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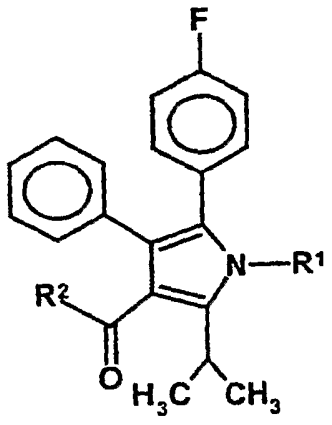
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(54) Title: PROCESS FOR PREPARING PYRROLE DERIVATIVES AND INTERMEDIATES



(I)

(57) Abstract: The present invention relates to a process for preparing pyrrole derivatives of a class that is effective at inhibiting the biosynthesis of cholesterol in humans, and more particularly to improved synthetic methods for preparing 3,5-dihydroxy-7-pyrrol-1-yl heptanoic acids from 1,4-diketo starting materials. The invention further relates to intermediates in this process formula (I).

WO 2006/066823 A1

Process for preparing pyrrole derivatives and intermediates

The present invention relates to a process for preparing pyrrole derivatives of a class that is effective at inhibiting the biosynthesis of cholesterol in humans, and more particularly to improved synthetic methods for preparing 3,5-dihydroxy-7-pyrrol-1-yl heptanoic acids from 1,4-diketo starting materials. The invention further relates to intermediates in this process.

It is known that certain 3,5-dihydroxy heptanoic acid derivatives are competitive inhibitors of the 3-hydroxy-3-methyl-glutaryl-coenzyme A ("HMG-CoA"). HMG-CoA is a key enzyme in the biosynthesis of cholesterol in humans. Its inhibition leads to a reduction in the rate of biosynthesis of cholesterol. The first HMG-CoA inhibitor to be described is compactin ([1*S*-[1α(*R**), 7β, 8β(2*S**, 4*S**),8αβ]]-1,2,3,7,8a-hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate), which was isolated from cultures of *Penicillium* in 1976. In 1987, lovastatin ([1*S*-[1α(*R**),3α, 7β, 8β(2*S**, 4*S**),8αβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoiate) became the first HMG-CoA reductase inhibitor approved by the Food and Drug Administration (FDA) for treatment of hypercholesterolemia. Both compactin and lovastatin are derived from bacterial cultures.

Two other naturally-derived HMG-CoA reductase inhibitors, simvastatin and pravastatin are structurally related to compactin and lovastatin.

In 1987, it was reported in U.S. patent No. 4,681,893 that compounds within a certain class of 3,5-dihydroxy-7-pyrrol-1-yl heptanoic acid (and the corresponding lactones) also were effective at inhibiting the HMG-CoA reductase enzyme. One such compound is [*R*(*R**,*R**)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid ("atorvastatin"), which was said to provide surprising inhibition in U.S. patent No. 5,273,995. Atorvastatin later received FDA approval as an adjunct to a low cholesterol diet to reduce elevated levels of total cholesterol, low density lipoprotein cholesterol, apo B and triglycerides and to increase levels of high density lipoprotein cholesterol in patients with hyperlipidemia.

In contrast to compactin, lovastatin, simvastatin and pravastatin, there is no known fermentation culture that produces atorvastatin. It, and other 3,5-dihydroxy-7-pyrrol-1-yl heptanoic acids, must be synthesized by traditional synthetic methods.

A number of processes for the synthesis of 3,5-trihydroxy-7-pyrrol-1-yl heptanoic acids and in particular atorvastatin are known. Some of the processes are concerned with the synthesis of the 3,5-dihydroxy heptanoic acid side chain of the pyrrole ring while others are concerned with the formation of the pyrrole ring.

For example, EP-A-0 330 172 teaches that the pyrrole ring can be formed by the Paal-Knorr reaction between an 1,4-diketone and a primary amine being a precursor of the 3,5-dihydroxy heptanoic acid side chain. The 1,4-diketone already bears those substituents required at the pyrrole ring of atorvastatin and in particular the (phenylamino)carbonyl group required at position 4 of the pyrrole ring.

WO 2004/046105 also discloses a process comprising the Paal-Knorr reaction between a ketal-protected 7-amino-3,5-dihydroxy-1-heptanol and an 1,4-diketone. Also this diketone already comprises the aminocarbonyl functionality required at position 4 of the pyrrole ring in atorvastatin.

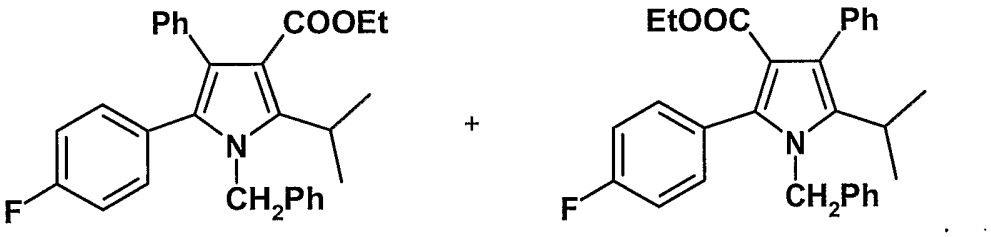
Similar reactions are disclosed in EP-A-0 687 263, WO 02/057274 and WO 03/004457. All these synthesis routes have in common that the Paal-Knorr reaction is conducted with an

1,4-diketone comprising an amino carbonyl moiety and in particular (phenylamino)carbonyl at the position required to finally obtain atorvastatin.

It is, however, difficult to obtain the required 1,4-diketone comprising the amino carbonyl moiety in good yield and purity. Moreover, even when starting from a commercially available 1,4-diketone precursor comprising the required (phenylamino)carbonyl side chain, it turned out to be difficult, if not impossible, to replace the phenylamino residue by other residues such as alkoxy or aryloxy residues without cleavage of the diketone. This limits the possible variation of the substituents and makes a screening for new compounds for inhibiting the biosynthesis of cholesterol in humans difficult.

