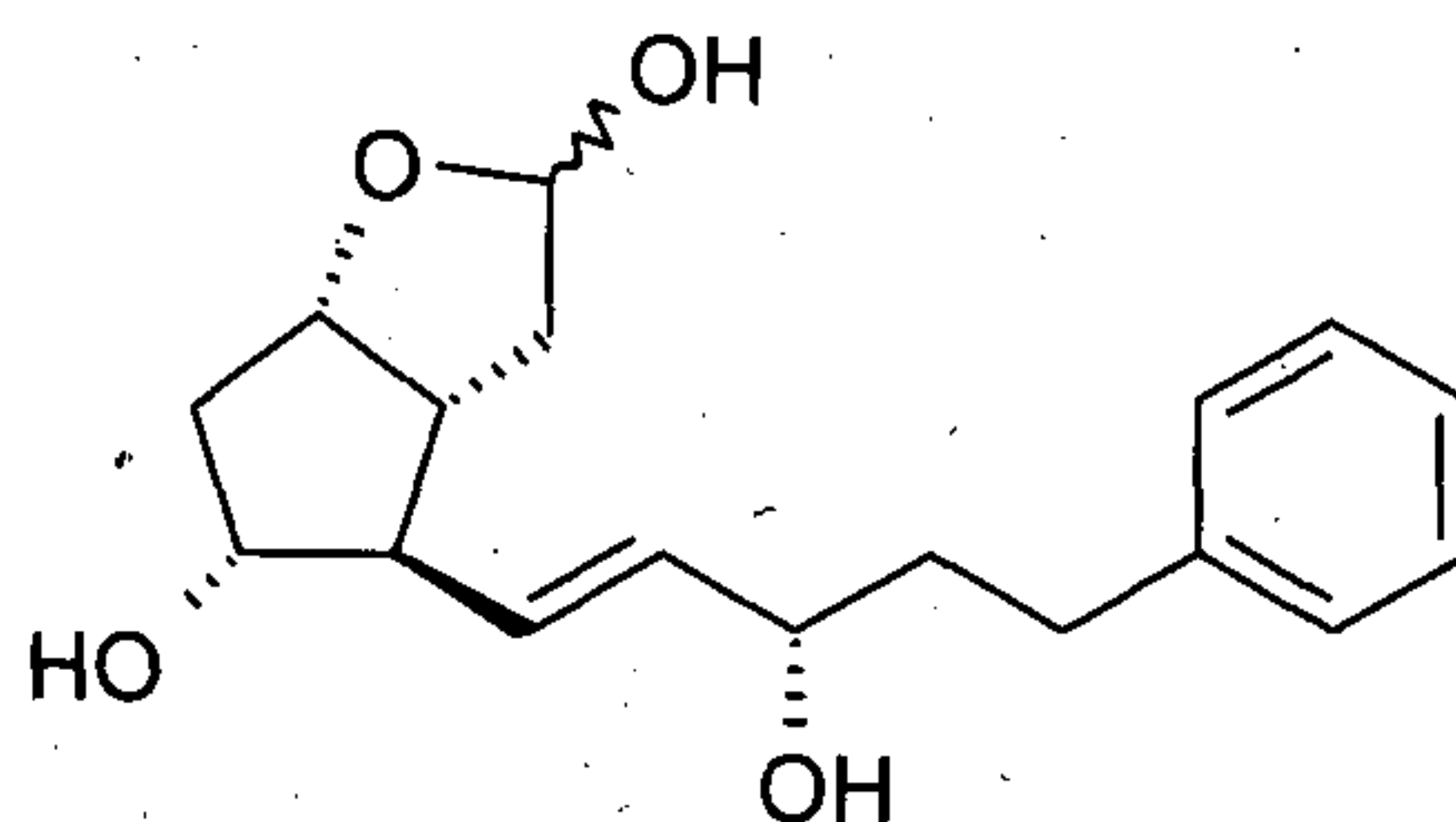
b.) Preparation of the (3aR,4R,5R,6aS)-hexahydro-4-[(1E,3S)-3-hydroxy-5-phenyl-1-penten-1-yl]-2H-cyclopenta[b]furan-2,5-diol, (lactoltriol):

10

46.2 g of [1,1'-Biphenyl]-4-carboxylic acid ((3aR,4R,5R,6aS)-hexahydro-4-[(1E,3S)-3-hydroxy-5-phenyl-1-penten-1-yl]-2-hydroxy-2H-cyclopenta[b]furan-5-yl) ester (PPB-lactoltriol) oil is dissolved in 230 ml of methanol and after adding 6.6 g of K₂CO₃ it is desacylated at 35-45°C. The pH of the reaction mixture is adjusted to 7-8 at (-)5-0°C with 0.5 M phosphoric acid solution. The precipitated crystals are filtered off and washed with methanol:water mixture. The mother liquor is evaporated, extracted with ethyl acetate, the organic phase is dried over Na₂SO₄, the drying material is filtered off and the product is crystallized by the addition of hexane. 26 g of white crystalline material is obtained.

15

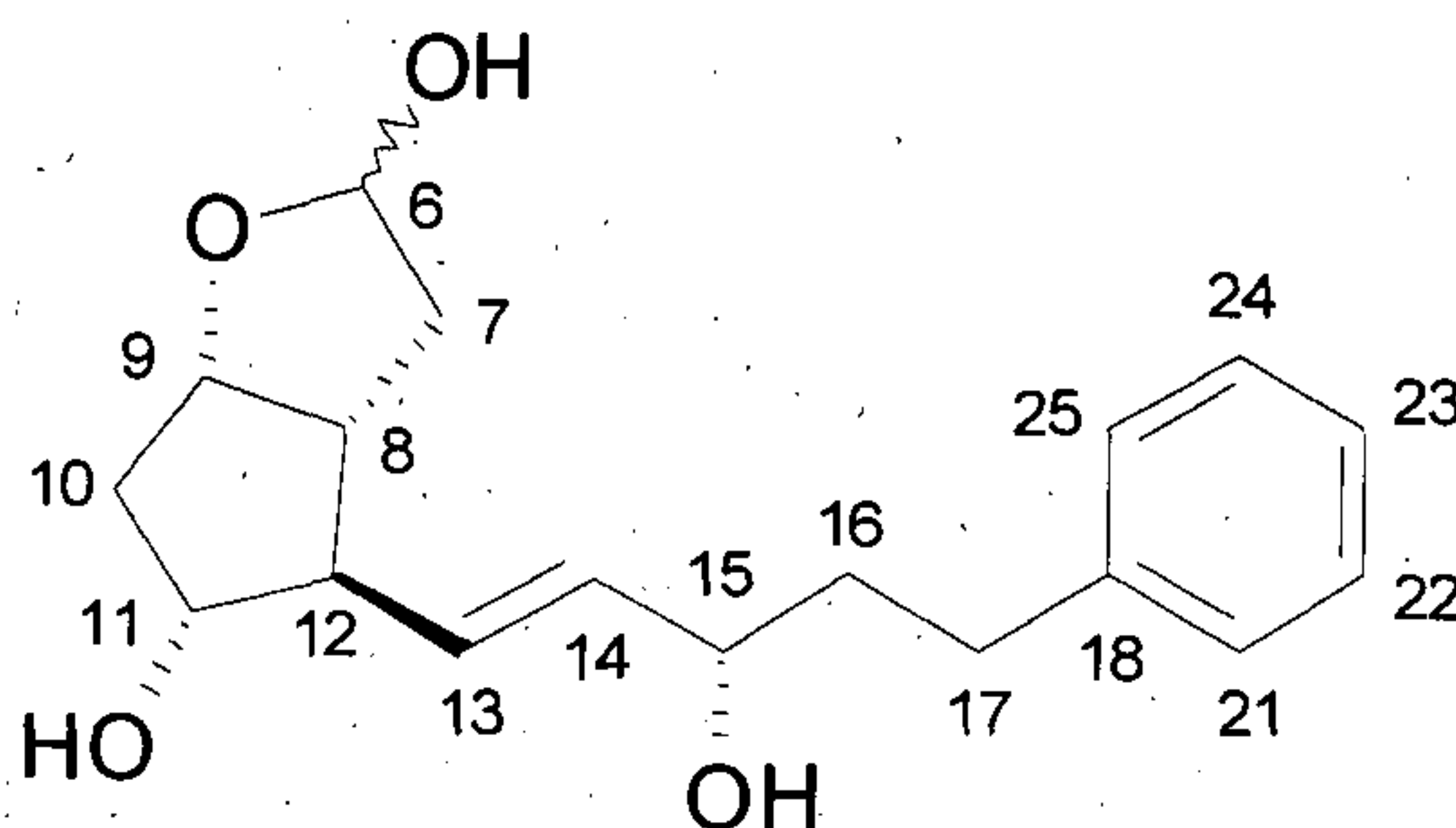
Structural formula of the product:



M: 304,39
 $C_{18}H_{24}O_4$

Melting point: 98-103 °C

^{13}C and 1H NMR data:



Position	^{13}C (ppm)	1H (ppm)	Number of the protons	Multiplicity	Coupling (Hz)
6; OH	99.65; 100.48	5.46* (8H); 5.40 OH: 5.92; 6.13	1 1	m d	$J_{6,OH}=4.65; 3.8$
7	39.94; 38.77	1.81* (26H) 1.97* (25H); 1.66* (27H)	1;1	m; m	
8	45.63; 45.81	2.29* (22H); 2.22* (24H)	1	m	
9	79.20; 80.97	4.38; 4.32	1	m	$J_{9,10a}=6.9; 7.3-7.55$
10	41.53; 43.795	2.27* (23H); 1.48 2.30* (22H); 1.76* (27H)	1; 1	m; m	$J_{9,10a}=6.4-6.8; 7.1-7.4$
11; OH	77.62; 77.06	3.70; 3.61 OH: 4.75; 4.80	1 1	m d	$J_{11,OH}=5.95; 5.85$
12	56.80; 55.86	1.97* (25H); 2.53* (21H)	1	m	
13	131.46; 132.11	5.54* (6H); 5.54* (6H)	1	m	$J_{13,14}=15.3$
14	135.39; 135.16	5.49* (7H); 5.49* (7H)	1	m	$J_{13,14}=16$
15; OH	71.14; 71.22	3.94* (16H); 3.94* (16H) OH: 4.72* (12H); 4.71* (13H)	1 1	m d	$J_{15,OH}=4.75; 4.35$
16	40.26	1.74* (27H); 1.66* (27H)	1; 1	m; m	
17	32.24; 32.27	2.63* (20H); 2.63* (20H)	1; 1	m	
18	143.23	-	-	-	
21*	129.20	7.22* (2H)	1	d	$J_{21,22}=7.3$
22*	129.18	7.30	1	t	$J_{21,22}=J_{22,23}=7.4-7.6$
23*	126.48	7.19* (3H)	1	t	$J_{22,23}=J_{23,24}=7.25$
24*	129.18	7.30	1	t	$J_{23,24}=J_{24,25}=7.4-7.6$
25*	129.20	7.22* (2H)	1	d	$J_{24,25}=7.3$

* Overlapping ^1H NMR signals. (The number in brackets signifies the position number of the signal group in the PMR spectrum, direction: towards decreasing shifts).

c.) Preparation of the 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-penten-1-yl]-cyclopentyl]-5-heptenic acid, (5Z)-(bimatoprost acid):

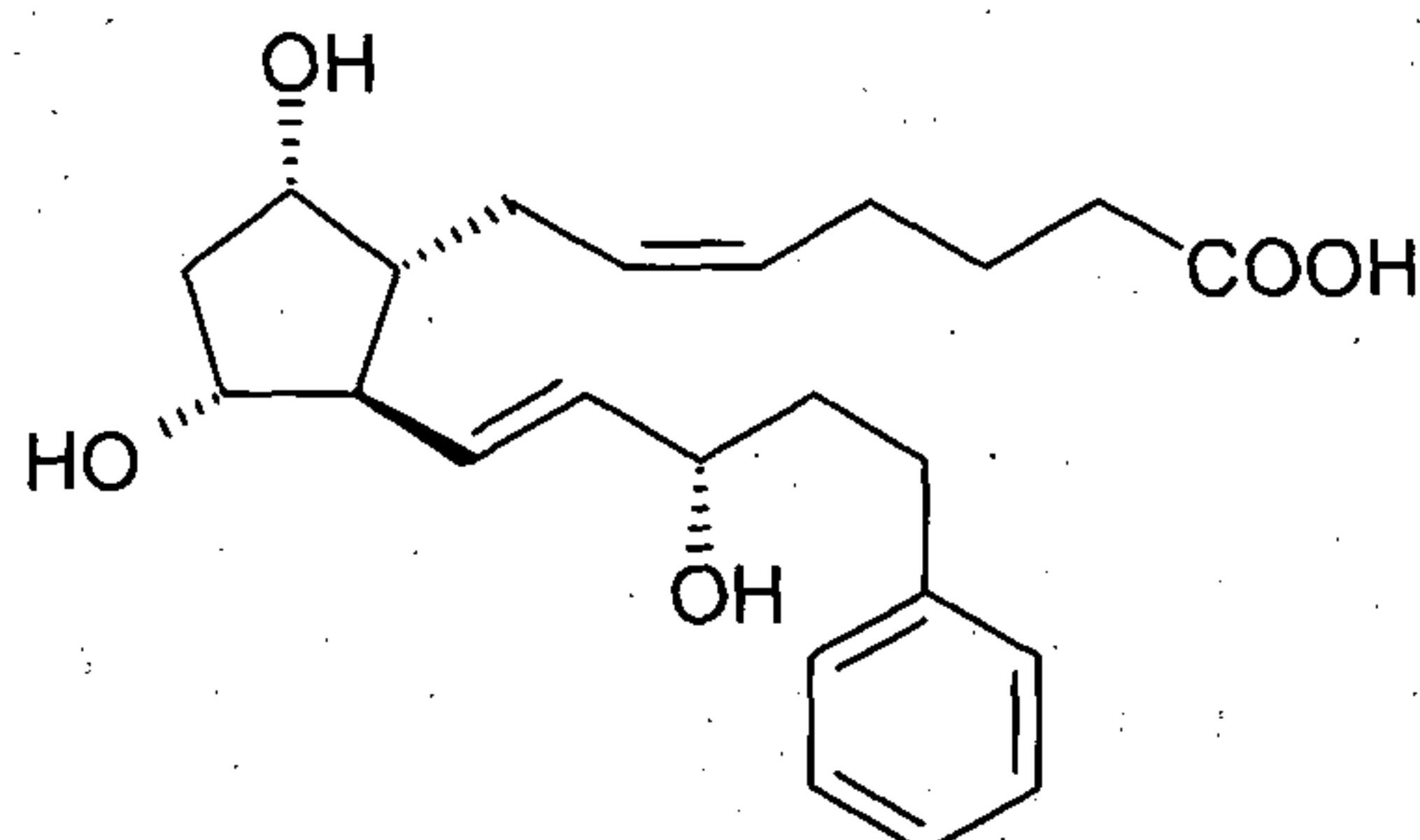
c1.) 108 g of 4-carboxybutylphosphonium bromide (KBFBBr) is dissolved in 800 ml of THF and the solution is cooled to 0 – (-5)°C. To this solution first 91 g of potassium tert-butyrate (KOTBu), and then after stirring and cooling to (-10) - (-15)°C, the solution of 25 g of lactoltriol in THF are added. When the expected conversion is reached the reaction mixture is destroyed with water, then EtOAc is added. The aqueous phase is washed with EtOAc. The aqueous layer is acidified with NaHSO_4 solution to pH=2 and extracted with EtOAc. The united organic phase is washed with 15% NaCl solution, dried over Na_2SO_4 , filtered and evaporated. The residue is crystallized from the mixture of ethyl acetate and diisopropyl ether. The crystals are filtered off and washed, the filtrate solution is evaporated. The resulting yellow oil is purified by chromatography on silica gel using diisopropyl ether – acetone eluent. 25.5g oil is obtained.

IR spectrum of the obtained Bimatoprost acid is shown in Figure II.

c2.) The product obtained in example 1/c1.) is dissolved in 60 ml of isopropyl-acetate and under stirring 40 ml of diethyl-ether is added to it. Small amount of bimatoprost acid seeding crystal is added to the reaction mixture. Under stirring gradually cooled to 0°C about 60 ml of diisopropyl-ether is added to it. The suspension is stirred at this temperature for a night thereafter it is filtered and washed with diisopropyl- ether and dried under vacuum. 20,4g crystalline bimatoprost acid is obtained.

DSC curve of the obtained Bimatoprost acid is shown in Figure X and X-ray powder diffraction curve in Figure IX.

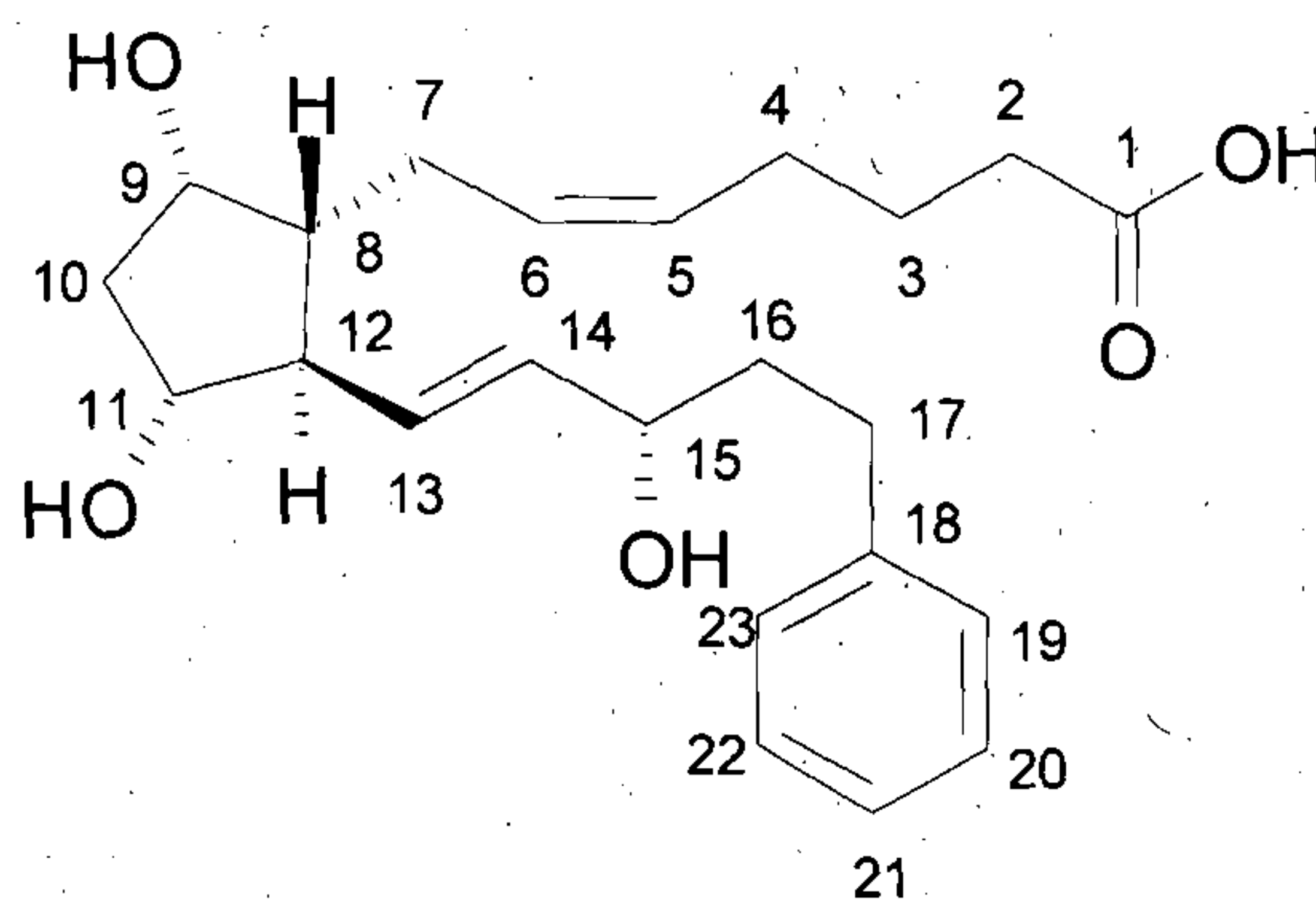
Structural formula of the product:



M: 388,51
C₂₃H₃₂O₅

Melting point: 63.0-65.5 °C

¹³C and ¹H NMR data:



Position	¹³ C (ppm)	¹ H (ppm)	Number of the protons	Multiplicity	Coupling (Hz)
1; COOH	175.30	-; COOH: 12.02	-; COOH: 1	-; COOH: broad	
2	34.10	2.23* (21H); 2.16* (22H)	1; 1	m; m	
3	25.45	1.54* (26H)	2	m	
4	27.09	2.01* (24H)	2	m	J _{4,5} =6.8-7.0
5	129.53	5.29	1	td	J _{4,5} =7.2 J _{5,6} =10.8
6	130.64	5.50* (7H)	1	td	J _{6,7} =7.8 J _{5,6} =10.6
7	25.74	2.15* (22H); 2.04* (24H)	1; 1	m; m	
8	49.81	1.34	1	m	J _{8,9} =5.75
9; OH	70.47	3.95* (13H); OH: 4.40	1	m; broad	J _{8,9} =5.75

10	44.89	2.24* (21H); 1.48* (26H)	1; 1	m; ddd	J _{10α,10β} =14.1; 5.65-5.85; 2.3-2.4
11; OH	76.69	3.71; OH: 4.55	1; OH: 1	m (ddd); broad	J _{11,12} =7.5
12	55.22	2.19* (21H)	1	m	
13	133.05	5.40* (7H)	1	dd	J _{12,13} =7.7-8.15; J _{13,14} =15.45
14	136.09	5.47* (7H)	1	dd	J _{14,15} =6.2-6.35; J _{13,14} =15.4
15; OH	71.53	3.94* (13H); OH: 4.71	1; OH: 1	m; broad	J _{14,15} =6.4
16	40.45*	1.75* (25H); 1.69* (25H)	1; 1	m; m	
17	32.29	2.64	2	m	
18	143.24	-	-	-	-
19*	129.15	7.21* (5H)	1	d	J _{19,20} =6.9
20*	129.20	7.30	1	t	J _{19,20} =J _{20,21} =7.5-7.55
21*	126.51	7.19* (5H)	1	t	J _{20,21} =J _{21,22} =6.7-7.3
22*	129.20	7.30	1	t	J _{21,22} =J _{22,23} =7.5-7.55
23*	129.15	7.21* (5H)	1	d	J _{22,23} =6.9

* Partly or fully overlapping ¹H NMR signals. (The number in brackets signifies the position number of the signal group in the PMR spectrum, direction: towards decreasing shifts).

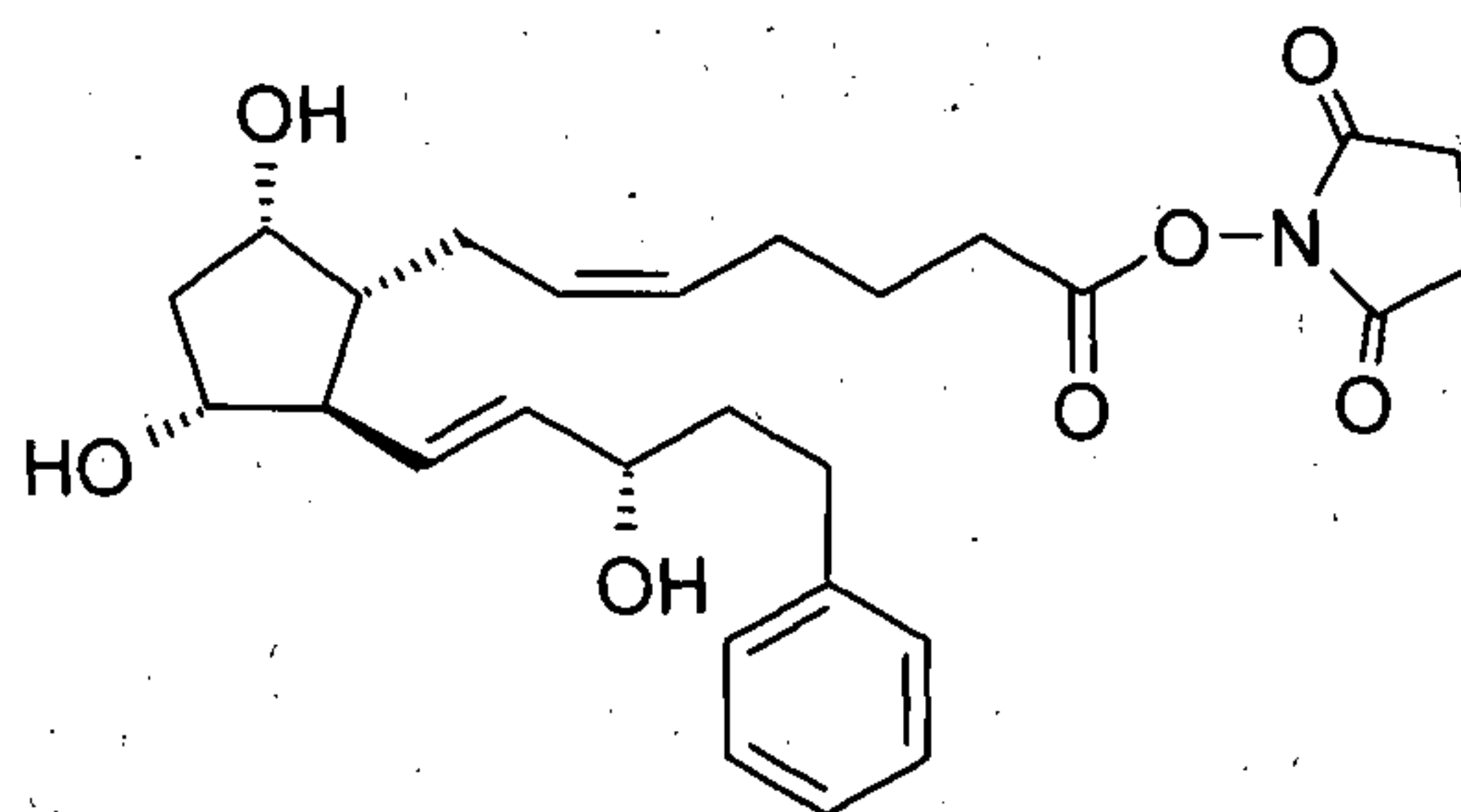
5

2. Preparation of 7-[3,5-Dihydroxy-2-(3-hydroxy-5-phenyl-pent-1-enyl)-cyclopentyl]-5-heptenoic acid (2,5-dioxo-pyrrolidin-1-yl) ester (activated ester)

27.5 g of bimatoprost acid of example 1/c2.) is dissolved in 270 ml of THF and to it are added at room temperature 13.7 g of N,N'-diisopropylcarbodiimide followed by 13.7 g of N-hydroxysuccinimide. The mixture is stirred at that temperature and then poured onto the mixture of 1N NaHSO₄ solution and tert-butyl methyl ether (TBME). The phases are separated. The organic phase is washed with 1N NaHCO₃ solution, the aqueous-alkaline phase is extracted with TBME. The united organic phase is dried over Na₂SO₄, filtered and evaporated. The residue is crystallized from hexane : acetone mixture to obtain 30.04 g white crystalline material.

15

Product:



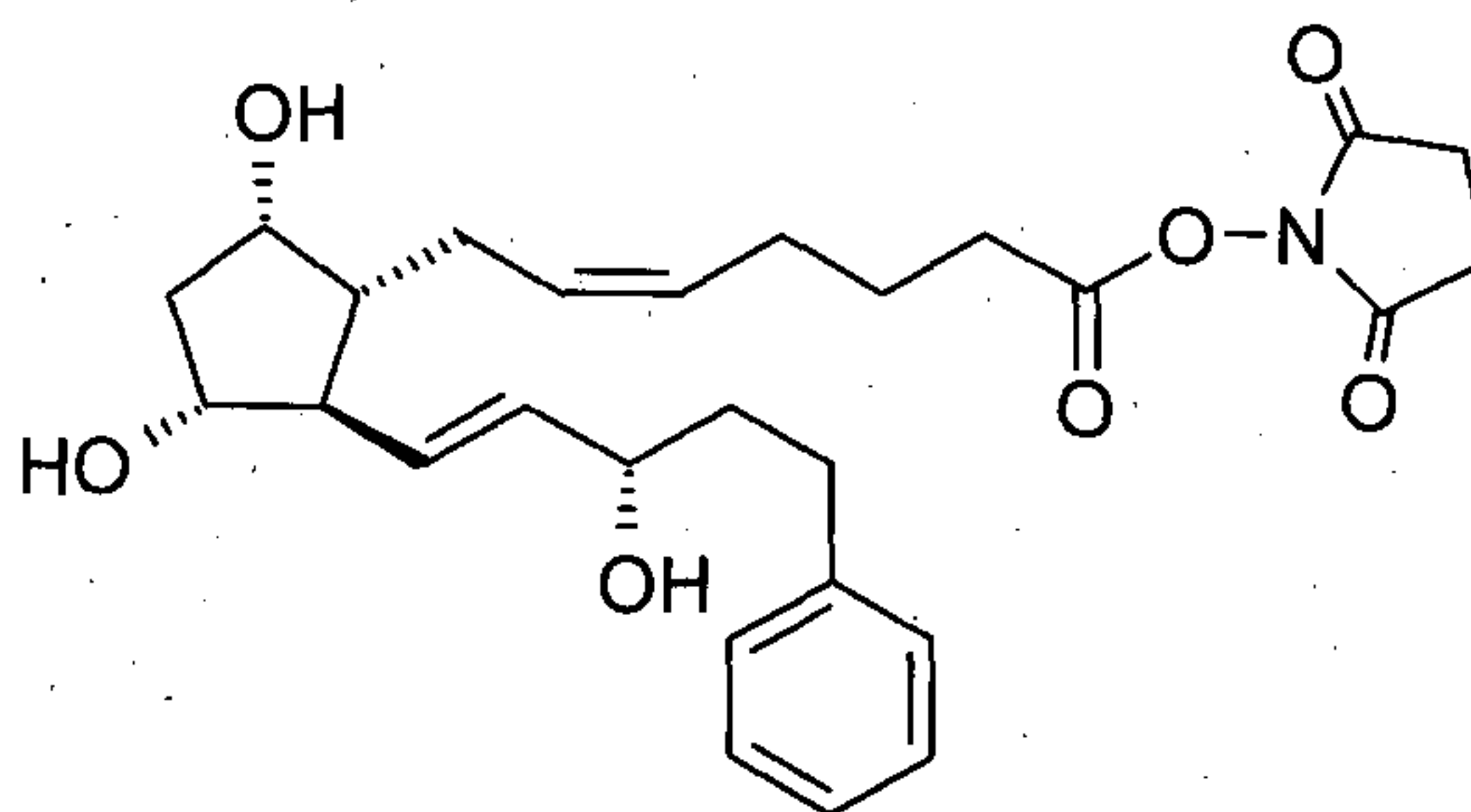
activated ester

 $C_{27}H_{35}NO_7$
 $M=485,58$

Melting point: 93.5-103.4°C

3.) 27.5 g of bimatoprost acid of example 1/c1.) is dissolved in 270 ml of THF and to this
 5 solution are added at room temperature 11.5 g of potassium carbonate and 19.6 g of N,N'-
 disuccinimidyl carbonate. The reaction mixture is under stirring gradually heated to 60°C
 and then poured onto the mixture of 1N NaHSO₄ solution and tert-butyl methyl ether
 (TBME). The phases are separated, the organic phase is washed with 1N NaHCO₃ solution
 and the aqueous-alkaline phase is extracted with TBME. The united organic phase is dried
 10 over Na₂SO₄, filtered and evaporated. The residue is crystallized from hexane : acetone
 mixture to obtain 30.9 g white crystalline material.

