Abstract: It comprises a preparation process of Valsartan from new salts of Valsartan having the tetrazole moiety protected with a protective group. The process leads to the elimination of the typical impurities due to the preparation process while avoiding its racemization, yielding a Valsartan with high purity and high yield. It also comprises the salts of Valsartan having the tetrazole moiety protected with a protective group, which are new intermediates, and also its preparation processes.
The present invention relates to new salts of Valsartan having the tetrazole moiety N-protected. It relates also to their preparation process, as well as to a process for the preparation of Valsartan from such intermediate salts.

BACKGROUND ART

Valsartan is the generic name of the N-pentanoyl-N-\{[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl\}-l-valine, having the formula (I).

\[
\text{(I)}
\]

Valsartan is an Angiotensin II (A-II) receptor antagonist known since the publication of the European patent EP 443.983-A. In this document two preparation processes of Valsartan are described. Both processes involve a coupling between the biphenyl moiety and the valine moiety which is carried out by reductive amination, and subsequently N-acylation to introduce the acyl moiety.

Valsartan could also be prepared by a process which involves the coupling of both phenyl moieties. In EP 994.881-A a preparation process of 2-substituted-1-(tetrazol-5-yl)benzenes by coupling a suitable bromophenyl derivative with an ortho-methylated (tetrazol-5-yl)benzene is described. According to this patent application, such compounds are useful intermediates for the preparation of several Angiotensin II antagonists.

Several attempts to purify Valsartan have been described in the art. In WO
2004/094391 different processes for the preparation of Valsartan or for its purification are described. The purification is carried out during the transformation of trityl Valsartan as free acid form to Valsartan using a cleaning mixture of solvents. According to this patent application said mixture can also be used to purify Valsartan. Nevertheless, the Valsartan obtained by these processes has a considerable amount of the D-isomer.

The isolation of Valsartan by crystallization from ethyl acetate results in low yields and also presents several problems associated with filtration and drying. WO 05/049588 describes a process for isolating Valsartan with a purity greater than 99% from a mixture of a solvent and antisolvent.

In any case, the main problem associated with the recrystallization of Valsartan is that the product may racemize, particularly with temperature. Other attempts to purify Valsartan consist of the formation of a salt thereof. Thus, WO05/049587 describes a process for the preparation of pure Valsartan by formation of a salt thereof which is isolated in a solid state and then converting again into Valsartan.

Despite the teaching of these prior art documents, the research of new preparation processes of pure Valsartan is still an active field, since Valsartan and its intermediates are difficult to purify by methods that avoid racemization. Thus, the provision of new preparation processes of Valsartan, in particular if they lead to Valsartan in a high degree of chemical and enantiomeric purity, is still a matter of great interest in industry.

SUMMARY OF THE INVENTION

Inventors have surprisingly found that the purification of Valsartan, as well as their salts and solvates, including hydrates, through the formation and isolation of a salt of Valsartan having the tetrazole moiety protected with an amino protective group, leads to the elimination of the typical impurities due to the preparation process while avoiding its racemization. As it is said above, racemization is the major problem of Valsartan and its intermediates having the carboxy group as free acid form. In contrast with such intermediates, the salts of the present invention are very stable compounds and no racemization is produced when they are heated. Therefore said salts can be easily purified
and are isolated in a highly enantiomerically pure form, and also highly enantiomerically pure Valsartan can be obtained from them.

Accordingly, a first aspect of the present invention refers to the provision of a salt of a compound of formula (H)-P,

\[
\text{(N)-P}
\]

wherein: P is an amino protective group. As previously mentioned, these salts are very stable which is advantageous not only to carry out the purification of Valsartan but also to work at industrial scale since they are easy to handle and can be stored for a long time. Furthermore, if necessary they can be recrystallized several times to purify crude Valsartan intermediates of low purity.

According to a second aspect of the present invention, a preparation process is provided of a salt of the compound of formula (H)-P as defined above, which comprises the coupling of a compound of formula (III), or a salt thereof,
wherein: $Y_1$ and $Y_2$ are each independently selected from the group consisting of hydroxy, $(\text{CrC}_4)$-alkoxy and phenoxy, the latter optionally substituted by a $(\text{CrC}_4)$-alkoxy, $(\text{CrC}_4)$-alkyl or an halogen group; or alternatively $Y_1$ and $Y_2$ are taken together with the boron atom to form a cyclic structure selected from the following ones,

![Cyclic Structure](image1)

wherein $Z$ is selected from the group consisting of $(\text{CH}_2)_n$, $(\text{CH}_2)r\text{CR}_u\text{Rv}(\text{CH}_2)_s$ and $\text{CR}_u\text{Rv}(\text{CH}_2)t\text{CR}_u\text{Rv}$; $n$ is an integer from 2 to 4; $r$ and $s$ are integers from 0 to 4 with the condition that $r$ and $s$ are not both 0; $t$ is an integer from 0 to 1, and $R_u$ and $R_v$ are each independently selected from the group consisting of H, $(\text{CrC}_4)$-alkyl, phenyl and mono- or di- substituted phenyl, the substituents being halogen, $(\text{C}-4\text{C}_4)$-alkyl and $(\text{C}-4\text{C}_4)$-alkoxy;

with a compound of formula (IV),

![Compound IV](image2)

wherein $Y$ is a leaving group such an halogen atom (Cl, Br and I) or a sulfonfyoxy radical such as methanesulfonfyoxy, toluensulfonfyoxy, benzenesulfonfyoxy or thfluoromethanesulfonfyoxy; and $P$ is a protective group; in an appropriate solvent system and in the presence of a metallic compound and a base; and optionally carrying out a further step which comprises crystallizing the salt obtained in an appropriate solvent system.