Therefore, there is still a need for further methods of synthesizing pyrrole derivatives and in particular 3,5-dihydroxy-7-pyrrol-1-yl heptanoic acids having HMG-CoA inhibitory activity.

1,3-dipolar cycloaddition reactions of mesoionic munchnone (1,3-oxazolium-5-olate) with ethyl phenylpropiolate and N1,3-diphenyl-2-propynamide are described by P.S. Pandey et al., in Bioorganic & Medicinal Chemistry Letters 14 (2004) 129-131. The reaction of mesoionic munchnone with ethyl phenylpropiolate is found to be regioselective giving 1:9 ratio of regioisomers 8a and 8b



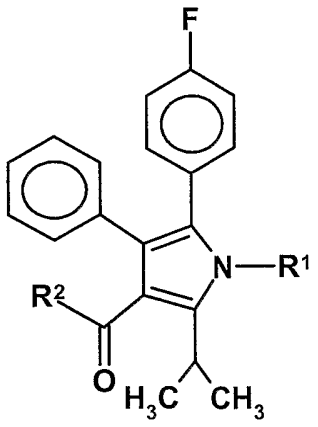
8a 8b

This reaction is, however, said to be undesirable, because 8a is the desired isomer for preparing atorvastatin. The document therefore suggests to carry out the reaction of the mesoionic munchnone with N1,3-diphenyl-2-propionamide, because this reaction is not regioselective and, thus, gives a higher yield of the desired isomer.

Thus, an object of the present invention is to provide a further process for preparing pyrrole derivatives and in particular 3,5-dihydroxy-7-pyrrol-1-yl heptanoic acids. The intermediates in the process should be obtainable in good yield and purity. Moreover, the process should

be suitable for an industrial scale. Furthermore, the process and the intermediates should provide the option to easily modify the side chain on the carbonyl substituent at position 4 of the pyrrole ring of atorvastatin to make the screening of compounds bearing different substituents easier.

It has now surprisingly been found that the above problems can be overcome by a process for preparing a pyrrole derivative of the formula I



I,

wherein

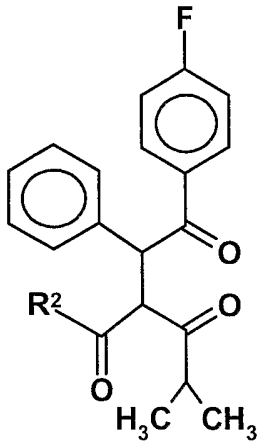
R^1 is hydrogen or a straight or branched, saturated or unsaturated C_{1-30} hydrocarbon group which may comprise 1-5 oxygen atoms, 1-5 nitrogen atoms, 1-2 sulfur atoms, 1 selenium atom and/or 1-5 $-NR^6-$ residues, which hydrocarbon group may be substituted with 1-5 optionally protected hydroxy groups, 1-5 $-OR^7$ residues, 1-5 $-NR^8R^9$ residues, 1-5 halogen atoms and/or 1-5 optionally protected carboxy groups, in which hydrocarbon group 1-5 carbon atoms may form carbonyl groups and which hydrocarbon group or part of which hydrocarbon group may form one or more rings (such as lactones, lactames or oxazolidines),

R^2 is $-OR^3$, $-NR^4R^5$, $-NR^{10}CONR^{11}R^{12}$, $-NR^{13}OR^{14}$, $-ONR^{15}R^{16}$ or halogen,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from hydrogen or a straight, branched and/or cyclic, saturated or unsaturated C_{1-10} alkyl residue or aryl residue, both residues being optionally substituted with 1-3 optionally protected hydroxy or carboxy groups, 1-3 $-OR^7$ residues, 1-3 $-NR^8R^9$ residues and/or 1-3 halogen atoms, the C_{1-10} alkyl residue optionally comprising 1-3 oxygen atoms, 1-3 nitrogen atoms and/or 1-3 $-NR^6-$ residues, the C_{1-10} alkyl residue further optionally comprising or being substituted with 1 or 2 aryl residues,

or a salt thereof,

which process comprises the steps of reacting a compound of the formula II



II,

wherein R^2 is defined as above, or a salt thereof with a compound of the formulae IIIa, IIIb or IIIc

R^1-NH_2 IIIa,

R^1-NH-COO^- H_3N^+-R^1 IIIb,

R^1-NH-$SiR^{17}R^{18}R^{19}$ IIIc,

or mixtures thereof, wherein R^1 is defined as above,

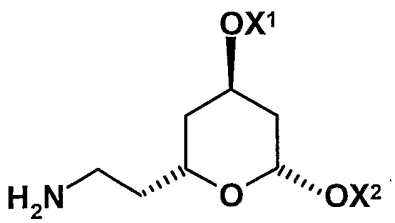
R^{17} and R^{18} are independently selected from straight, branched and/or cyclic C_{1-10} alkyl residues or aryl residues, and

R^{19} is straight, branched and/or cyclic C_{1-10} alkyl residue, aryl residue or -NH-R^1,

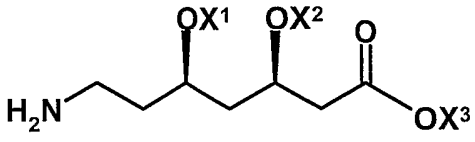
and, if necessary, converting the obtained pyrrole derivative having the substituent R^1 into a pyrrole derivative having a different substituent R^1,

provided that if R^2 is $-NR^4R^5$ the compound of the formula IIIa is NH_3.

Preferably the compound of the formula IIIa is not



or



wherein X^1, X^2 and X^3 are hydrogen or protecting groups, in particular if R^2 is $-OR^3$ (such as $-OCH_2CH_3$).