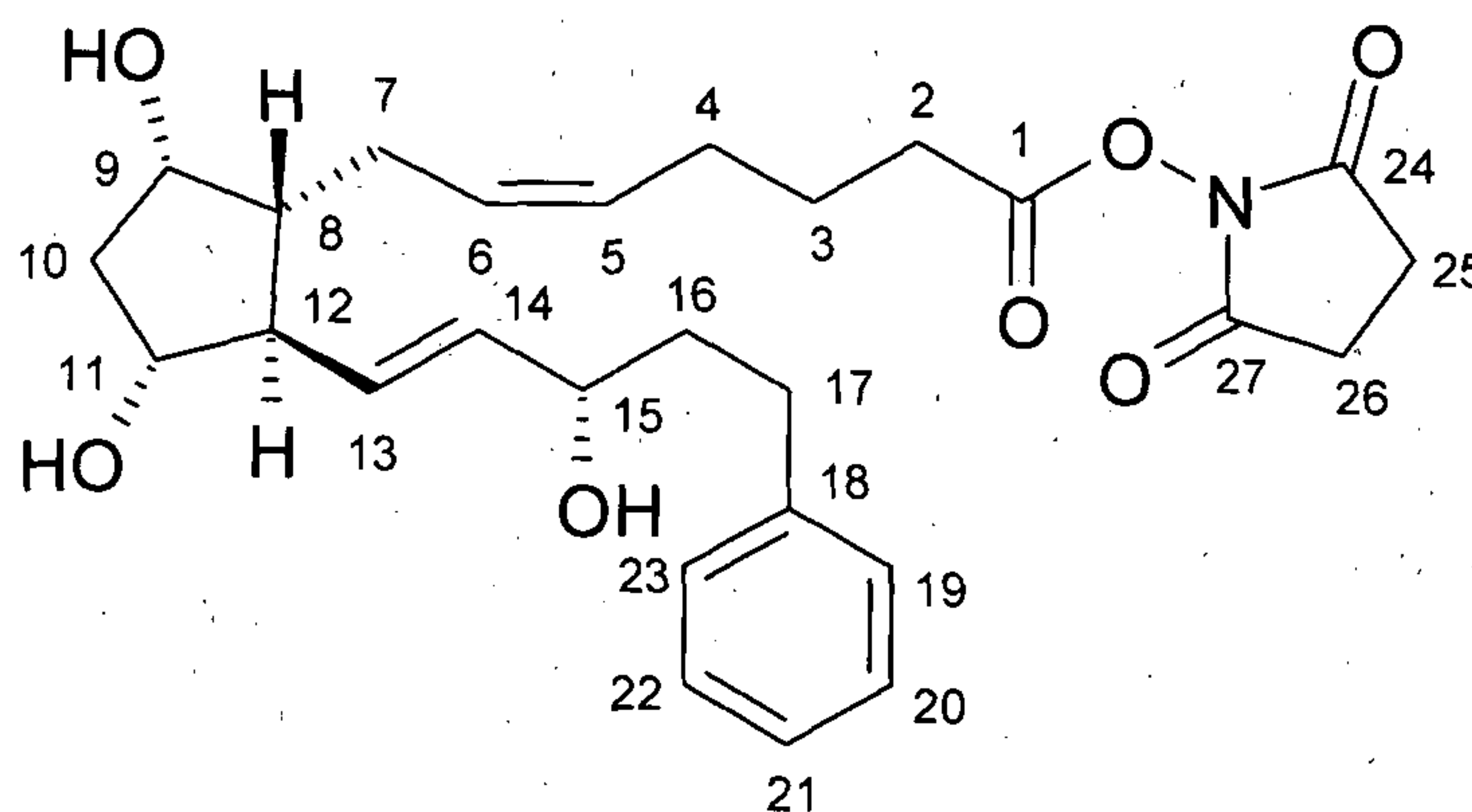
Product:



activated ester

 $C_{27}H_{35}NO_7$
 $M=485,58$

Melting point: 93.5-103.4 °C

¹³C and ¹H NMR data:

Numbering	¹³ C (ppm)	¹ H (ppm)	Number of ¹ H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
1	168.80	-	-	-	
2	29.70	2.55**	2	t	J _{2,3} =7.4
3	24.29	1.61***	2	m (tt)	J _{3,4} =7.4
4	25.70	2.06	2	m	J _{4,5} =7.2
5	127.87	5.28	1	dt	J _{5,6} =10.7
6	130.27	5.48 ⁺	1	dt (ddd)	J _{6,7} =7.4
7	24.83	7a: 2.14 ⁺⁺ 7b: 2.00	1 1	m m	
8	48.78	1.32	1	m (dddd)	10.4; 10.4; 5.1; 5.1
9	69.53	3.915 ⁺⁺⁺	1	m	
9-OH		4.35	1	d	J _{9,OH} =5.0
10	43.94	β: 2.20 ⁺⁺ α: 1.44	1 1	m (ddd) ddd	J _{gem} =14.1; 8.2; 5.9 5.6; 2.3
11	75.37	3.68	1	m (dddd)	~7.9; ~7.9; ~5.8; ~5.8
11-OH		4.50	1	d	J _{11,OH} =5.8
12	54.22	2.16 ⁺⁺	1	m	7.8; 3.8
13	132.02	5.37	1	dd	J _{13,14} =15.4; J _{12,13} =8.1
14	135.16	5.44 ⁺	1	m (dd)	J _{14,15} =6.3
15	70.56	3.909 ⁺⁺⁺	1	m	
15-OH		4.65	1	d	J _{15,OH} =4.7
16	39.49*	1.71 ^{***} 1.65 ^{***}	1 1	m m	
17	31.35	2.60 ^{**}	2	m	
18	142.31	-	-	-	
19, 23	128.19/128.24	7.17 [#]	2	d	J _{19,20} =7.4
20, 22	128.24/128.19	7.26	2	t	J _{20,21} =7.4
21	125.55	7.15 [#]	1	t	
24, 27	170.18	-	-	-	
25, 26	25.42	2.80	4	s	

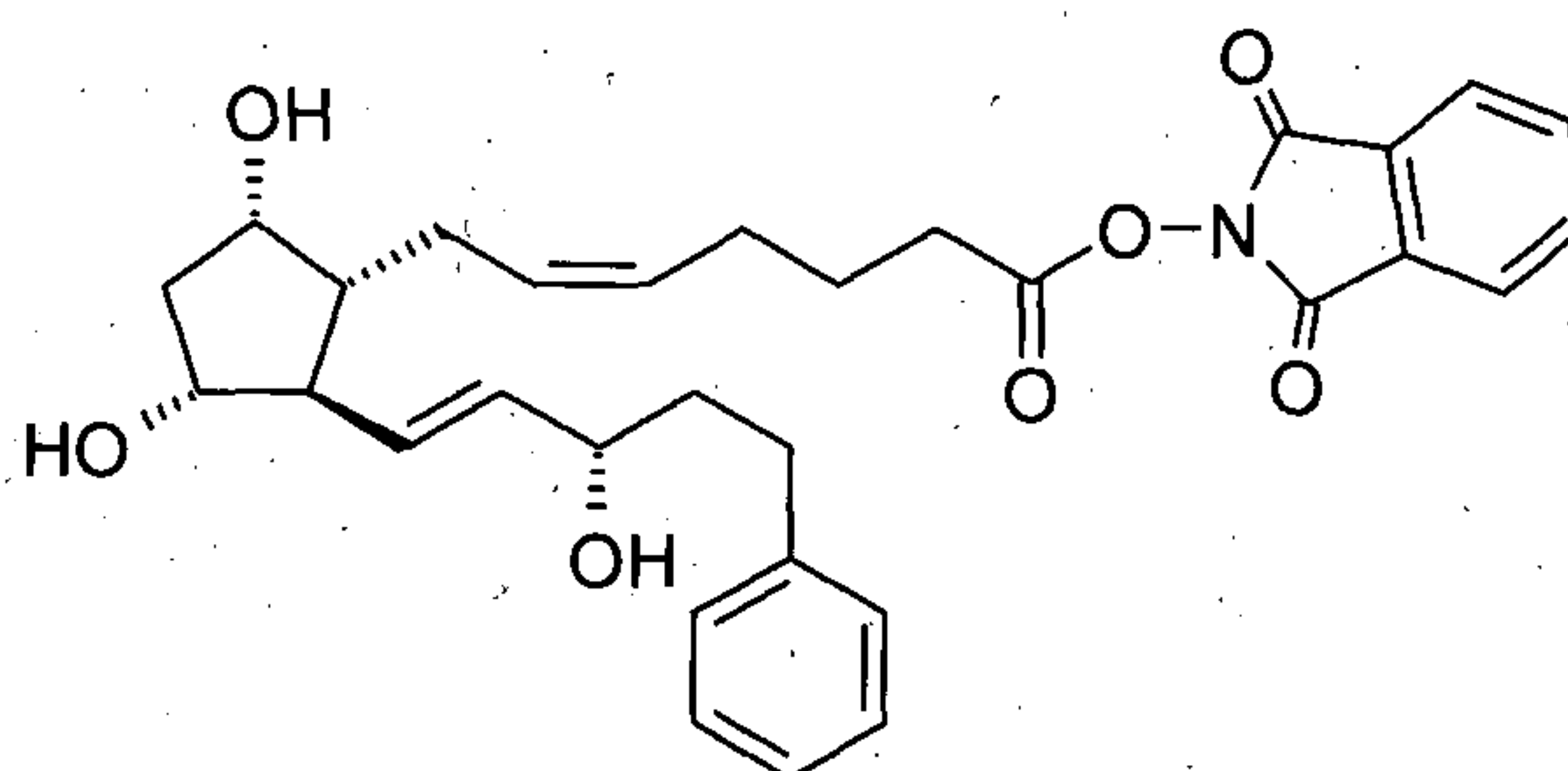
*Overlapped ¹³C NMR by the DMSO signal. **, ***, ⁺, ⁺⁺, ⁺⁺⁺, [#]: Overlapped ¹H NMR signals.

5

4.) Preparation of 7-[3,5-Dihydroxy-2-(3-hydroxy-5-phenyl-pent-1-enyl)-cyclopentyl]-5-heptenoic acid 1,3-dioxo-1,3-dihydro-isoindol-2-yl ester (activated ester)

2 g of bimatoprost acid is dissolved in 20 ml of THF and to this solution are added at room temperature 1g of N-hydroxy-phthalimide and 1 ml of N,N'-diisopropylcarbodiimide. The reaction mixture is stirred for 2 hours and then poured onto the mixture of 1N NaHSO₄ solution and tert-butyl methyl ether (TBME). The phases are separated, the organic phase
5 is washed with 1N NaHCO₃ solution and the aqueous-alkaline phase is extracted with TBME. The united organic phase is dried over Na₂SO₄, filtered and evaporated. The residue is crystallized from hexane : acetone mixture to obtain 1.5 g white crystalline material.

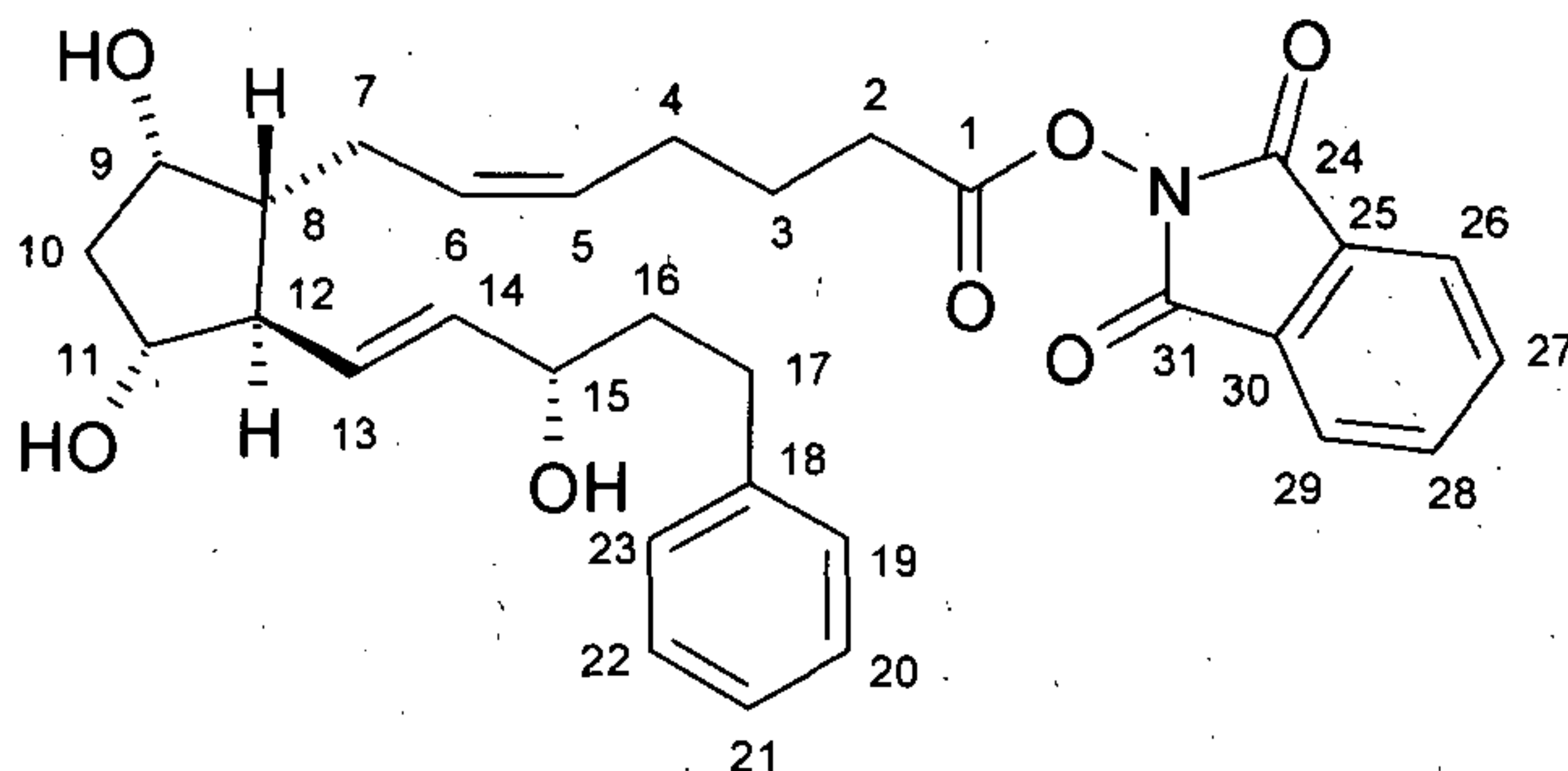
Product:



M: 533,63
C₃₁H₃₅NO₇

10

Melting point: 83.2-84.5°C

¹³C and ¹H NMR data:

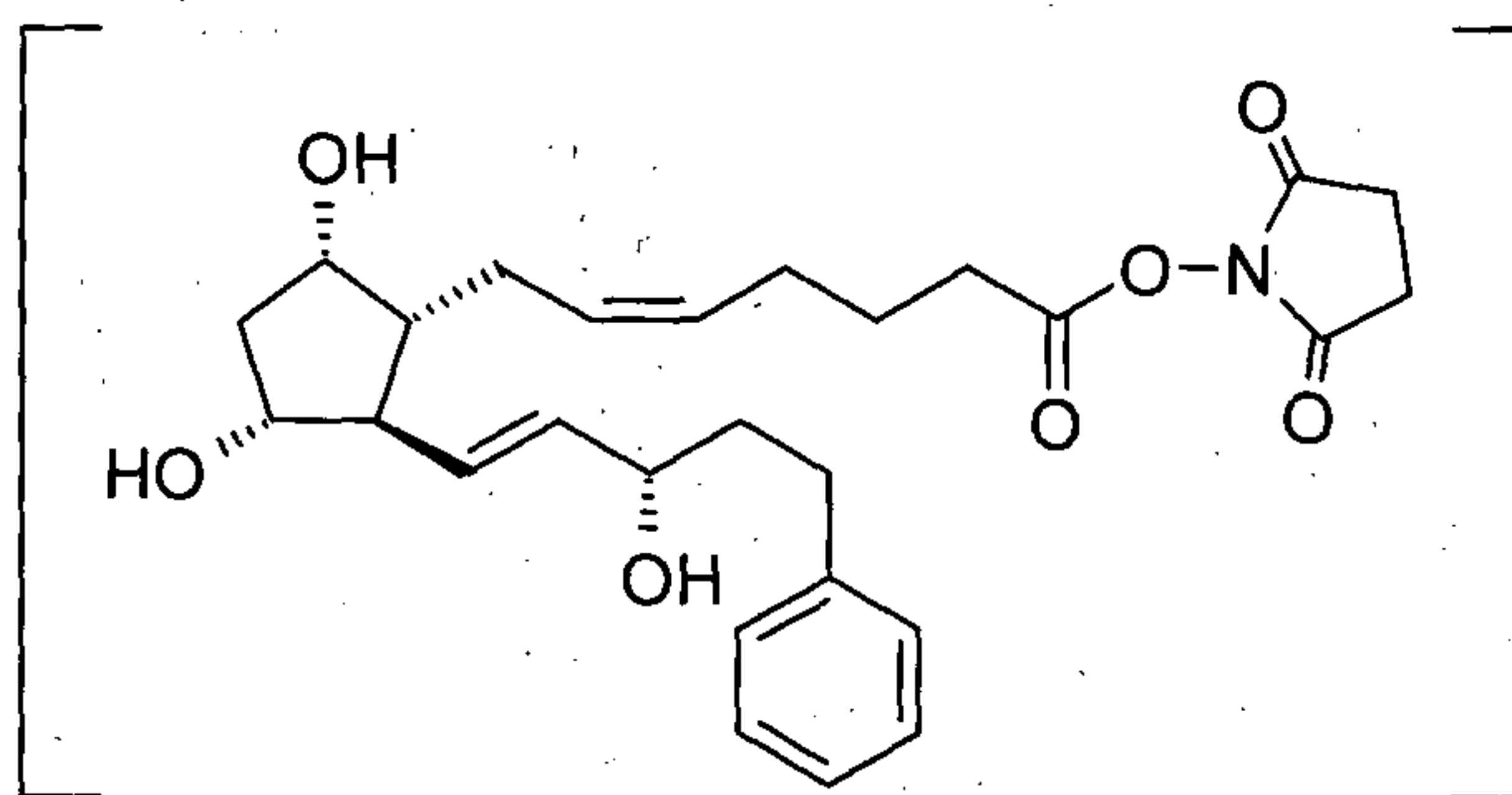
Numbering	¹³ C (ppm)	¹ H (ppm)	Number of ¹ H	Multiplicity	Coupling constant (Hz) (+/- 0.2Hz)
1	169.82	-	-	-	
2	29.63	2.64	2	t	J _{2,3} =7.4
3	24.29	1.65*	2	m (tt)	J _{3,4} =7.4
4	25.71	2.09	2	m	J _{4,5} =7.2
5	127.84	5.30	1	dt	J _{5,6} =10.5
6	130.33	5.50	1	dt (ddd)	J _{6,7} =7.5
7	24.83	a: 2.16** b: 2.01	1 1	m m (ddd)	J _{gem} =12.6
8	48.79	1.325	1	m (dddd / tt)	10.7, 10.0; 5.3; 4.7
9	69.52	3.92***	1	m	
9-OH		4.38	1	d	J _{9,OH} =4.9
10	43.95	β: 2.205** α: 1.44	1 1	m(ddd) ddd	J _{gem} =14.1; J _{10β} = 8.4 and 6.0 J _{10α} = 5.6 and 2.1
11	75.74	3.68	1	m (dddd/tt)	~7.8; ~7.8; ~6.0; ~6.0
11-OH		4.52	1	d	J _{11,OH} =5.8
12	54.23	2.165**	1	m	
13	132.08	5.37	1	dd	J _{13,14} =15.4; J _{12,13} =8.3
14	135.18	5.44	1	m (dd)	J _{14,15} =6.4
15	70.56	3.89***	1	m	
15-OH		4.66	1	d	J _{15,OH} =4.6
16	39.47 [§]	a: 1.69* b: 1.64*	1 1	m m	
17	31.34	2.58**	2	m (td)	10.1 and 6.3
18	142.28	-	-	-	
19, 23	128.16 [§] /128.20	7.15 ⁺	2	d	J _{19,20} =7.5
20, 22	128.20/128.16 [§]	7.24	2	t	J _{20,21} =7.3
21	125.52	7.13 ⁺	1	t	
24, 31	161.81	-	-	-	
25, 30	~128.1 [§]	-	-	-	
26, 29	123.97	7.97 ⁺⁺	2	m	
27, 30	135.51	7.94 ⁺⁺	2	m	

[§]Overlapped ¹³C NMR by the DMSO signal. ^{§§}Overlapped ¹³C NMR signals. *, **, ***, +, ++: Overlapped ¹H NMR signals.

5.) Preparation of 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]-cyclopentyl]-N-ethyl-5-heptenamide, (5Z(-)-bimatoprost)

through the activated ester

27.5 g of bimatoprost acid is dissolved in 270 ml of THF and to the solution are added at room temperature 13.7 g N,N'-diisopropylcarbodiimide and then 13.7 g of N-hydroxysuccinimide. The mixture is stirred at room temperature. The resulting activated ester is not isolated.



activated ester

C₂₇H₃₅NO₇

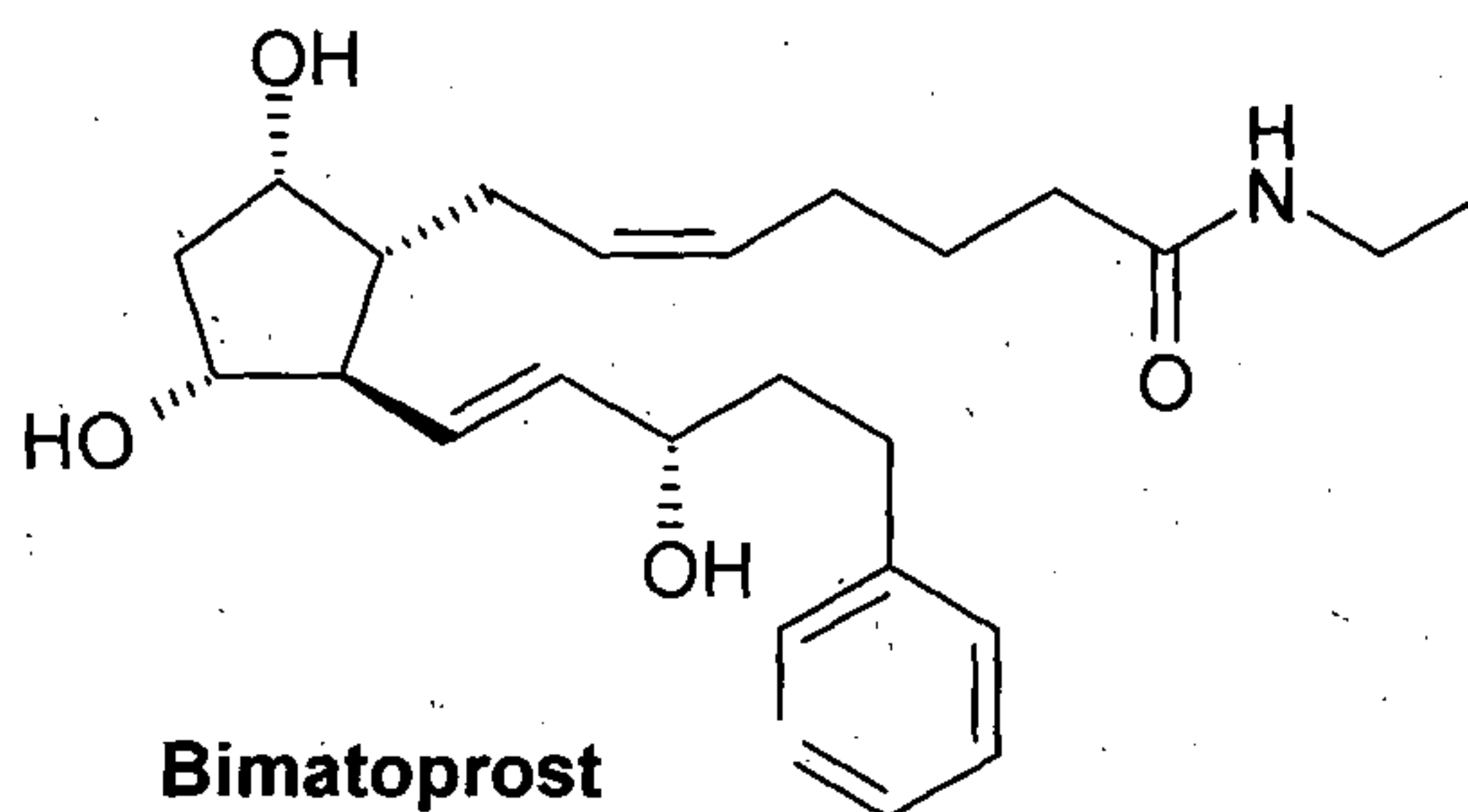
M=485,58

5

After the completion of the ester formation 70 ml of 2M ethylamine in THF solution is added to the reaction mixture. The mixture is stirred until the expected conversion is reached, then it is poured onto the mixture of 1N NaHSO₄ solution and tert-butyl methyl ether (TBME). The phases are separated, the organic phase is washed with 1N NaHCO₃ solution and the aqueous-alkaline phase is extracted with TBME. The united organic phase is dried over Na₂SO₄, filtered and evaporated to obtain 25.4 g of oil.

10

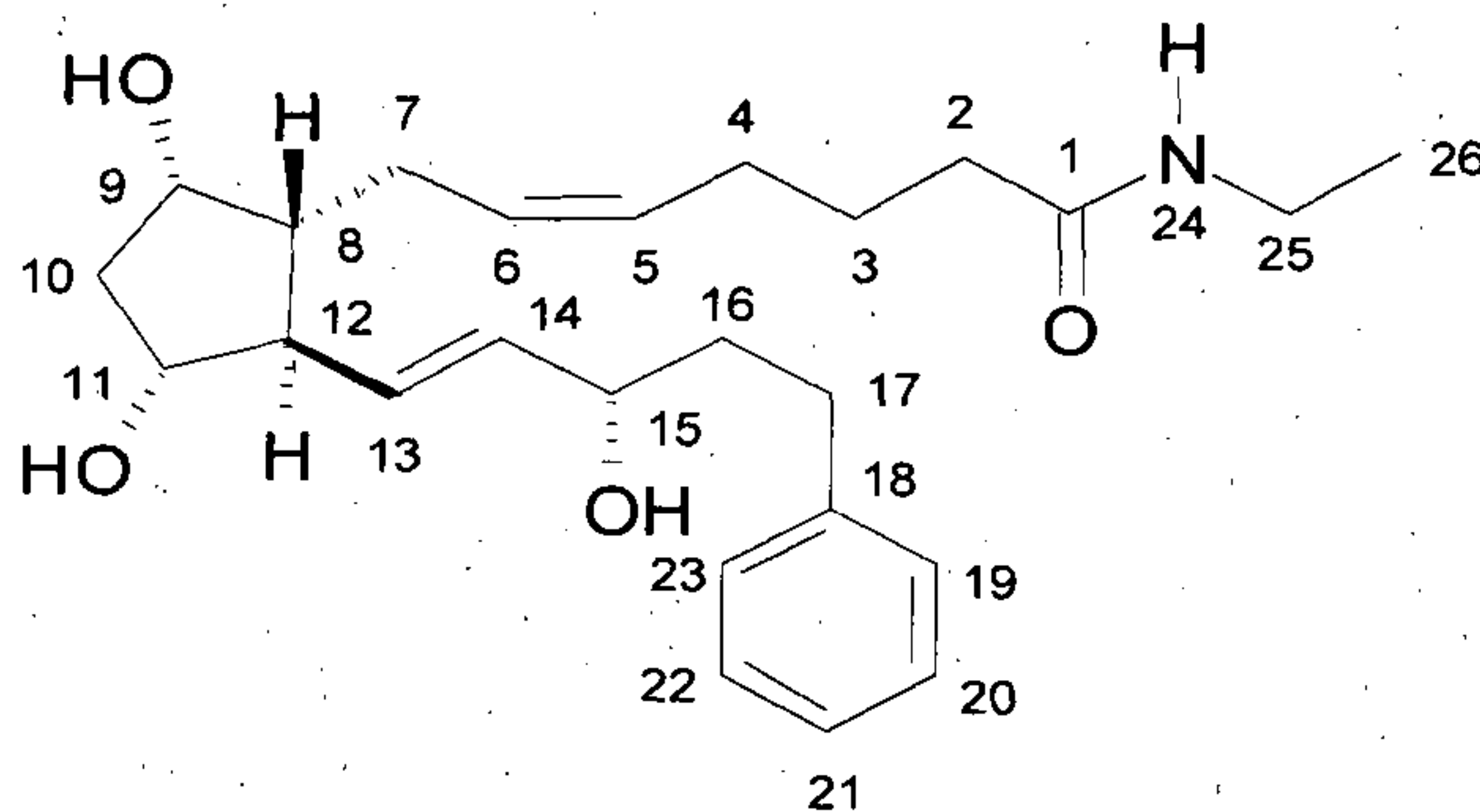
Product:



Bimatoprost

M: 415,58

C₂₅H₃₇NO₄

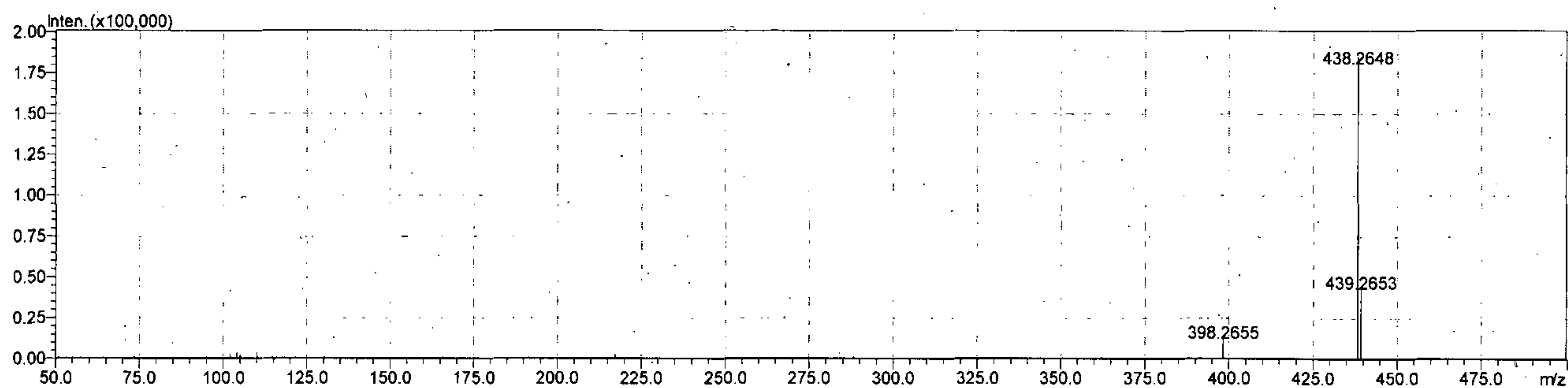
¹³C and ¹H NMR data:

