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(71) Applicant: **ZENTIVA, K.S.** [CZ/CZ]; U Kabelovny 130, 102 37 Praha 10 (CZ).

(72) Inventors: **CERNA, Igor**; Vyrava 109, 067 16 Vyrava (SK). **VLASAKOVA, Ruzena**; Na Cihelne 1332, 282 01 Cesky Brod (CZ). **KRULIS, Radim**; Primeticka 6, 140 00 Praha 4 (CZ).

(74) Agents: **JIROTKOVA, Ivana** et al.; Rott, Ruzicka & Guttmann, Vinohradska 37, 120 00 Praha 2 (CZ).

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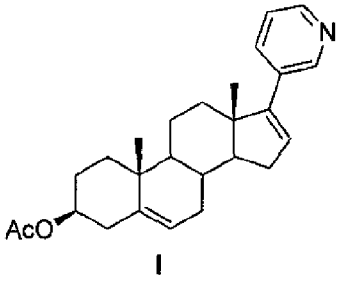
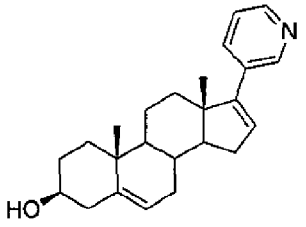
[Continued on next page]

(54) Title: METHOD OF PREPARING ABIRATERONE ACETATE OF HIGH PURITY APPLICABLE ON INDUSTRIAL SCALE

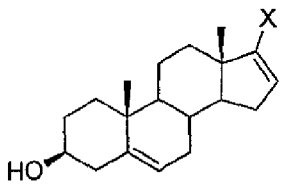
(57) Abstract: The solution relates to a method of preparing abiraterone acetate of formula I, which comprises: a) preparation of abiraterone of formula II by the Suzuki reaction of 3-pyridyldiethylborane and a halo steroid of formula VI or VII in the presence of a palladium catalytic system, a base, and a solvent; b) acetylation of abiraterone with formation of abiraterone acetate of formula I; c) isolation of abiraterone acetate by crystallization, wherein the palladium catalytic system consists of the catalyst palladium acetate - $Pd(OAc)_2$ and the ligand triphenylphosphine - Ph_3P.



I



II



VI X=I
VII X=Br

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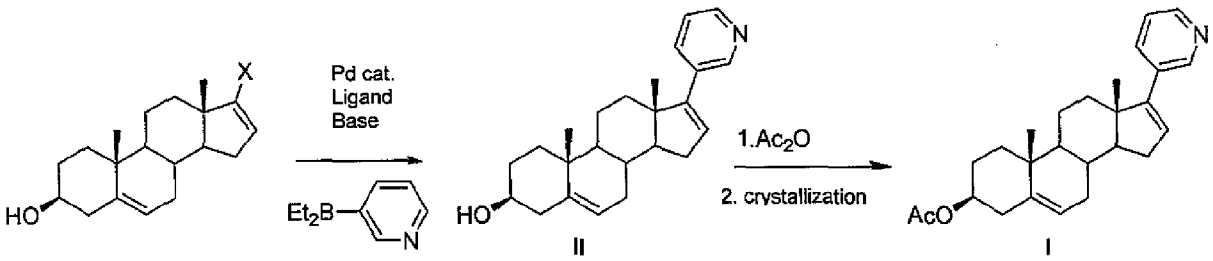
Method of preparing Abiraterone acetate of high purity applicable on industrial scale

Technical Field

The invention relates to an improvement of the method for the preparation of abiraterone acetate of formula **I**. The improvement relates to the Suzuki cross-coupling reaction, subsequent acetylation, and crystallization (Scheme 1). The method is focused on using the most affordable raw materials, reagents, catalysts, and ligands while maintaining yield and quality of the product. Secondly, the improvement is focused on applicability of the process in synthesis on a larger, industrial scale. The developed process of preparing abiraterone of formula **II** demonstrably leads to eliminating the formation of impurities and, thus, to formation of a satisfactory active pharmaceutical substance of formula **I** in a high yield, even when prepared on a larger scale.

Scheme 1



VI X=I
VII X=Br

3-PyBEt$_2$

II

I

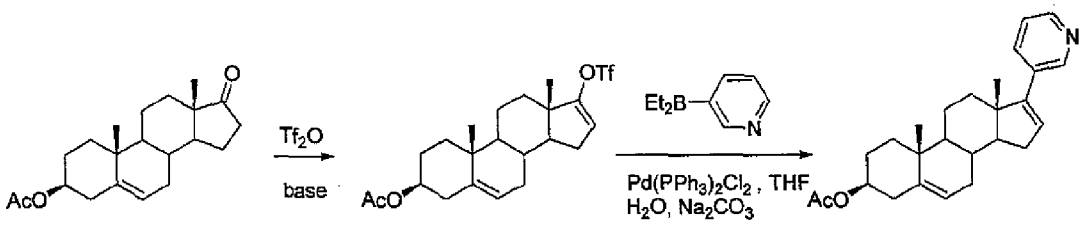
Background Art

Abiraterone acetate is a product which is used in treatment of the metastasis stage of the prostate cancer in men for whom the treatment by pharmacological or surgical castration was not effective.

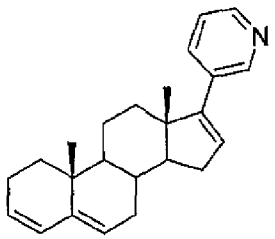
Abiraterone acetate was first described in patent EP00633893B1. The method of preparing according to this patent is also disclosed in the publication of Potter, G. A.; Barrie, S. E.; Jarman, M.; Rowlands, M. G. *J. Med. Chem.* **1995**, 38, 2463–2471. A key step of the three-stage synthesis is the Suzuki cross-coupling reaction of enol triflate of formula **III** with diethyl 3-pyridylborane (**3-PyBEt$_2$**) in the presence of a palladium catalyst (Scheme 2). Enol triflate **III** is prepared by the reaction of acetylated dehydroepiandrosterone (**Ac-DHEA**) with trifluoromethanesulphonic acid anhydride in a basic environment. Disadvantage of this

reaction include both the use of toxic and corrosive trifluoromethanesulphonic acid anhydride and the necessity of using expensive, sterically protected base (2,6-di-*tert*-butyl-4-methylpyridine). Moreover, in this step, a competitive reaction can also run under the given conditions, i.e. elimination of acetic acid form compound of formula **III** which, in the following step, leads to formation of impurity of formula **IV**. In the end result, this means necessity of purifying the product by chromatography, which in the case of preparation on a larger scale, would entail a principal obstacle of the process.