One advantage of the process of the present invention is that if R^2 is $-OR^3$ or halogen the compound of the formula II is easy to produce in good yield and purity. A further advantage is that if R^2 is $-OR^3$ or halogen the intermediate compound of the formula II provides the possibility of easy substitution of the R^2 residue, thereby providing higher flexibility for example for screening substituted pyrrole compounds for their pharmaceutical activity. This finding is particularly unexpected, since the corresponding known diketone anilide (2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid phenylamide) turned out to be stable to hydrolysis. It reacts with base and hydrogen peroxide not to the expected acid but it breaks to 1-(4-fluorophenyl)-2-phenylethan-1-one (compound of formula VIII). This problem does not arise when using the corresponding diketone ester or acid halogenide (compound of the formula II).

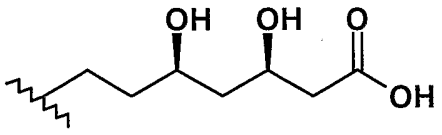
Moreover, if using NH_3 as the compound of the formula IIIa in the process of the present invention, the yield of the ring-forming reaction is significantly higher compared to reactions with compounds of the formula IIIa, wherein R^1 is other than hydrogen.

In the process of the present invention a compound of the above formula II is reacted with a compound of the above formulae IIIa, IIIb or IIIc. In the compound of the formulae IIIa, IIIb and IIIc R^1 is either hydrogen or a hydrocarbon group. If in the compound of formula IIIa R^1 is hydrogen, liquid ammonia, aqueous ammonia or a solution of an ammonium salt such as NH_4Cl or CH_3COONH_4 can be used. Thus, NH_3 as one compound of the formula IIIa also includes NH_4^+ ions which will always be present in the reaction solution in dependence of the pH value of the solution. Preferably the diketone of the formula II is reacted with CH_3COONH_4. The reaction can be carried out in any common inert solvent such as THF preferably at elevated temperatures, such as, for example, under reflux.

In one embodiment the reaction is conducted with ammonium acetate in refluxing THF for about 6 hours. The yield of this reaction is considerably higher than the yield of the similar reaction with benzylamine instead of ammonium acetate.

Instead of NH_3 a primary amine (formula IIIa), an amine derivative with carbon dioxide (formula IIIb) or a silylated amine (formula IIIc) can be employed in the process of the present invention. In this case the substituent R^1 is not particularly limited and can be chosen among the hydrocarbon groups defined above for R^1. Preferably R^1 is a straight or branched, saturated or unsaturated C_{1-20} hydrocarbon group, in particular C_{1-20} alkyl group, which may comprise 1-5 oxygen atoms, may be substituted with 1-5 optionally protected hydroxy groups, 1 or 2 $-NR^8R^9$ residues (wherein R^8 and R^9 are defined as above) and/or 1 or 2 optionally protected carboxy groups, in which hydrocarbon group 1-5 carbon atoms may form carbonyl groups and which hydrocarbon group or part of which hydrocarbon group may form 1 or more rings.

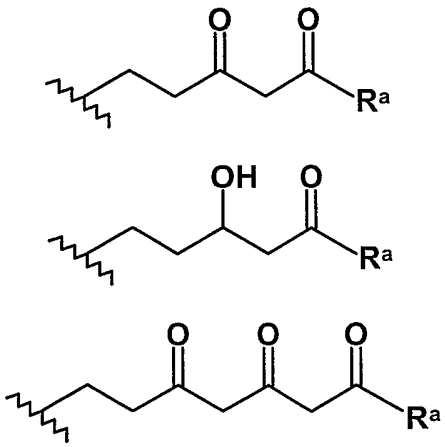
In one embodiment of the process of the present invention R^1 is a residue of the formula X

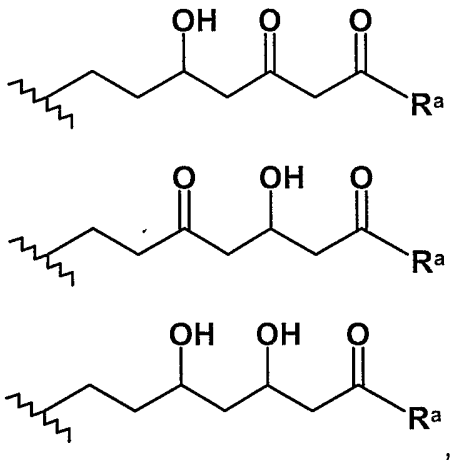


X

which may optionally be protected or is chosen such that it can easily be converted into a residue of the formula X. Residues which can be converted into residues of the formula X are for example known from WO 2004/046105, WO 94/20492, WO 02/057274, WO 02/055519, EP-A-0 330 172, EP-A-0 179 559, EP-A-0 247 633 and EP-A-0 409 281. The disclosures of these documents are therefore incorporated by reference herein.

Preferred residues for R^1 are selected from the following residues:





wherein R^a is $-OR^b$, $-SR^c$, SeR^d or $-NR^eR^f$;

R^b, R^c and R^d are independently selected from straight, branched and/or cyclic, saturated or unsaturated C_{1-10} alkyl residue, aryl residue or arylalkyl residue;

R^e and R^f are independently selected from straight, branched and/or cyclic, saturated or unsaturated C_{1-10} alkyl residue, aryl residue or arylalkyl residue or

R^e and R^f taken together are

$-(CH_2)_4-$

$-(CH_2)_5-$

$-(CH(R^g)-CH_2)_3-$

$-(CH(R^g)-CH_2)_4-$

$-(CH(R^g)-(CH_2)_2-CH(R^g))-$

$-(CH(R^g)-(CH_2)_3-CH(R^g))-$

$-CH_2-CH_2-A-CH_2-CH_2-$

$-CH(R^g)-CH_2-A-CH_2-CH_2-$

$-CH(R^g)-CH_2-A-CH_2-CH(R^g)-$,

wherein R^g is C_{1-4} alkyl residue and A is O, S or NR^h, wherein R^h is hydrogen or C_{1-4} alkyl residue;

and each hydroxy group may independently be protected with a suitable protecting group whereby two hydroxy groups together with their protecting group may form a ring. It is understood that any of the residues R^1 can be, if possible, in its lactone or lactame form.