Position	¹³ C (ppm)	¹ H (ppm)	Number of the protons	Multiplicity	Coupling (Hz) (+/- 0.2Hz)
1	172.51	-	-	-	
2	35.88	2.02**	2	t	J _{2,3} =7.5
3	26.27	1.53***	2	m (tt)	J _{3,4} =7.5
4	27.25	1.99**	2	m	J _{4,5} =7.2
5	129.78	5.30	1	dt	J _{5,6} =10.5
6	130.38	5.48 ⁺	1	Dt (ddd)	
7	25.72	2.15 ⁺⁺	1	m	
		2.03**	1	m	
8	49.78	1.35	1	m (dddd)	10.6; 10.6; 4.7; 4.7
9	70.45	3.95 ⁺⁺⁺	1	m	
9-OH		4.40	1	d	J _{9,OH} =4.9
10	44.85	β: 2.23 ⁺⁺	1	m	
		α: 1.48***	1	ddd	J _{gem} =14.2; 5.5; 2.2
11	76.67	3.71	1	m (dddd)	~7.5; ~7.5; ~7.5; 6.5
11-OH		4.54	1	d	J _{11,OH} =5.8
12	55.15	2.19 ⁺⁺	1	m	
13	132.91	5.41	1	dd	J _{13,14} =15.4; J _{12,13} =8.0
14	136.00	5.47 ⁺	1	M (dd)	
15	71.41	3.94 ⁺⁺⁺	1	m	
15-OH		4.71	1	d	J _{15,OH} =4.6
16	40.36*	1.74 [#]	1	m	
		1.70 [#]	1	m	
17	32.25	2.61	1	m	
		2.675	1	m	
18	143.21	-	-	-	
19, 23	129.13	7.21 ^{##}	2	d	J _{19,20} =7.4
20, 22	129.15	7.30	2	t	J _{20,21} =7.4
21	126.46	7.19 ^{##}	1	t	
24 (NH)		7.72	1	broad, t	J _{24,25} =5.5
25	34.13	3.07	2	qd	J _{25,26} =7.2
26	15.70	1.02	3	t	

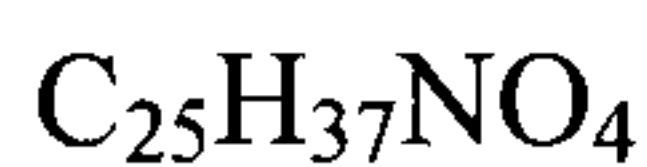
MS data

MS spectrum:

Positive ionization:



5 Expected formula:



Measured exact mass: 438.2648 [M+Na]⁺

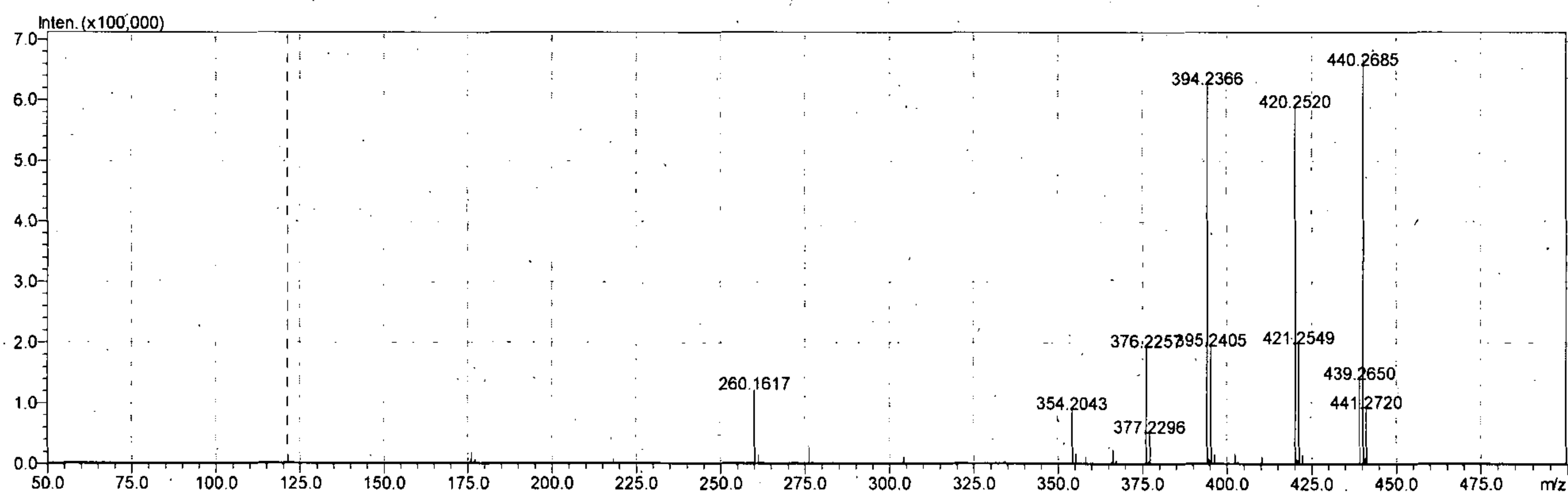
Expected exact mass: 438.2615 [M+Na]⁺ $\Delta M = 3.3$ mDa and 7.53 ppm



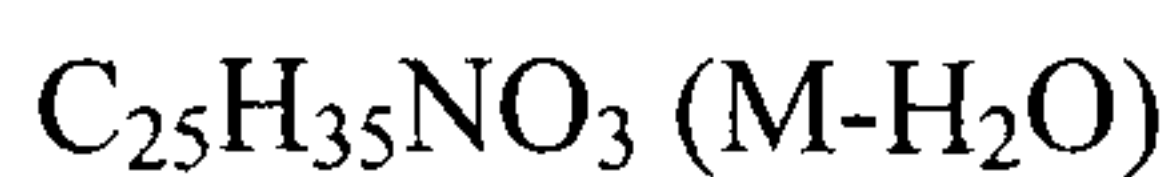
10 Measured exact mass: 398.2655 [M-H₂O+H]⁺

Expected exact mass: 398.2690 [M-H₂O+H]⁺ $\Delta M = -3.5$ mDa and 8.79 ppm

MSMS (precursor ion: 438.26):



15 Expected formula:



Measured exact mass: 420.2520 [M-H₂O+Na]⁺

Expected exact mass: 420.2509 [M-H₂O+Na]⁺

$\Delta M = 1.1$ mDa and 2.62 ppm

C₂₅H₃₂NO₃ (M-H₂O-5H)

Measured exact mass: 394.2366 [M-H₂O-5H]⁺

5 Expected exact mass: 394.2377 [M-H₂O-5H]⁺

$\Delta M = -1.1$ mDa and 2.79 ppm

C₂₅H₃₀NO₂ (M-2xH₂O-5H)

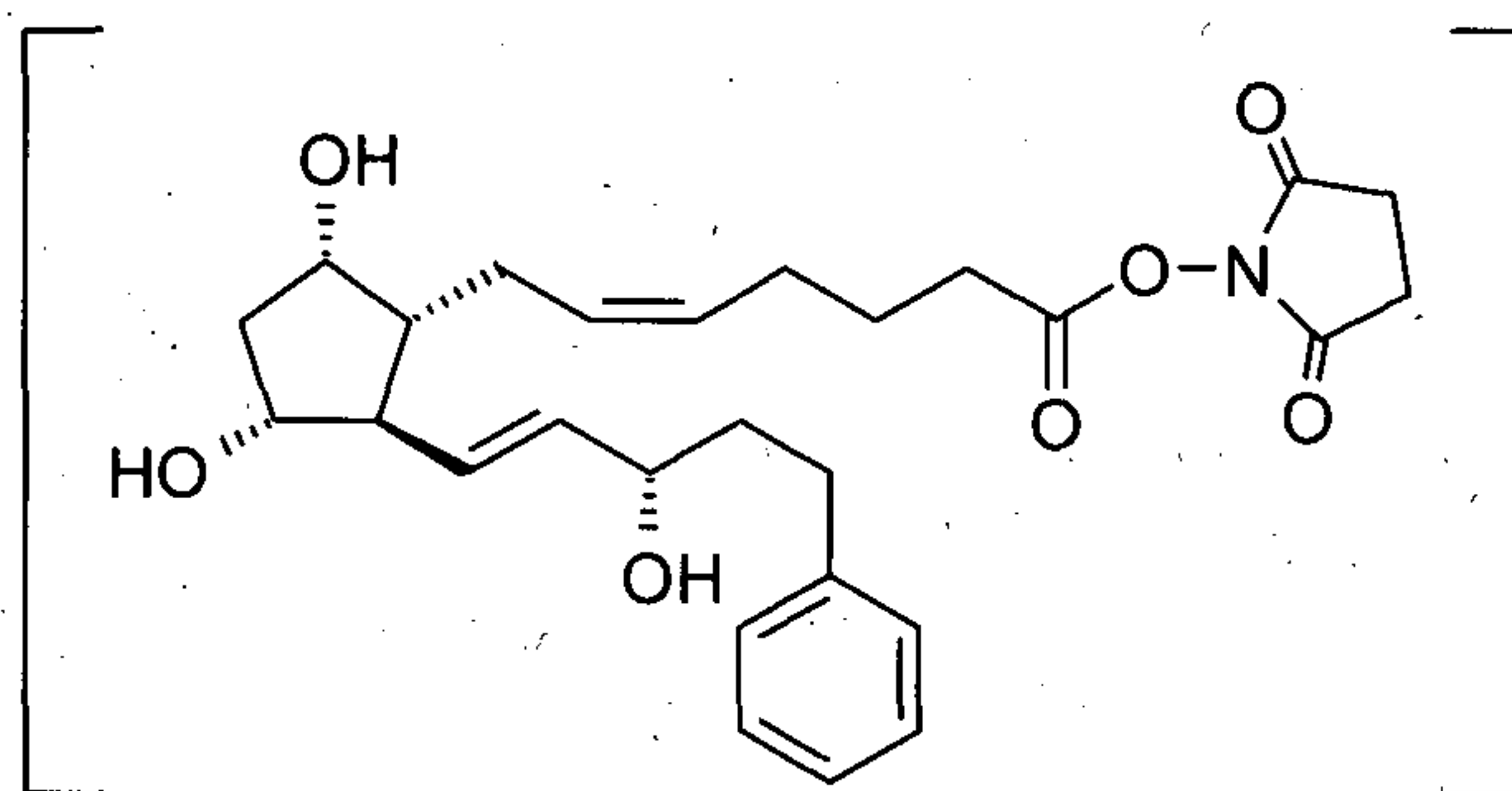
Measured exact mass: 376.2258 [M-2xH₂O-5H]⁺

Expected exact mass: 376.2271 [M-2xH₂O-5H]⁺

$\Delta M = -1.3$ mDa and 3.46 ppm

10 6.) Preparation of Bimatoprost through the activated ester

27.5 g of bimatoprost acid is dissolved in 270 ml of THF and to this solution are added at room temperature 11.5 g of potassium carbonate and 19.6 g of N,N'-disuccinimidyl carbonate. The reaction mixture is gradually heated to 60°C under stirring. The resulting
15 activated ester is not isolated.



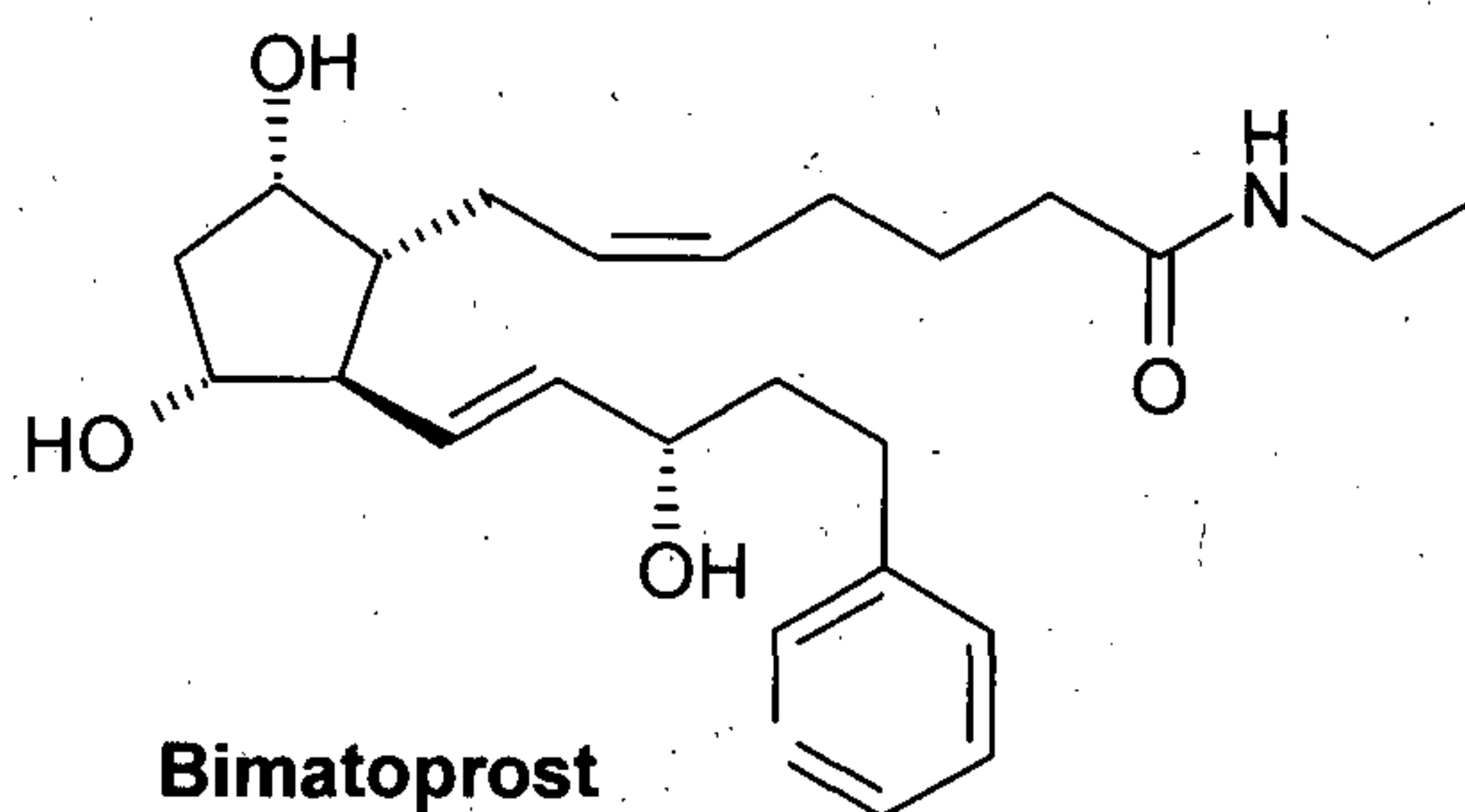
activated-ester

C₂₇H₃₅NO₇
M=485,58

After the formation of the activated ester, 70 ml of 2M ethylamine in THF solution is added to the reaction mixture. When the reaction is completed the mixture is poured onto the mixture of 1N NaHSO₄ solution and EtOAc. The organic phase is washed with 1N

NaHCO₃ solution, the aqueous-alkaline phase is extracted with EtOAc. The united organic phase is washed with NaCl solution and dried over Na₂SO₄. The drying material is filtered off, the filtrate is evaporated to obtain 25.7 g of oil.

Product:



M: 415,58

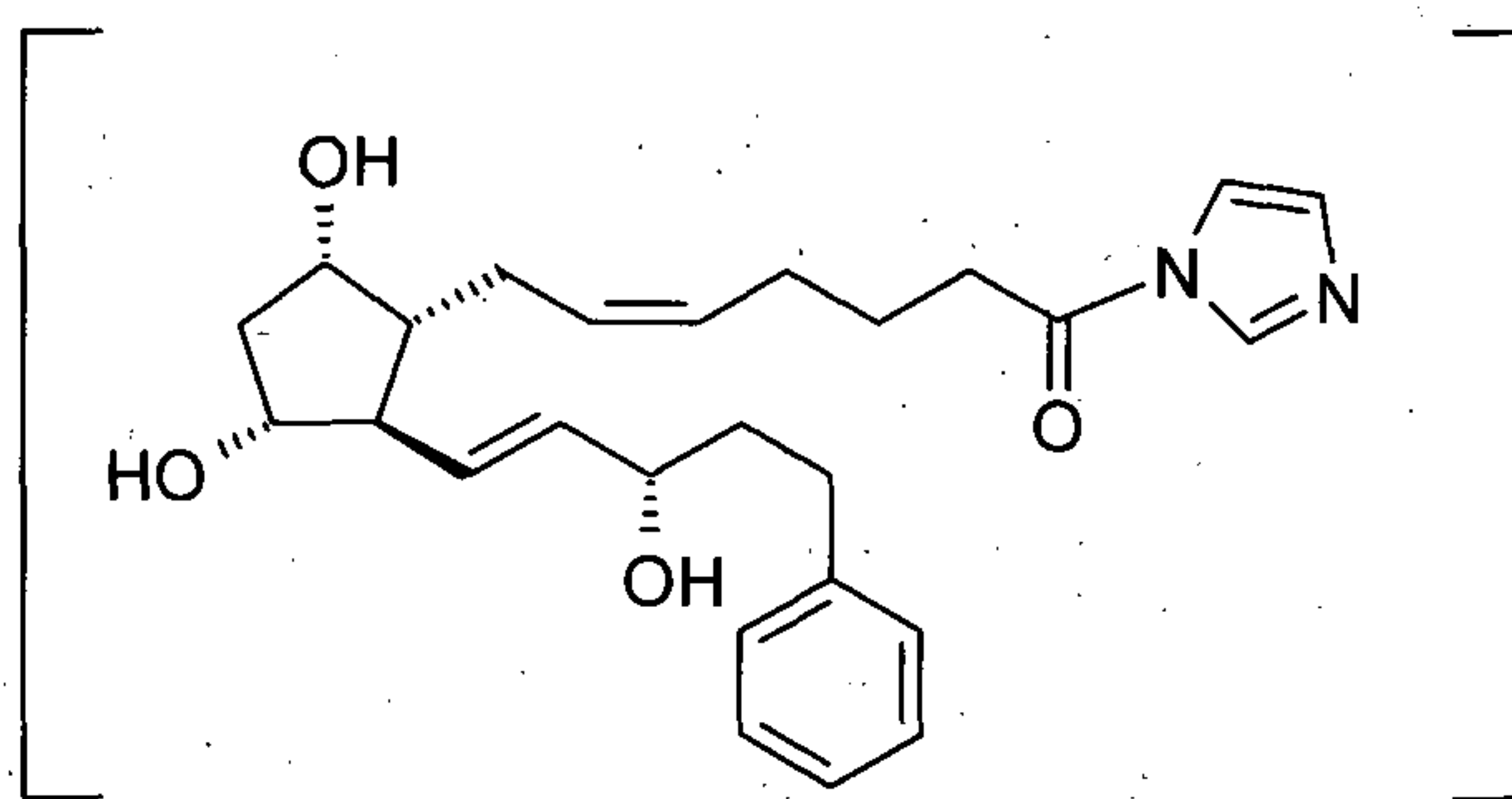
C₂₅H₃₇NO₄

5

7.) Preparation of Bimatoprost through the activated amide

27.5 g bimatoprost acid is dissolved in 270 ml of pyridine and 13.7 g of 1,1'-carbonyldiimidazole is added to it. The mixture is stirred at 20-25°C until the activated amide formation takes place. The resulting activated amide is not isolated.

10



activated amide

C₂₆H₃₄N₂O₄

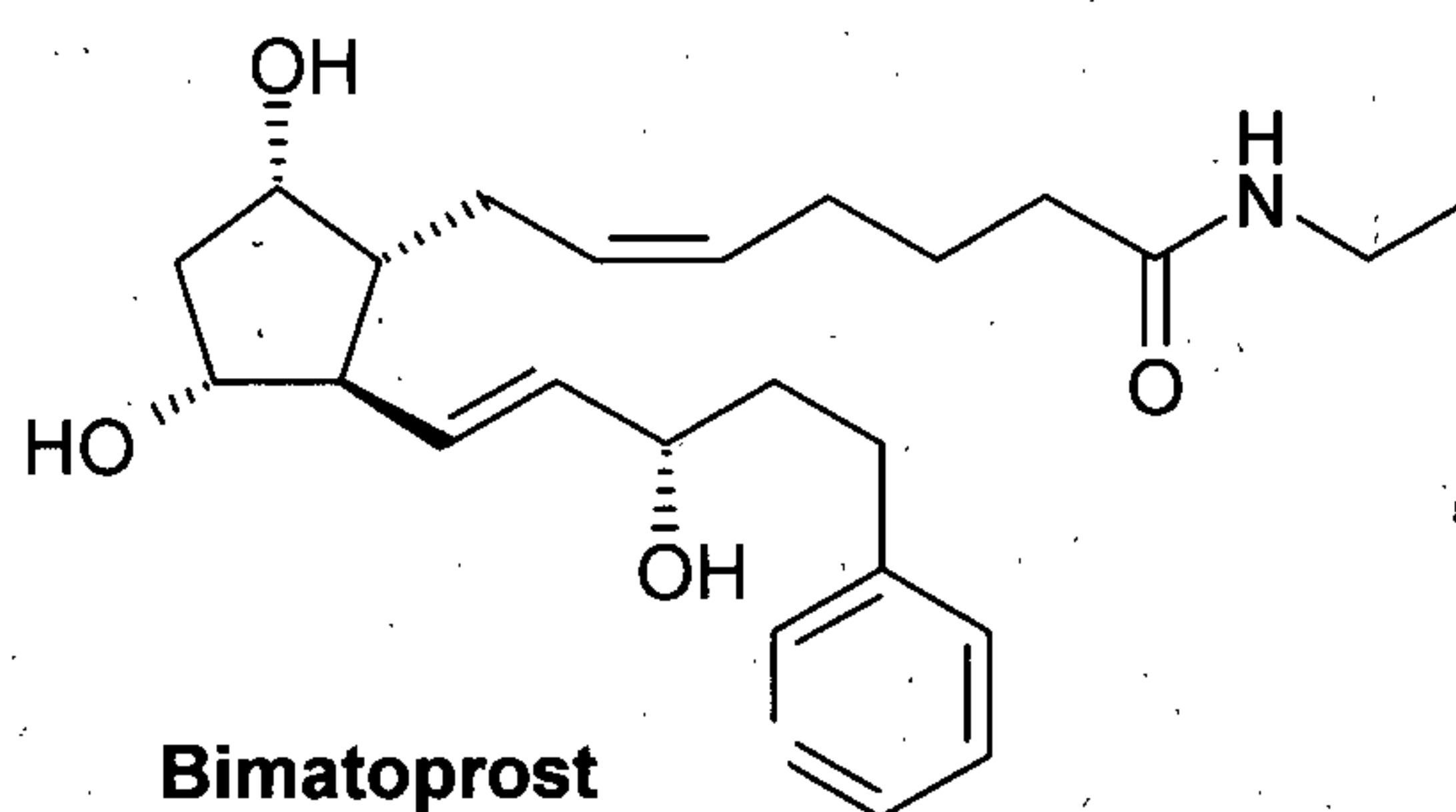
M=438,57

15

70 ml of 2M ethylamine in THF solution is added to the reaction mixture at room temperature and the mixture is stirred until the expected conversion is reached. The mixture is then poured onto the mixture of 1N NaHSO₄ solution and tert-butyl methyl ether

(TBME). The phases are separated, the organic phase is washed with 1N NaHCO₃ solution and the aqueous-alkaline phase is extracted with TBME. The united organic phase is dried over Na₂SO₄, filtered and the filtrate is evaporated to obtain 23.82 g of oil.

Product:



Bimatoprost

M: 415,58

C₂₅H₃₇NO₄

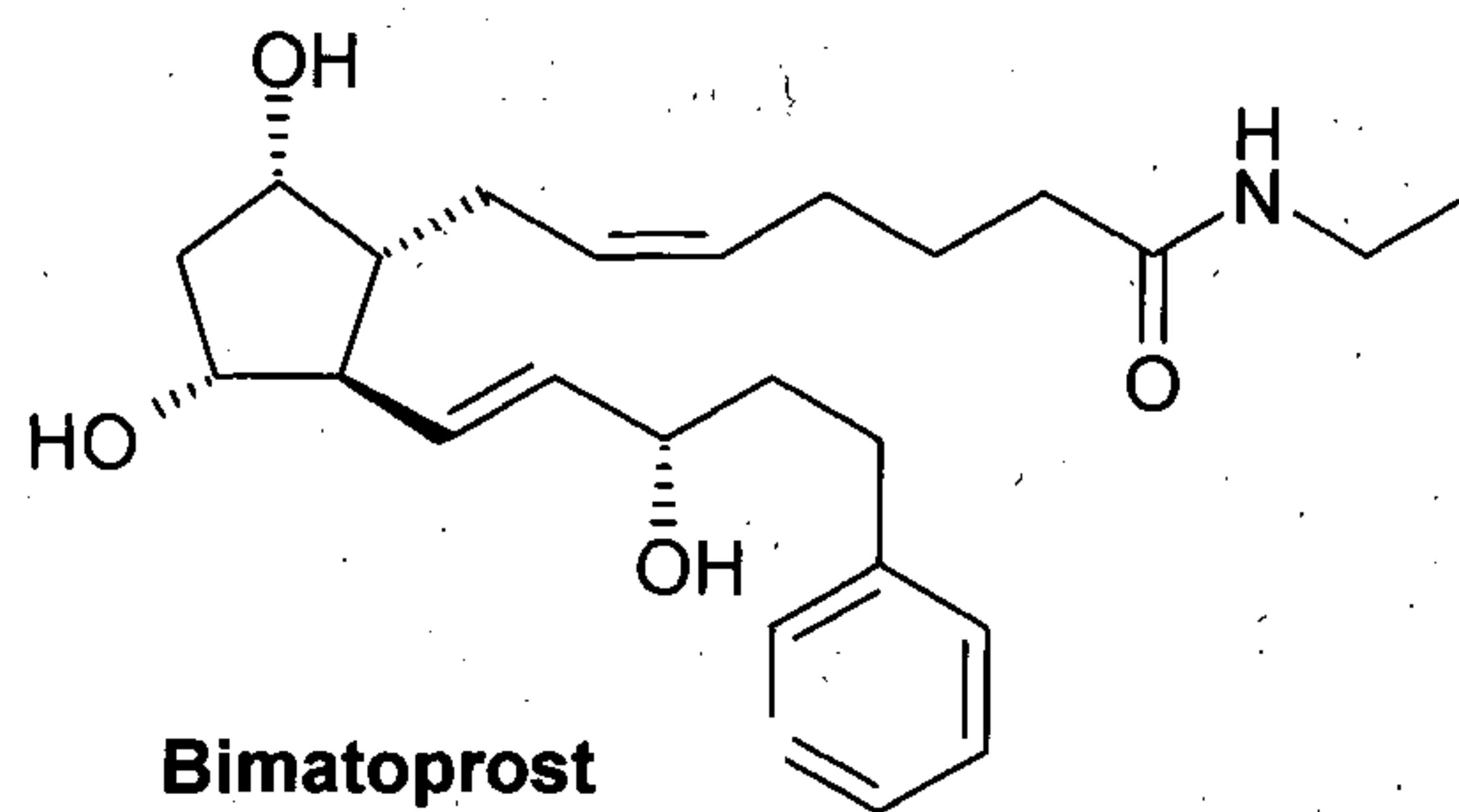
5

8.) Preparation of Bimatoprost from the purified activated ester

30.9 g of the activated ester according to Example 3. is dissolved in 270 ml of THF and to this solution 70 ml of 2M ethylamine dissolved in THF is added. After the completion of the reaction the mixture is poured onto the mixture of 1N NaHSO₄ solution and EtOAc. The organic phase is washed with 1N NaHCO₃ solution. The aqueous-alkaline phase is extracted with EtOAc. The united organic phase is washed with NaCl solution and dried over Na₂SO₄. The drying material is filtered off and the filtrate is evaporated. To the resulting oil 35 mass% of water is added and the product is crystallized. 24.8 g of white bimatoprost crystals of higher than 99.5% purity are obtained.

15

Product:



M: 415,58
 $C_{25}H_{37}NO_4$

Melting point: 71.9-72.5 °C

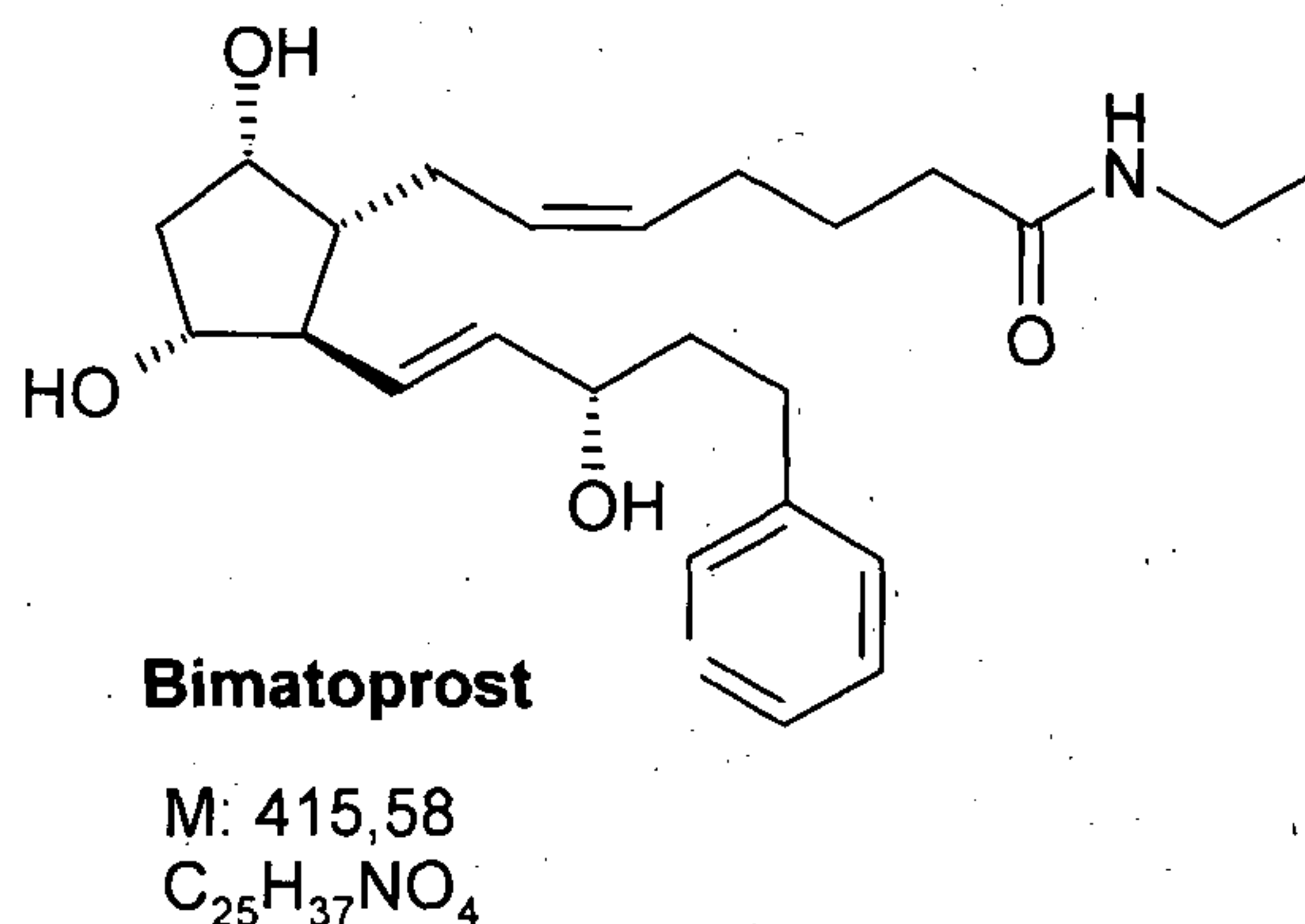
HPLC: 99.6 % bimatoprost, less than 0.3% trans-bimatoprost, 0.1% other impurity

5 9.) Preparation of Bimatoprost according to method iii.)

2.00 g of Bimatoprost acid is dissolved in 20 ml of tetrahydrofuran (THF) and at 30°C first 1.29 g of 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and 1.44 ml of triethylamine, then after 10 minutes of stirring 2.57 ml of 2M ethylamine in THF solution are added. The reaction mixture is gradually, in 1 hour, heated to 70°C and the mixture is stirred at that temperature until the starting material disappears (approx. 1 hour). The reaction is followed by TLC.

After the completion of the reaction the mixture is poured onto the mixture of 1N NaHSO₄ solution and isopropyl acetate (iPrOAc). The organic phase is washed with 1N NaHCO₃ solution, the aqueous-alkaline phase is extracted with iPrOAc. The united organic phase is washed with NaCl solution and dried over Na₂SO₄. The drying material is filtered off and the filtrate is evaporated to obtain 1.41 g of oil.