Scheme 2



Ac-DHEA **III** **I**

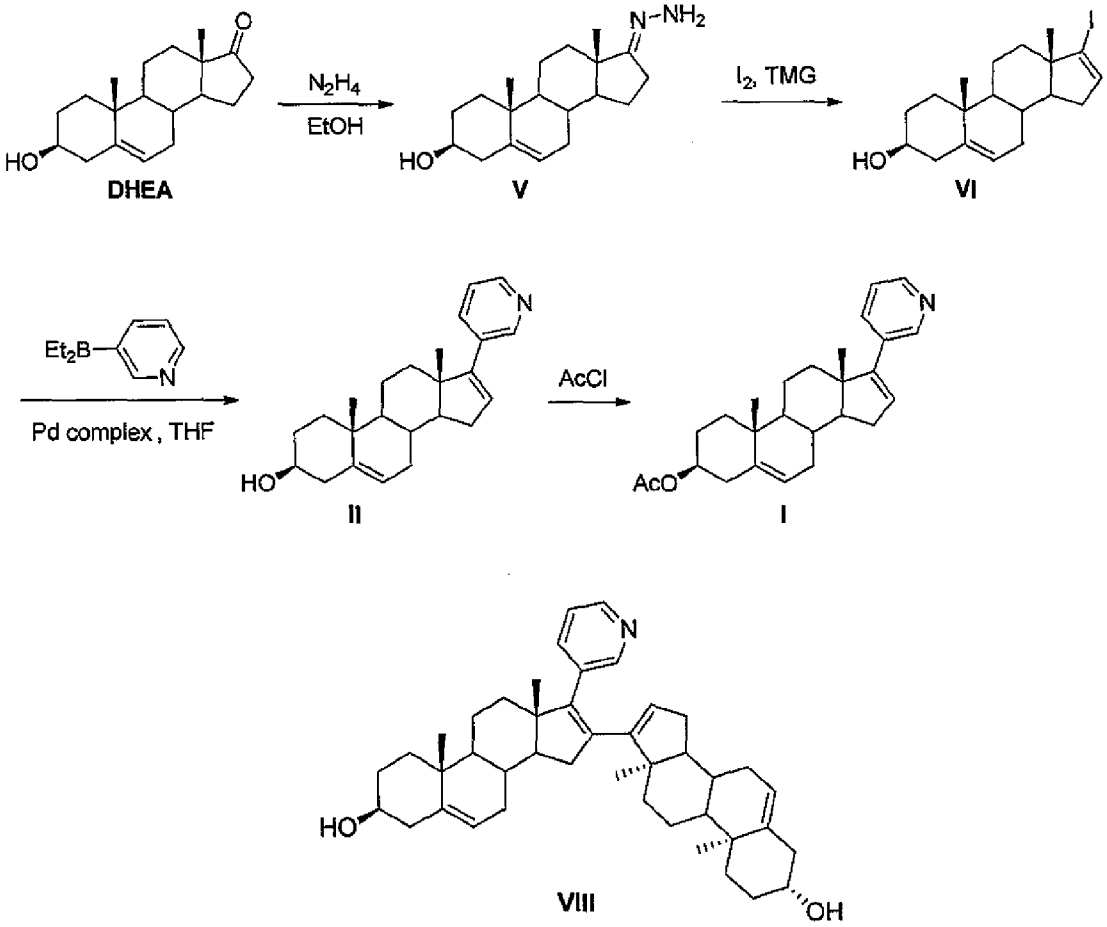


IV

Patent application WO06021777A1 refers about using of a more affordable bases (tertiary or heterocyclic amines, for instance, 2,6-lutidine or triethylamine) in preparing enol triflate of formula **III** and also in purification and isolation of final product **I** after the Suzuki reaction from the reaction mixture (also containing incompletely reacted ketone **Ac-DHEA** from the previous step in the ratio 1 : 3 in favour of product **I**) via its salt with methanesulphonic acid, by crystallization from methyl *tert*-butyl ether. By introduction of these modifications, it is possible to obtain the product without chromatography, however, in insufficient purity of the salt of product **I** (96.4%), even after two crystallizations. Very low yields resulting from the necessary multiple recrystallization in order to obtain satisfactory product **I** are also problematic. Another disadvantage is a danger of partial hydrolysis of the acetyl group during releasing the abiraterone acetate of formula **I** from its salt and therewith connected necessity of additional acetylation of the resulting side product **II**, which makes further complication of the process.

Patent EP0721461B1 and also the publication (Potter, G. A.; Hardcastle, I. R.; Jarman, M. *Org. Prep. Proced. Int.* **1997**, 29, 123–134) describe a four-stage synthesis of abiraterone acetate starting from the commercially available steroid **DHEA** (dehydroepiandrosterone, Scheme 3). The first step is conversion of the steroid ketone **DHEA** to hydrazone of formula **V** by reaction with hydrazine in ethanol. The second step is preparation of a halo derivative and subsequent Suzuki reaction of the iodo formula **VI** or bromo formula **VII** steroid with diethyl 3-pyridylborane, catalyzed with a palladium complex. The final step is acetylation of the hydroxy group of abiraterone of formula **II** using acetyl chloride with formation of abiraterone acetate of formula **I**.

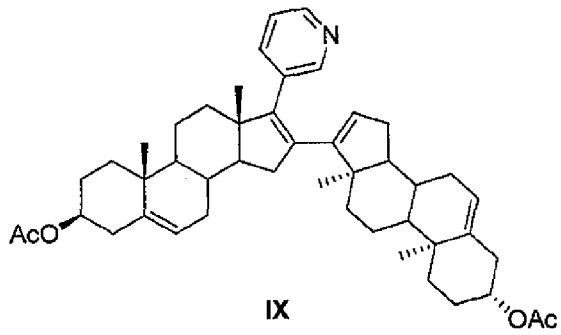
Scheme 3



The key step - the Suzuki reaction - is described by means of a reaction of the iodo steroid of formula **VI** with diethyl(3-pyridyl)borane (1.2 equivalent) in tetrahydrofuran, catalyzed with bis(triphenylphosphine) palladium chloride (0.01 equivalent) in a basic environment of a 2M aqueous solution of sodium carbonate. The mentioned method has a disadvantage that,

under these specific conditions, conversion of the reaction is slow and, therefore, it requires stirring at high temperature (azeotrope reflux ~ 80°C) for up to four days. This is connected both with higher costs from the viewpoint of the process and also with one principal disadvantage, namely the amount of the bis-steroid of formula **VIII** increasing with the reaction time. This impurity is formed by the reaction of product abiraterone of formula **II** with 17-iodoandrosta-15,16-diene-3β-ol of formula **VI** catalyzed with palladium (Heck's coupling as competitive reaction). So far, the only efficient method of removing impurity of formula **VIII** is reverse-phase chromatography, which is almost inapplicable as a purifying method in manufacturing product **II** on a larger scale. In this case, crystallization provides just a very limited space for reducing the amount of impurity of formula **VIII**.