As protecting groups for the optionally protected hydroxy groups and the optionally protected carboxy groups usual protecting groups known to the person skilled in the art may be used. Suitable protecting groups are exemplified in WO 03/044011, which therefore is incorporated by reference herein.

In the compound of the formula II R^2 may be $-OR^3$, $-NR^4R^5$ or halogen, preferably $-OR^3$ or halogen and most preferred $-OR^3$. Herein R^3, R^4 and R^5 are defined as above.

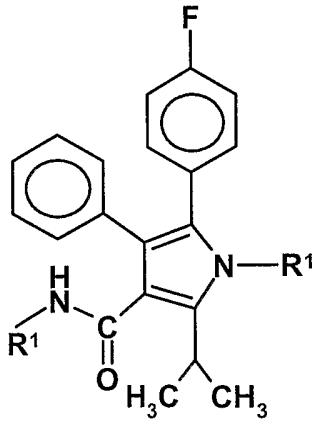
For R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^b, R^c, R^d, R^e and R^f the alkyl residue is preferably a straight or branched, saturated or unsaturated C_{1-6} alkyl residue or a cyclic C_{3-6} alkyl residue, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, n-hexyl or cyclohexyl. Preferred aryl residues are phenyl and naphthyl, particularly preferred phenyl. The aryl residue furthermore includes heteroaryl residues such as pyrrole or pyridine. The preferred arylalkyl residue is benzyl.

For R^{17}, R^{18} and R^{19} the alkyl residue is preferably a straight or branched C_{1-6} alkyl residue or a cyclic C_{3-6} residue, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, n-hexyl or cyclohexyl. Preferred aryl residues are phenyl and naphthyl, particularly preferred phenyl. The aryl residue furthermore includes heteroaryl residues such as pyrrole or pyridine.

In the present application halogen stands for fluoro, chloro, bromo or iodo, preferably chloro or bromo.

The primary amine of the formula IIIa or the amines of the formulae IIIb or IIIc are reacted with a diketone of the formula II. This reaction can for example be carried out under the same conditions as described above for the reaction, wherein the compound of the formula IIIa is NH_3. Further detailed reaction conditions can for example be found in WO 2004/046105, WO 94/20492 and EP-A-0 330 172. For example, the reaction can be conducted under heating with azeotropical water removed in an appropriate solvent or mixture of solvents catalyzed with an acid, such as, for example, pivalic acid. As suitable solvents n-heptane, toluene and THF or mixtures thereof can be mentioned. Alternatively the reaction can be conducted without any solvent (neat) under heating the reactants to for example about 120°C to 140°C.

When reacting a compound of the formula II, wherein R^2 is $-OR^3$ or halogen with a compound of the formulae IIIa, IIIb or IIIc a by-product of the following formula IV

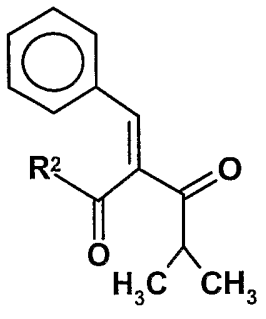


IV,

wherein R^1 at both occurrences are identical and defined as above may be obtained. In this case the desired pyrrole derivative of the formula I may be separated from the reaction by-product of the formula IV, and the reaction by-product can subsequently be converted into a pyrrole derivative of the formula I, wherein R^2 is $-OR^3$, $-NR^4R^5$ or halogen and R^3, R^4 and R^5 are defined as above, provided that $-NR^4R^5$ is different from $-NHR^1$. This reaction route is effective for recycling undesired by-products obtained in the reaction between the diketone of the formula II and the amine of the formula III.

In a further embodiment of the process of the present invention the compound of the formula II is obtained by

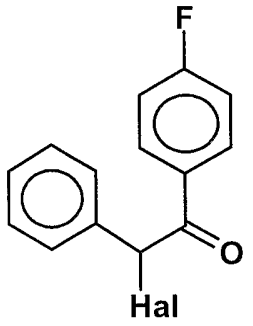
a) reacting a compound of the formula V



V,

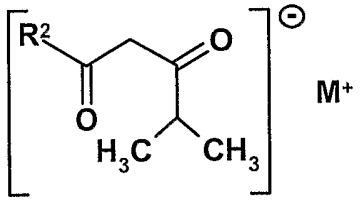
wherein R^2 is defined as in claim 1,
with 4-fluorobenzaldehyde or

b) reacting a compound of the formula VI



VI,

wherein Hal is halogen, preferably bromo with a compound of the formula VII



VII,

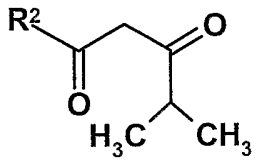
wherein R^2 is defined as in claim 1 and M^+ is selected from H^+, Li^+, Na^+ and K^+, preferably Na^+.

The above reaction route a) has the advantage that the compound of the formula V, wherein R^2 is $-OR^3$ can be easily purified by distillation. Thus, this intermediate can be employed in the following reaction in a highly pure form.

The above reaction route b) has the advantage that the compound of the formula VI can easily be obtained from the commercially available 2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid phenylamide by cleavage with hydrogen peroxide in the presence of a base such as NaOH.

Above reaction a) can for example be carried out under solvent-free conditions catalyzed by 2-(2-hydroxyethyl)-3-methyl-4-ethylthiazolium bromide in the presence of triethylamine under heating to for example to a temperature of about 60°C to about 80°C.