Product:



10.) Preparation of crystal form II. of bimatoprost from crude bimatoprost oil

- 5 To the bimatoprost oil prepared according to Example 6., 35 mass% amount of purified water is added. The mixture is intensively stirred and then dried in vacuum at max. 35°C temperature, while every 2 hour it is agitated and scratched. After complete dryness the mixture is homogenized. IR spectrum of this product is shown in Figure IV and the DSC curve of this product is shown in Figure VI. The X-ray diffraction curve of produced Form
- 10 II is shown in Figure VIII.

Yield: 96.9%

Mp.: 78°C

DSC onset: 73.56 °C

15 11.) Preparation of crystal form II. of bimatoprost

- The crude bimatoprost prepared according to Example 5. is dissolved under heating in 3000-fold amount of diethyl ether. The solvent is then removed at (-)20-(-)30°C by slowly passing through nitrogen gas. The resulting crystals are
- 20 homogenized, or first exposed to mechanical effect and then homogenized.

Yield: 94.4%

Mp.: 75.9°C

DSC onset: 72.92 °C

12.) Preparation of crystal form II. of bimatoprost

5

To the crude bimatoprost prepared according to Example 6., 35 mass% amount of methanol is added. The mixture is intensively stirred and then dried in vacuum at max. 35°C temperature, while every 2 hour it is agitated and scratched. After complete dryness the mixture is homogenized.

10 Yield: 95.8%

Mp.: 77.2 °C

DSC onset: 73.07 °C

13.) Preparation of crystal form II of bimatoprost

15

To the crude bimatoprost prepared according to Example 6., 17.5 mass% amount of purified water and 17.5 mass% amount of ethanol are added. The mixture is intensively stirred and then dried in vacuum at max. 35°C temperature, while every 2 hour it is agitated and scratched. After complete dryness the mixture is homogenized.

20 Yield: 92.3%

Mp.: 72.9 °C

DSC onset: 72.96 °C

14.)

25 a.) Preparation of Bimatoprost crystal form I. (according to Example 38 of patent application US 20090163596)

5.2 g of crude bimatoprost is crystallized from 106 g of acetonitrile: the mixture is heated to a temperature near the boiling point, the hot solution is cooled to room temperature and the mixture is stirred at that temperature for 1 hour, then at 0-5°C for 2 hours. The precipitated crystals are filtered off, washed with 20 g of cold (0-5°C) acetonitrile and dried in vacuum at 0-5°C for 1 hour, at room temperature for half an hour and at 30-40°C for 2 hours.

4.3 g of crystal form I. of bimatoprost is obtained. Its IR spectrum is shown in Figure III, its DSC curve is shown in Figure V and its X-ray diffraction curve of Form I is shown in Figure VII.

Yield: 83%

Mp.: 62.1°C

DSC onset: 63.61 °C

b.) Preparation of Bimatoprost crystal form II. started from form I.

To crystal form I. of bimatoprost prepared according to Example 14a., 35 mass% amount of purified water is added. The mixture is intensively stirred and then dried in vacuum at max. 35°C temperature, while every 2 hour it is agitated and scratched. After complete dryness the mixture is homogenized.

Yield: 97.3%

Mp.: 77.7°C

DSC onset: 73.14 °C

15. .) Preparation of crystal form II. of a mixture of bimatoprost crystal form II. and I.

To a 50%-50% mixture of crystal form II. and I. of bimatoprost 35 mass% amount of purified water is added. The mixture is intensively stirred and then dried in vacuum at max. 35°C temperature, while every 2 hour it is agitated and scratched. After complete dryness the mixture is homogenized.

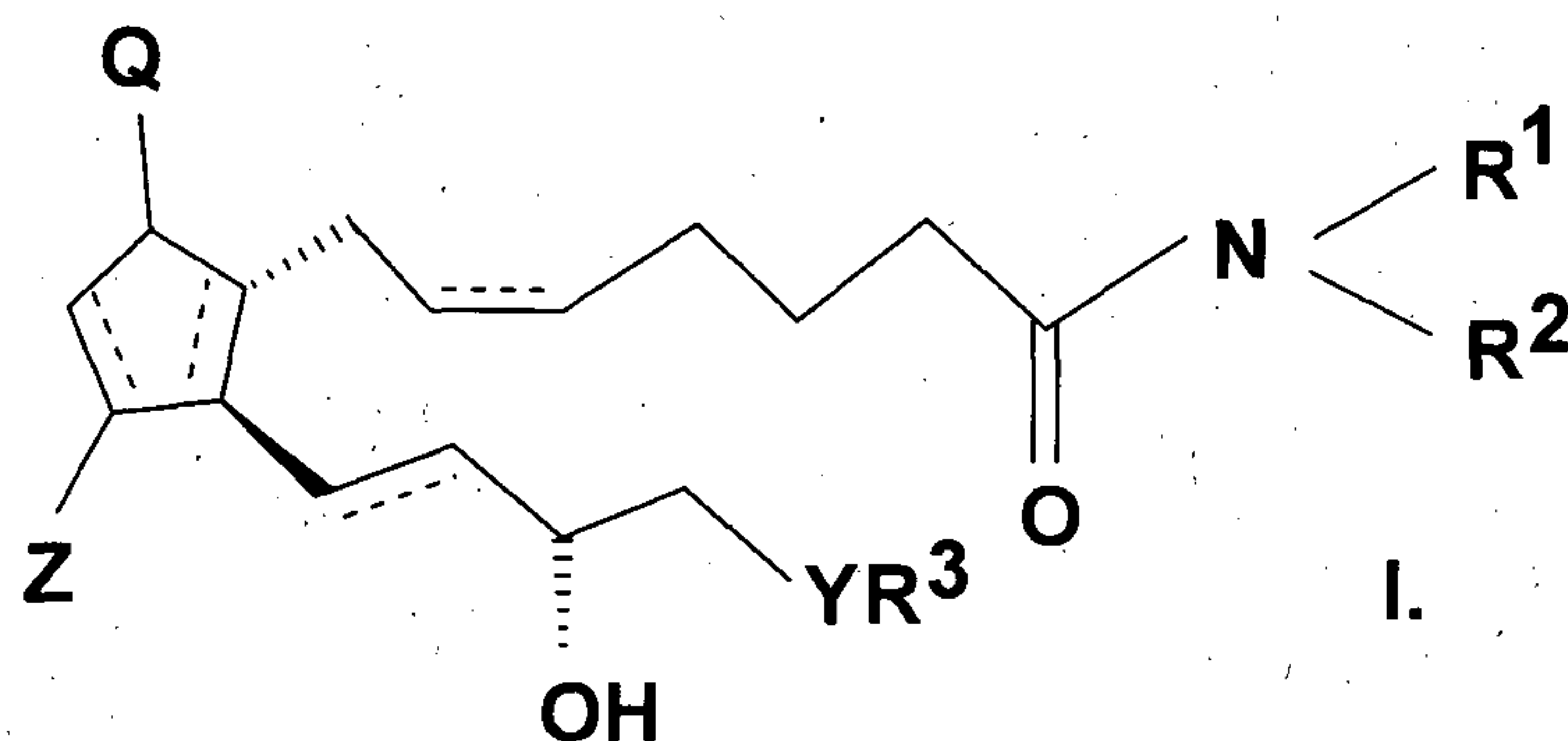
5 Yield: 97.6%

Mp.: 78.2 °C

DSC onset: 73.77 °C

Claims

1. Process for the preparation of prostaglandin amides of the general formula (I),



- 5 - where in the formula

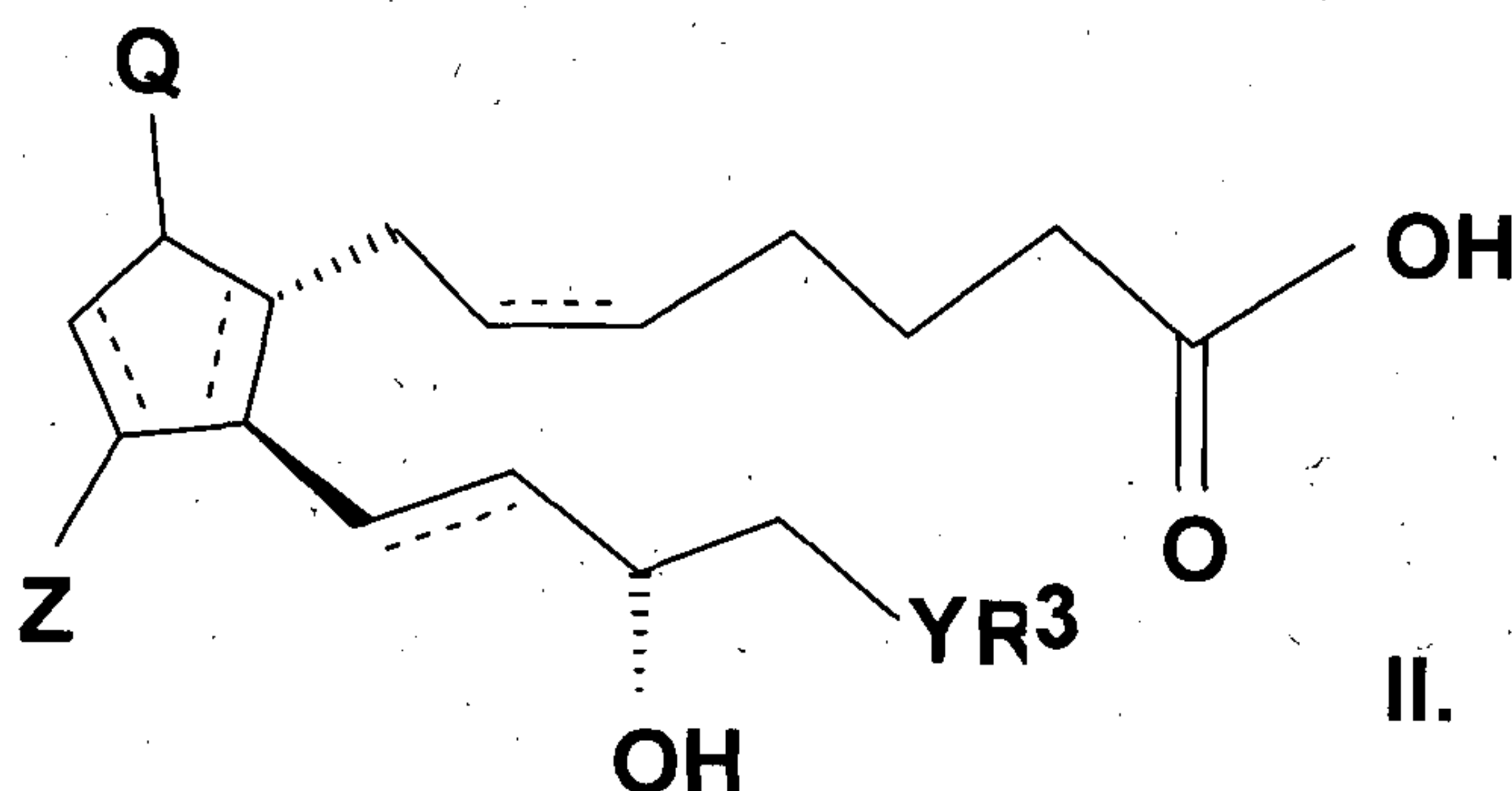
the bonds marked with dotted lines may be single or double bonds, in the case of double bonds at positions 5,6 and 13,14 they may be in cis or in trans orientation,

Q represents hydroxyl-group and Z represents hydroxyl- or oxo- group,

- 10 R¹ and R² independently represent hydrogen atom or a straight or branched C₁₋₁₀ alkyl- or aralkyl- group, optionally substituted with -ONO₂ group, or an aralkyl- or aryl- group, which contains heteroatom,

R³ represents a straight or branched, saturated or unsaturated C₄₋₆ hydrocarbon group, or a C₄₋₁₀ alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C₇₋₁₀ alkylaryl- or hetaryl- group,

- 15 Y represents (CH₂)_n group or O atom or S atom, and where n=0-3,
characterized in that an acid of the general formula (II),



where in the formula

the bonds marked with dotted lines may be single or double bonds, in the case of double bonds at positions 5,6 and 13,14 they may be in cis or in trans orientation,

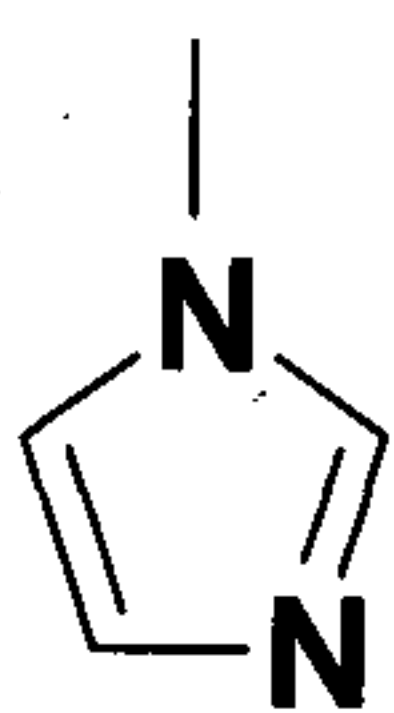
5 Q represents hydroxyl-group and Z represents hydroxyl- or oxo- group,

R³ represents a straight or branched, saturated or unsaturated C₄₋₆ hydrocarbon group, or a C₄₋₁₀ alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C₇₋₁₀ alkylaryl- or hetaryl- group,

Y represents (CH₂)_n group or O atom or S atom, and where n=0-3,

10 is reacted

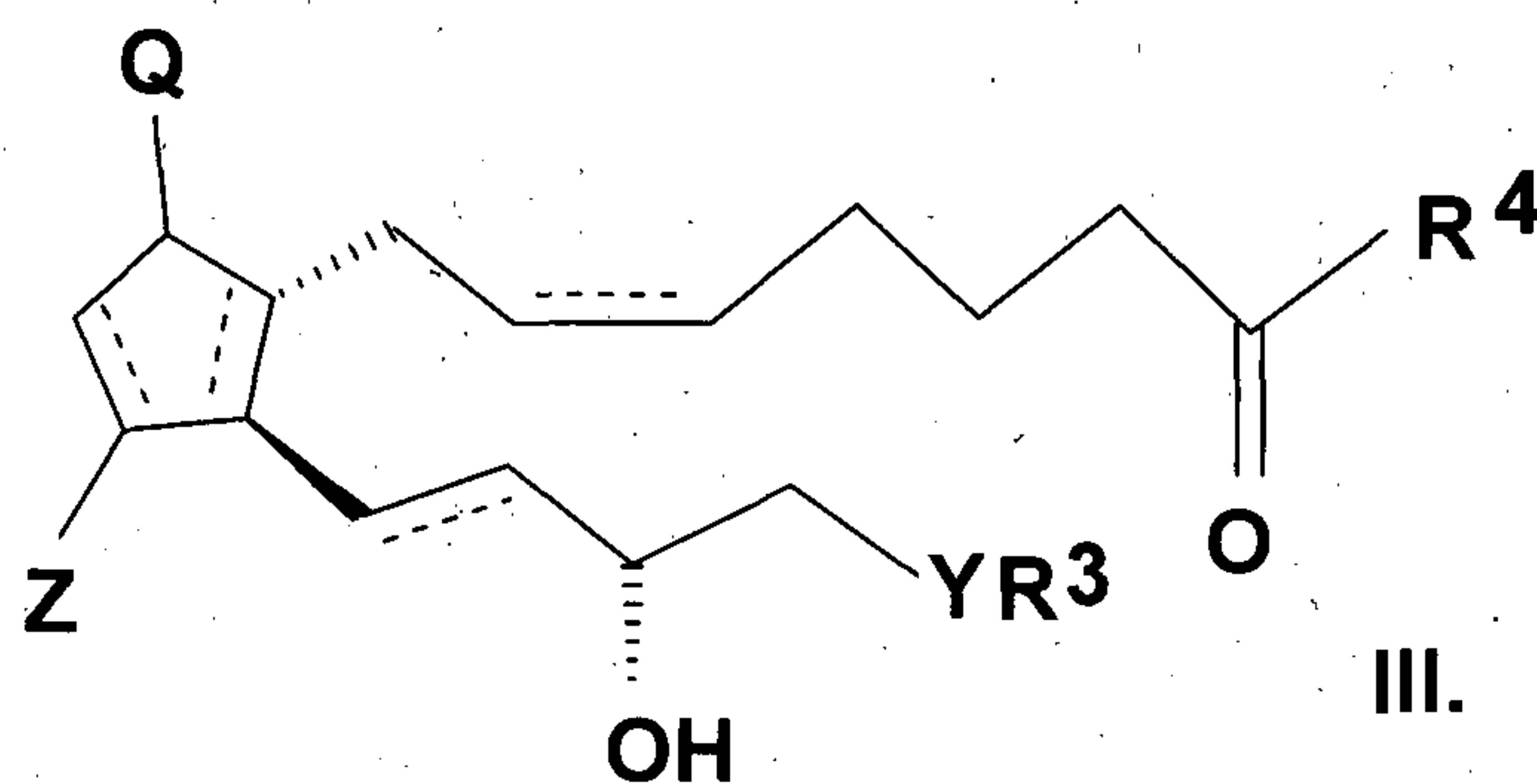
i.) with a compound suitable to introduce group R⁴, where R⁴ represents



a.)

the group of formula a.)

and reacting the amide of the general formula (III) , thus obtained



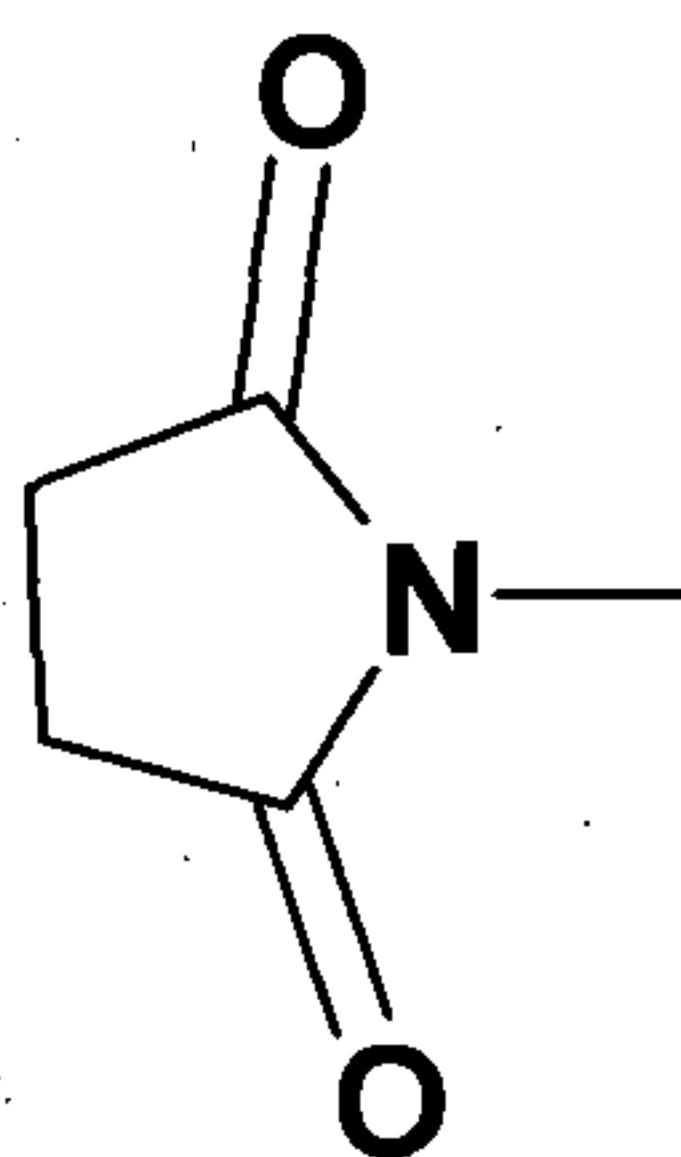
where the meanings of Q, Z, R³, R⁴, Y and n are as defined above, with an amine of the general formula (IV)



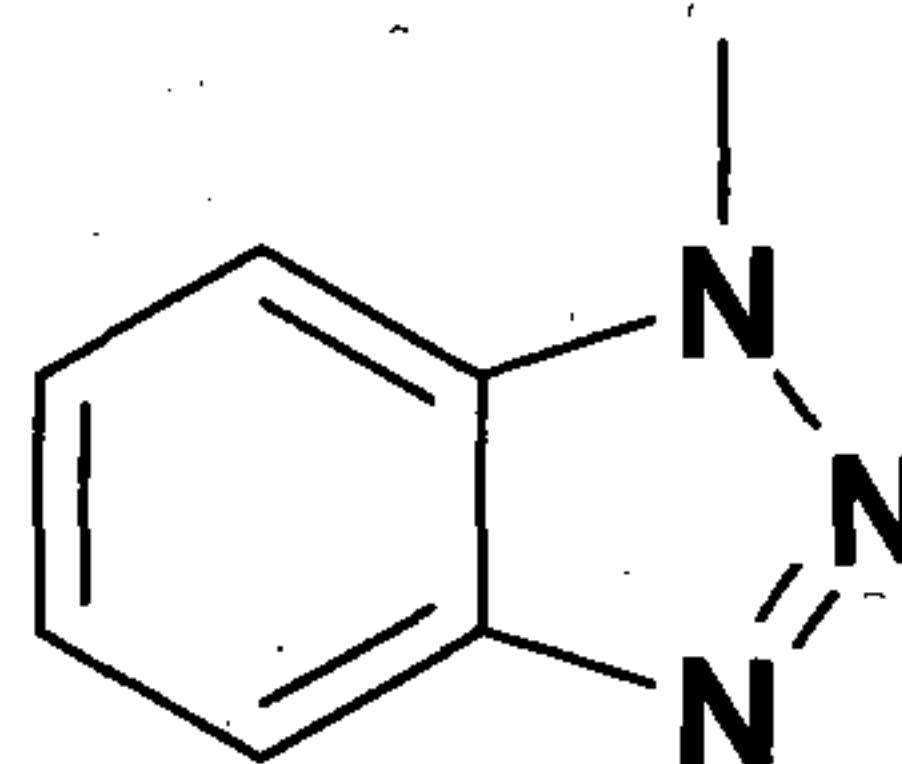
5

- where R¹ and R² have the meanings as defined above, or

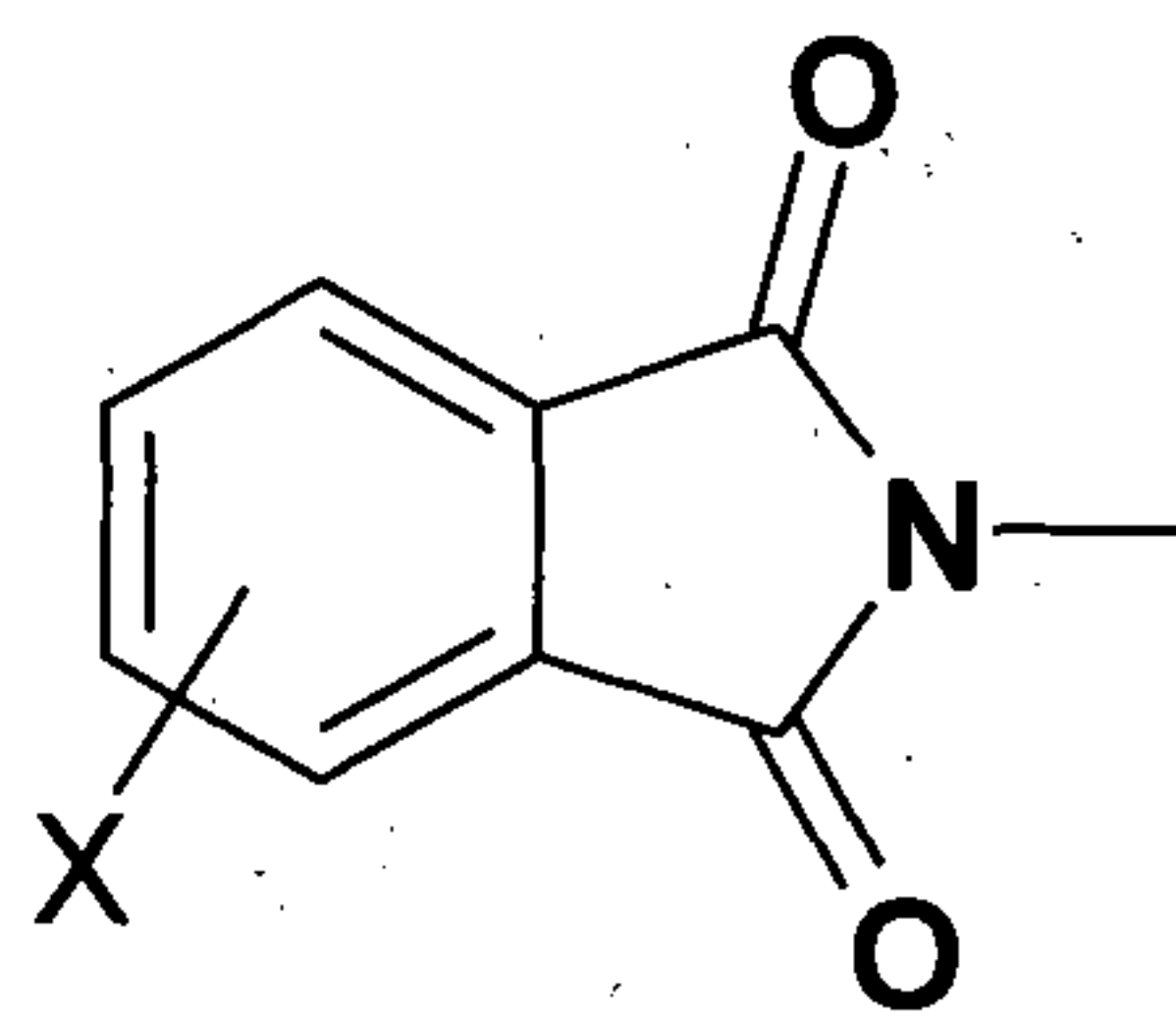
ii.) with a compound suitable to introduce group R⁵, where R⁵ represents



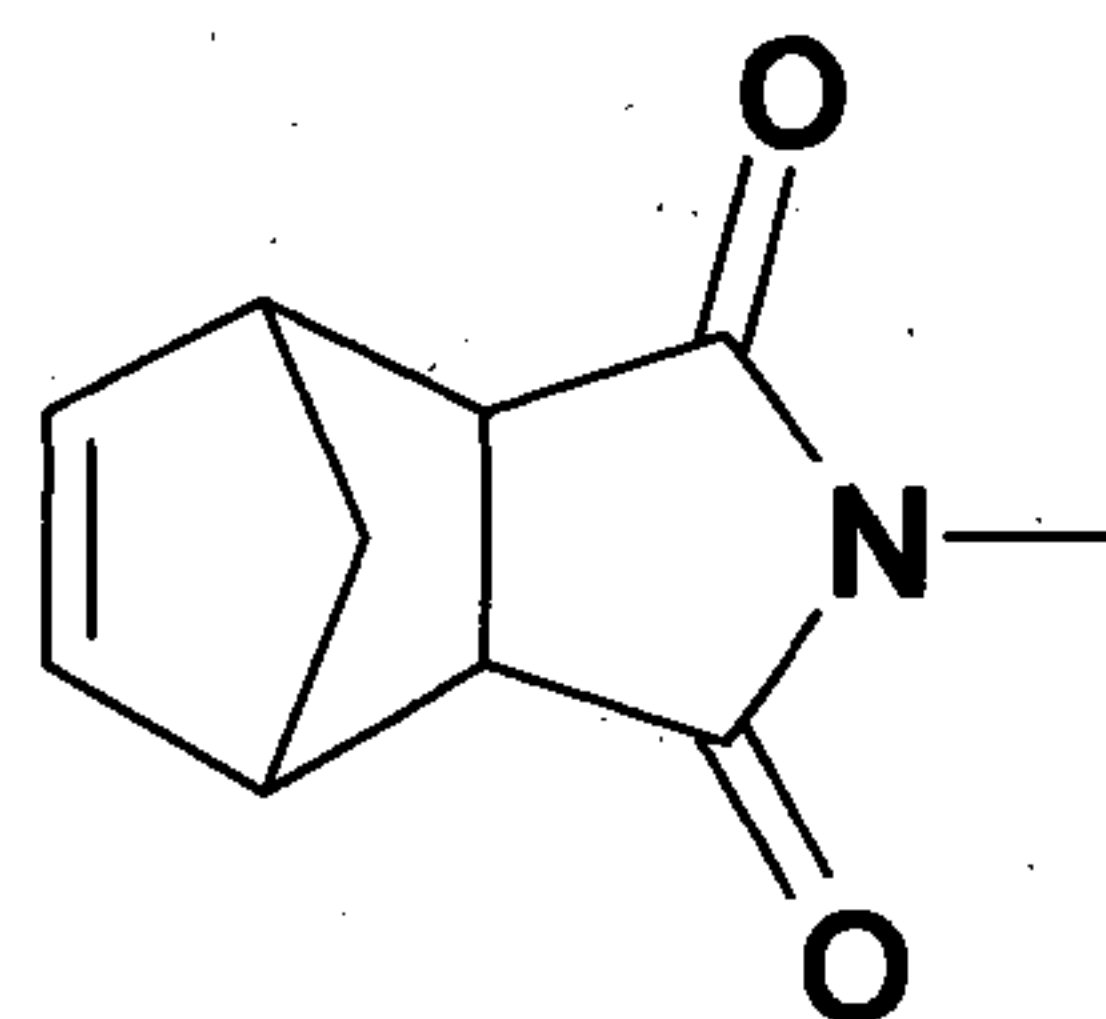
b.)



c.)



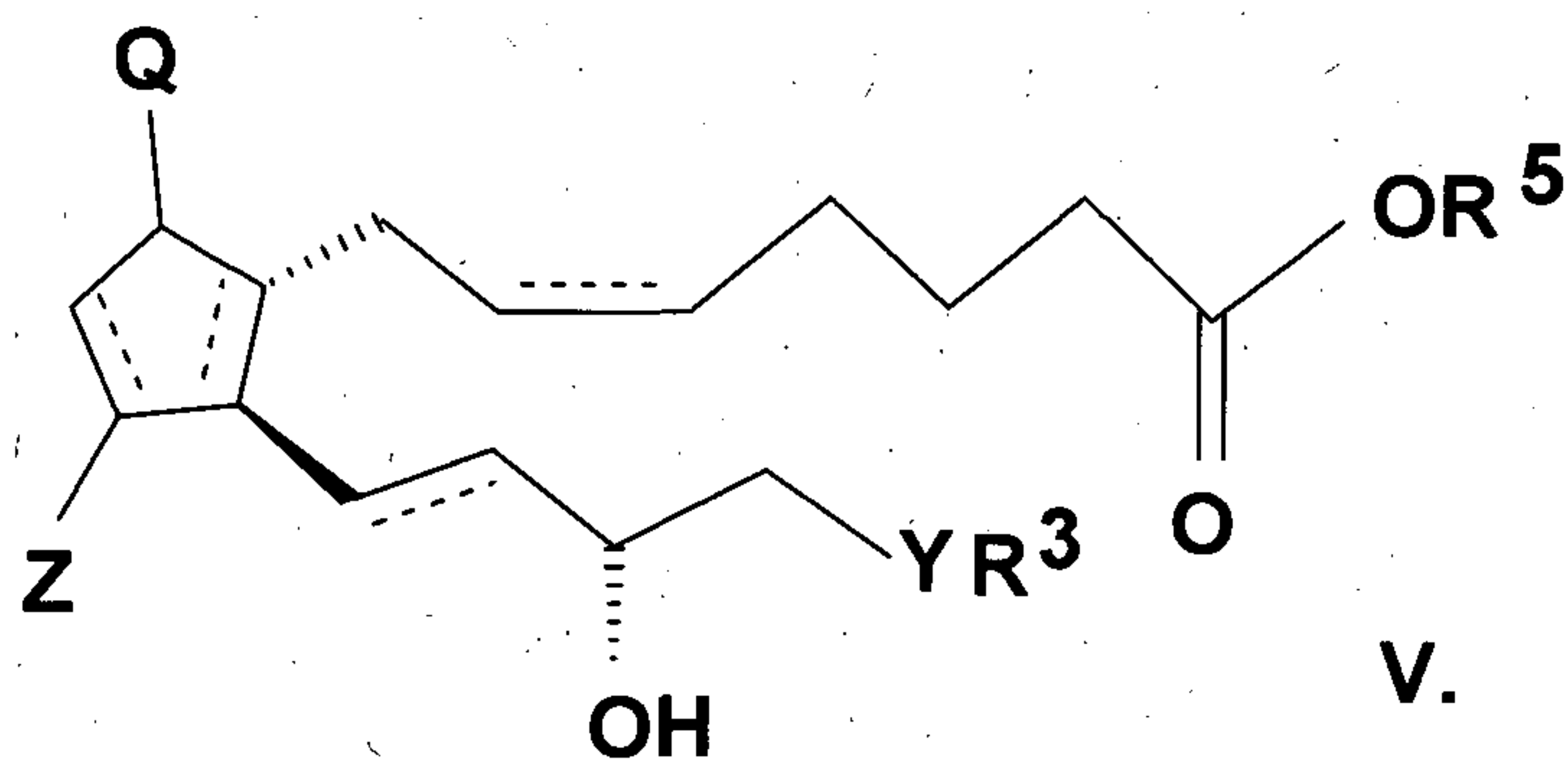
d.)



e.)