Compounds of formula (III) or a salt thereof, as well as its solvates, including hydrates are new. Thus, a third aspect of the present invention is the provision of said compounds.
According to a fourth aspect of the present invention it is provided another preparation process of the compound of formula (H)-P as defined above, which comprises the steps of:

a) coupling a compound of formula (V),

\[
\begin{align*}
\text{O} & \quad \text{R}_1 \\
\text{N} & \quad \text{Y}_1 \\
\text{B} & \quad \text{Y}_2 \\
\end{align*}
\]

(V)

wherein: \( \text{R}_1 \) represents a group which may be converted into a carboxy group; and \( \text{Y}_1 \) and \( \text{Y}_2 \) have the same meaning as mentioned above for the compound of formula (III),

with a compound of formula (IV), wherein \( \text{Y} \) and \( \text{P} \) have the meaning mentioned above,

\[
\begin{align*}
\text{Y} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{P} \\
\end{align*}
\]

(IV)

in an appropriate solvent system and in the presence of a metallic compound and a base; to yield the compound of formula (VI);
wherein R₁ and P have the same meaning as above;

b) submitting the compound of formula (VI) to a hydrolysis, thermolysis, or hydrogenolysis reaction, in the presence of a base, and thereafter as necessary converting the salt obtained into a different salt form.

Unless otherwise indicated, the term "carboxy" is used herein to refer to the radical -COO⁻ as free acid (i.e. -COOH) or in salt form.

A fifth aspect of the present invention is the provision of a process for the preparation of a salt of the compound of formula (N)-P, which comprises reacting a compound of formula (N)-P with a base in an appropriate solvent system and recovering the salt.

The formation of a salt of the compound of formula (N)-P from Valsartan can be used as a method of purification of Valsartan. Thus, according to a sixth aspect of the present invention, another process is provided for the preparation of a salt of the compound of formula (N)-P as defined above, which comprises submitting Valsartan or a pharmaceutically acceptable salt thereof, to a protection reaction of the nitrogen of the tetrazole moiety, preferably in the presence of a base and an appropriate solvent system.

Finally, a last aspect of the present invention refers to the provision of a preparation process of Valsartan of formula (I), or a pharmaceutically acceptable salt thereof,
which comprises: a) first converting a salt of a compound of formula (II)-P,

wherein P is an amino protective group, into its free acid form by reaction with
an acid, and then submitting the compound obtained to a deprotection
reaction to remove the protective group P, yielding the Valsartan as free acid
or in salt form, or alternatively, submitting a salt of the compound of formula
(N)-P to a deprotection reaction to remove the protective group P, yielding a
salt of Valsartan, and if desired, converting the resulting salt of Valsartan into
the free acid form of Valsartan by reaction with an acid; and c) if desired,
converting a resulting free acid form of Valsartan into a salt thereof, or
converting a resulting salt of Valsartan into the free acid form of Valsartan, or
converting a resulting salt of Valsartan into a different salt.
The processes for the preparation of Valsartan of the present invention present several advantages: they proceed with good yield and high enantiomeric purity; they make easier the purification of Valsartan avoiding further purification steps, and there is no need to use chromatographic separations.

DETAILED DESCRIPTION OF THE INVENTION

Preferred salts of the compound of formula (N)-P are those where the cation is selected from the group consisting of a quaternary ammonium cation of formula \( +N(R_3)_4 \), \( R_3 \) being a radical, same or different, independently selected from the group consisting of \( \text{H} \), \((\text{C}_1-\text{C}_4)\)-alkyl, \((\text{C}_5-\text{C}_7)\)-cycloalkyl, phenyl, benzyl, phenyl \((\text{C}_1-\text{C}_4)\)-alkyl, and \((\text{C}_1-\text{C}_4)\)-alkylbenzyl, or alternatively, two of the \( R_3 \) are taken together with the N atom to form a cyclic structure having between 5-7 carbon atoms; a morpholinium cation; alkaline metal cation, and alkaline earth metal cation.

Preferred salts of the compound of formula (N)-P are the sodium salt or the potassium salt. Also preferred salts of the compound of formula (N)-P are the diethylammonium salt and the triethylammonium salt. Preferably, the protective group is the triphenylmethyl (trityl), but other protective groups from those known in the art can be used for purposes of the present invention.

As has been described above, a salt of a compound of formula (N)-P can be prepared by several processes. Thus, they can be prepared by the process summarized in Scheme 1.

**Scheme 1:**

![Scheme 1 Diagram]

(V) \( \rightarrow \) (III) or a salt thereof \( \rightarrow \) salt of (II)-P
In Scheme 1, R-i, Y-i, Y_2, P, and Y have the meaning mentioned above, D^+ is H^+ or an organic or inorganic cation, and A^+ is an inorganic or organic cation.

In a preferred embodiment, in formula (V) R_i is a radical of formula COOR_2 where R_2 is selected from the group consisting of (d-C_6)-alkyl, substituted methyl, 2-substituted ethyl, 2,6-dialkyl-phenyl, benzyl, substituted benzyl and silyl. Preferably, R_2 is benzyl.

In another preferred embodiment, compounds of formula (V) and compounds of formula (III) are those where Y_i and Y_2 are independently selected from hydroxy, methoxy, ethoxy and phenoxy, or alternatively, Y_i and Y_2 together with the boron atom form a cyclic structure, wherein Z is selected from the group consisting of \((\text{CH}_2)_i\text{CR}_u\text{R}_v(\text{CH}_2)_s\) and \(\text{CR}_u\text{R}_v(\text{CH}_2)_t\text{CR}_u\text{R}_v\); r and s are integers from 0 to 4 with the condition that r and s are not both 0; t is an integer from 0 to 1 and R_u and R_v are each independently selected from methyl and phenyl. In a more preferred embodiment compounds of formula (V) are those where Y_i and Y_2 are hydroxy. In another more preferred embodiment, compounds of formula (V) are those where Y_i and Y_2 together with the boron atom form a cyclic structure, wherein Z is \(\text{CH}_2\text{C(CH}_3)_2\text{CH}_2\). In another more preferred embodiment, compounds of formula (V), are those where Y_i and Y_2 together with the boron atom form a cyclic structure, where Z is \(\text{C(CH}_3)_2\text{C(CH}_3)_2\).