In reaction route a) the compound of the formula V can be obtained by reacting a compound of the formula IX



IX,

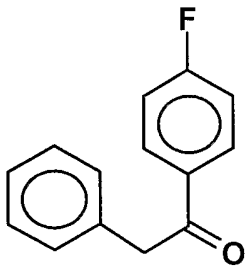
wherein R^2 is defined as above with benzaldehyde. This reaction can be carried out in the presence of a catalyst such as, for example, piperidine and glacial acetic acid, ethylene diamine and glacial acetic acid, β-alanine and glacial acetic acid, and the like in an inert solvent such as, for example, toluene, heptane, hexane, and the like for about 24 to about 36 hours at about 60°C to about 120°C with the removal of water to afford a compound of the formula V.

If in the compound of the formula V R^2 is $-OR^3$, this compound is heat-stable and can be distilled as to separate the desired compound of the formula V from undesired by-products of the reaction. In a preferred embodiment of the process of the present invention the reaction between the compound of the formula IX and benzaldehyde is catalyzed with β-alanine in the presence of acetic acid, preferably glacial acetic acid, in toluene. The reaction mixture is heated under reflux with azeotropic removal of water for about 24 hours. After usual workup the product can be distilled under reduced pressure.

In the alternative embodiment according to above route b) the compound of the formula II is obtained by reacting the compounds of the formula VI and VII with each other. This addition reaction can be carried out in any suitable inert organic solvent, preferably anhydrous inert organic solvent, such as, for example, ethers, e.g. diethyl ether, 1,2-diethoxyethane, 1,2-dimethoxyethane, THF or mixtures thereof. Preferably the reaction is carried out in THF. The reaction temperature may be in the range of for example about 0°C to about 40°C, preferably from about 0°C to about room temperature.

In a preferred embodiment the compound of the formula VII is prepared in situ.

The compound of the formula VI can be obtained by halogenating the compound of the formula VIII

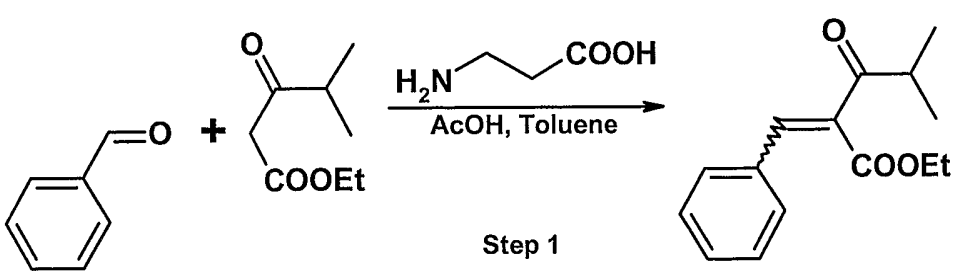


VIII.

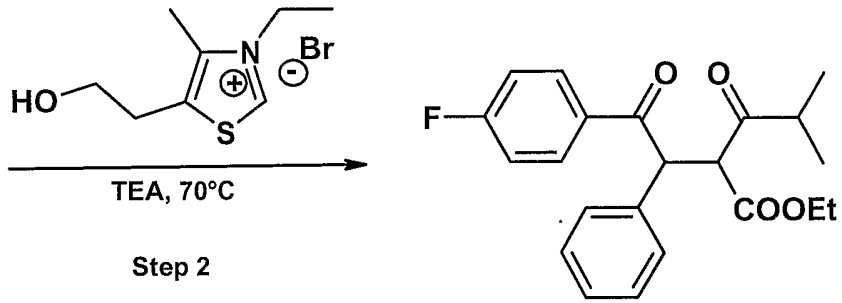
Halogenation, preferably bromination of the compound of the formula VIII can be carried out with for example bromine in an inert organic solvent, preferably an anhydrous inert organic solvent, such as, for example, halogenated lower alkane solvents, e.g. CCl_4, $CHCl_3$, 1,1-dichloroethane, 1,2-dichloroethane, methylene chloride, 1,1,2-trichloroethane or mixtures thereof. A preferred solvent is $CHCl_3$. The reaction can be carried out for example at a temperature of about 0°C to about 40°C.

The compound of the formula VIII can be obtained by cleavage of a compound of the formula II, wherein R^2 is $-NR^4R^5$, and R^4 and R^5 are defined as above, such as the commercially available 2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid phenylamide. The cleavage can be carried out for example with hydrogen peroxide in the presence of a base such as NaOH.

A particularly advantageous route for the synthesis of a compound of the formula II is shown in the following scheme:



Step 1



Advantages of the synthesis of diketone ethyl ester by this route are:

- no need of reaction solvent in step 2 (environmental, economic);
- no need of recrystallization process in step 1 (environmental, economic), product is isolated by distillation;
- this is the shortest synthetic route (only 2 steps) in comparison with other known processes (3-5 steps required);
- in the process for the step 1 nontoxic catalyst (β-alanine) is used (environmental);
- no need of toxic a corrosive reagents (like bromine in alternative route);
- all starting materials are commercially available.

The present invention further relates to compounds of the formula I, II and IV, wherein R^2 is $-OR^3$ or halogen and R^1 at both occurrences are identical and defined as above, respectively. These compounds are useful intermediates in the preparation of atorvastatin.

The present invention will now be further illustrated by the following examples which are not intended to be limiting.

Examples

1. Synthesis of ethyl-2-benzylidene-4-methyl-3-oxopentanoate (compound of formula V)

A mixture of benzaldehyde (33.8 g, 319 mmol), ethyl isobutyrylacetate (50.4 g, 319 mmol), β-alanine (1.0 g) and acetic acid (10 ml) in 600 ml of toluene was stirred and heated under reflux with azeotropic removal of water (Dean-Stark adapter) until GC analysis showed no presence of starting material (24 h). The solution was cooled, poured into ethylacetate (400

ml), washed with 1 M HCl solution (2 x 100 ml), saturated $NaHCO_3$ solution (2 x 100 ml) and brine (100 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield 76.3 g of brown oil which was further distilled under reduced pressure (bp 105 - 120°C/0.06 mm Hg) to afford 58.9 g (75%) of ethyl 2-benzylidene-4-methyl-3-oxopentanoate as a mixture of isomers (major ~ 70%).