10

a group of formula b.), c.), d.) or e.), where (X) stands for halogen or hydrogen atom – and reacting the activated ester of the general formula (V), thus obtained

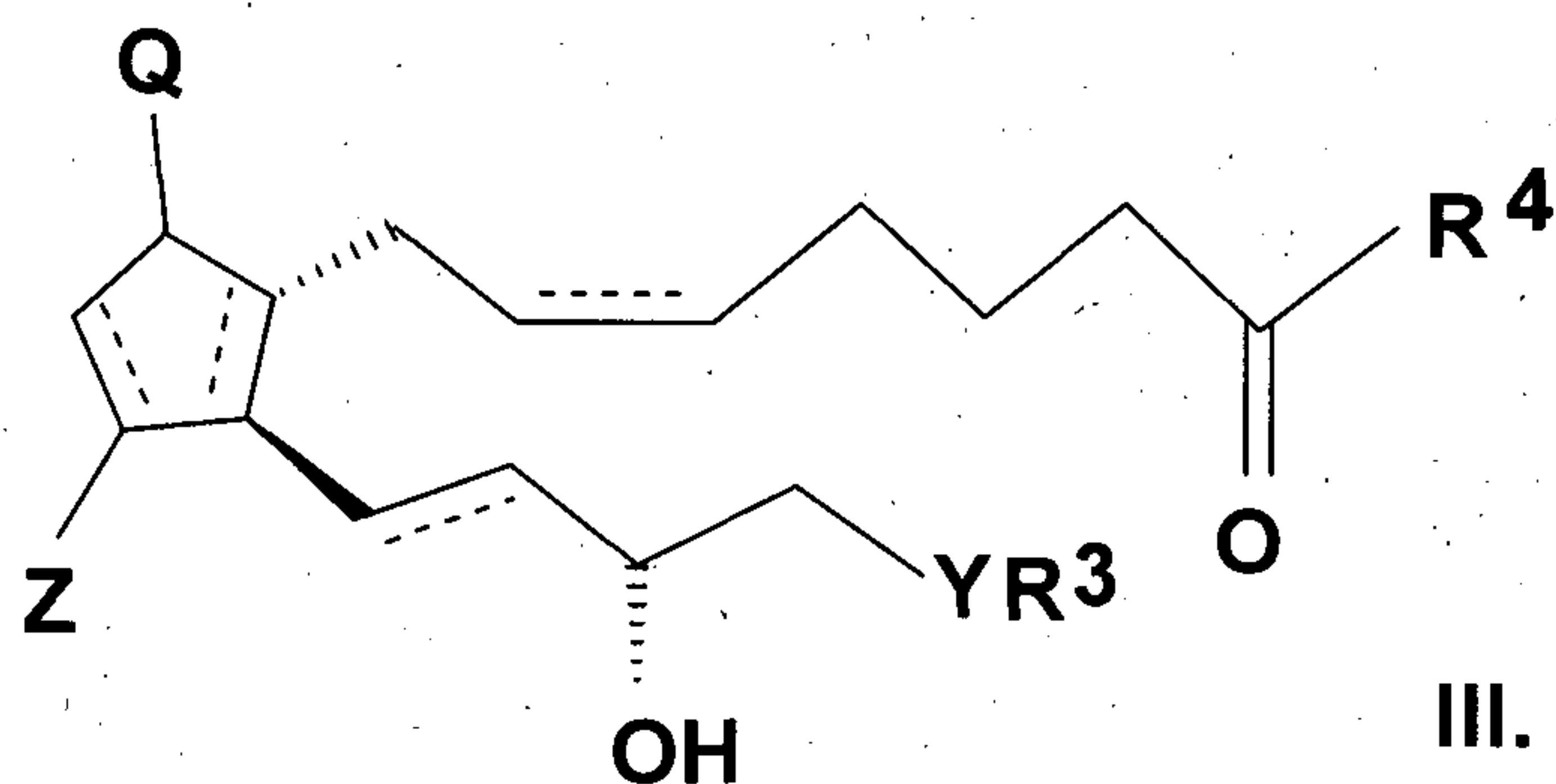


where the meanings of Q, Z, R³, R⁵, Y and n are as defined above, with an amine of the general formula (IV), where the meanings of R¹ and R² are as defined above, or

5

- iii.) with an amine of the general formula (IV), - where the meanings of R¹ and R² are as defined above - in the presence of 2-chloro-1,3-dimethylimidazolinium chloride and a base.

10 . 2.) The compounds of the general formula (III),



where in the formula

the bonds marked with dotted lines may be single or double bonds, in the case of double bonds at positions 5,6 and 13,14 they may be in cis or in trans orientation,

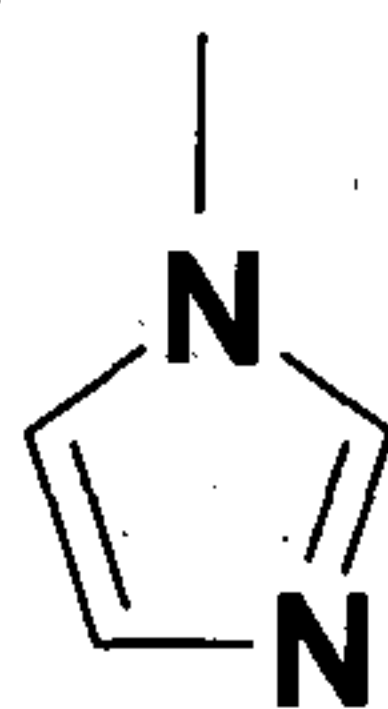
15 Q represents hydroxyl-group and Z represents hydroxyl- or oxo- group,

R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

Y represents $(CH_2)_n$ group or O atom or S atom, and $n=0-3$,

5 and

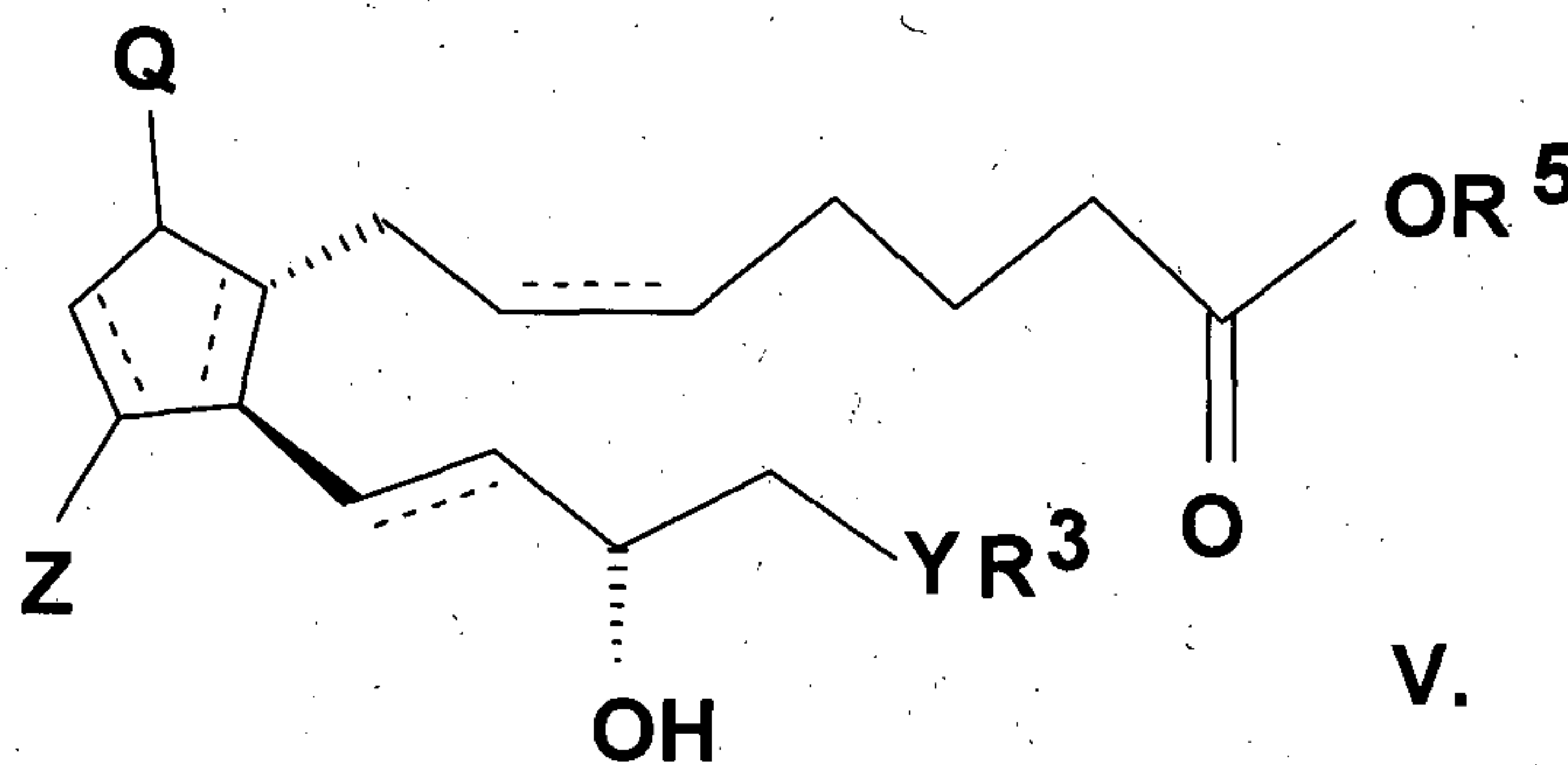
R^4 represents



a.)

the group of formula a.).

10 3.) The compounds of the general formula (V),



- where in the formula

the bonds marked with dotted lines may be single or double bonds, in the case of double bonds at positions 5,6 and 13,14 they may be in cis or in trans orientation,

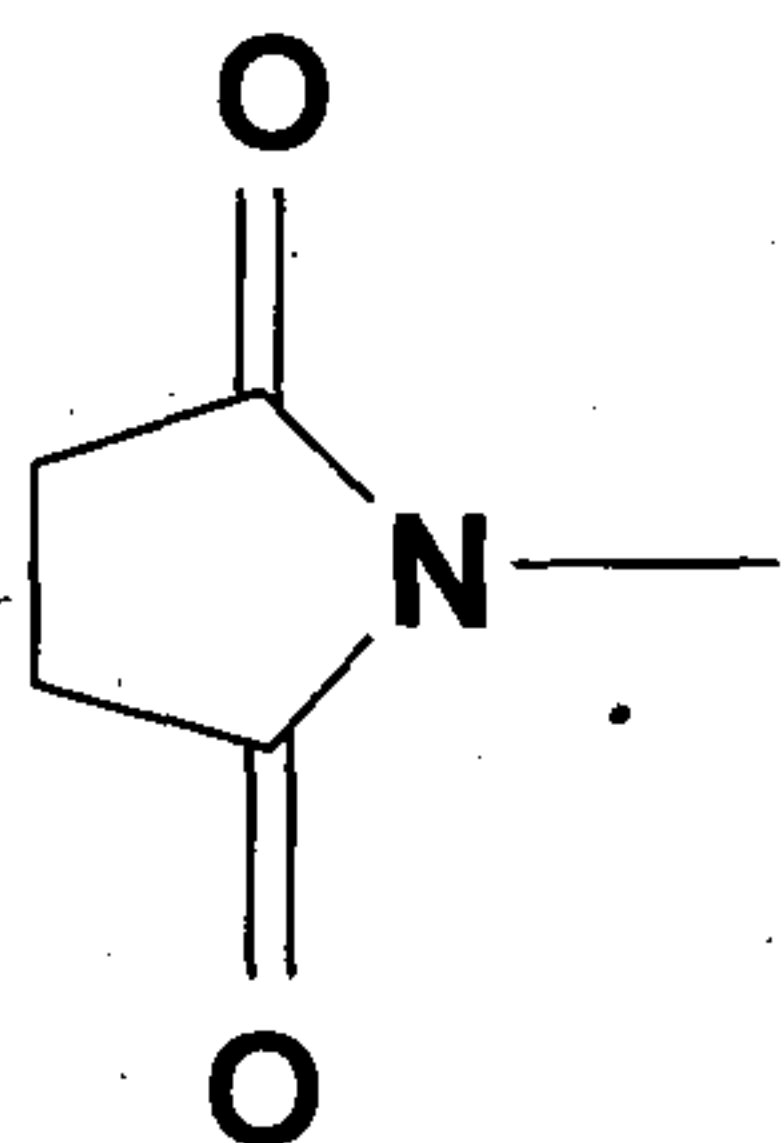
15 Q represents hydroxyl-group and Z represents hydroxyl- or oxo- group,

R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

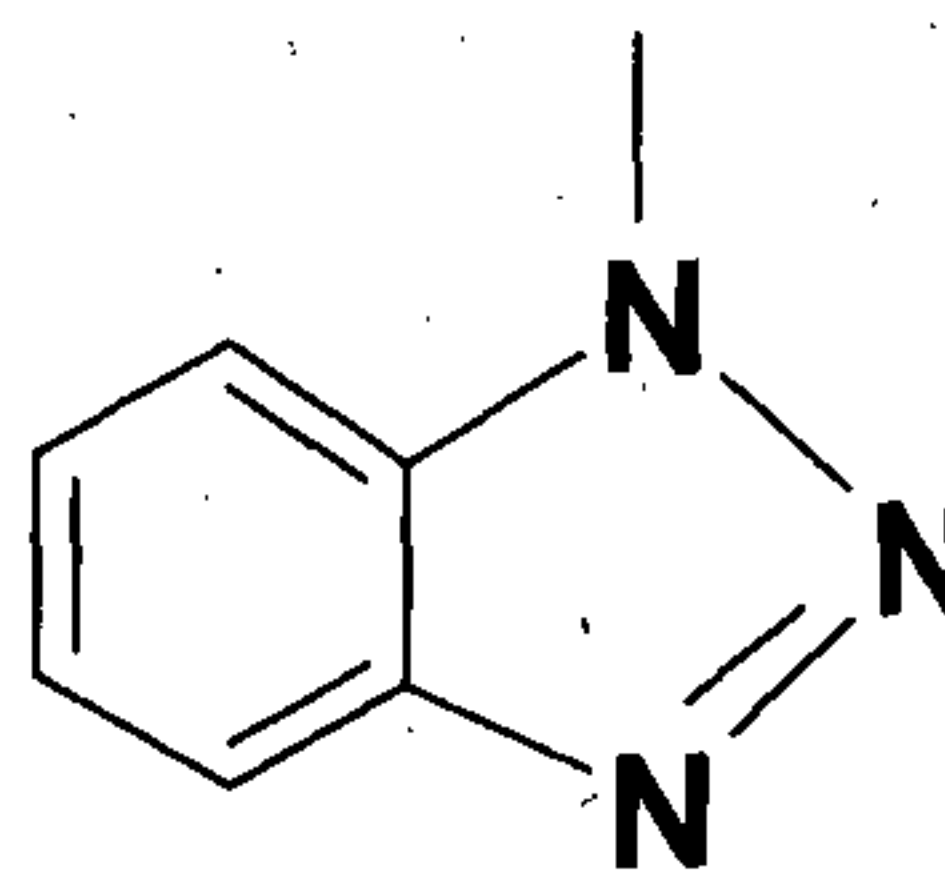
Y represents $(CH_2)_n$ group or O atom or S atom, and $n=0-3$,

and

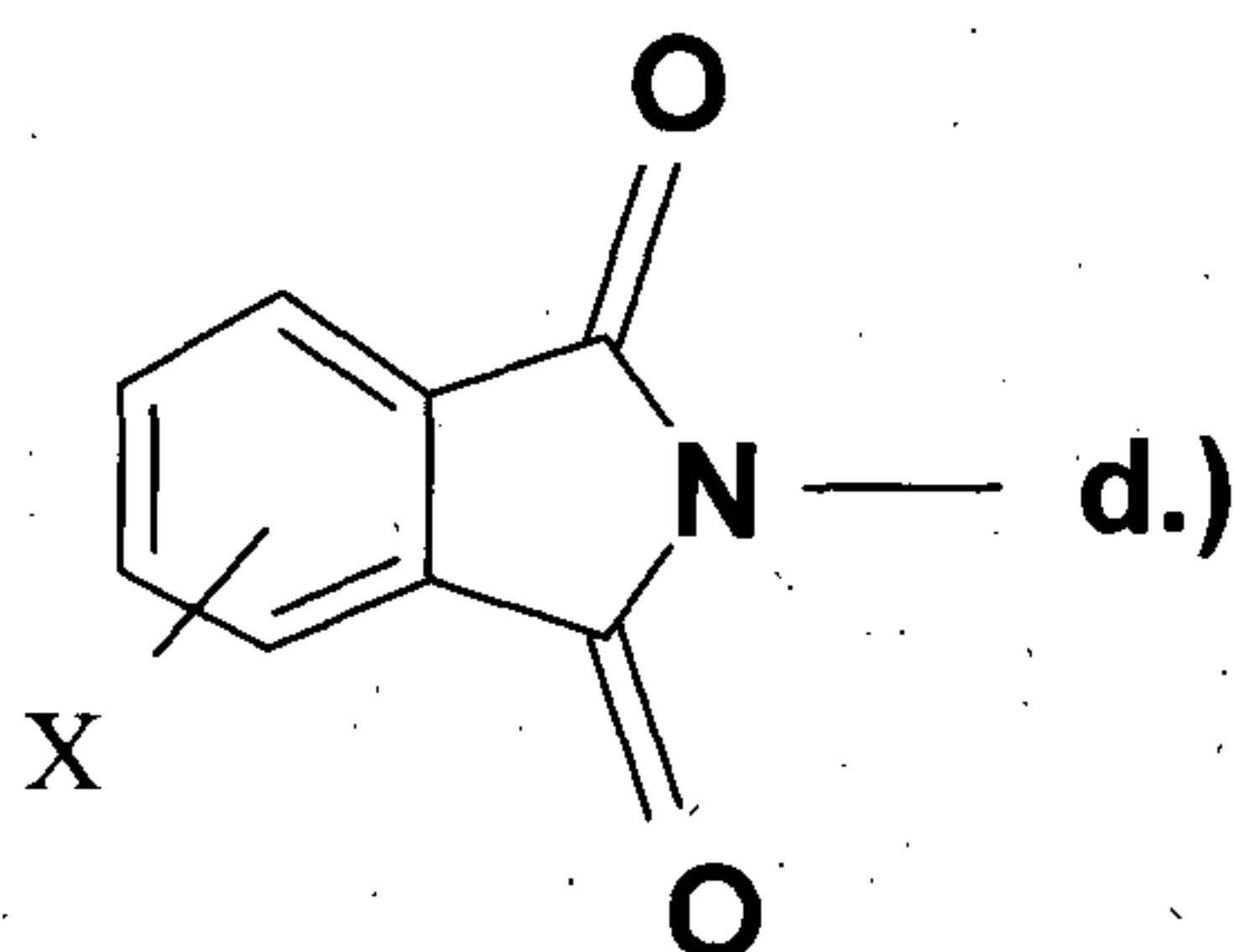
R^5 represents



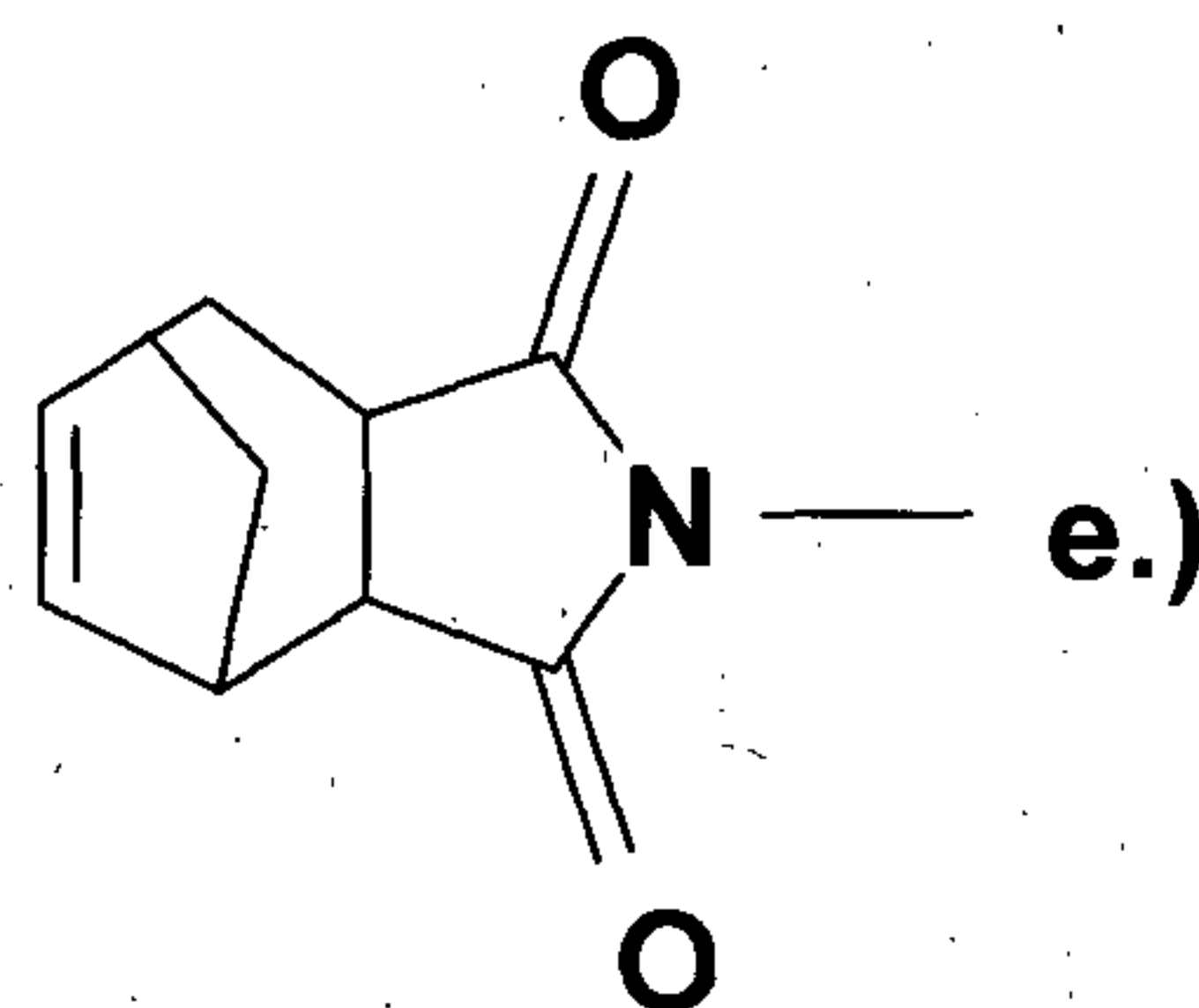
b.)



c.)



d.)



e.)

5 a group of formula b.), c.), d.) or e.), where X stands for halogen atom or hydrogen atom.

4.) Process according to method i.) of Claim 1., characterized in that the compound suitable to introduce the group R^4 , is 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole.

10

5.) Process according to method ii.) of Claim 1., characterized in that for the introduction of group R^5 , N-hydroxysuccinimide, N-hydroxyphthalimide, N-hydroxy-5-norben-endo-2,3-dicarboxamide, 1-hydroxybenzotriazole, (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate, N,N'-disuccinimidyl carbonate or N,N'-disuccinimidyl oxalate are used, in a given case in the presence of an activating agent.

15

6.) Process according to Claim 5., characterized in that the applied activating agent is N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide or 2-chloro-1,3-dimethylimidazolinium chloride.

5

7.) Process according to Claim 1., characterized in that the reaction is carried out in an ether-type, or aromatic, or polar-aprotic solvent, or in the mixture of them.

8.) Process according to Claim 1., characterized in that the introduction of group R^4 is performed at a temperature between 20-80°C, preferably at 70°C.

10

9.) Process according to method i.) of Claim 1., characterized in that the reaction of the compounds of formulae (III) and (IV) is carried out at a temperature between 20-80°C.

15

10.) Process according to method ii.) of Claim 1., characterized in that the reaction is carried out in an ether-type or aromatic or polar-aprotic solvent, or in the mixture of them.

11.) Process according to method ii.) of Claim 1., characterized in that the introduction of group R^5 is carried out at a temperature between 0-80°C.

20

12.) Process according to method ii.) of Claim 1., characterized in that the reaction of the compounds of formulae (V) and (IV) is carried out at a temperature between 20-80°C, preferably at room temperature.

13.) Process according to methods i.) or ii.) of Claim 1., characterized in that the activated carboxylic acid derivatives of formulae (III) or (V) are purified by crystallization and/or by chromatography.

5 14.) Process according to method iii.) of Claim 1., characterized in that the reaction is carried out in an ether-type or aromatic or polar-aprotic solvent, or in the mixture of them.

15.) Process according to Claims 7., 10. or 14., characterized in that tetrahydrofuran is used as solvent.

10

16.) Process according to method iii.) of Claim 1., characterized in that the reaction is carried out at a temperature between 0-70°C.

15

17.) Process according to method iii.) of Claim 1., characterized in that the applied base is N-methylmorpholine, N,N-diisopropylethylamine, 1,5-diazabicyclo[4,3,0]non-5-ene or 1,8-diazabicyclo[5,4,0]undec-7-ene.

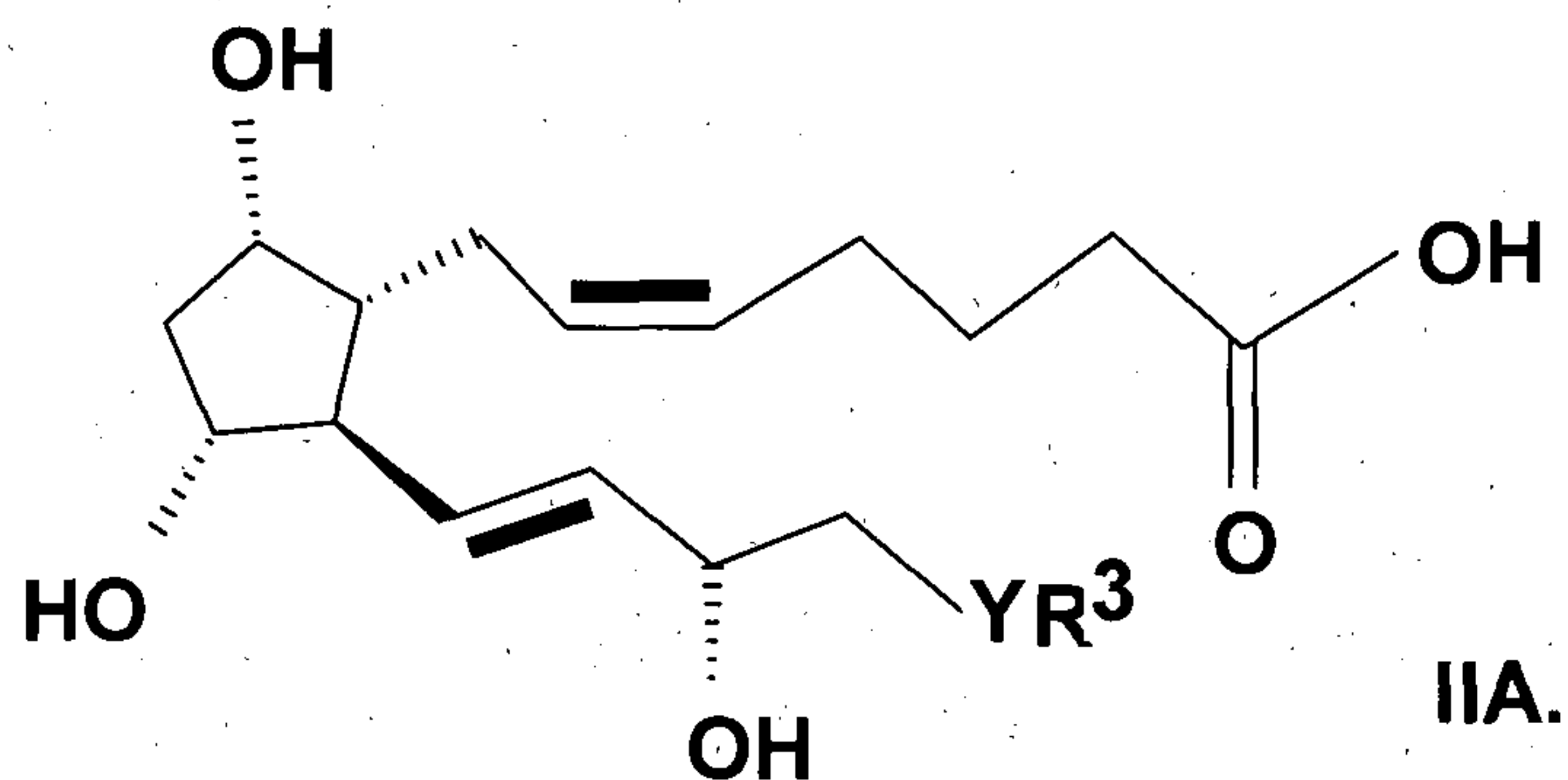
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18.) Process according to Claim 1., characterized in that the applied base of formula (IV) is ethylamine.

19.) Process according to methods i., ii or iii.) of Claim 1., characterized in that the reaction is carried out under „one pot” conditions.