The compound of formula (III) can be prepared by submitting a compound of formula (V) to a hydrolysis, acidolysis, thermolysis, or hydrogenolysis reaction, optionally in the presence of a base; and thereafter as necessary, converting the compound (III) obtained into a salt form. When R_2 is benzyl, p-methoxybenzyl or benzhydryl, the conversion of the compound of formula (V) into compound of formula (III) or a salt thereof is carried out by hydrogenolysis in the presence of a suitable hydrogenation catalyst. Examples of suitable hydrogenation catalyst are Pd black, Pd on charcoal, Pd(OH)_2, Pt, PtO_2 and Raney Nickel. When R_2 is t-butyl, the conversion can be carried out by treating the tert-butyl ester with an acid, under mild conditions. When R_2 is methyl or ethyl, the conversion can be achieved by hydrolysis in suitable acid or basic conditions.
Preferred bases to carry out the conversion of compound of formula (III) as free acid into salt form and also to carry out the conversion of the compound of formula (V) to the compound of formula (III) when said conversion is carried out in the presence of a base are the following: an organic base, for instance a base of formula N(R₃)₃, R₃ being a radical, same or different, independently selected from the group consisting of H, (Ci-C₄)-alkyl, (Cs-C₇)-cycloalkyl, phenyl, benzyl, phenyl (Ci-C₄)-alkyl, and (Ci-C₄)-alkylbenzyl, or alternatively, two of the R₃ are taken together with the N atom to form a cyclic structure having between 5-7 carbon atoms; a morpholine; or an inorganic base such as alkaline metal hydroxide, alkaline earth metal hydroxide, alkaline metal carbonate or alkaline earth metal carbonate.

Compound (III) is then reacted with compound (IV) to afford a salt of the compound of formula (N)-P. In a preferred embodiment of this process, the compound of formula (III) is in form of sodium salt, potassium salt, triethylammonium salt, or diethylammonium salt. In another preferred embodiment, compounds of formula (III) are those where Y₁ and Y₂ together with the boron atom form a cyclic structure, wherein Z is CH₂C(CH₃)₂CH₂. In an also preferred embodiment, compounds of formula (IV) are those where the leaving group Y is Br. In another preferred embodiment, compounds of formula (IV) are those where the protective group P is trityl.

The reaction between a compound of formula (III) and (IV) is known as Suzuki coupling reaction. It is carried out in an appropriate solvent system and in the presence of a metallic compound. Preferably, the reaction is carried out at a temperature between ambient temperature and the reflux of the solvent used. More preferably, the reaction is carried out at reflux temperature of the solvent used. The best conditions to carry out the process vary according to the parameters considered by the person skilled in the art, such as the starting materials, temperature, solvent and similar. Such reaction conditions may be easily determined by the person skilled in the art by routine tests, and with the teaching of the examples included in this document.

Preferably, the metallic compound is selected from palladium, nickel, a metallic salt and a metallic complex. More preferably, the metallic compound is a Pd complex, added or formed in situ, selected from the group consisting of PdX₂, PdXVPAr₃, PdX₂P(Cic-C₆)₃, PdX₂N(CrC₆)₃, PdL₄, and PdX₂L₂; X′
is a leaving group independently selected from the group consisting of Cl, Br and OCOCH₃; Ar is an aromatic group selected from the group consisting of phenyl, tolyl and furyl; L is a ligand selected from the group consisting of NR’s, SR’₂ and PR’₃; or alternatively in formula PdX’₂L₂ both L form a diphosphine of formula PR’₂-U-PR’₂; R’ is independently selected from phenyl, tolyl, furyl, ferrocenyl and (d-C₆)₆-alkyl; and U is selected from ferrocenyl and (Ci-C₄)-alkyl. Still more preferably, the metallic compound is selected from tetrakis(triphenylphosphine)palladium (O), (Pd(PPh₃)₄); dichloro[1,1’-bis(diphenylphosphino)ferrocene]palladium (II), (PdCl₂(dppf)); 1,4-bis(diphenylphosphino)butane palladium (II) chloride, (PdCl₂(dppb)); dichlorobis(tricyclohexylphosphine) palladium (II), (PdCl₂(PCy₃)₂); dichloro[1,1’-bis(di-tert-butylphosphino)ferrocene]palladium (II), (PdCl₂(dtbp)); palladium black; palladium (II) chloride; palladium (II) acetate; mixtures of the previously mentioned catalysts with phosphines; and palladium catalysts over polymeric supports. The most preferably metallic compounds are Pd(PPh₃)₄, PdCl₂(dppf), and Pd(OAc)₂/PPh₃.

Preferably, the solvent system is selected from water, an organic solvent selected from aromatic (C₆-C₈) hydrocarbons, an aprotic polar solvent, and aliphatic (C₂-C₈) ethers; and mixtures of water and one or more organic solvents from those mentioned. More preferably, the solvent system is selected from tetrahydrofuran and a mixture of dimethylformamide/toluene/water.

Preferably, the base is selected from an alkaline metal carbonate and alkaline metal phosphate. More preferably, the base is potassium carbonate and potassium phosphate.

Compounds of formula (N)-P can also be prepared by the process summarized in Scheme (II):
In the previous formulae, $R_i$, $Y_i$, $Y_2$, $P$, and $A$ have the meaning mentioned above. Preferred values of the substituents are the same as those described for the compounds of Scheme 1.