2. Synthesis of ethyl 2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxopentanoate (compound of formula II)

To a stirred mixture of ethyl 2-benzylidene-4-methyl-3-oxopentanoate (52.5 g, 0.213 mol), 4-fluorobenzaldehyde (39.7 g, 0.320 mol) and 2-(2-hydroxyethyl)-3-methyl-4-ethylthiazolium bromide (8.11 g, 0.032 mol) was added dropwise triethylamine (21.3 ml). The solution turned dark and precipitation of solid particles was observed. A mixture was then heated at 70°C until the reaction mixture did not contain starting ethyl 2-benzylidene-4-methyl-3-oxopentanoate (HPLC monitoring). After cooling to room temperature, the mixture was diluted with ethylacetate (500 ml) and water (100 ml). The organic phase was washed with 1 M HCl solution (2 x 100 ml), saturated $NaHCO_3$ solution (2 x 100 ml) and brine (100 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield 100.2 g of impure oily product which was then dissolved in dichloromethane (400 ml) and silicagel (50 g) was added. The mixture was stirred for 10 minutes and the silicagel was filtered off and washed with dichloromethane (500 ml). Air was bubbled through the combined filtrates for 24 hours in order to oxidize remaining 4-fluorobenzaldehyde. Additional 200 ml of dichloromethane was added to the reaction mixture to compensate losses due to evaporation and the solution was washed with saturated $NaHCO_3$ solution (2 x 100 ml) and water (100 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield 87 g yellow oily product which slowly solidified. The oily product contains 85% of ethyl 2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxopentanoate and the calculated yield was then 94%.

3. Synthesis of ethyl 5-(4-fluorophenyl)-2-isopropyl-1-phenethyl-4-phenyl-1*H*-pyrrole-3-carboxylate (compound of the formula I)

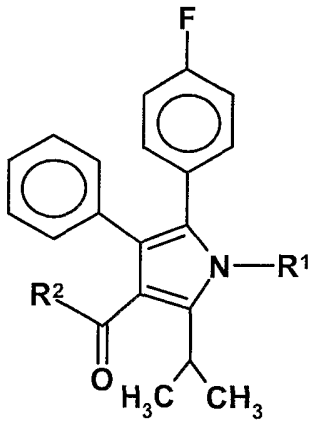
Ethyl 2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxopentanoate (reagent 1) was reacted with 2-phenylethylamine (reagent 2) under the conditions summarized in the following table 1.

Table 1

Exp. No.:	Ratio of reagents 1:2:catalyst	Catalyst	Solvents	Conditions	Reaction time [h]	Yield [%]
1	1:1:1	Pivalic acid	*n*-heptane, THF, toluene	Reflux with azeotropic water removal	96	72.4
2	1:1:2	Pivalic acid	-	Heating neat at 125-130°C	48	65.0
3	1:1.5:1.5	Pivalic acid	*n*-heptane, THF, toluene	Reflux with azeotropic water removal	24	68.5

Claims:

1. Process for preparing a pyrrole derivative of the formula I



I,

wherein

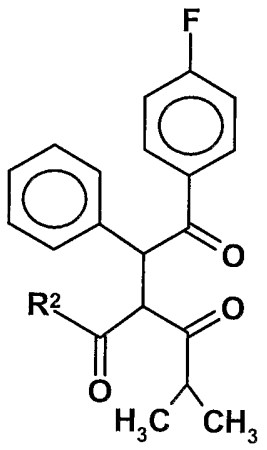
R^1 is hydrogen or a straight or branched, saturated or unsaturated C_{1-30} hydrocarbon group which may comprise 1-5 oxygen atoms, 1-5 nitrogen atoms, 1-2 sulfur atoms, 1 selenium atom and/or 1-5 $-NR^6-$ residues, which hydrocarbon group may be substituted with 1-5 optionally protected hydroxy groups, 1-5 $-OR^7$ residues, 1-5 $-NR^8R^9$ residues, 1-5 halogen atoms and/or 1-5 optionally protected carboxy groups, in which hydrocarbon group 1-5 carbon atoms may form carbonyl groups and which hydrocarbon group or part of which hydrocarbon group may form one or more rings,

R^2 is $-OR^3$, $-NR^4R^5$, $-NR^{10}CONR^{11}R^{12}$, $-NR^{13}OR^{14}$, $-ONR^{15}R^{16}$ or halogen,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently selected from hydrogen or a straight, branched and/or cyclic, saturated or unsaturated C_{1-10} alkyl residue or aryl residue, both residues being optionally substituted with 1-3 optionally protected hydroxy or carboxy groups, 1-3 $-OR^7$ residues, 1-3 $-NR^8R^9$ residues and/or 1-3 halogen atoms, the C_{1-10} alkyl residue optionally comprising 1-3 oxygen atoms, 1-3 nitrogen atoms and/or 1-3 $-NR^6-$ residues, the C_{1-10} alkyl residue further optionally comprising or being substituted with 1 or 2 aryl residues,

or a salt thereof,

which process comprises the steps of reacting a compound of the formula II



II,

wherein R^2 is defined as above, or a salt thereof with a compound of the formulae IIIa, IIIb or IIIc

R^1-NH_2 IIIa,

R^1-NH-COO^- H_3N^+-R^1 IIIb

R^1-NH-$SiR^{17}R^{18}R^{19}$ IIIc,

or mixtures thereof, wherein R^1 is defined as above,

R^{17} and R^{18} are independently selected from straight, branched and/or cyclic C_{1-10} alkyl residue or aryl residue; and

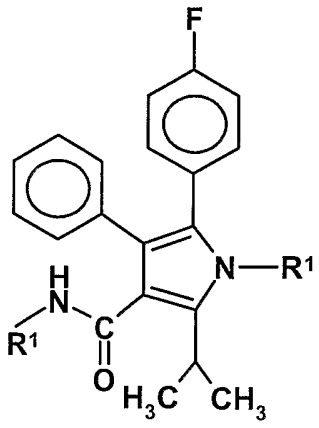
R^{19} is straight, branched and/or cyclic C_{1-10} alkyl residue, aryl residue or -NH-R^1,

and, if necessary, converting the obtained pyrrole derivative having the substituent R^1 into a pyrrole derivative having a different substituent R^1,

provided that if R^2 is -NR^4R^5 the compound of the formula IIIa is NH_3.