20.) Process for the preparation of the compounds of the general formula (IIA)

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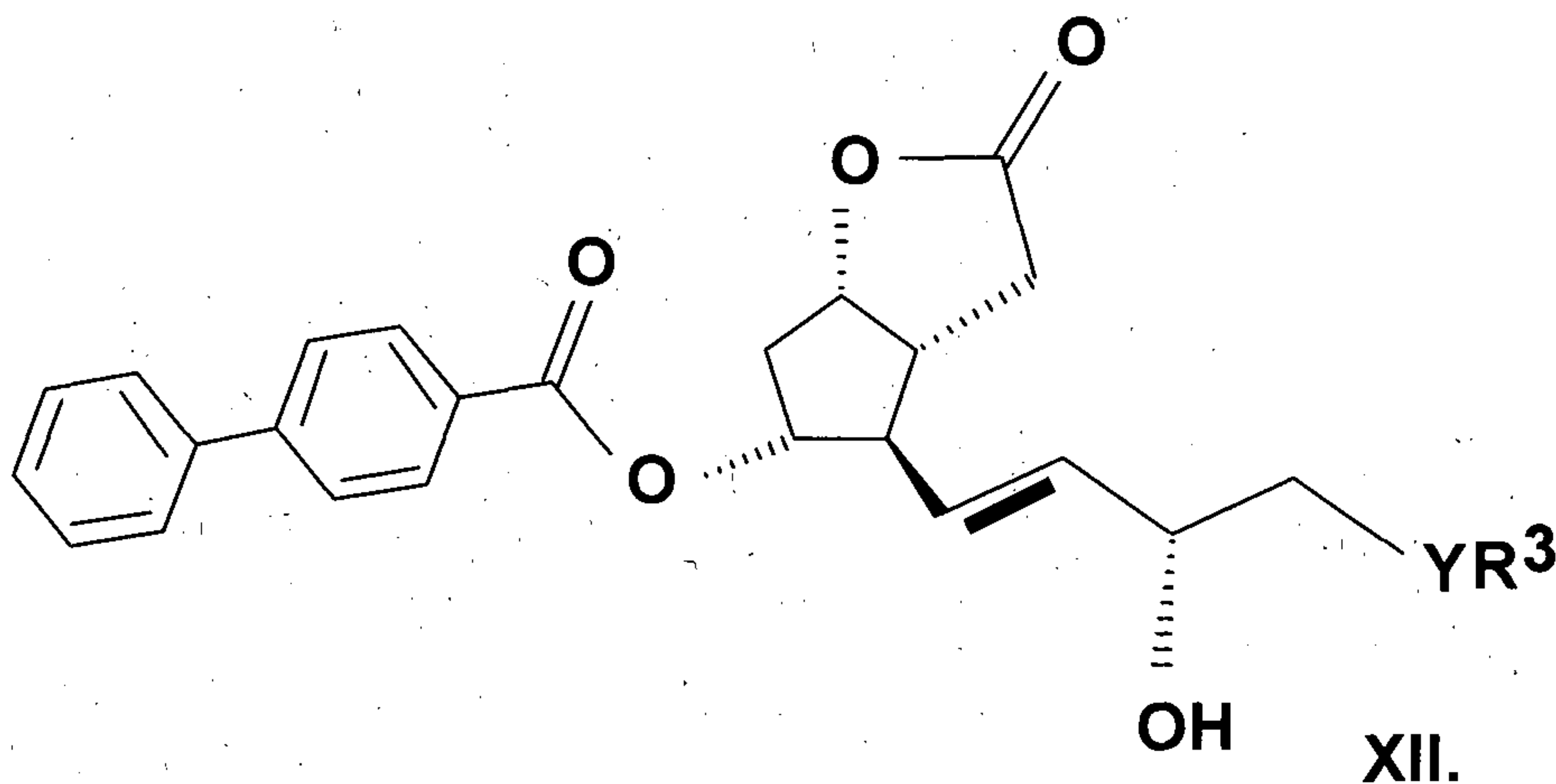


- where in the formula

R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

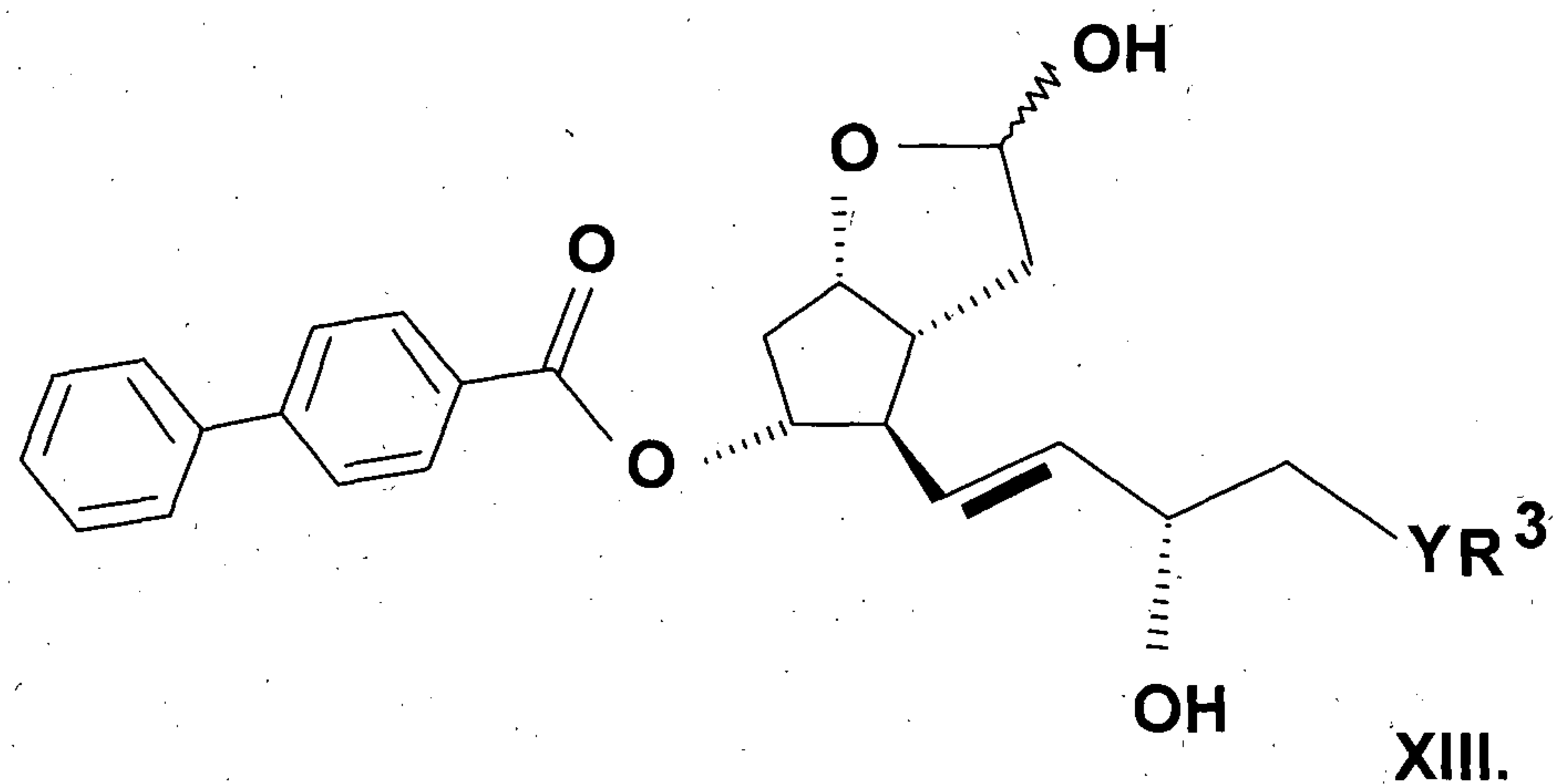
Y represents $(CH_2)_n$ group or O atom or S atom, and $n=0-3$,

characterized in that, a lactondiol of the general formula (XII),



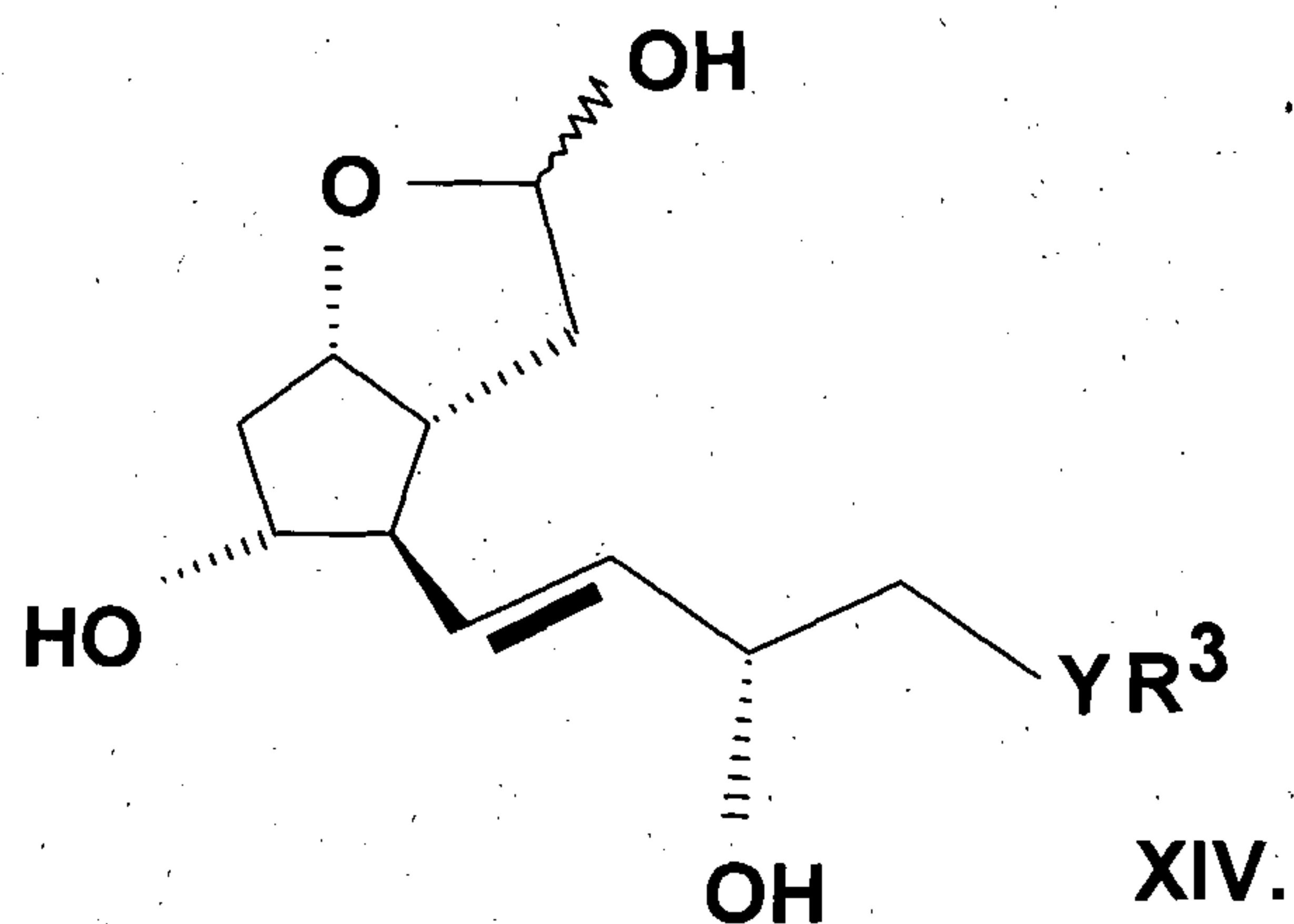
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where the meanings of R^3 , Y and n are as defined above, is reduced into the lactondiol of the general formula (XIII)



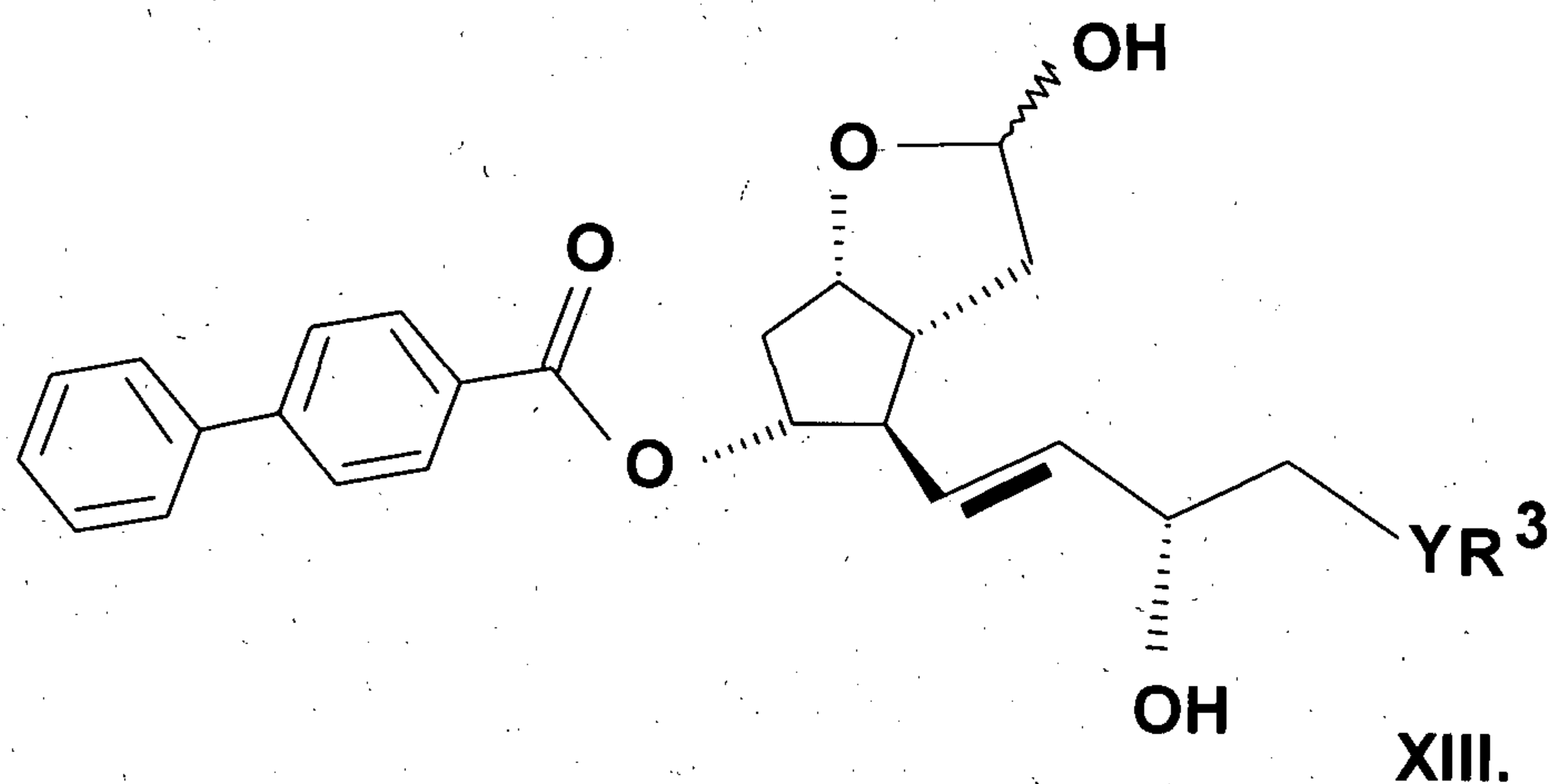
where the meanings of R^3 , Y and n are as defined above,

the protecting group of the compound of formula (XIII) is removed, and the resulting compound of the general formula (XIV),



where the meanings of R^3 , Y and n are as defined above, is transformed by Wittig reaction into the compound of the general formula (IIA).

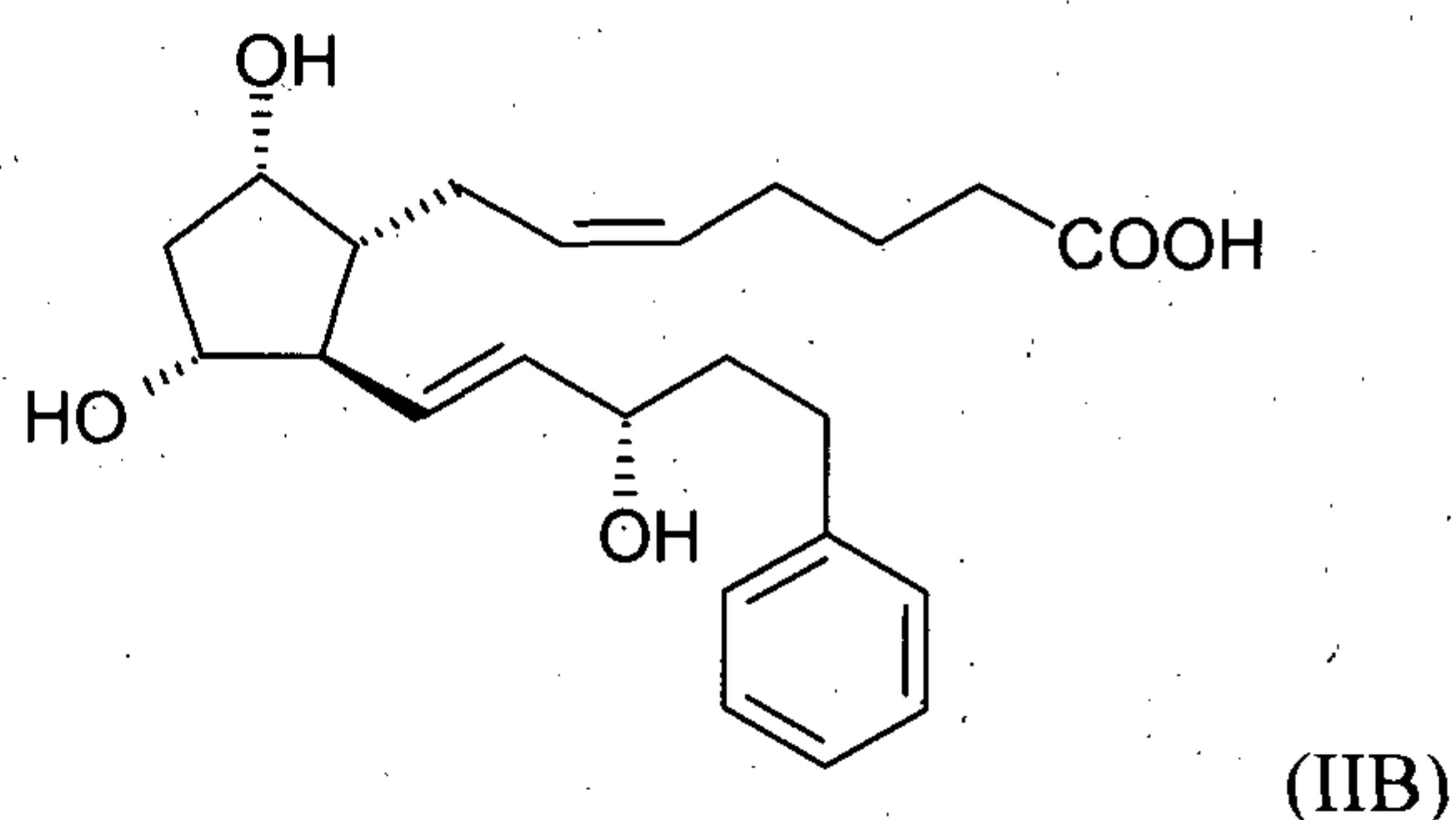
21.) The lactonatriol of the general formula (XIII),



where R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group,

5 Y represents $(CH_2)_n$ group or O atom or S atom, and $n=0-3$.

22.) Compound of the formula (IIB) in crystalline form



10

23.) Process for the preparation of the compound of the formula (IIB) in crystalline form, characterized in that to a mixture containing the compound of the formula (IIB) a mixture of ester type and ether type solvents is added.

24.) Process according to Claim 23., characterized in that dimethyl ether, diethyl ether, diisopropyl ether, preferably diethyl-ether and diisopropyl ether are used as ether-type solvents.

5 25.) Process according to Claim 23., characterized in that ethyl-acetate, methyl-acetate, isopropyl-acetate, preferably isopropyl-acetate are used as ester-type solvents.

26.) Process according to Claims 23., characterized in that crystallisation is performed between (-)30°C and 30°C, preferably between 0-25°C.

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27.) Process according to Claims 23., characterized in that the suspension of crystals is stirred 1-24 hours, preferably 8 hours.

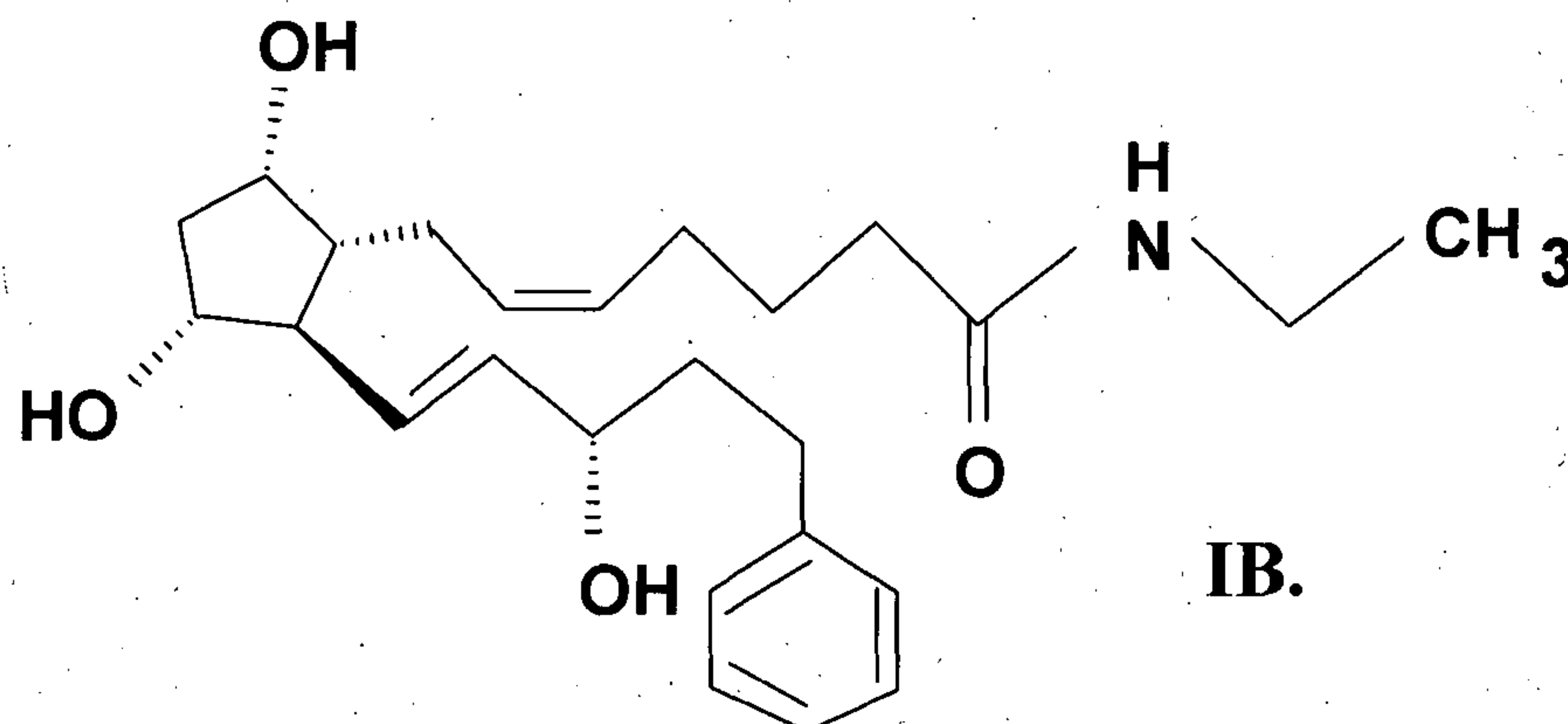
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28.) Process according to Claims 23., characterized by that the crystal suspension is filtered and washed with ether type solvent, preferably with diisopropyl ether.

29.) Process according to Claims 23., characterized in that the filtered crystals are dried under vacuum between 25-50°C, preferably at 35-40°C.

20

30.) Process for the preparation of crystal form II. of bimatoprost of formula (IB),



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characterized in that to a reaction mixture containing bimatoprost, after work-up and evaporation, or to any crystalline or non-crystalline form of bimatoprost or to their mixtures of any ratio, calculated amount of ether-type or protic solvent is added, if desired it is exposed to mechanical effect, and then dried and homogenized.

5

31.) Crystal form II. prepared by the process according to claim 30., characterized in that its melting point is between 72-78°C.

32.) Crystal form II. prepared by the process according to claim 30., characterized in that on the basis of DSC investigation the endothermic peak is between 72-79°C and its melting heat is higher than 75 J/g.

15

33.) Process according to Claim 30., characterized in that 20-60 mass% amount, preferably 35 mass% amount of protic solvent is applied.

34.) Process according to Claim 30., characterized in that alcohols and/or water are used as protic solvents.

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35.) Process according to Claim 34., characterized in that methanol or ethanol is used as alcohol.

36.) Process according to Claim 34., characterized in that water is used as protic solvent.

25

37.) Process according to Claim 30., characterized in that 2000-8000 mass% amount of ether-type solvent is applied.

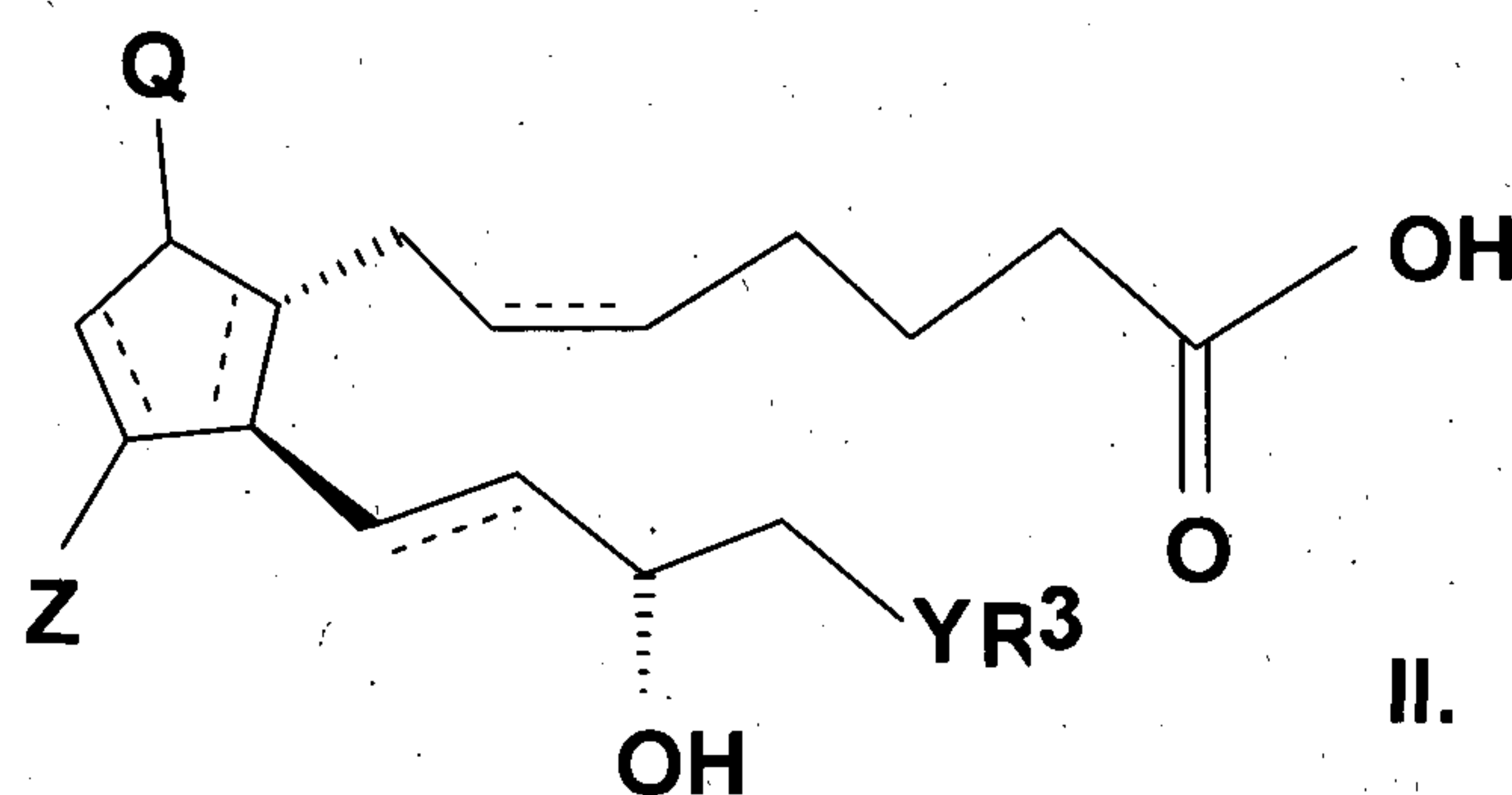
38.) Process according to Claim 30., characterized in that dimethyl ether, diethyl ether, diisopropyl ether are used as ether-type solvents.

39.) Process according to Claim 30., characterized in that stirring or scratching, or both
5 are applied as mechanical effect.

40.) Process according to Claim 30., characterized in that the added solvent is removed
by drying.

10 41.) Process according to Claims 33 and 40., characterized in that drying is performed
in vacuum, at a temperature between (-) 60°C and 70°C.