In a preferred embodiment, in formula (V) $R_1$ is a radical of formula $COOR_2$ where $R_2$ is selected from the group consisting of (d-$C_6$-alkyl, substituted methyl, 2-substituted ethyl, 2,6-dialkyl-phenyl, benzyl, substituted benzyl and silyl. In a more preferred embodiment, compounds of formula (V) are those where $R_2$ is a benzyl radical. In another preferred embodiment, compounds of formula (V) are those where $Y_1$ and $Y_2$ together with the boron atom form a cyclic structure, wherein $Z$ is $CH_2C(CH_3)_2CH_2$. In another preferred embodiment, compounds of formula (IV) are those where the leaving group $Y$ is Br. In another preferred embodiment, compound of formula (IV) are those where the protective group $P$ is trityl.

The coupling of a compound of formula (V) with a compound of formula (IV) is carried out in the presence of an appropriate solvent system, a metallic compound, preferably selected from palladium, nickel, a metallic salt and a metallic complex, and a base preferably selected from the group consisting of an alkaline metal carbonate and an alkaline metal phosphate. The more preferred metallic compounds, bases and solvent systems are the same as those mentioned to the process of scheme 1 described above.

The transformation of compound of formula (VI) to a salt of a compound of formula (N)-P can be carried out by hydrolysis, thermolysis, acidolysis or hydrogenolysis reaction, in the presence of a base, in appropriate conditions.
to avoid or minimize deprotection.

Examples of suitable bases which may be present in the conversion of the compound of formula (VI) into a salt of the compound of formula (N)-P are the following: an organic base, for instance a base of formula N(R₃)₃, R₃ being a radical, same or different, independently selected from the group consisting of H, (d-C₄)-alkyl, (C₅-C₇)-cycloalkyl, phenyl, benzyl, phenyl (C₃-C₄)-alkyl, and (Ci-C₄)-alkylbenzyl, or alternatively, two of the R₃ are taken together with the N atom to form a cyclic structure having between 5-7 carbon atoms; a morpholine; or an inorganic base such as alkaline metal hydroxide, alkaline earth metal hydroxide, alkaline metal carbonate or alkaline earth metal carbonate.

The starting compound of formula (V) of both processes described in Scheme 1 and Scheme 2 can be prepared by condensing a compound of formula (VII) with a compound of formula (VIII) or a salt thereof, then removing the water present, followed by reducing the condensation product. This two-step reaction is known as reductive amination.

In formulae (VII) and (VIII), R₁, Y₁ and Y₂ are a group as defined above, or alternatively, Y₁ and Y₂ is an intermediate form thereof which can be transformed to such Y₁ and Y₂ groups. In a preferred embodiment, in formula (VIII) R₁ is a radical of formula COOR₂ where R₂ is selected from the group consisting of (C-t-C₆)-alkyl, substituted methyl, 2-substituted ethyl, 2,6-dialkyl-phenyl, benzyl, substituted benzyl and silyl. In a more preferred embodiment, compounds of formula (V) are those where R₁ is a radical of formula COOR₂ where R₂ is a benzyl radical.
Thereafter, as necessary, transforming said intermediate forms of \( Y_1 \) and \( Y_2 \) groups to \( Y_i \) and \( Y_2 \) groups as previously defined, and optionally submitting the compound obtained to an acylation reaction using a pentanoyl halide to give a compound of formula (V).

The elimination of water can be performed by azeotropic removal or using a water scavenger. Preferably, the condensation reaction is carried out in the presence of a base, for instance, a tertiary amine such as triethylamine, diisopropylethylamine, N-methylmorpholine and pyridine, and an appropriate solvent. The reduction can be carried out without isolation of the imine intermediate obtained in the condensing reaction, by reaction with a reducing agent in the presence of a suitable solvent. The reducing agent is preferably selected from the group consisting of an alkali metal borohydride such as sodium borohydride, an alkali metal cyanoborohydride such as sodium cyanoborohydride or lithium cyanoborohydride, an alkali metal tri-(\( \text{C}_x \))alkoxy borohydride such as sodium tri-methoxyethoxy-borohydride; a tetra-\( \text{C}_x \)-alkylammonium-(cyano)borohydride such as tetrabutylammonium borohydride or tetrabutylammonium cyanoborohydride. A suitable catalyst for the reductive amination with hydrogen or a hydrogen donor is, for example, nickel, such as Nickel Raney, and noble metals or their derivatives such as palladium, platinum or platinum dioxide.

When \( Y_1 \) and \( Y_2 \) are intermediates forms of \( Y_1 \) and \( Y_2 \), the preparation process includes, as necessary, transforming said intermediate forms of the \( Y_1 \) and \( Y_2 \) groups to \( Y_1 \) and \( Y_2 \) groups as previously defined.

The acylation reaction is preferably carried out with pentanoyl chloride in the presence of a base, for instance, a tertiary amine such as triethylamine, diisopropylethylamine, N-methylmorpholine and pyridine, and a suitable solvent such as dichloromethane, toluene, dioxane or a mixture of tetrahydrofuran with water. Generally, the reaction is carried out between room and reflux temperature. Preferably, it is carried out at room temperature.

Compounds of formula (VII) may be obtained from 4-formylphenylboronic acid by methods known in the art. For instance, Example 1 illustrates the preparation of 4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-benzaldehyde by
reaction of 4-formylphenylboronic acid with 2,2-dimethyl-1,3-propanediol.

Another way of preparing a salt of the compound of formula (H)-P is by reaction of the compound of formula (N)-P with a base in an appropriate solvent system and recovering the salt.

Examples of suitable bases are the following: an organic base, for instance a base of formula N(R₃)₃, R₃ being a radical, same or different, independently selected from the group consisting of H, (Cᵢ-C₄)-alkyl, (C₅-C₇)-cycloalkyl, phenyl, benzyl, phenyl (Cᵢ-C₄)-alkyl, and (C₅-C₇)-alkylbenzyl, or alternatively, two of the R₃ are taken together with the N atom to form a cyclic structure having between 5-7 carbon atoms; a morpholine; or an inorganic base such as alkaline metal hydroxide, alkaline earth metal hydroxide, alkaline metal carbonate or alkaline earth metal carbonate.