2. Process according to claim 1, wherein R^2 is -OR^3 or halogen.

3. Process according to claim 2, which comprises the additional step of separating the pyrrole derivative of the formula I from the reaction by-product of the formula IV



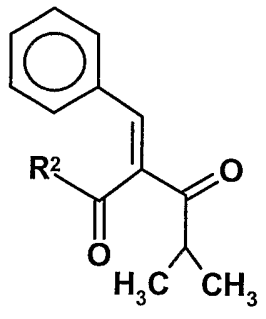
IV,

wherein R^1 at both occurrences are identical and defined as in claim 1.

4. Process according to claim 3, which comprises the additional step of converting the separated reaction by-product of the formula IV into a pyrrole derivative of the formula I, wherein R^2 is $-OR^3$, $-NR^4R^5$ or halogen and R^3, R^4 and R^5 are defined as in claim 1, provided that $-NR^4R^5$ is different from $-NHR^1$.

5. Process according to any of the preceding claims, wherein the compound of formula II is obtained by

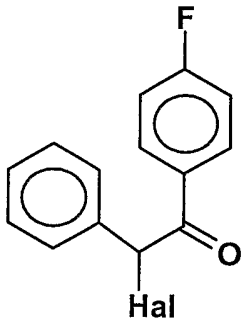
a) reacting a compound of the formula V



V,

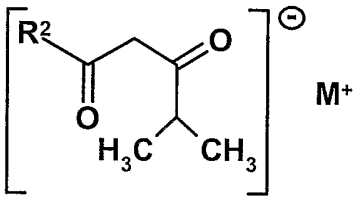
wherein R^2 is defined as in claim 1,
with 4-fluorobenzaldehyde or

b) reacting a compound of the formula VI



VI,

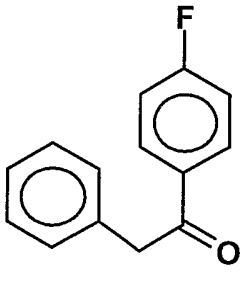
wherein Hal is halogen, with a compound of the formula VII



VII,

wherein R^2 is defined as in claim 1 and M^+ is selected from H^+, Li^+, Na^+ and K^+, preferably Na^+.

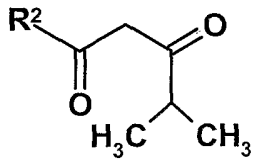
6. Process according to claim 5, wherein the compound of the formula VI is obtained by halogenating the compound of the formula VIII



VIII.

7. Process according to claim 6, wherein the compound of the formula VIII is obtained by cleavage of a compound of the formula II, wherein R^2 is $-NR^4R^5$, and R^4 and R^5 are defined as in claim 1.

8. Process according to claim 5, wherein the compound of the formula V is obtained by reacting a compound of the formula IX



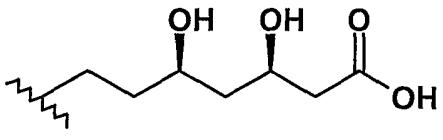
IX,

wherein R^2 is defined as in claim 1 with benzaldehyde.

9. Process according to any of the preceding claims, wherein R^1 is a straight or branched, saturated or unsaturated C_{1-20} hydrocarbon group which may comprise 1-5 oxygen atoms, may be substituted with 1-5 optionally protected hydroxy groups, 1 or 2 $-NR^8R^9$ residues (wherein R^8 and R^9 are defined as in claim 1) and/or 1 or 2 optionally protected carboxy groups, in which hydrocarbon group 1-5 carbon atoms may form carbonyl groups and which hydrocarbon group or part of which hydrocarbon group may form one or more rings.

10. Process according to any of the preceding claims, wherein R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are independently selected from hydrogen, a straight or branched, saturated or unsaturated C_{1-6} alkyl residue, a cyclic C_{3-6} alkyl residue or phenyl.

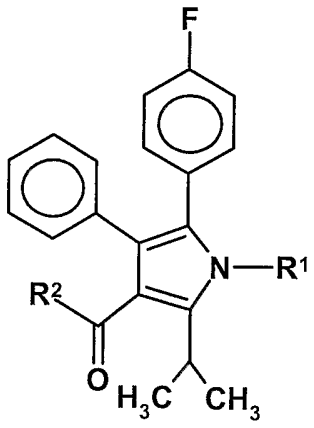
11. Process according to any of the preceding claims, wherein in the compound of the formula I R^2 is or is converted to -NH-phenyl and R^1 is or is converted to a residue of the formula X



X

which may optionally be protected.

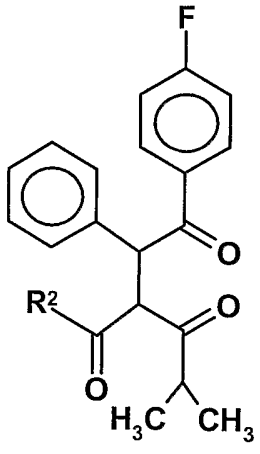
12. Compound of the formula I



I,

wherein R^2 is $-OR^3$ or halogen and R^1 and R^3 are defined as in claim 1, or a salt thereof, provided that if R^3 is ethyl R^1 is not $-CH_2$-phenyl.