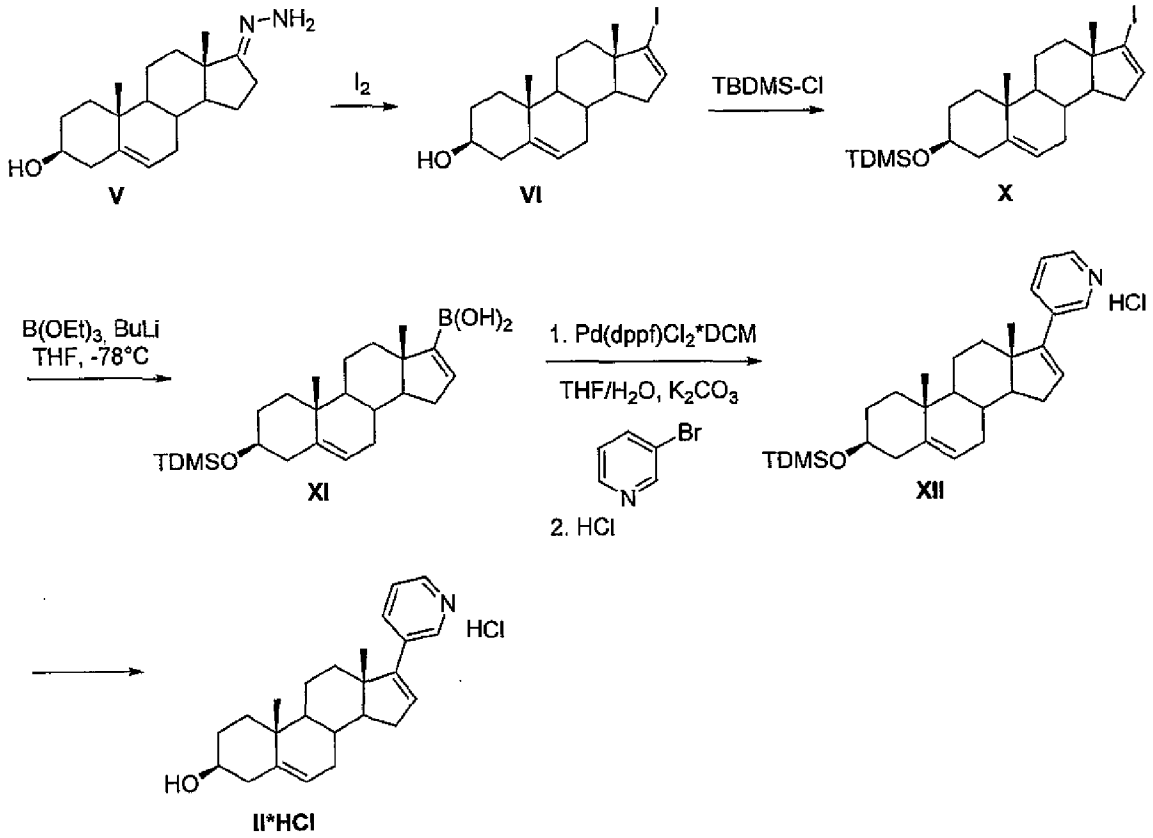
In case impurity of formula **VIII** is present in product **II**, impurity **VIII** is also acetylated in the next step (acetylation), which results in formation of a diacetylated bis-steroid of formula **IX**, where a problem again arises with just very limited space for purification because of similarity of physical properties of the bis-steroid of formula **IX** with the product of formula I.



IX

Patent WO2013/030410 describes the Suzuki coupling of boronic acid of formula **XI**, derived from steroid **DHEA** with 3-pyridylbromide (Scheme 4). However, preparation of the intermediate of formula **XI** requires application of cryogenic conditions (lithiation and transmetallation of the iodide of formula **X**).

Scheme 4



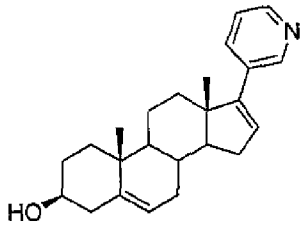
Optimization of conditions of the Suzuki coupling between 3-pyridyldiethylborane and the bromo steroid of formula **VII** focused on shortening the reaction time and increasing efficiency of the isolation has recently been published in the literature (*Org. Process Res. Dev.* **2014**, 18, 555–558). However, the remaining disadvantage is using of expensive tetrakis(triphenyl phosphine)palladium of only limited stability as a catalytic complex. The necessary purification of product **I** via the acido-basic extraction could be deemed another disadvantage of this method of preparing abiraterone acetate of formula **I** since this mainly serves for removing impurities, in particular for reducing the amount of diethyl 3-pyridylborane identified in final product **I**.

It is obvious from the above given list of methods and conditions of preparing both abiraterone of formula **II** and the final API abiraterone acetate of formula **I** that all methods include shortcomings that can present problems in preparing the product on a larger scale in terms of technology, operating costs, and/or above-limit amounts of impurities in the final API.

Disclosure of Invention

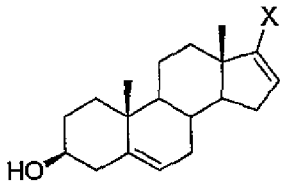
The invention relates to an efficient, competitive, and industrially applicable method of preparing abiraterone acetate of formula **I**, which comprises the following steps:

a) Preparation of abiraterone of formula **II** of high purity



II

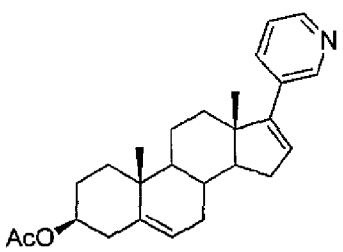
by the Suzuki reaction of 3-pyridyldiethylborane (1 to 1.2 equivalent, preferably 1.1 equivalent) and a halogenated steroid of formulas **VI** and **VII**



VI X=I
VII X=Br

in the presence of palladium acetate (0.1 to 1.5 mol %, preferably 1 mol %) as a catalyst, and of triphenylphosphine (0.2 to 3 mol %, preferably 2 mol %) as a ligand in a basic environment of potassium phosphate or caesium carbonate (1 to 3 equivalents, preferably 2 equivalents) at temperatures higher than 50°C, preferably at the reflux temperature of the azeotropic mixture of solvents (THF/water, MeTHF/water, or toluene/water, preferably THF/water or MeTHF/water, in a ratio 2 : 1.5 or 2 : 1), for the period not exceeding 24 hours, preferably 4 hours.