Preferably, the solvent system is selected from the group consisting of methyl isobutyl ketone, toluene, and their mixtures with water.

The formation of a salt of a compound of formula (H)-P from Valsartan can be used as a method of purification of Valsartan. The process comprises submitting Valsartan or a pharmaceutically acceptable salt thereof, to a protection reaction of the nitrogen of the tetrazole moiety, preferably in the presence of a base and an appropriate solvent system. Preferably the protective group is a trityl group. Preferably, the base is selected from an organic base, for instance a base of formula N(R₃)₃, R₃ being a radical, same or different, independently selected from the group consisting of H, (Cᵢ-C₄)-alkyl, (C₅-C₇)-cycloalkyl, phenyl, benzyl, phenyl (d-C₄)-alkyl, and (Cᵢ-C₇)-alkylbenzyl, or alternatively, two of the R₃ are taken together with the N atom to form a cyclic structure having between 5-7 carbon atoms; a morpholine; or an inorganic base such as alkaline metal hydroxide, alkaline earth metal hydroxide, alkaline metal carbonate or alkaline earth metal carbonate. Preferably, the organic base is selected from triethylamine and diethylamine. Preferably, the inorganic base is selected from sodium hydroxide or potassium hydroxide.

Preferably, the solvent system is selected from methyl isobutyl ketone and toluene and their mixtures with water. By way of example, Valsartan is
reacted with trityl chloride in the presence of triethylamine to yield the triethylammonium salt of tritylated Valsartan.

The salts of the compounds of formula (N)-P are useful intermediates for the preparation of Valsartan or its pharmaceutically acceptable salts. As it has been mentioned above, the process comprises converting a salt of the compound of formula (H)-P into its free acid form by reaction with an acid, and then submitting the compound obtained to a deprotection reaction to remove the protective group P yielding the Valsartan as free acid or in salt form, or alternatively, submitting a salt of the compound of formula (N)-P to a deprotection reaction to remove the protective group P yielding a salt of Valsartan, and if desired, converting the resulting salt of Valsartan into the free acid form of Valsartan by reaction with an acid; and c) if desired, converting the resulting free acid form of Valsartan into a salt thereof, or converting a resulting salt of Valsartan into the free acid form of Valsartan, or converting a resulting salt of Valsartan into a different salt.

In a preferred embodiment, the salt of the compound of formula (N)-P is the sodium salt or the potassium salt. In another preferred embodiment, the salt of the compound of formula (N)-P is the diethylammonium salt or the triethylammonium salt.

A suitable protective group for the tetrazole moiety is selected from those known in the art. Preferably, the protective group is the triphenylmethyl (trityl). Likewise, the protective group of the tetrazole moiety can be introduced and removed by procedures known in the art (cf. Protective Groups in Organic Synthesis, Wiley-Interscience, (1999)). The specific reaction conditions depend on the protective group used. For instance, when trityl group is used as the protective group of the tetrazole moiety, it can be deprotected either in acidic or basic conditions. Preferably, the deprotection is carried out in acidic, basic or neutral conditions, for example, in methanol or HCl in a suitable solvent such as methanol or a mixture of dioxane/water.

Some of the steps of the present invention may be carried out in one pot, as illustrated in the examples.

Throughout the description and claims the word "comprise" and variations of
the word, such as "comprising", are not intended to exclude other technical features, additives, components, or steps. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention.

The following examples and drawings are provided by way of illustration, and are not intended to be limiting of the present invention.

EXAMPLES

Enantiomeric excess (ee) of trityl-Valsartan or its salts has been determined by transformation to Valsartan and HPLC analysis of it (Chiralcel OD).

Example 1: Preparation of 4-(5,5-dimethyl-H,3,21dioxaborinan-2-yl)-benzaldehyde

To a mixture of 4-formylphenylboronic acid (50 g) in toluene (250 mL) was added 2,2-dimethyl-1,3-propanediol (34.39 g) and the dispersion was heated at reflux for 2 h. The water while formed was azeotropically separated and the residue (330 mL) was used directly in the next step. 1H-NMR (400 MHz, CDCl3): δ 1.04 (s, 6 H, 2 CH3), 3.79 (s, 4 H, 2 CH2), 7.84 (d, J = 6.4 Hz, 2 H, H-Ar), 7.96 (d, J = 8 Hz, 2 H, H-Ar), 10.04 (s, 1 H, CHO) ppm.

Example 2: Preparation of 4-(4A5,5-tetramethyl-H,3,21dioxaborolan-2-yl)-benzaldehyde

To a solution of 4-formylphenylboronic acid (1 g) in anhydrous THF (10 mL) was added 2,3-dimethyl-butane-2,3-diol (0.867 mg) and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated to dryness. The residue was dissolved in dichloromethane (40 mL), washed with water (25 mL x 3), dried and evaporated under vacuum to obtain 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (1.41 g, 91% yield). 1H-NMR (400 MHz, CDCl3): δ 1.34 (s, 12 H, 4 CH3), 7.86 (d, J = 8.4 Hz, 2 H, H-Ar), 7.96 (d, J = 8 Hz, 2 H, H-Ar), 10.05 (s, 1 H, CHO) ppm.

Example 3: Preparation of (benzyl N-r4-(5,5-dimethyl-H,3,21dioxaborinan-2-yl)phenyl-4-yl-methylL-valinate)

A mixture of L-Valine benzyl ester tosylate (132.7 g), 4-(5,5-dimethyl-
[1,3,2]dioxaborinan-2-yl)-benzaldehyde (330 mL), Et₃N (48.4 mL) and toluene (413 mL) was heated at reflux temperature for 1 h. The water while formed was azeotropically separated. Then, the mixture was cooled to room temperature and the solution was washed with aqueous NaHCO₃ (317 mL x 2) and water (317 mL). The residual water was azeotropically removed. The toluene was partially distilled (134 mL) and MeOH (134 mL) was added. The solution was then cooled to 0-5 °C and NaBH₄ (6.5 g) was slowly added. The reaction mixture was stirred at room temperature overnight. Then the solvent was partially distilled (half volume) and the residue was washed with aqueous NaHCO₃ (270 mL). The separated aqueous phase was extracted with toluene (135 mL x 2). The combined organic phases were then washed with water (135 mL). The residual water in the organic layer was azeotropically removed and the residue (aprox. 730 mL) was used directly in the next step.