42.) Process according to Claims 37 and 40., characterized in that drying is performed at
low temperature, preferably between 0-(-)50°C, by passing through nitrogen gas.



where in the formula

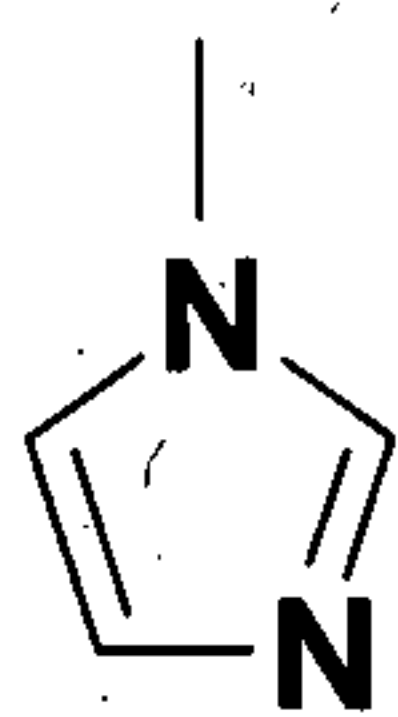
the bonds marked with dotted lines may be single or double bonds, in the case of double bonds at positions 5,6 and 13,14 they may be in cis or in trans orientation,

5 Q stands for a hydroxyl-group and Z stands for a hydroxyl- or oxo-group,

R^3 represents a straight or branched, saturated or unsaturated C_{4-6} hydrocarbon group, or a C_{4-10} alkylcycloalkyl- or cycloalkyl- group, or an optionally with alkyl group or halogen atom substituted phenyl-, C_{7-10} alkylaryl- or hetaryl- group, Y represents $(CH_2)_n$ group or O atom or S atom, and where $n=0-3$,

10 is reacted

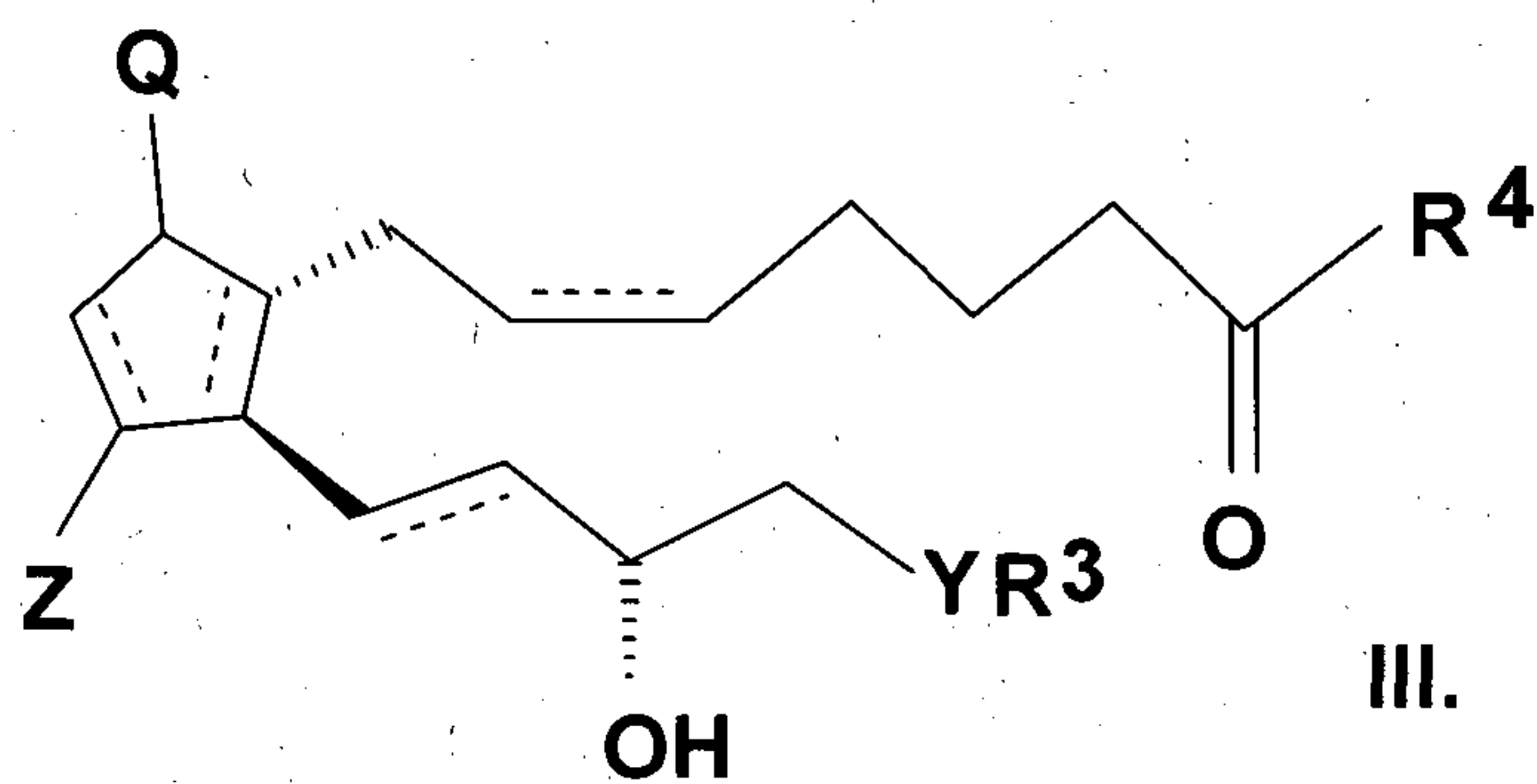
i) with a compound suitable to introduce the group R^4 , where R^4 represents



a.)

the group of formula a.),

and the resulting amide of the general formula (III),



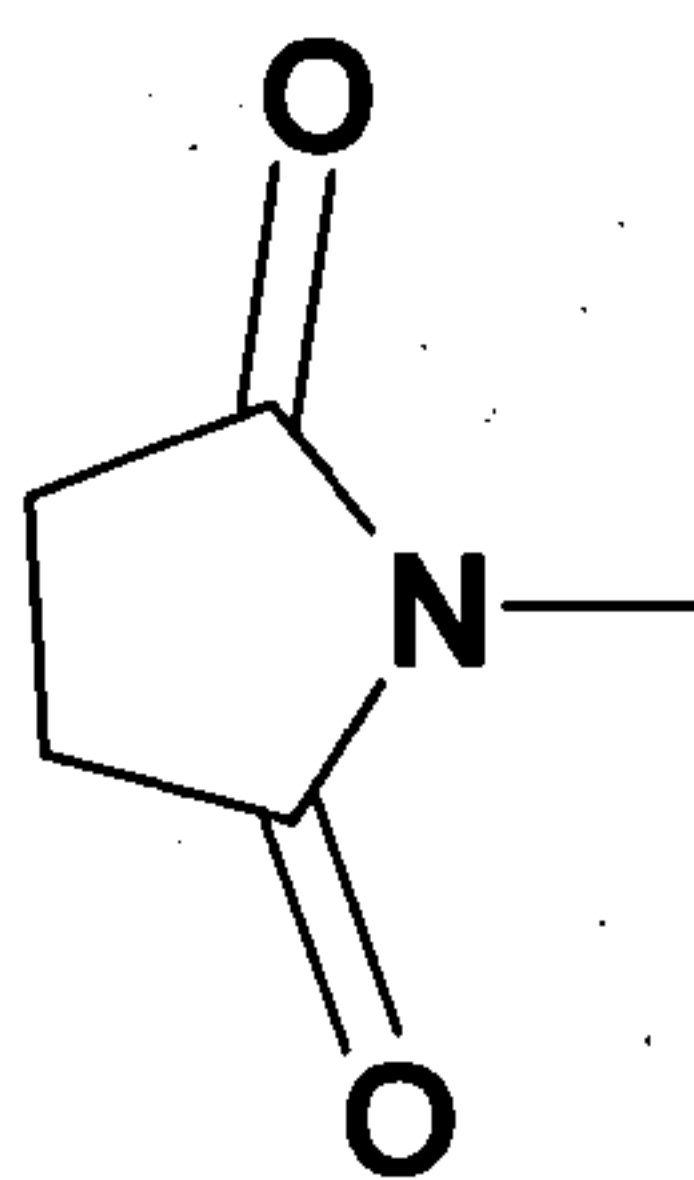
where the meanings of R^3 , R^4 , Y and n are as defined above, is reacted with an amine of the general formula (IV),



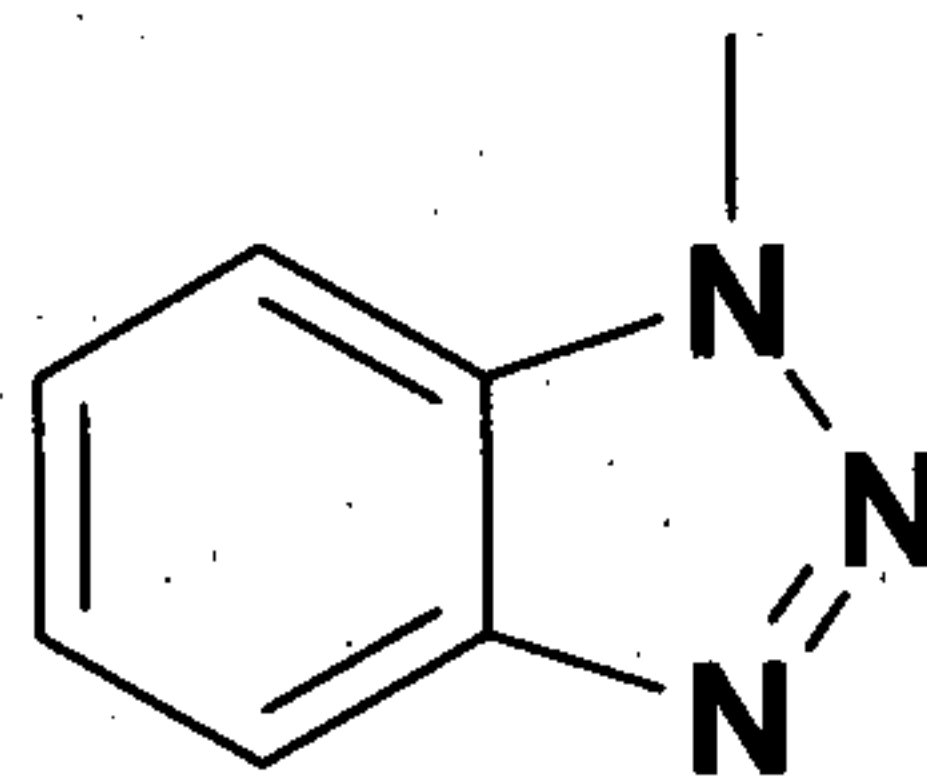
- where the meanings of R^1 and R^2 are defined above, or

ii) with a compound suitable to introduce the group R^5 – where R^5 represents

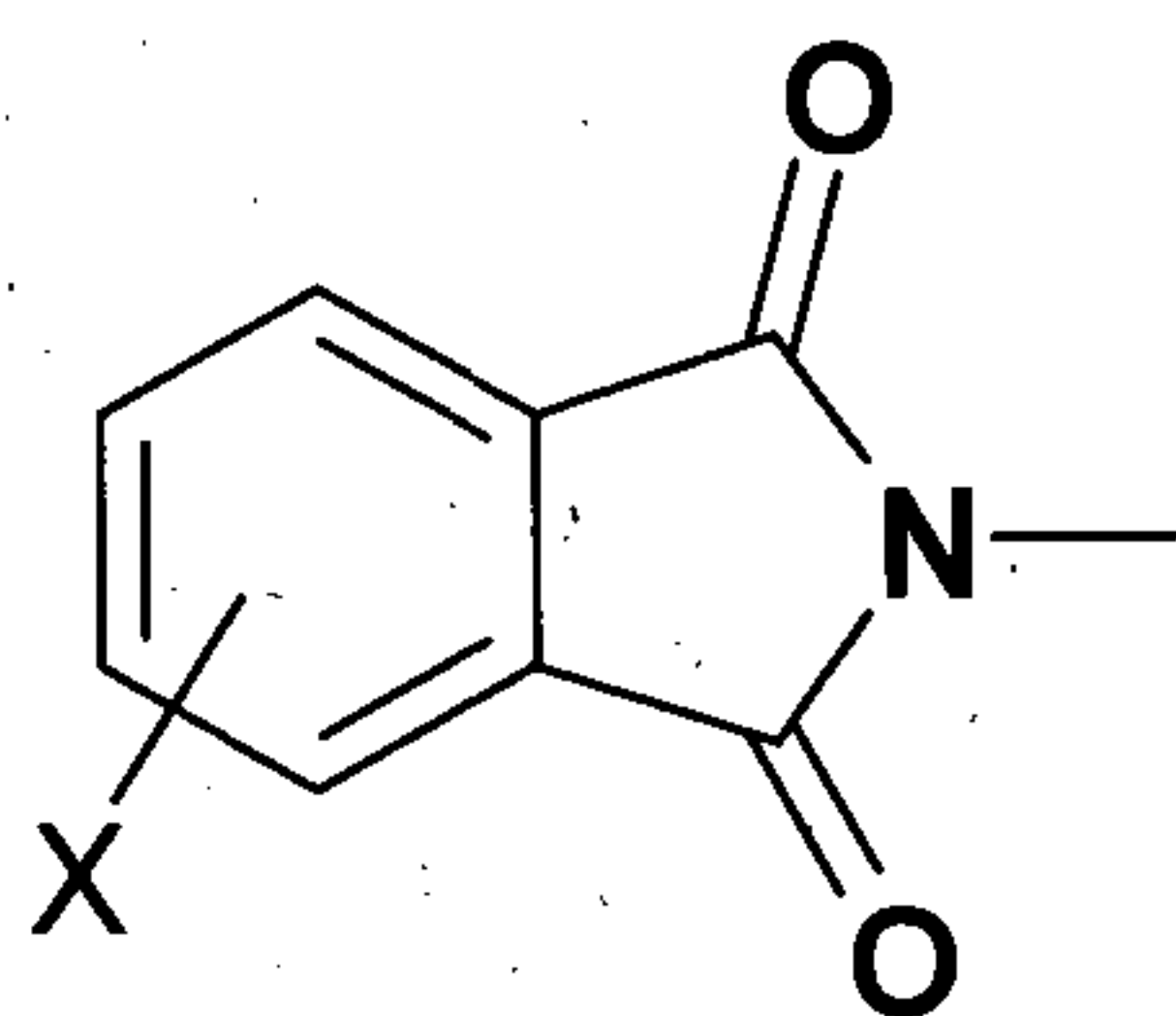
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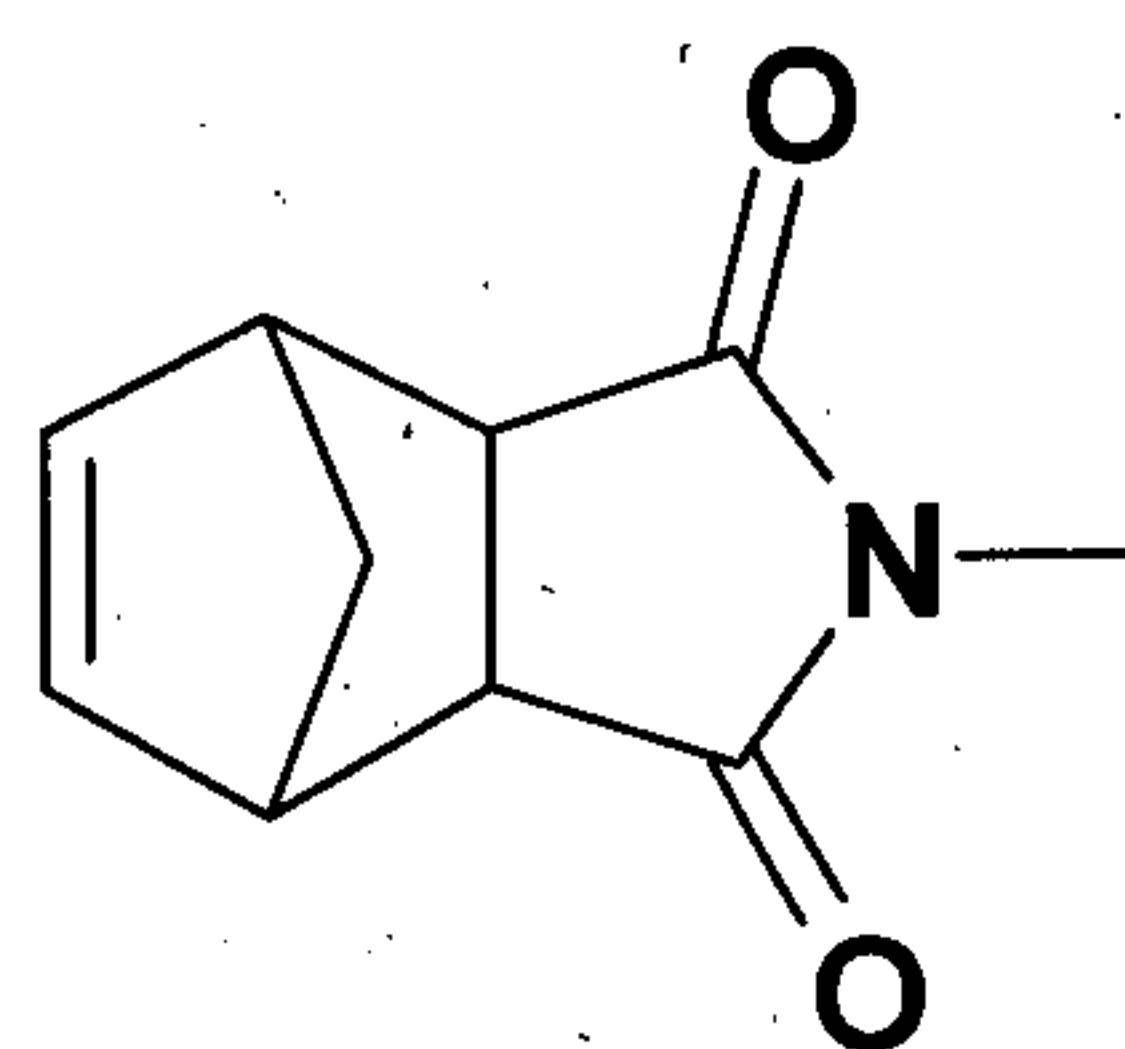
b.)



c.)

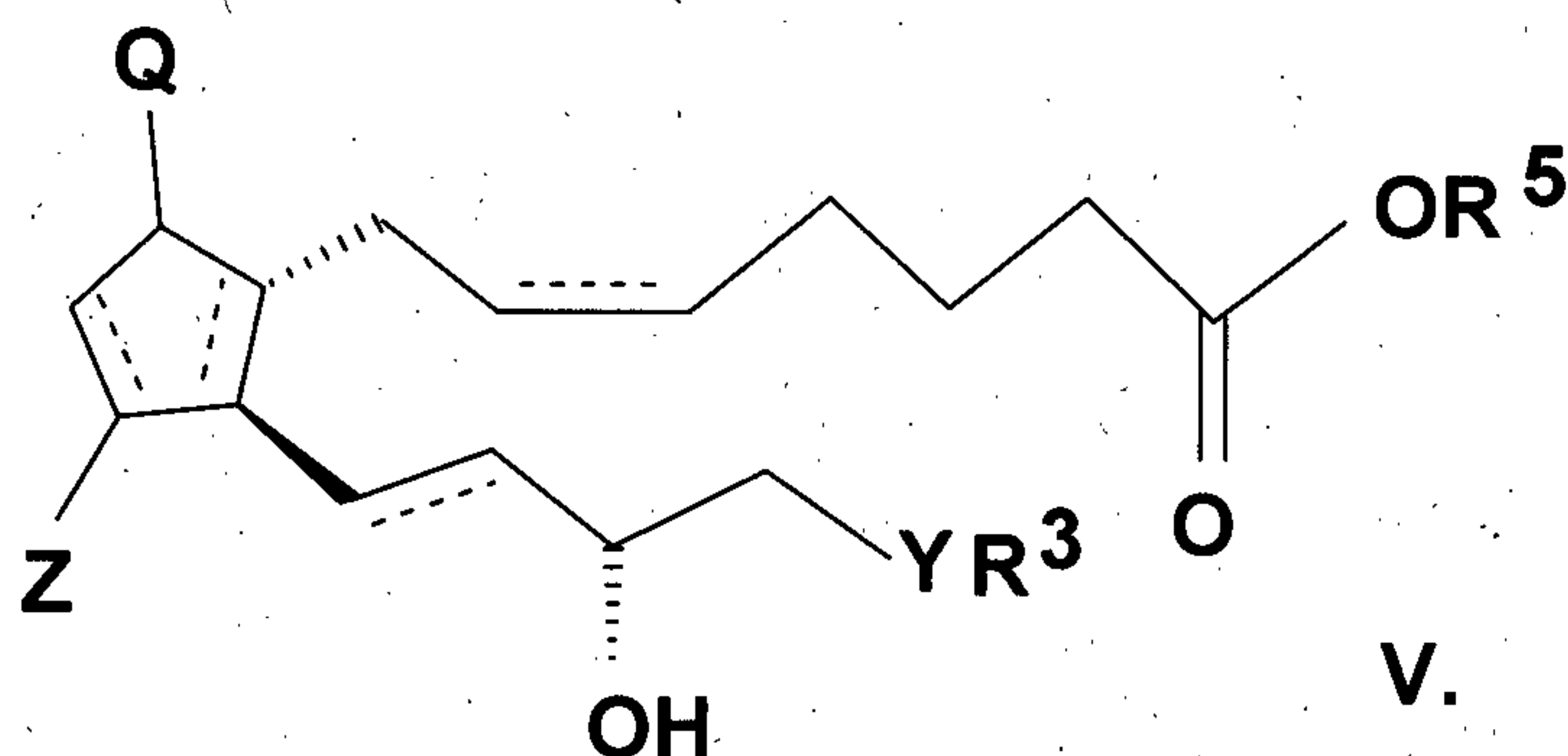


d.)



e.)

a group of formula b.), c.), d.) or e.), where (X) stands for halogen atom or hydrogen atom, and the resulting activated ester of the general formula (V),

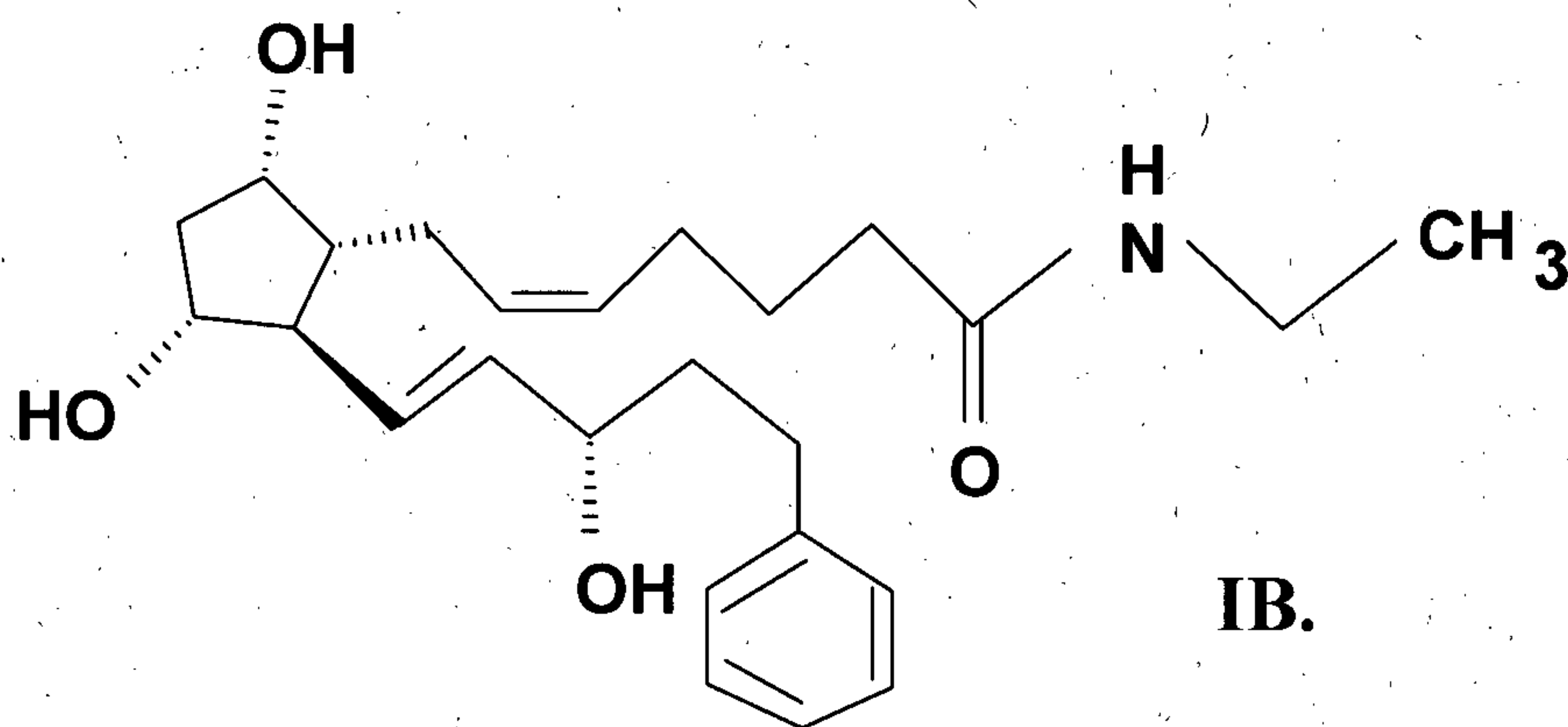


where the meanings of R^3 , R^5 , Y and n are as defined above- is reacted

with an amine of the general formula (IV), or

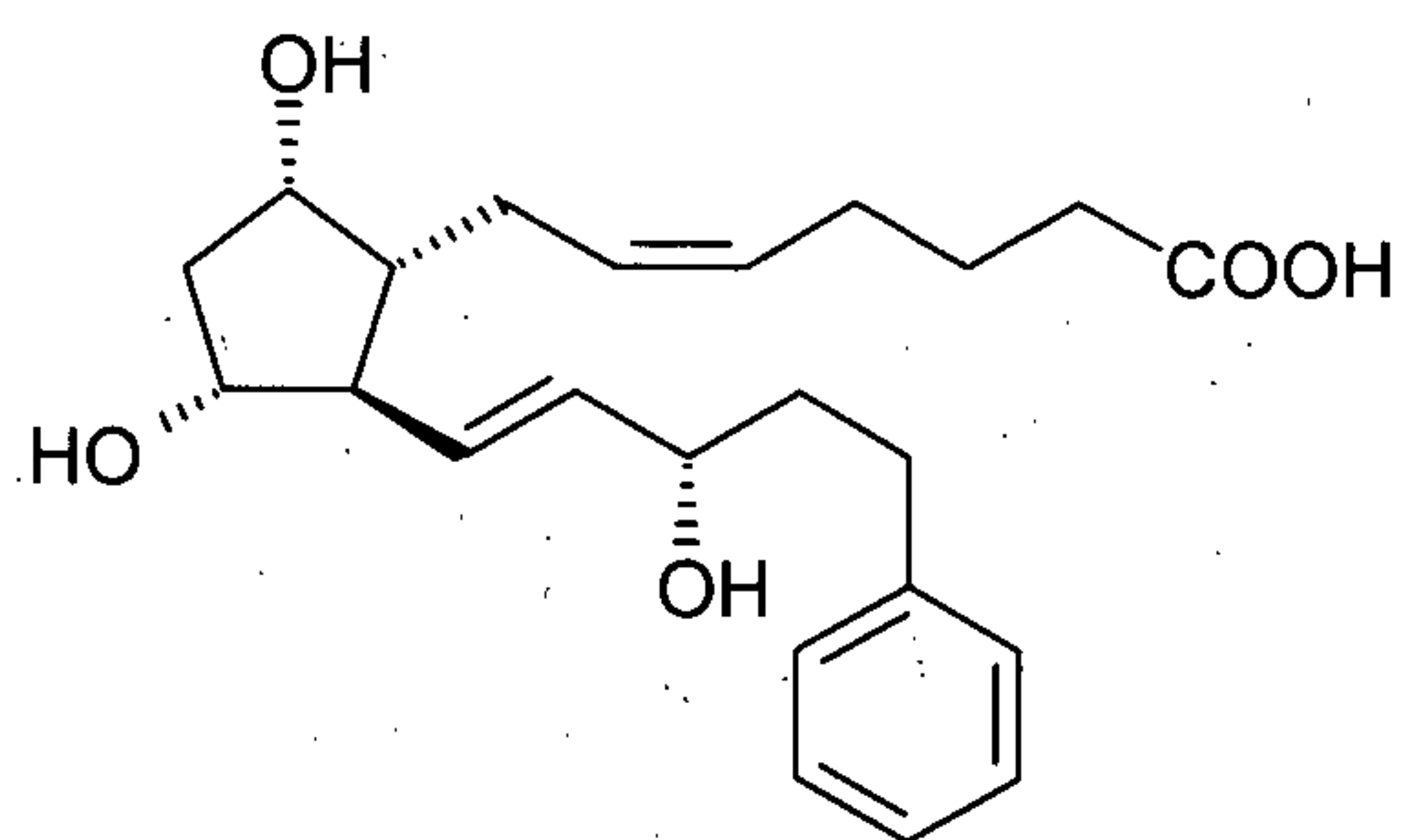
- iii.) with an amine of the general formula (IV) - where the meanings of R^1 and R^2 are as defined above- in the presence of 2-chloro-1,3-dimethylimidazolinium chloride and a base.

Further embodiment of our invention is a process for the preparation of a high melting crystal form II of bimatoprost of the formula (IB).



Further embodiment of invention is a process for the preparation of a compound of the formula (IIB) in crystalline form.

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(IIB)

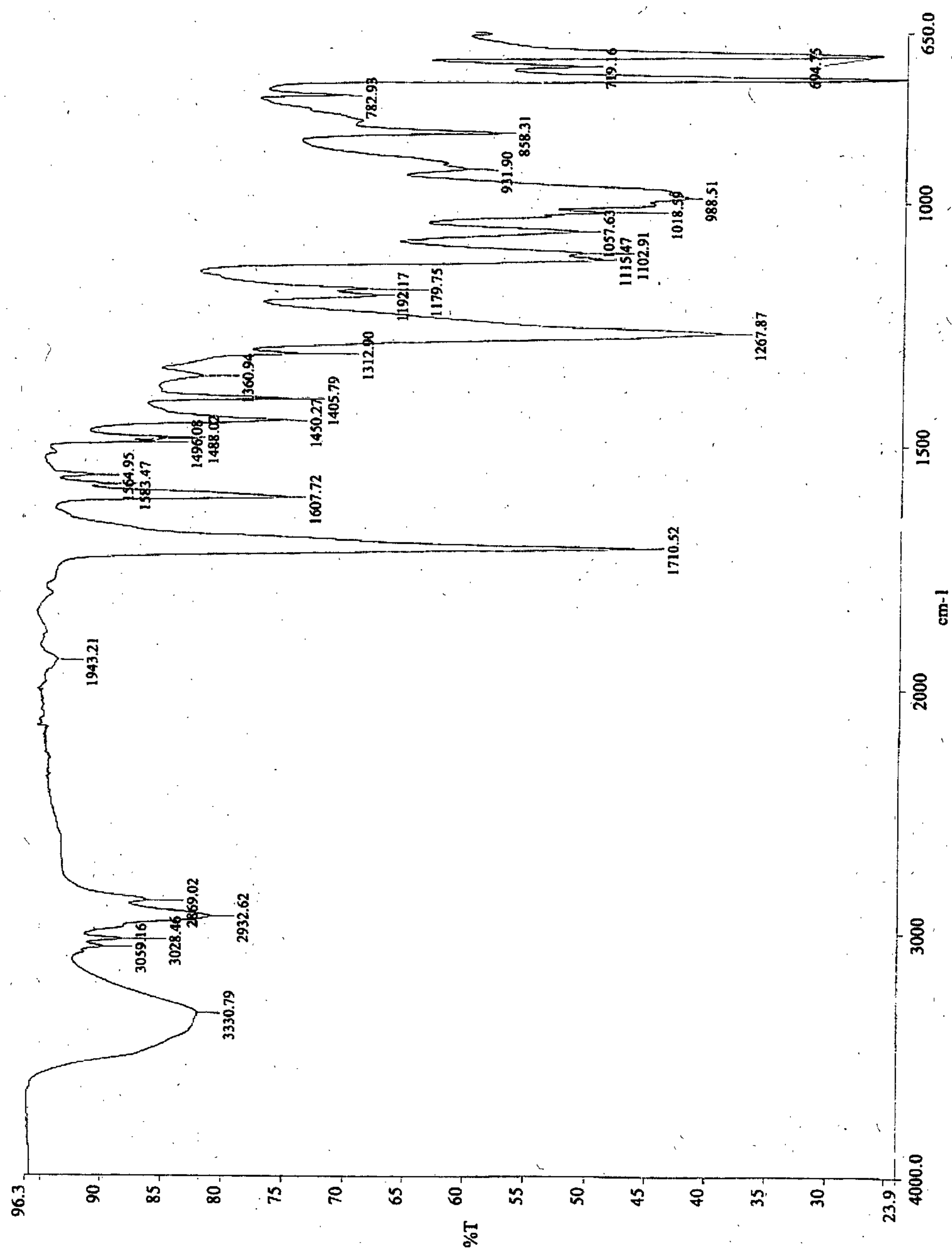


Figure I

IR spectrum of the lactoltriol of example 1a.

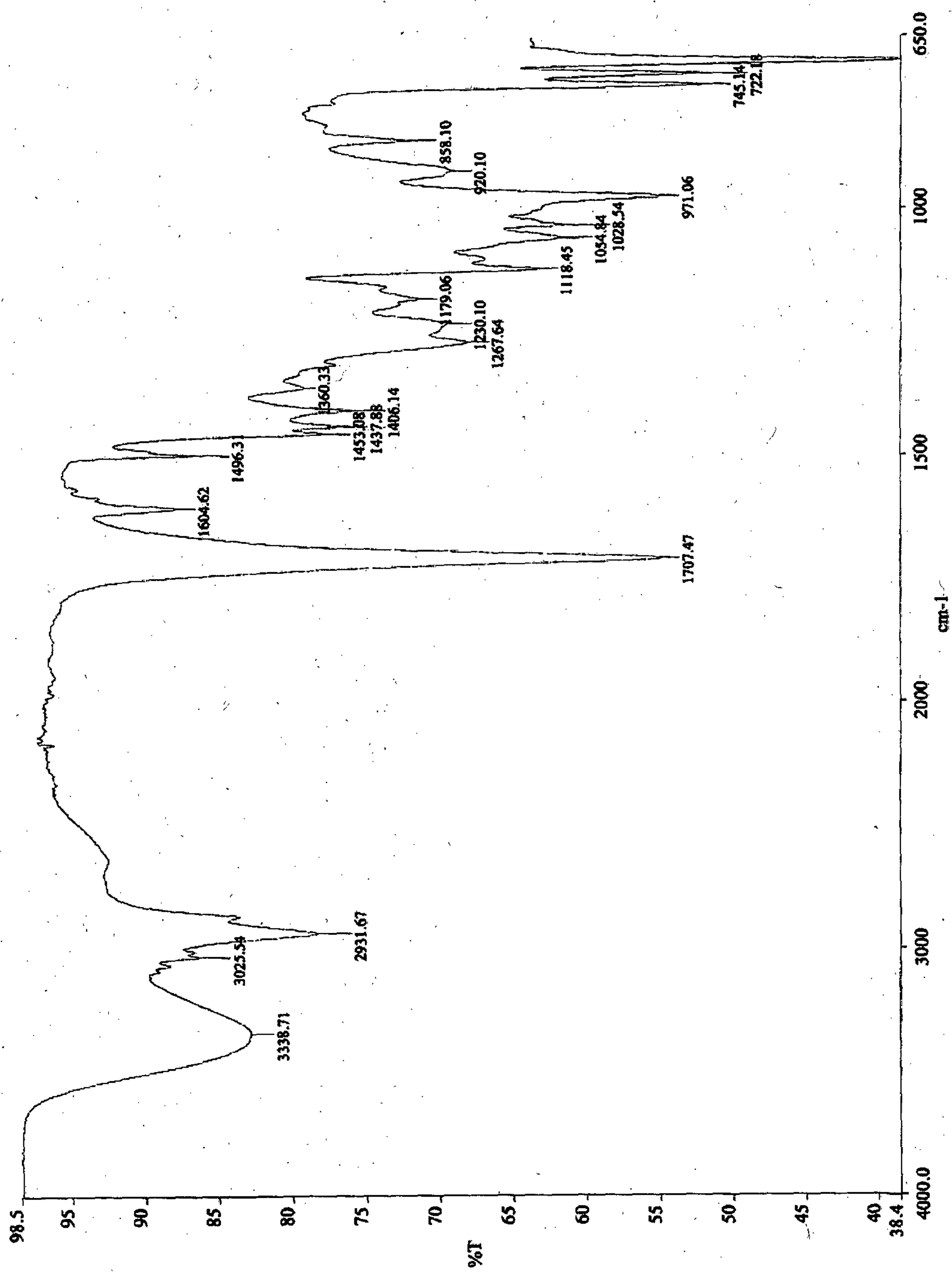


Figure II

IR spectrum of Bimatoprost acid of example 1/c1.