b) Preparation of abiraterone acetate of formula **I** of high purity



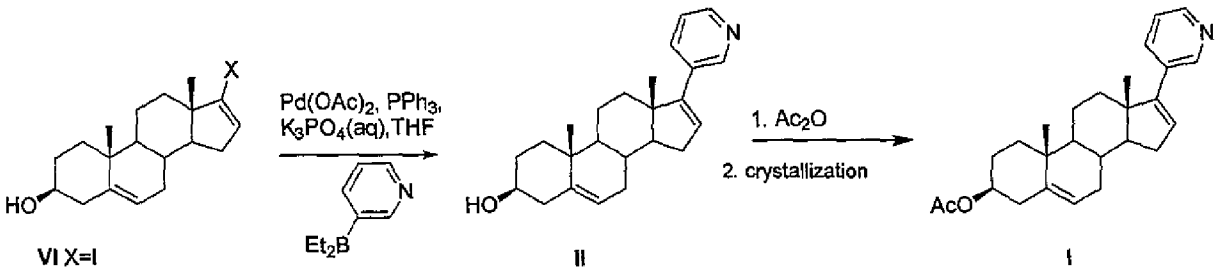
I

by crystallization of crude abiraterone acetate **I** from a suitable solvent. Abiraterone acetate **I** is prepared by acetylation of abiraterone **II** under standard conditions (for instance, by means of acetanhydride or acetyl chloride in a basic environment of pyridine or triethylamine, in the presence of a catalytic amount of *N,N*-dimethylaminopyridine).

Suitable solvents for crystallization, from the viewpoint of reduced content of the bis-steroid impurity of formula **IX,** include acetonitrile, $C_1 - C_4$ alcohols, or mixtures of a $C_1 - C_4$ alcohol and water, preferably the alcohols and their mixtures with water are selected from the mixture of ethanol with water, mixture of 2-propanol with water, or pure 2-propanol.

The improved method of preparing abiraterone acetate of formula **I** is shown in the following scheme 5.

Scheme 5



VI X=I
VII X=Br

II

I

Table 1 shows selection of most important experiments that have led to the invention.

Table 1

Experiment*	Base	Proportion of individual components in reaction mixture (%); determined by UPLC											
		II (Abiraterone)			VI (Iodo derivative)			VIII (Bis-steroid)			Bipyridine		
		12 h	48 h	120h	12 h	48 h	120h	12h	48h	120h	12h	48h	120h
1	3 eq. Na_2CO_3	42.1	51.4	92.0	40.1	28.3	0.7	0.6	1.1	1.5	1.6	2.3	-
2	3 eq. K_3PO_4	90.6	82.3	85.7	1.7	1.7	1.4	0.2	1.1	1.9	0.5	0.9	0.8
3	3 eq. Cs_2CO_3	67.5	75.5	78.2	10.3	1.6	1.3	1.2	1.4	2	1.9	3.9	4.1

*1.1 eq. of 3-$PyBEt_2$, 1 mol % of $Pd(PPh_3)_2Cl_2$, THF/H_2O, reflux; note: eq.= equivalent

Extensive experiments have surprisingly revealed that using of potassium phosphate as the base in the Suzuki cross-coupling reaction of the halo steroid of formulas **VI** or **VII** with diethyl 3-pyridylborane resulted in dramatic increase in the conversion in time, which enables the reaction time to be shortened from days (experiment 1, Table 1 - reference experiment under applied conditions from patent EP0721461B1 – almost complete conversion attained after five days; after 12 hours, the conversion was only 60%) to several hours (experiment 2 – according to the invention – 98% conversion was attained already after 12 hours). Using of caesium carbonate (experiment 3 – according to the invention) makes it also possible to shorten the reaction time to less than 48 hours (1.6 % of the starting iodo derivative of formula **VI** after 48 hours).

This aspect is also very important concerning formation of impurities, particularly in the case of formation of the impurity of formula **VIII**.

In fact, the shortened reaction time demonstrably leads to a reduced content of the impurity of formula **VIII** in the product abiraterone of formula **II**. This is evident from monitoring the amount of the impurity of formula **VIII** in time, where the same trend was observed in all experiments (Table 1); thus, the amount of the impurity of formula **VIII** increases with longer reaction time.

Moreover, it has been surprisingly found that this effect is maintained even when the affordable catalytic system $Pd(OAc)_2/PPh_3$ is used and competitiveness of this method is increased in comparison with methods utilizing catalysts such as tetrakis(triphenylphosphine) palladium, bis(triphenylphosphine)palladium chloride, or [1,1'-bis(diphenylphosphino)

ferrocene]palladium dichloride (complex with dichloromethane), used in the art for the Suzuki cross-coupling reaction of the halo steroid of formulas **VI** or **VII** with diethyl 3-pyridylborane.

Table 2 shows comparison of the experiments that have led to this finding.

Table 2.

Experiment*	Catalytic system	Base	Proportion of individual components in reaction mixture (%); determined by UPLC			
			II	VI	VIII	Bipyridine
1	1 mol % of $PdCl_2(PPh_3)_2$	3 eq. of K_3PO_4	90.6	1.70	0.20	0.50
2	1 mol % of $Pd(OAc)_2$/2 mol % of PPh_3	3 eq. of K_3PO_4	80.1	1.00	0.80	0.90
3	1 mol % of $PdCl_2(PPh_3)_2$	3 eq. of Cs_2CO_3	67.5	10.3	1.20	1.90
4	1 mol % of $Pd(OAc)_2$/2 mol % of PPh_3	3 eq. of Cs_2CO_3	82.3	1.20	1.20	1.10

*1.1 eq. of 3-$PyBEt_2$, THF/H_2O, 12 hours, reflux

The reaction mentioned in the fourth experiment (experiment 4, Table 2) shows even better conversion with the used catalytic system $Pd(OAc)_2/PPh_3$ = 1/2 in combination with caesium carbonate, where an excellent conversion above 98% was attained already in 12 hours.

In order to better explain the limits of using such conditions, several experiments have been carried out with the particular focus on the amount of the catalyst and ligand {$Pd(OAc)_2/PPh_3$} used, excess of K_3PO_4 and diethyl(3-pyridyl)borane, but also on the possibility of using a different halo derivative than iodide **VI**. The results are summarized in Table 3.

Table 3

Experiment	Change against original method	Time (h)	Isolated yield (%)	Purity of crystalline product II (%)	Content of impurities in product (%)	
					VI (VII)	VIII
1*	-	21	88	97.3	0.47	0.10
2	1 eq. of K_3PO_4	20	81	73.4	17.4	0.32
3	2 eq. of K_3PO_4	22	84	97.9	0.55	-
4	0.5 mol % of $Pd(OAc)_2$, 1 mol % of PPh_3, 2 eq. of K_3PO_4	20	80	97.4	0.98	0.12
5	1 eq. of **3-PyBEt$_2$**	45	89	88.9	2.25	0.62
6	**VII** instead of **VI**; 2 eq. of K_3PO_4	21	73	95.6	1.11	-

* 1.1 eq. of **3-PyBEt$_2$**, 1 mol % of $Pd(OAc)_2$, 2 mol % of Ph_3P, 3 eq. of K_3PO_4, THF/water, reflux.