Example 4: Preparation of benzyl N-r4-(5,5-dimethyl-H ,3,21dioxaborinan-2-yl)phenyl-4-yl-methyl-N-pentanoyl-L-valinate

To the toluene solution of benzyl N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-L-valinate (730 mL) at room temperature was added ethyl-diisopropyl-amine (Hönnig base, 66.4 mL) and DMAP (4.03 g). The mixture was then cooled to 0-5 °C and valeryl chloride (42 mL) was added dropwise. The mixture was stirred at room temperature overnight. The reaction mixture was washed with 1M HCl, followed by washing with water, with saturated sodium hydrogen carbonate, with saturated sodium chloride (488 mL each washing) and with water again (244 mL). The residual water in the organic layer was azeotropically removed and the toluene was evaporated to dryness under reduced pressure to obtain crude benzyl N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-N-pentanoyl-L-valinate (140.1 g, 86% yield, three steps).

Example 5: Preparation of N-r4-(5,5-dimethyl-H,3,21dioxaborinan-2-yl)phenyl-4-yl-methyl-N-pentanoyl-L-valine

A mixture of benzyl N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-N-pentanoyl-L-valinate (20 g) in AcOEt (160 mL) containing 4.9% palladium on activated Charcoal (Pd/C, 2.25 g) was hydrogenated at room temperature for 4 h. Celite® (2.25 g) was added and the resulting mixture was filtered and the solvent was evaporated to furnish the desired product (15.9 g,
$^{1}$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.85 and 0.98 (2 d, 3 H each, $J = 6.8$ Hz, 2 CH$_3$ (iPr)), 0.89 (t, 3 H, $J = 7.4$ Hz, CH$_3$ (pentanoyl)), 1.02 (s, 6 H, CHMe$_2$), 1.33 (m, 2 H, CH$_2$Me), 1.64 (m, 2 H, CH$_2$Et), 2.44 (m, 2 H, CH$_2$CO), 2.73 (m, 1 H, CH(iPr)), 3.58 (d, 1 H, $J = 10.4$ Hz, CHN), 3.76 (s, 4 H, CH$_2$O), 4.42 and 4.74 (2 d, 1 H each, $J = 16.8$ Hz, CH$_2$-Ph), 7.17 and 7.79 (2d, 2 H each, $J = 8$ Hz, H-Ar) ppm. $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 13.7, 19.4, 19.7 and 21.8 (CH$_3$), 22.3 (CH$_2$), 27.1 (CH$_2$), 27.2 (CH), 31.8 (C), 33.9 (CH$_2$), 54.1 (CH$_2$), 70.7 (CH), 72.2 (CH$_2$), 125.9 (CH-Ar), 134.5 (CH-Ar), 137.9 (C-/pso-Ar), 172.2 and 177.1 (CO) ppm. IR (v): 2959 (broad band, OH), 1724 (CO-acid) cm$^{-1}$. Mp (AcOEt): 132.3-134.6 °C.

Example 6: Preparation of Sodium N-r4-(5,5-dimethyl-1'H,3,2-dioxaborinan-2-yl)phenyl-4-yl-methyl-N-pentanoyl-L-valinate

A solution of N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-N-pentanoyl-L-valine (1.5 g) in THF (6 ml) was treated with NaOH (141 mg). The formed suspension was stirred at room temperature for 5 min, until the solid dissolved. After stirring for 10 min. quantitative white solid appeared. THF (1.5 ml) was added and the mixture was stirred for 20 min. This was filtered under vacuum and the solid was washed with cold THF (1 ml). The solid was dried to give sodium N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-N-pentanoyl-L-valinate (0.9 g, 60%). $^{1}$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.71 and 0.91 (2d, 3 H each, $J = 6.4$ Hz, 2 CH$_3$ (iPr)), 0.77 (t, 3 H, $J = 7.2$ Hz, CH$_3$ (pentanoyl)), 0.99 (s, 6 H, CHMe$_2$), 1.18 (m, 2 H, CH$_2$Me), 1.49 (m, 2 H, CH$_2$Et), 2.17 (m, 3 H, CH$_2$CO and CH(iPr)), 3.72 (s, 4 H, CH$_2$O), 4.11 (d, 1 H, $J = 10$ Hz, CHN), 4.66 and 4.73 (2 d, 1 H each, $J = 17.6$ Hz, CH$_2$-Ph), 7.25 and 7.72 (2d, 2 H each, $J = 7.8$ Hz, H-Ar) ppm. $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 13.7, 20.1, 20.7 and 21.8 (CH$_3$), 22.3 (CH$_2$), 27.3 (CH$_2$), 27.5 (CH), 31.8 (C), 34.0 (CH$_2$), 50.4 (CH$_2$), 68.7 (CH), 72.2 (CH$_2$), 126.0 and 134.0 (CH-Ar), 140.8 (C-/pso-Ar), 176.2 and 177.3 (CO) ppm. IR (v): 3485 (broad band, OH), 1584 (CO-amide and carboxylate) cm$^{-1}$. Mp (THF): 156-158 °C.