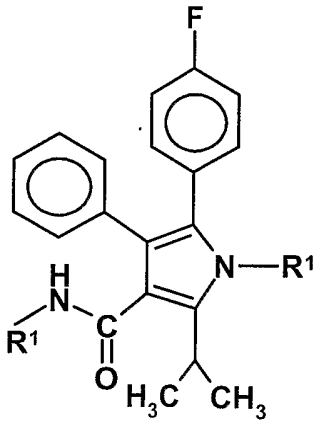
13. Compound of the formula II



II,

wherein R^2 is $-OR^3$ or halogen and R^3 is defined as in claim 1, or a salt thereof, provided that R^3 is not ethyl.

14. Compound of the formula IV



IV,

wherein R^1 at both occurrences are identical and defined as in claim 1, or a salt thereof.

15. Use of a compound of the formula I as defined in claim 12 for the preparation of atorvastatin.

16. Use of a compound of the formula II as defined in claim 13 for the preparation of atorvastatin.

17. Use of a compound of the formula IV as defined in claim 14 for the preparation of atorvastatin.

INTERNATIONAL SEARCH REPORT

PCT/EP2005/013588

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D207/34 C07C69/738

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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/106299 A (RANBAXY LABORATORIES LIMITED; SALMAN, MOHAMMAD; SATTIGERI, JITENDRA; K) 9 December 2004 (2004-12-09) * page 51, line 1 - page 52, line 23; scheme II on page 20; claims 81-90,92 *	1-12,14, 15,17
X	scheme II, compound XX wherein R2 is -OR3=-OBenzyl, p.20	13,16
X	WO 03/044011 A (CIBA SPECIALTY CHEMICALS HOLDING INC; OEHRLEIN, REINHOLD; BAISCH, GABR) 30 May 2003 (2003-05-30) cited in the application example 6	12,15
X	example 6, intermediate III	13,16

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 May 2006	26/05/2006

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schuemacher, A

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROTH B D ET AL: "INHIBITORS OF CHOLESTEROL BIOSYNTHESIS. 3. TETRAHYDRO-4-HYDROXY-6-(2-(1H-PYRROL-1-YL)ETHYL)-2H-PYRAN-2-ONE INHIBITORS OF HMG-COA REDUCTASE. 2. EFFECTS OF INTRODUCING SUBSTITUENTS AT POSITIONS THREE AND FOUR OF THE PYRROLE NUCLEUS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 1, January 1991 (1991-01), pages 357-366, XP002922115 ISSN: 0022-2623 * compounds 11d,16a,16b,17a,17b,3g in schemes III, IV and tables I, II, III and on pages 363, 364 *	12,15
X	PROCOPIOU P A ET AL: "INHIBITORS OF CHOLESTEROL BIOSYNTHESIS. 2. 3,5-DIHYDROXY-7-(N-PYRROLY L)-6-HEPTENOATES, A NOVEL SERIES OF HMG-COA REDUCTASE INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, no. 23, 1993, pages 3658-3662, XP002303229 ISSN: 0022-2623 * abstract; compound 6b and step iv in scheme I *	1,12
P,X	WO 2005/012246 A (AVECIA LIMITED; MOODY, DAVID, JOHN; WIFFEN, JONATHAN, WILLIAM) 10 February 2005 (2005-02-10) page 8, line 1 - line 4; claim 1; example 5	1,2, 9-12,15
P,X	page 8	13,16
Y	WO 03/004457 A (CIBA SPECIALTY CHEMICALS HOLDING INC; SCHOENING, KAI-UWE; HARTWIG, JEM) 16 January 2003 (2003-01-16) cited in the application page 13 - page 15; claims	1-12,14, 15,17
Y	GRAUL A ET AL: "ATORVASTATIN CALCIUM" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 22, no. 9, 1997, pages 956-968, XP000904817 ISSN: 0377-8282 page 958 - page 960	1-12,14, 15,17

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INTERNATIONAL SEARCH REPORT

PCT/EP2005/013588

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PANDEY P S, RAO T S: "An efficient synthesis of N3,4-diphenyl-5-(4-fluorophenyl)-2-isopropyl-1H-3-pyrrolecarboxamide, a key intermediate for atorvastatin synthesis" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 1, 5 January 2004 (2004-01-05), pages 129-131, XP002328323 cited in the application Compound 10 in scheme 2 and on page 130, column 2, lines 12 - 18	1-17
P,X	WO 2005/118536 A (RANBAXY LABORATORIES LIMITED; SATTIGERI, JITENDRA, A; SALMAN, MOHAMMAD) 15 December 2005 (2005-12-15) formula IV, scheme 1, p.3 the whole document	13,16

INTERNATIONAL SEARCH REPORT

PCT/EP2005/013588

Box II ***Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)***

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III ***Observations where unity of invention is lacking (Continuation of item 3 of first sheet)***

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12,14,15,17

   The process according to claims 1-11, the products of formula I according to claim 12, the side-product of formula IV according to claim 14 and the use of the said two compound types of formulae I and IV, namely claims 15 and 17.

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2. claims: 13,16

   Compounds II according to claim 13 and the use thereof (claim 16).

INTERNATIONAL SEARCH REPORT

PCT/EP2005/013588

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004106299 A	09-12-2004	AU 2004242777 A1	09-12-2004
		CA 2526730 A1	09-12-2004
WO 03044011 A	30-05-2003	AU 2002342909 A1	10-06-2003
		CA 2464314 A1	30-05-2003
		JP 2005520792 T	14-07-2005
		US 2005014954 A1	20-01-2005
WO 2005012246 A	10-02-2005	AU 2004261468 A1	10-02-2005
		CA 2530163 A1	10-02-2005
		EP 1648866 A1	26-04-2006
WO 03004457 A	16-01-2003	NONE	
WO 2005118536 A	15-12-2005	NONE	