It follows from the results that the amount of the base potassium phosphate can be reduced from the original excess of 3 equivalents to an excess of 2 equivalents, without principal limitation of yield or purity (comparison of experiments 1 and 3, Table 3).

Concerning the amount of catalyst, almost identical result can be observed (comparison of experiments 1 and 4, Table 3), even with the half amount of the catalyst used {0.5 mol % of $Pd(OAc)_2$, 1 mol % of Ph_3P}.

Under these conditions, the bromo derivative of steroid **VII** can also be used into the reaction (experiment 6, Table 3); then, under the reaction conditions that are a part of the invention, a yield of 73% of Abiraterone **II** of purity 95.6% has been attained. The invention provides an improved method of preparing abiraterone acetate **I** of high purity and in high yield.

The method includes a reaction of iodide **VI** or bromide **VII** of the steroid in the presence of the catalytic system $Pd(OAc)_2$ /Ph_3P.

The ratio of catalyst $Pd(OAc)_2$ to ligand Ph_3P is 1 : 2.

The amount of the catalyst is 0.1 to 1.5 mol %, preferably 1 mol % of the catalyst is used.

The base used for the reaction is potassium phosphate or caesium carbonate, in an excess of 1 to 3 equivalents; preferably 2 equivalents of potassium phosphate are used.

The reaction is carried out in a mixture of solvents selected from THF/water, MeTHF/water, toluene/water. Preferably a mixture THF/water or MeTHF/water is used in the ratio 2 : 1.5 or 2 : 1.

The reaction is carried out at temperature higher than 50°C, preferably at the reflux temperature of the azeotropic mixture of solvents.

The maximum reaction time is 24 hours; preferably the reaction is carried out for 4 hours.

Brief Description of Drawings:

Fig. 1 - *Evaluation:* by the method of internal peak normalization

Fig. 2 - *Evaluation:* by the method of internal peak normalization

Examples

The invention is explained in more details in the following working examples. These are of an exclusively illustrative character and do not limit the scope of the invention in any respect.

Method of analysis of intermediate of formula II

Liquid chromatography is carried out *(Ph. Eur. 2.2.29)*:

Chromatographic conditions:

Instrument:	UPLC system with UV/VIS or PDA detector
Chemicals:	acetonitrile R1
	water for chromatography R
	ammonium dihydrogen phosphate R
	tetrahydrofuran for chromatography R
Column:	
- *dimensions:*	length = 100 mm, internal diameter = 4.6 mm
- *stationary phase:*	Ascentis Express Phenyl-Hexyl 2.7 µm
- *temperature:*	30 °C
Mobile phase:	A: 0.58 g of ammonium dihydrogen phosphate R is dissolved in 1000 ml of water for chromatography R.
	B: acetonitrile R1
- *elution:*	gradient

Time [min]	Mobile phase A [% vol./vol.]	Mobile phase B [% vol./vol.]
0	75	25
1	75	25
10	10	90
16	0	100
17.5	75	25
19	75	25

Flow rate: 0.8 ml/min

Injection: 2.0 µl

Sample temperature: 15 °C

Detection: UV 215 nm

Time: 19.0 min

Solvent for sample: tetrahydrofuran for chromatography R : acetonitrile = 10 : 30 (vol./vol.)

Sample concentration: 2 mg/ml

Typical retention and relative retention times (reference peak RRT 1 is **II***):*

II: ca 8.1 min

VIII	RRT 0.82
VI	RRT 1.23
IV	RRT 1.41
3-PyBEt$_2$	RRT 1.90

Correction factor: **VI** 1.6

IV 0.42

3-PyBEt$_2$ 0.25

other impurities 0.8 – 1.2 (without correction)

Evaluation: method of internal peak normalization– Fig. 1

Method of analysis of Abiraterone acetate **I**

Liquid chromatography is carried out *(Ph. Eur. 2.2.29)*:

Chromatographic conditions:

Instrument: UPLC system with UV/VIS or PDA detector

Chemicals: acetonitrile R1
water for chromatography R
ammonium dihydrogen phosphate R

Column:

- *dimensions:* length = 100 mm, internal diameter = 4.6 mm
- *stationary phase:* Ascentis Express Phenyl-Hexyl 2.7 µm
- *temperature:* 30 °C

Mobile phase: A: 0.58 g of ammonium dihydrogen phosphate R is dissolved in 1000 ml of water for chromatography R.
B: acetonitrile R1

- *elution:* gradient

Time [min]	Mobile phase A [% vol./vol.]	Mobile phase B [% vol./vol.]
0	75	25
1	75	25
10	10	90
16	0	100
17.5	75	25
19	75	25

Flow rate: 0.8 ml/min
Injection: 2.0 µl
Sample temperature: 15 °C
Detection: UV 255 nm
Time: 19.0 min
Solvent for sample: acetonitrile R1
Sample concentration: 2 mg/ml

Typical retention and relative retention times (reference peak RRT 1 is Abiraterone acetate I):

Abiraterone acetate I: ca 10.3 min

II	RRT 0.78
IX	RRT 1.42

Evaluation: method of internal peak normalization - Fig. 2.

Preparation of intermediate of abiraterone of formula **II**

Example 1 (General method of carrying out experiments 1 to 3 from Table 1)

600 mg (1.51 mmol) of the iodo derivative of formula **VI**, 244 mg (1.1 eq., 1.66 mmol) of diethyl(3-pyridyl)borane, 3 equivalents (4.52 mmol) of the base (according to Table 1), and 10.6 mg of bis(triphenylphosphine)palladium chloride (1 mol %) are weighed into a flask. The flask was closed with a septum and subsequently evacuated 3-times and inertized (argon). 6 ml of tetrahydrofuran and 4.5 ml of distilled water are added to this mixture under the inert argon atmosphere. The reaction mixture is heated in a bath at 80°C. Samples are continuously taken from the reaction mixture; results of the analysis of purity for respective experiments and samplings are shown in Table 1.