Example 7: Preparation of benzyl N-pentanoyl-N-r-{2'-H-(thphenylmethyl)-1'H-tetrazol-5-yl-1,1'-biphenyl-4-yl }methyl-L-valinate
A solution of Pd(OAc)$_2$ (9 mg) and PPh$_3$ (40 mg) in toluene (5 mL) and tetrahydrofuran (3 mL) was degassed by argon purge (5 min.) and stirred at room temperature for 30 min. under argon atmosphere. Then, 5-(2-Bromophenyl)-1-triphenylmethyl-1H-tetrazole (1.8 g), anhydrous K$_3$PO$_4$ (1.25 g) and a solution of benzyl N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-N-pentanoyl-L-valinate (2 g) in toluene (7 mL) were added. The mixture was degassed by argon purge (5 min.) and heated at 85 °C overnight. The reaction mixture was cooled, and water (5 mL) was added. The aqueous layer was extracted with toluene (3.5 mL x 2). The water of the combined organic layers was azeotropically removed and the solvent was evaporated to dryness under reduced pressure to obtain crude benzyl N-pentanoyl-N-[2'-[1-(triphenylmethyl)]-iH-tetrazol-5-yl]-1,1'-biphenyl-4-yl-methyl]-L-valinate (3.07 g, quantitative).

Example 8: Preparation of N-pentanoyl-N-(r2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-ylmethyl]-L-valine

A solution of Pd(OAc)$_2$ (10 mg) and PPh$_3$ (47 mg) in tetrahydrofuran (15 mL) was degassed by argon purge (5 min.) and stirred at room temperature for 30 min. under argon atmosphere. Then, 5-(2-Bromophenyl)-1-triphenylmethyl-1H-tetrazole (2.09 g), anhydrous K$_3$PO$_4$ (2.91 g) and N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-N-pentanoyl-L-valine (1.9 g). The mixture was degassed by argon purge (5 min.) and heated at 60 °C overnight. The reaction mixture was cooled, passed through a pad of Celite® and the filtrate evaporated under vacuum. 1 g of the previous residue in MeOH (15 mL) was heated under reflux for 3 h. The solvent of the resulting solution was distilled under reduced pressure. The residue was dissolved in AcOEt (4 mL) and washed with saturated aqueous NaHCO$_3$ (4 mL). The aqueous layer was acidified with 1 M HCl and extracted with AcOEt (5 mL x 3). The combined organic layers were dried with anhydrous Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure to give Valsartan (470 mg, 77 %, ee 98%).

Example 9: Recrystallization of (N-pentanoyl-N-r(2'-H-(thphenylmethyl)-1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methylL-valine)
A mixture of (N-pentanoyl-N-[(2'-)-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valine (2 g, ee 74%) in toluene (10 ml) was heated until a clear solution was obtained. The solution was cooled slowly till room temperature and then was stirred at 0-5°C for 1 h. The solid was filtered under vacuum, washed with cold toluene (1 ml) and dried at 60°C for 3 h to yield the product (1.79 g, 90%, ee: null).

Example 10: Preparation of Sodium N-pentanoyl-N-[(2'-H-(triphenylmethyl)-1 H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-L-valinate

A mixture of N-pentanoyl-N-[(2'-)-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valine (1 g, ee 74%) in toluene (7 ml) and 1 N NaOH (10 ml) was stirred at 80°C until the solid was dissolved. The mixture was cooled to room temperature overnight. The solid was filtered under vacuum and dried at 60°C for 4 h to give sodium N-pentanoyl-N-[(2'-)-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valinate (0.75 g, 75%, ee 74%).

Example 11: Preparation of Sodium N-pentanoyl-N-[(2'-ri-(thphenylmethyl)-1 H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-L-valinate

A mixture of N-pentanoyl-N-[(2'-)-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valine (1 g, ee 74%) in MIK (3 ml) and 1 N NaOH (3 ml) was stirred at 60°C until the solid was dissolved. The mixture was cooled to 45-50°C, stirred for 25 min., and then cooled to room temperature and stirred for 2 h. The solid was filtered under vacuum, washed with cold MIK (1 ml) and cold water (1 ml) and dried at 40°C under vacuum to give sodium N-pentanoyl-N-[(2'-H-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valinate (0.99 g, 96%, ee 74%).

Example 12: Preparation of Sodium N-pentanoyl-N-[(2'-H-(triphenylmethyl)-1 H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-L-valinate

To a mixture of Valsartan (0.5 g, ee 99.4%) in MIK (3 ml) was added solid NaOH (0.1 g) at room temperature under inert atmosphere and the mixture was stirred for 1 h. Then TrCl (0.35 g) was added and the reaction mixture was stirred for 4 h. Water (3 ml) was added and the mixture was stirred at 60°C until clear layers were obtained. The mixture was then allowed to reach
room temperature, while a white solid precipitated. The mixture was stirred overnight at room temperature and then was filtered under vacuum. The solid was washed with cold MIK (1 ml) and with cold water (1 ml). The solid was dried under vacuum at room temperature to yield the desired product (0.4 g, 50%, ee 99.4%). 

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.62 and 0.89 (2 d, 3 H each, J = 6.4 Hz, 2 CH$_3$ (iPr)), 0.74 (t, 3 H, J = 7.2 Hz, CH$_3$ (pentanoyl)), 1.13 (m, 2 H, CH$_2$Me), 1.47 (m, 2 H, CH$_2$Et), 2.18 (m, 3 H, CH$_2$CO and CH(iPr)), 3.7 (d, 1 H, J = 9.2 Hz, CHN), 4.57 (s, 2 H, CH$_2$-N), 6.92-7.84 (m, 23 H, H-Ar).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 13.8, 20.4 and 21.1 (CH$_3$), 22.3 (CH$_2$), 27.4 (CH$_2$), 27.6 (CH), 33.9 (CH$_2$), 50.9 (CH$_2$), 68.9 (CH), 82.9 (CH), 126.2-141.7 (CH- and C-/pso-Ar), 164.2 (CN), 175.9 and 177.5 (CO) ppm. IR (υ): 1599 (broad band, CO-carboxylate and amide) cm$^{-1}$. Mp (MIMH$_2$O): 108-109 °C.