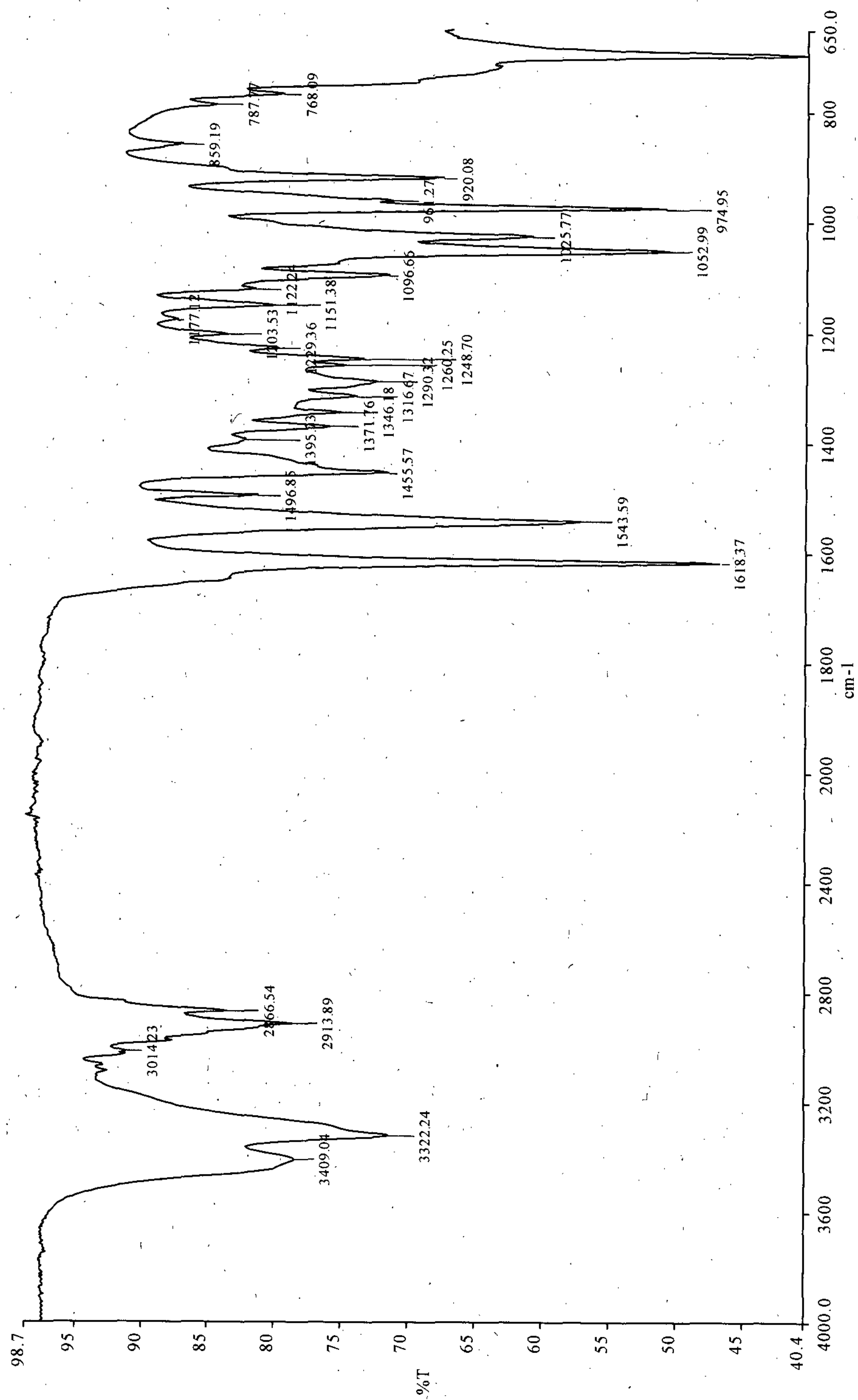


Figure III.

IR spectrum of form I. of example 14/a.

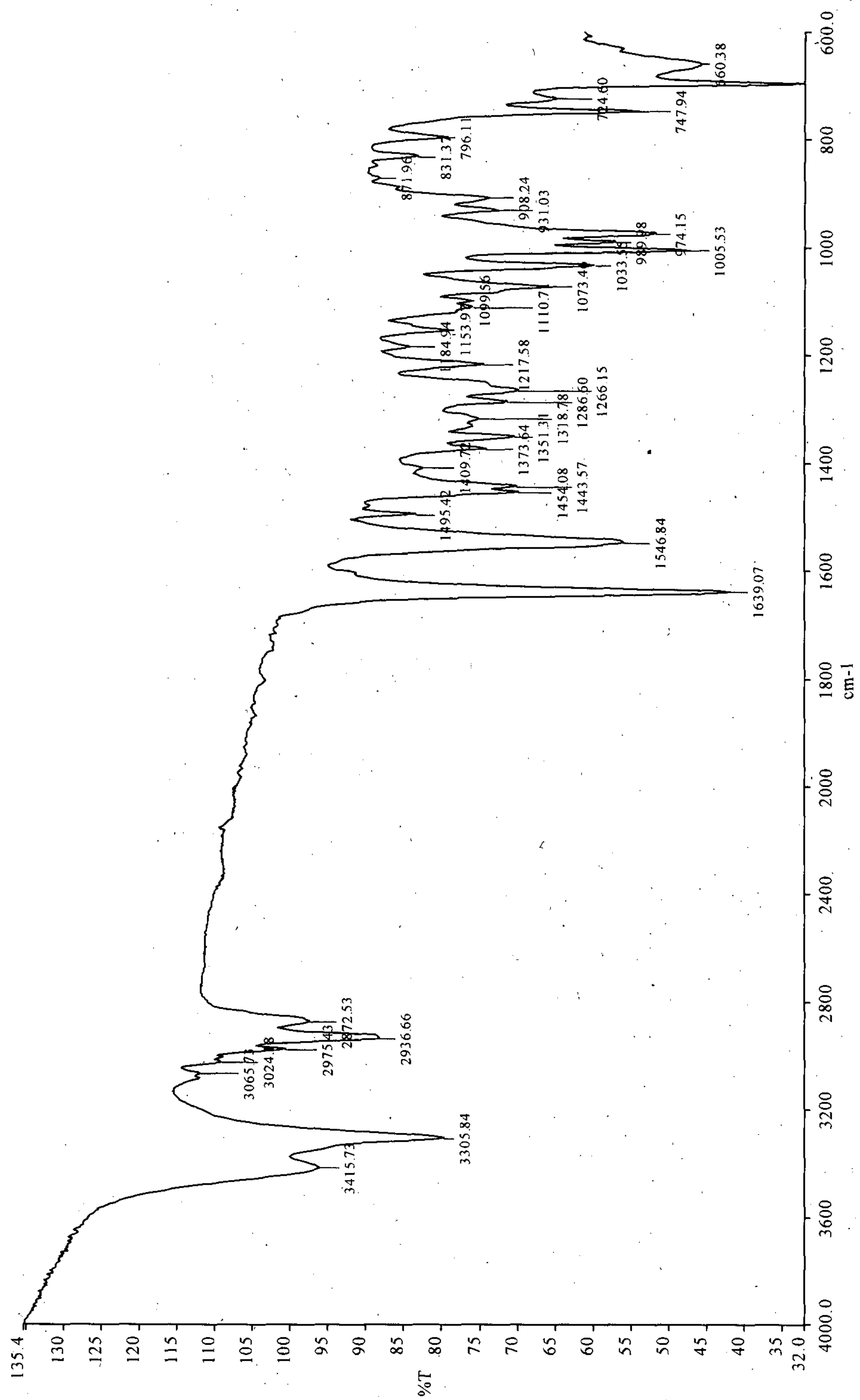


Figure IV.

IR spectrum of form II. of example 10.)

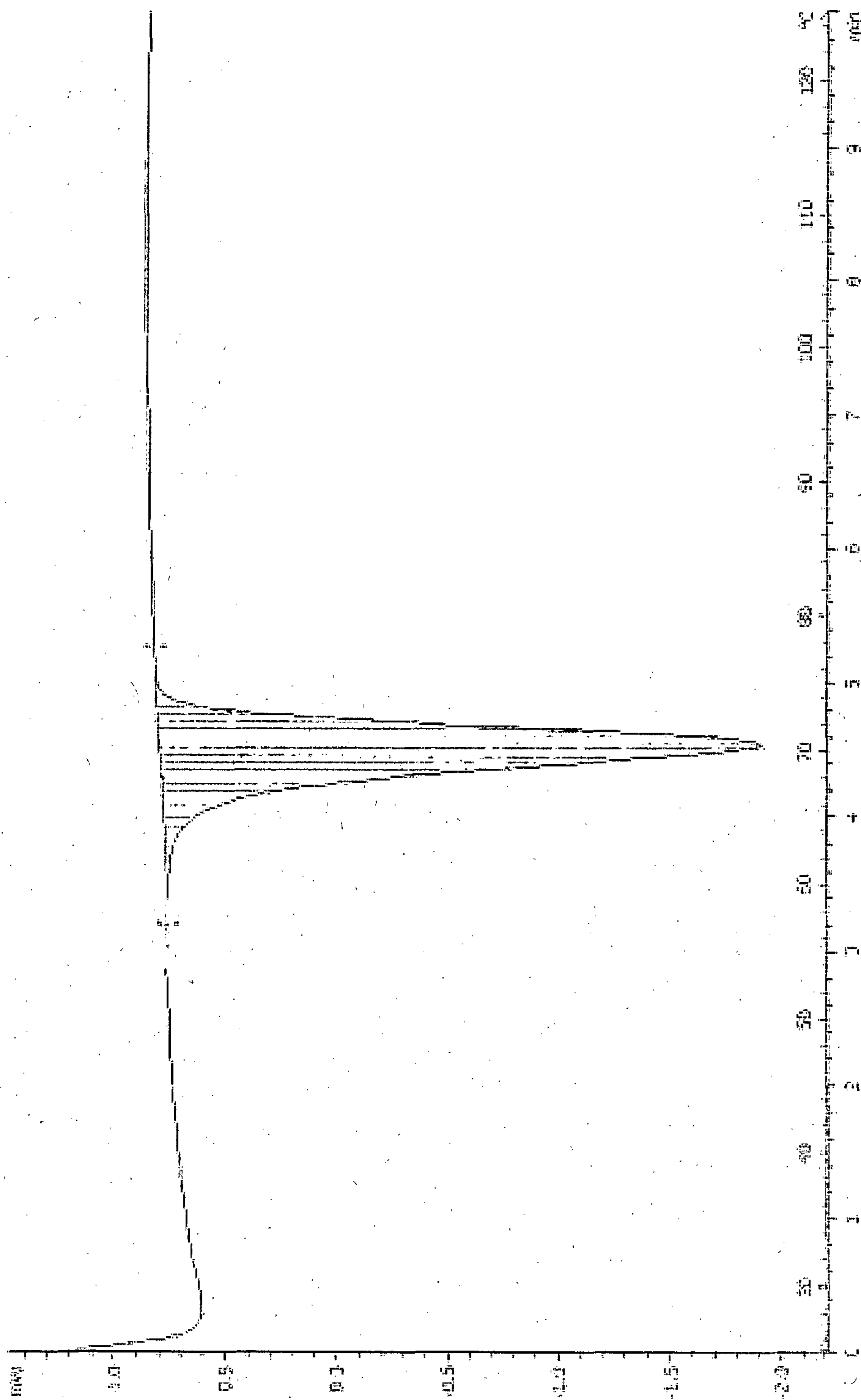


Figure V.

DSC curve of form I. of example 14/a.

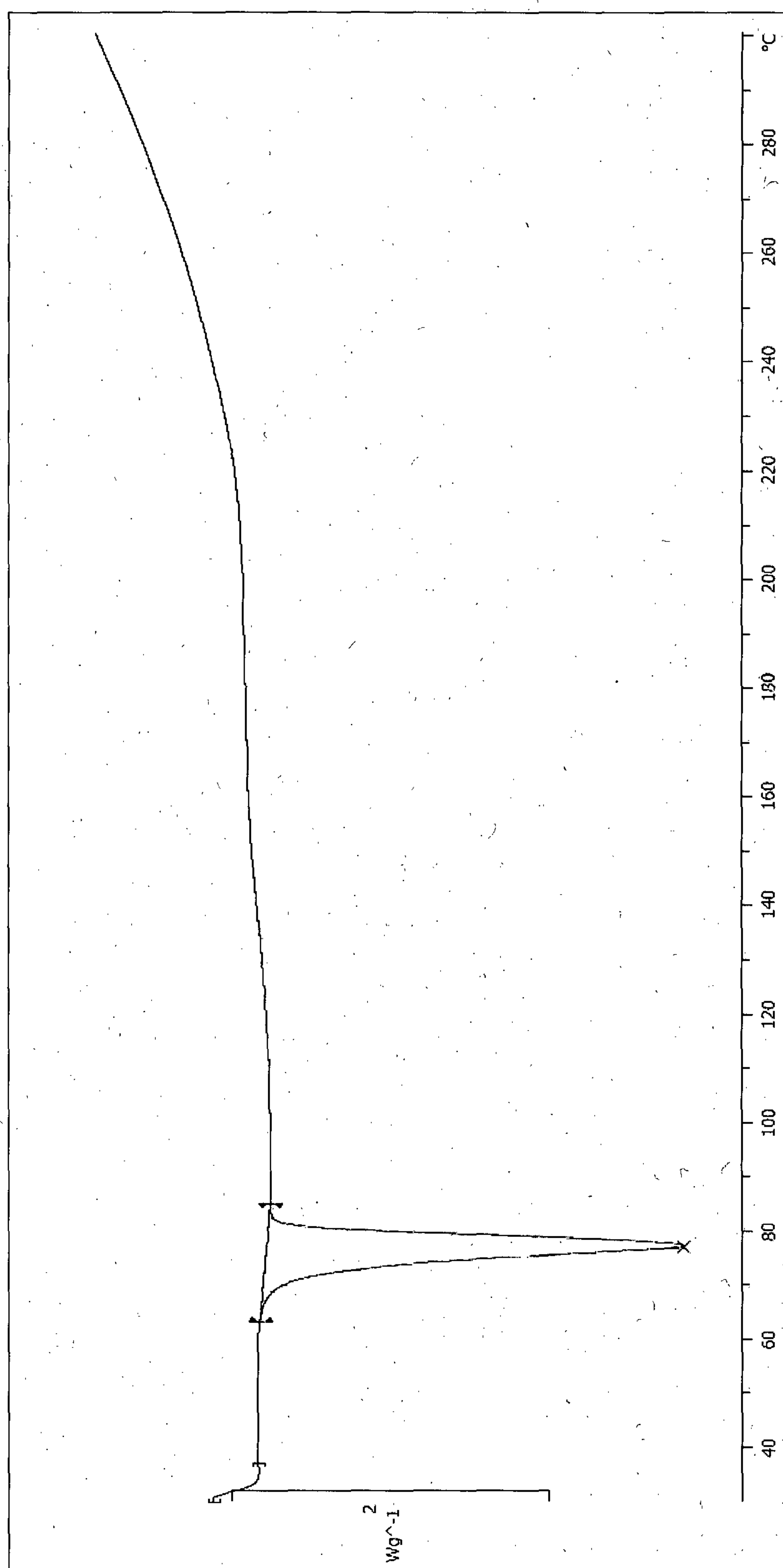


Figure VI.

DSC curve of form II. of example 10.

Bimatoprost F1

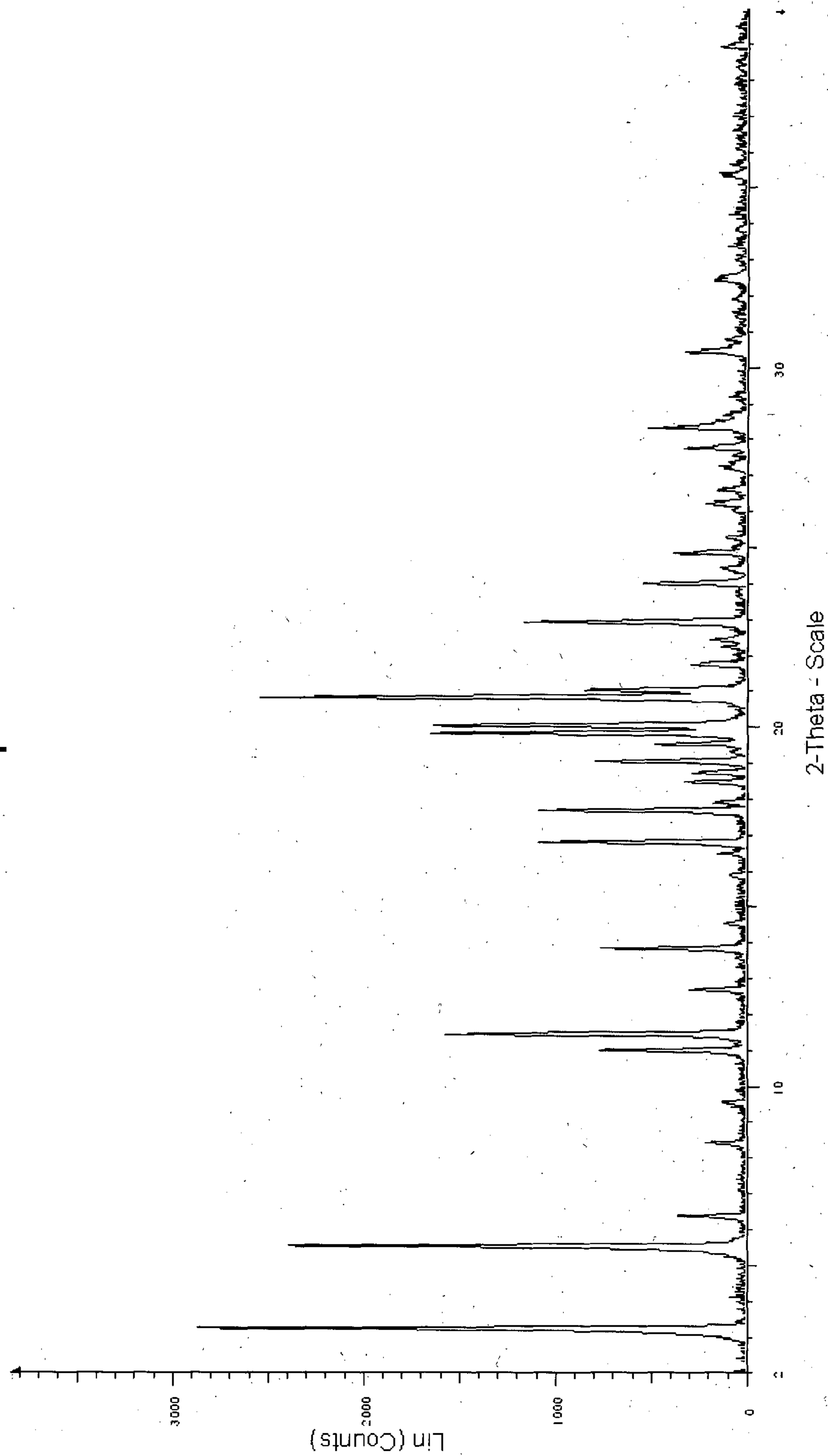


Figure VII.

X-ray diffraction curve of form I. of example 14/a.

Bimatoprost F2

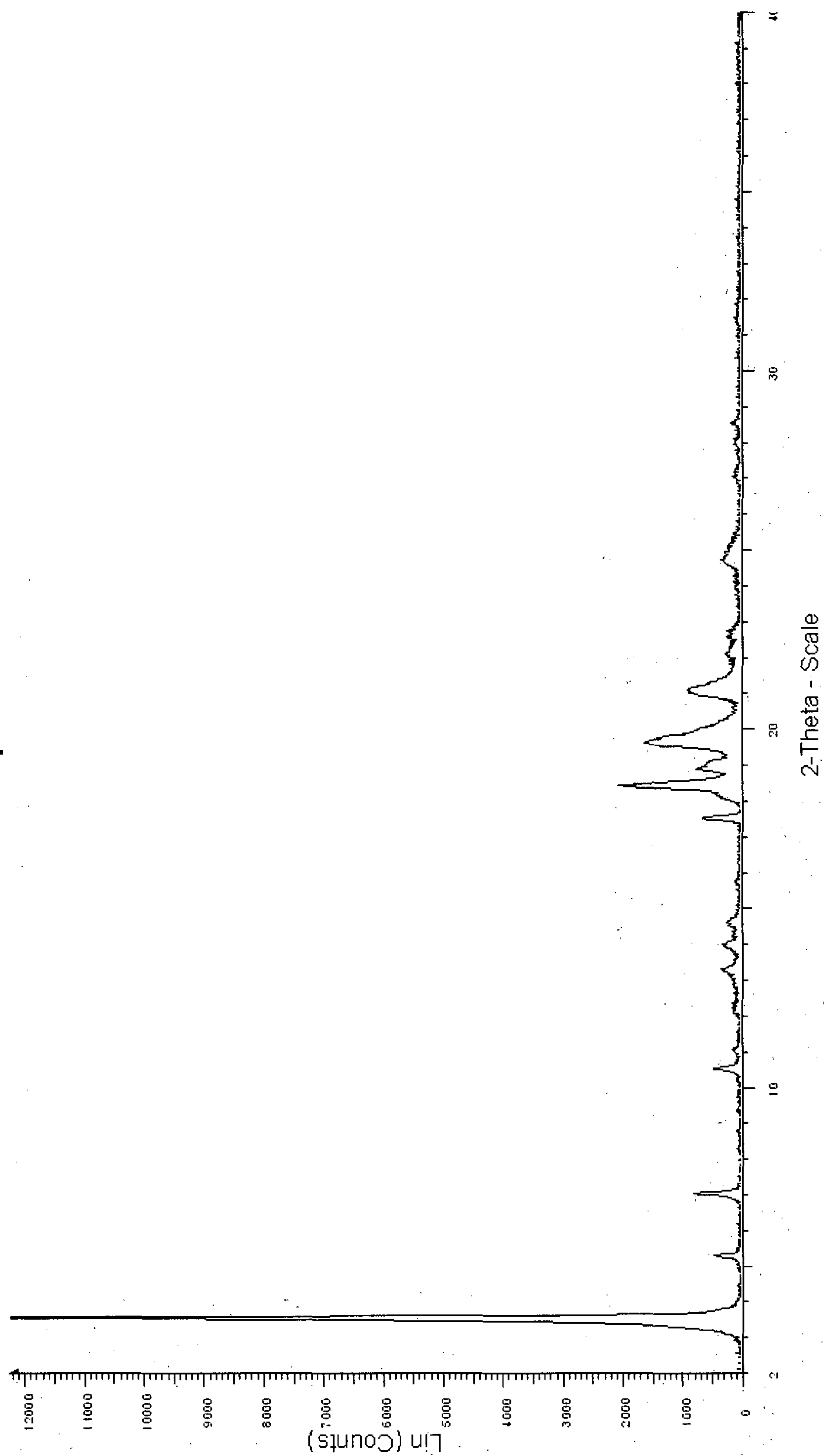


Figure VIII.

X-ray diffraction curve of form II. of example 10.

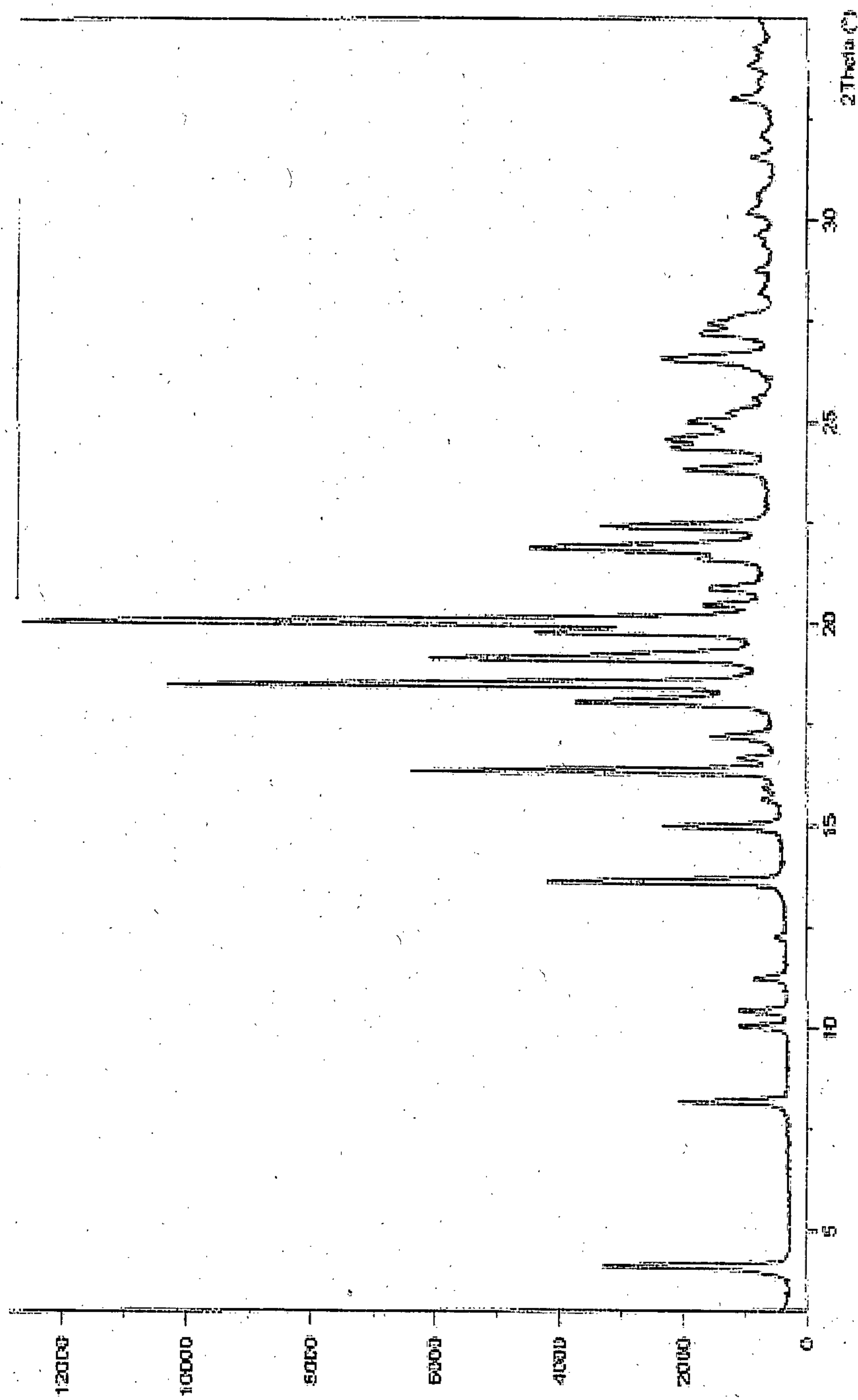


Figure IX

X-ray diffraction curve of bimatoprost acid of example 1/c2.)

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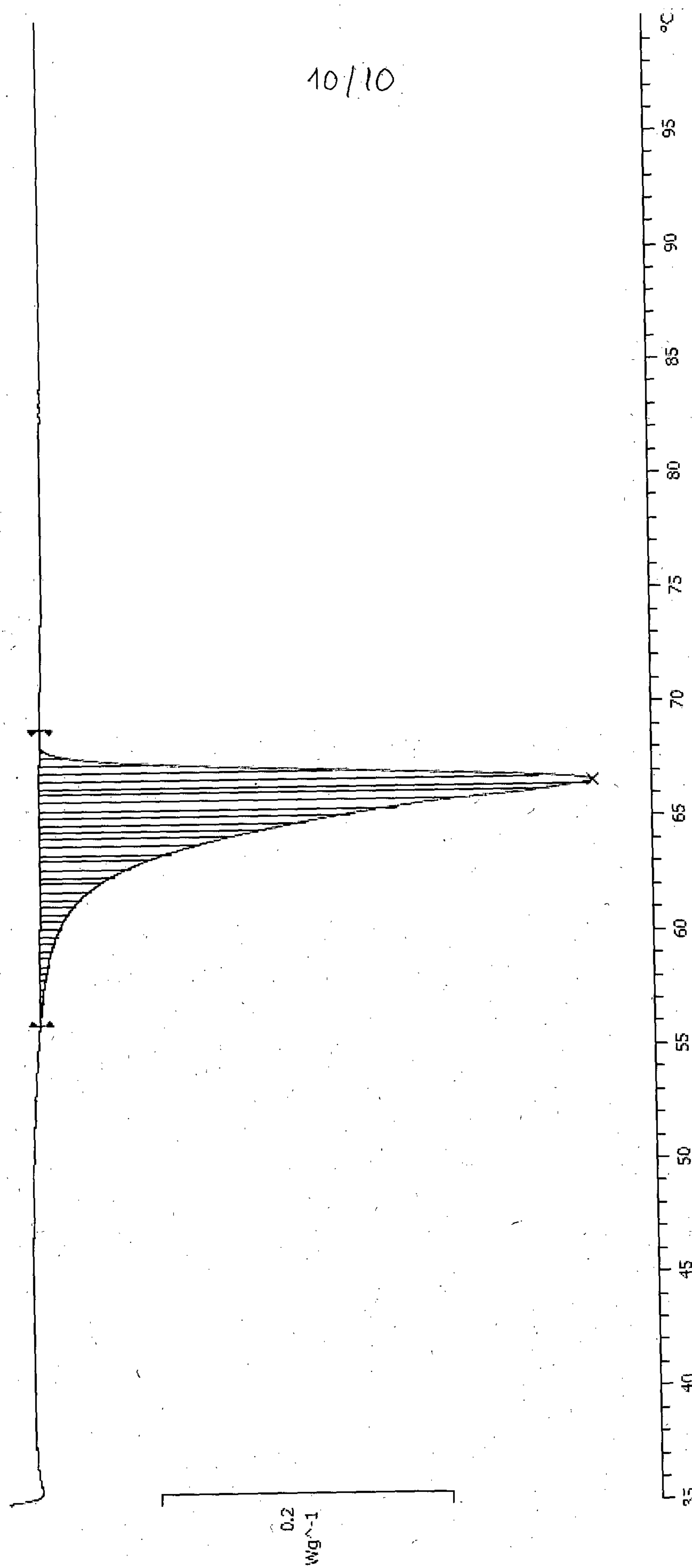


Figure X

DSC curve of bimatoprost acid of example 1/c2.)