^{1}H NMR (500.13 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.6 Hz, 1H), 8.46 (dd, *J* = 4.7, 1.1 Hz, 1H), 7.65 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.22 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.00 – 5.99 (m, 1H), 5.40 – 5.38 (m, 1H), 3.56 – 3.51 (m, 1H), 2.39 – 2.21 (m, 3H), 2.13 – 2.00 (m, 3H), 1.91 -1.84 (m, 2H), 1.76 (dt, *J* = 10.8, 4.9 Hz, 1H), 1.71 – 1.42 (m, 7 H), 1.14 – 1.04 (m, 2H), 1.07 (s, 3H), 1.04 (s, 3H);

^{13}C NMR (125.76 MHz, CDCl3) δ 151.6, 147.9, 147.8, 141.1, 133.7, 132.9, 129.2, 123.0, 121.3, 71.6, 57.5, 50.3, 47.3, 42.3, 37.1, 36.7, 35.2, 31.8, 31.6, 31.5, 30.4, 20.8, 19.3, 16.6.

Example 2 (Experiment No. 4, Table 2)

600 mg (1.51 mmol) of the iodo derivative of formula **VI**), 244 mg (1.66 mmol) of diethyl(3-pyridyl)borane, 3.5 mg of palladium acetate (1 mol %), and 10 mg (2 mol %) of triphenylphosphine are weighed into a flask. The mixture is diluted with 6 ml of tetrahydrofuran and a solution of caesium carbonate [1.47 g Cs_2CO_3 (4.5 mmol) in 4.5 ml of water] is added. The reaction mixture is heated under a reflux condenser in a bath at 80°C in the nitrogen atmosphere for 12 hours. After cooling down, the mixture is diluted with 2 ml of water. The formed suspension is stirred in an ice bath for 1 hour. After suction off, washing with water, and final drying (in a vacuum drier at 45°C for 16 h), 0.45 g (85%) of abiraterone of formula **II** is obtained, purity 88.21% (determined by UPLC). Its NMR spectrum corresponds to the NMR record of abiraterone of formula **II**.

Example 3 (Experiment No. 1, Table 3)

6 g (15 mmol) of the iodo derivative **VI**, 2.44 g (16.6 mmol) of diethyl(3-pyridyl)borane, 34 mg of palladium acetate (1 mol %), and 79 mg (2 mol %) of triphenylphosphine are weighed into a flask. The mixture is diluted with 60 ml of tetrahydrofuran and a solution of potassium phosphate [5.55 g K_3PO_4 (45 mmol) in 45 ml of distilled water] is added. The reaction mixture is heated under a reflux condenser in a bath at 80°C in the inert nitrogen atmosphere for 21 hours. After cooling down, the mixture is diluted with 20 ml of distilled water. The formed suspension is stirred in an ice bath for 1 hour. After suction off, washing with water, and final drying (in a vacuum drier at 45°C for 16 h), 4.65 g (88%) of abiraterone is obtained, purity 97.25% (determined by UPLC; the content of formula **VI** 0.47%, the content of formula **VIII** is 0.10%). The NMR spectrum corresponds to the NMR record of abiraterone of formula **II**.

Example 4 (Experiment No. 6, Table 3)

1.5 g (4.3 mmol) of the bromo derivative of formula **VII**, 0.69 g (4.7 mmol) of diethyl(3-pyridyl) borane, 10 mg of palladium acetate (1 mol %), and 25 mg (2 mol %) of triphenylphosphine are weighed into a flask. The mixture is diluted with 17 ml of tetrahydrofuran and a solution of potassium phosphate [1.83 g K_3PO_4 (8.6 mmol) in 13 ml of water] is added. The reaction mixture is heated under a reflux condenser in a bath at 80°C in the inert nitrogen atmosphere for 21 hours. After cooling down, the mixture is diluted with 6 ml of water. The formed suspension is stirred in an ice bath for 1 hour. After suction off, washing with water, and final drying (in a vacuum drier at 45°C for 16 h), 1.10 g (73%) of abiraterone is obtained, purity 95.59% (determined by UPLC; content of **3-PyBEt$_2$** 1.14%, content of **VII** is 1.11%). The NMR spectrum corresponds to the NMR record of abiraterone **II**.

Preparation of final product Abiraterone acetate I

Example 5

2.35 ml (25 mmol) of acetanhydride is dropwise-added to a suspension of 4.35 g (12.5 mmol) of abiraterone of formula **II** and 18 mg (1 mol %) of dimethylaminopyridine in 18 ml of pyridine at room temperature within 15 minutes. The mixture is stirred at room temperature for 2 hours. Activated charcoal is added to the resulting solution and the stirring proceeds for additional 30 minutes. After suction off through diatomaceous earth and washing with 5 ml of pyridine, 35 ml of water is dropwise-added to the filtrate cooled down in an ice bath. The formed suspension is stirred in an ice bath for 1 hour. After suction off, washing with water, and final drying (in a vacuum drier at 45°C for 16 h), 3.73 g (77%) of abiraterone acetate of

formula I is obtained, purity 99.17%; melting point = 141.3 – 142.8°C. If necessary, the product is re-purified by crystallization from acetonitrile or from an ethanol/water mixture.

1H NMR (500.13 MHz, CDCl3) δ 8.62 (d, J = 1.6 Hz, 1H), 8.47 (dd, J = 4.7, 1.2 Hz, 1H), 7.65 (dt, J = 7.9, 1.8 Hz, 1H), 7.22 (dd, J = 7.8, 4.8 Hz, 1H), 6.00 – 5.98 (m, 1H), 5.43 – 5.41 (m, 1H), 4.64 – 4.58 (m, 1H), 2.40 – 2.30 (m, 2H), 2.27 (ddd, J = 15.8, 6.5, 3.3 Hz, 1H), 2.10 – 2.01 (m, 3H), 2.04 (s, 3H), 1.92 – 1.84 (m, 2 H), 1.85 – 1.55 (m, 6H), 1.49 (td, J = 12.3, 4.9, 1H), 1.20 – 1.12 (m ,1H) 1.11 – 1.05 (m, 1H) 1.09 (s, 3H), 1.05 (s, 3H);

13C NMR (125.76 MHz, CDCl3) δ 170.5, 151.6, 147.9, 147.8, 140.0, 133.6, 132.9, 129.2, 123.0, 122.3, 73.8, 57.4, 50.2, 47.3, 38.1, 36.9, 36.7, 35.2, 31.8, 31.5, 30.4, 27.7, 21.4, 20.8, 19.2, 16.5.

Example 6

0.12 ml (0.86 mmol) of triethylamine is added to a suspension of 300 mg (0.86 mmol) of abiraterone II and 4 mg (4 mol %) of dimethylaminopyridine in 3 ml of methylethylketone and 0.12 ml (1.29 mmol) of acetanhydride is dropwise-added at room temperature within 10 minutes. The mixture is heated in a bath at 80°C for 2 hours. After cooling down, the solution is filtered through a layer of activated charcoal. 6 ml of water is dropwise-added to the filtrate cooled down in an ice bath. After stirring in an ice bath for 2 hours, the resulting suspension is sucked off and 243 mg of abiraterone acetate is obtained, purity 99.41%; melting point = 144.0 – 145.2°C. Its NMR spectrum corresponds to the NMR record of abiraterone acetate of formula I. If necessary, the product is re-purified by crystallization from acetonitrile or from an ethanol/water mixture.

Example 7

0.12 ml (0.86 mmol) of triethylamine is added to a suspension of 300 mg (0.86 mmol) of abiraterone of formula II and 6 mg (6 mol %) of dimethylaminopyridine in 3 ml of 2-methyltetrahydrofuran; then, 0.12 ml (1.29 mmol) of acetanhydride is dropwise-added at room temperature within 10 minutes. The mixture is heated in a bath at 80°C for 2 hours. After cooling down, the solution is filtered through a layer of activated charcoal. The solvent is distilled off from the filtrate under reduced pressure and the crude product is stirred up in 2 ml of acetonitrile. After suction off, 194 mg of abiraterone acetate is obtained, purity 99.26%; melting point = 145.8 – 146.6°C. Its NMR spectrum corresponds to the NMR record of abiraterone acetate of formula I. If necessary, the product is re-purified by crystallization from acetonitrile or from an ethanol/water mixture.

Example 8

Abiraterone acetate (1 g) of purity 99.17% (0.22% **IX**) is dissolved in 5 ml of acetonitrile under reflux. During spontaneous cooling, crystallization takes place. The resulting suspension is stirred in an ice bath for 1 hour. After suction off and washing with 1 ml of acetonitrile, 0.87 g of abiraterone acetate is obtained; purity 99.83% (0.09% **IX**); melting point = 146.2 -147.3°C.

Example 9

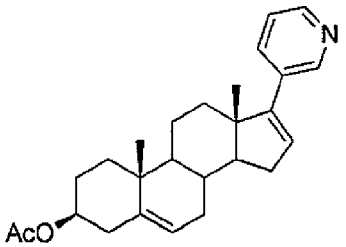
Abiraterone acetate (120 mg) of purity 84.63% (0.17% **IX**) is dissolved in 5 ml of a mixture EtOH/water (1:1) under reflux. The hot solution is filtered through a layer of active charcoal and after cooling down, crystallization takes place. The resulting suspension is stirred in an ice bath for 1 hour. After suction off and washing with 1 ml of the mixture EtOH/water (1:1), 40 mg of abiraterone acetate is obtained; purity 84.03% (0.02% **IX**).

Example 10

Abiraterone acetate (1 g) of purity 99.17% (0.22% **IX**) is dissolved in 60 ml of a mixture EtOH/water (1:1) under reflux. During spontaneous cooling, crystallization takes place. The resulting suspension is stirred in an ice bath for 1 hour. After suction off and washing with 5 ml of a mixture EtOH/water (1:1), 0.95 g of abiraterone acetate is obtained; purity 99.70% (0.16% **IX**); melting point = 145 5 – 146.6°C.

CLAIMS

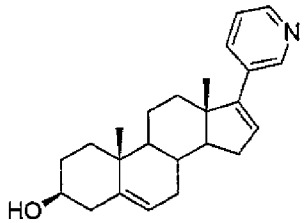
1. A method of preparing abiraterone acetate of formula I,



I

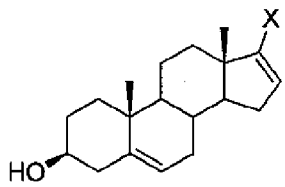
comprising

a) preparation of abiraterone of formula II



II

by the Suzuki reaction of 3-pyridyldiethylborane and a halo steroid of formula VI or VII



VI X=I
VII X=Br

in the presence of a palladium catalytic system, a base, and a solvent;

b) acetylation of abiraterone with formation of abiraterone acetate of formula I;

c) isolation of abiraterone acetate by crystallization,

characterized in that the palladium catalytic system consists of the catalyst palladium acetate - $Pd(OAc)_2$ and the ligand triphenylphosphine - Ph_3P.

2. The method according to Claim 1, characterized in that the ratio of the catalyst $Pd(OAc)_2$ to the ligand Ph_3P is 1 : 2.

3. The method according to Claims 1 to 2, characterized in that the catalyst is used in an amount of 0.1 to 1.5 mol %, preferably 1 mol %.

4. The method according to Claim 1, characterized in that the base is potassium phosphate or caesium carbonate and is used in an amount of 1 to 3 equivalents.

5. The method according to Claim 4, characterized in that the base is potassium phosphate and is used in the amount of 2 equivalents.

6. The method according to Claims 1 to 5, characterized in that the solvent is selected from the group consisting of mixed solvents tetrahydrofuran-THF/water, methyltetrahydrofuran-MeTHF/water, and toluene/water, preferably a mixture THF/ water or MeTHF/water, used in a ratio 2 : 1.5 or 2 : 1.

7. The method according to Claims 1 to 6, characterized in that the reaction of 3-pyridyldiethylborane and the halo steroid of formula **VI** or **VII** is carried out at temperatures higher than 50°C, preferably at the reflux temperature of the azeotropic mixture of solvents, for maximum 24 hours, preferably for 4 hours.

8. The method according to Claim 1, characterized in that abiraterone acetate is crystalized from acetonitrile or a $C_1 - C_4$ alcohol, or from a mixture of a $C_1 - C_4$ alcohol and water.

9. The method according to Claim 8, characterized in that abiraterone acetate is crystalized from a mixture of ethanol and water, or a mixture of 2-propanol and water, or from pure 2-propanol.

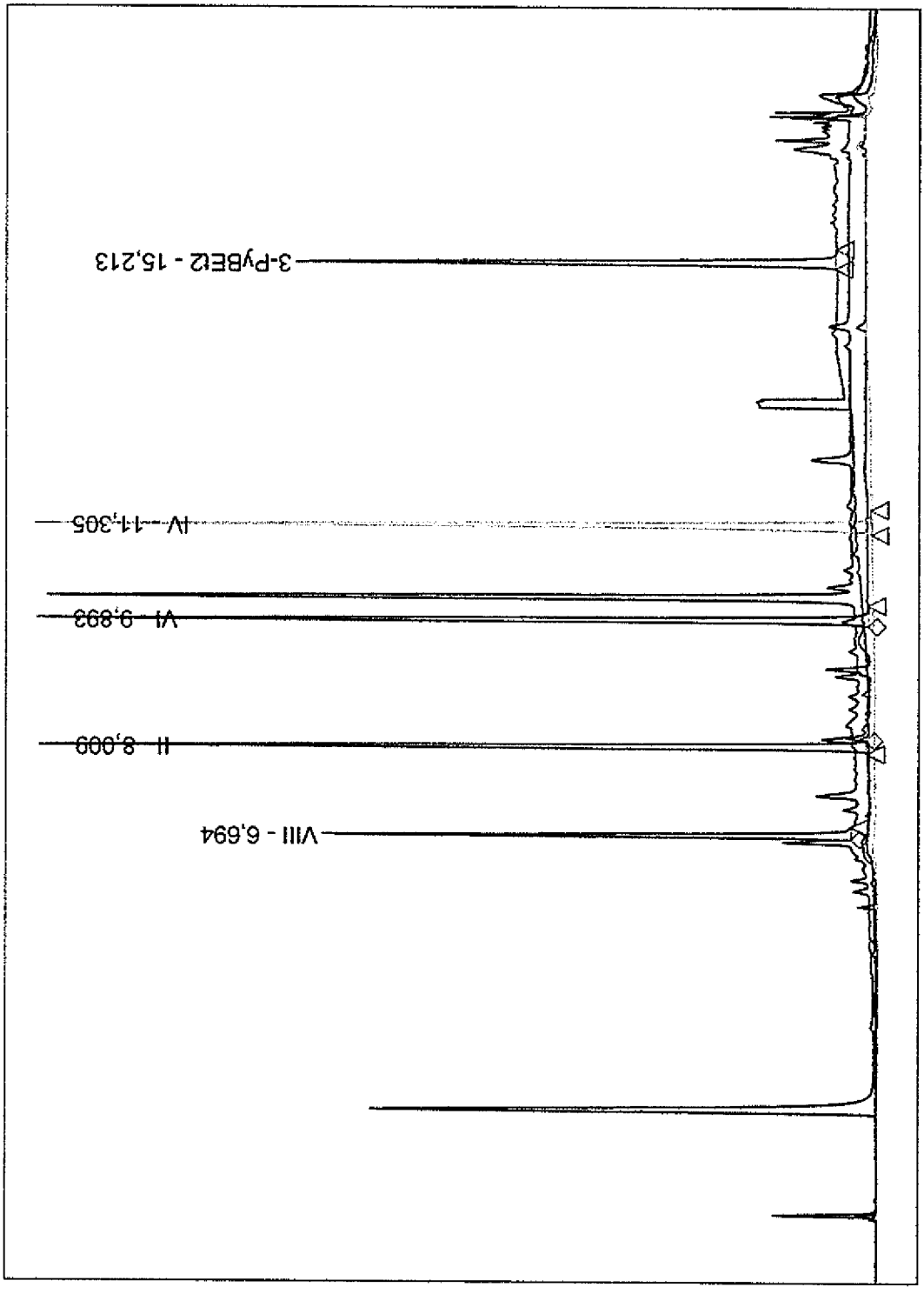
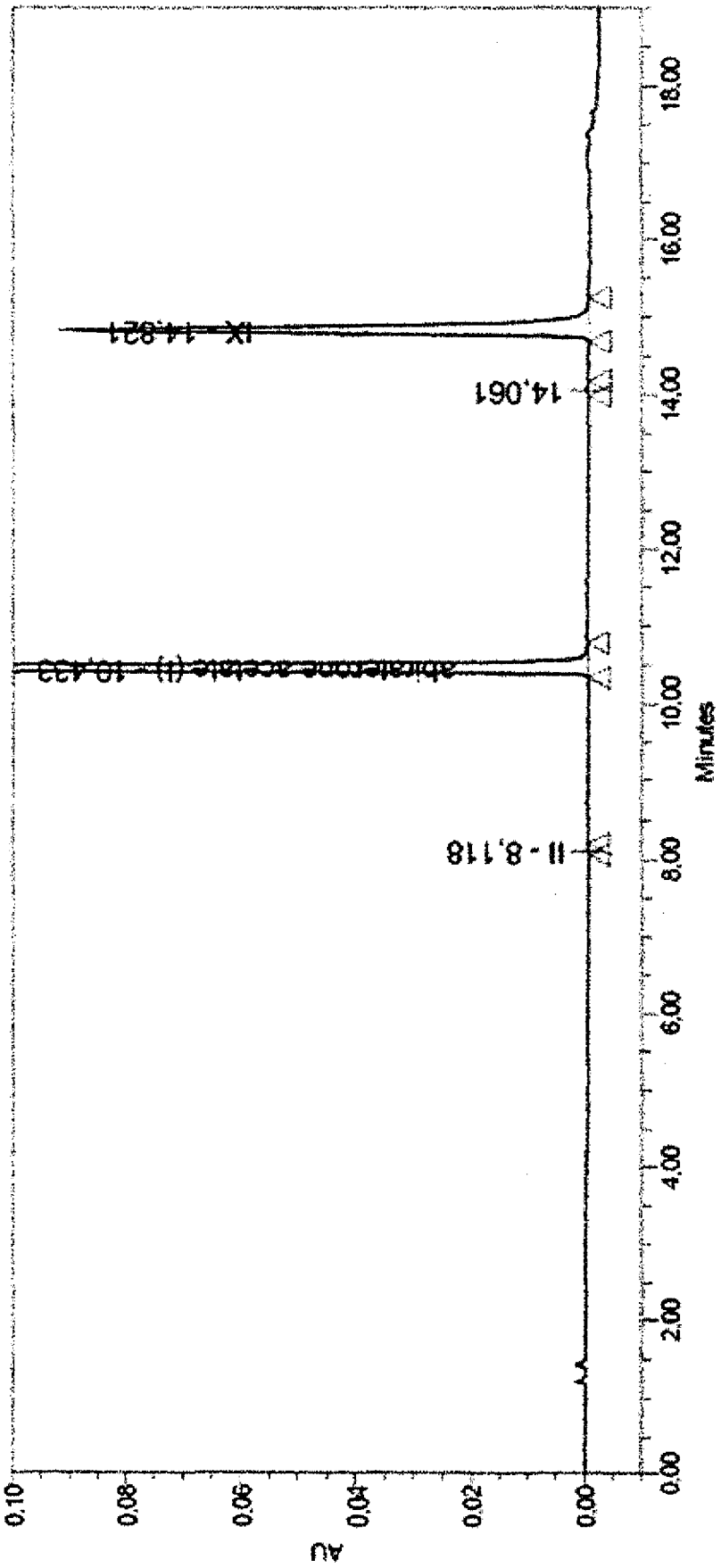


Fig. 1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10,00
12,00
14,00
16,00
18,00
Minutes
II - 8,118
14,061
IX - 14,821

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2015/000075

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J13/00 C07J43/00
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)
C07J

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, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2014/064032 A1 (OLON S P A [IT]) 1 May 2014 (2014-05-01) examples 2, 6	1-9

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

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2015	18/09/2015

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	Watchorn, Peter

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2015/000075

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