Example 13: Preparation of Potassium N-pentanoyl-N-(2'-H-triphenylmethyl)-1'-biphenyl-4-yl)methyl-L-valinate

A mixture of N-pentanoyl-N-[2'-[1-(triphenylmethyl)]-1 H-tetrazol-5-yl]-1' biphenyl-4-yl]methyl]-L-valine (1 g, ee 74%) in MIK (3 ml) and 1 N KOH (3 ml) was stirred at 61 °C until the solid was dissolved. The mixture was cooled to 50-55 °C, stirred for 25 min., and then cooled to room temperature and stirred for 2 h. The solid was filtered under vacuum, washed with cold MIK (1 ml) and cold water (1 ml) and dried at 40 °C under vacuum to give potassium N-pentanoyl-N-[2'-[1-(triphenylmethyl)]-1 H-tetrazol-5-yl]-1' bipheryl-4-yl)methyl]-L-valinate (0.91 g, 87%, ee 74%).

$^1$H-NMR (400 MHz, CDCl$_3$): Mixture of two rotamers $\delta$ 0.8-1 (m, 9 H, 2 CH$_3$ (iPr), CH$_3$ (pentanoyl)), 1.1-1.8 (m, 4 H, CH$_2$Me, CH$_2$Et), 2.2-2.2 (m, 2 H, CH$_2$CO), 2.4-2.6 and 2.6-2.8 (2 m, 1 H, CH(iPr)), 3.79 and 3.90 (2 d, J = 10 Hz, J = 9 Hz, 1 H, CHN), 4.29, 4.52 and 4.84 (3 d, J = 16 Hz, J = 7 Hz, J = 16 Hz, 2 H, CH$_2$-N), 6.8-7.9 (m, 23 H, H-Ar) ppm. $^{13}$C-NMR (100 MHz, CDCl$_3$):

Major rotamer $\delta$ 13.8, 20.1 and 21.2 (CH$_3$), 22.4 (CH$_3$), 27.5 (CH$_2$), 27.8 (CH), 33.8 (CH$_2$), 50.6 (CH$_2$), 68.5 (CH), 82.9 (CH), 126.1-141.6 (CH- and C-/ipso-Ar), 164.3 (CN), 175.1 and 177.5 (CO) ppm. IR (υ): 1593 (broad band, CO-carboxylate and amide) cm$^{-1}$. Mp (MIMH$_2$O): 115-119 °C.

Example 14: Preparation of N-pentanoyl-N-[2'-[1 H-tetrazol-5-yl]-1' biphenyl-4-yl]methyl]-L-valine


A solution of Pd(OAc)$_2$ (3 mg) and PPh$_3$ (12 mg) in toluene (3.2 ml) and tetrahydrofuran (0.8 ml) was degassed by argon purge (5 min.) and stirred at room temperature for 30 min. under argon atmosphere. Then, 5-(2-Bromophenyl)-1-triphenylmethyl-1 H-tetrazole (0.52 g), anhydrous K$_3$PO$_4$ (0.7 g), tetrabutylammonium bromide (18 mg) and sodium N-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl-4-yl-methyl]-N-pentanoyl-L-valinate (0.5 g) were added. The mixture was degassed by argon purge (5 min.) and heated at 80 °C overnight. Water (3 ml) and toluene (1 ml) were added. The organic layer was separated and the solid formed was filtered under vacuum, washed with cold toluene (1 ml) and dried to give crude potassium N-pentanoyl-N-[2'-[1-(triphenylmethyl)-i H-tetrazol-5-yl]-1',1'-biphenyl-4-yl-methyl]-L-valinate (0.5 g, 63%). Some of the previous crude (0.3 g) in MeOH (6 ml) was heated under reflux for 3 h. The solvent of the resulting solution was distilled under reduced pressure. The residue was dissolved in AcOEt (3 ml) and washed with saturated aqueous NaHCO$_3$ (3 ml). The aqueous layer was acidified with 1 M HCl and extracted with AcOEt (5 ml x 3). The combined organic layers were dried with anhydrous MgSO$_4$, filtered and the solvent was removed under reduced pressure to give Valsartan (120 mg, 66% from the salt, ee 99%).

Example 15: Preparation of Thethylammonium N-pentanoyl-N-[][]{2'-H-(triphenylmethyl)-i H-tetrazol-5-ylH ,1'-biphenyl-4-yl)methyl-L-valinate

A mixture of N-pentanoyl-N-[[2'-[1-(triphenylmethyl)-i H-tetrazol-5-yl]-1',1'-biphenyl-4-yl)methyl]-L-valine (1 g) in toluene (1.5 ml) was stirred at room temperature. Then Et$_3$N (0.41 ml) was added and the solid was dissolved. The solution was cooled to 0-5 °C for 2 h, but no solid appeared. The solvent was removed under reduced pressure to give triethylammonium N-pentanoyl-N-[[2'-[1-(triphenylmethyl)-i H-tetrazol-5-yl]-1',1'-biphenyl-4-yl)methyl]-L-valinate (1.06 g, 92 %). $^1$H-NMR (400 MHz, CDCl$_3$): Minor rotamer $\delta$ 0.71 and 0.99 (2 d, 3 H each, $J = 6.6$ Hz, 2 CH$_3$ (iPr)), 0.93 (t, 3 H, $J = 7.2$ Hz, CH$_3$ (pentanoyl)), 1.07 (t, 9 H, $J = 7.4$ Hz, (CH$_3$)$_3$), 1.21 (m, 2 H, CH$_2$Me), 1.54 (m, 2 H, CH$_2$Et), 2.21 (m, 2 H, CH$_2$CO), 2.67 (m, 1 H, CH(iPr)), 2.81 (q, 6 H, $J = 7.3$ Hz, (CH$_3$)$_3$), 4.13 (d, 1 H, $J = 10.4$ Hz, CHN), 4.37 and 4.73 (2 d, $J = 17$ Hz, 1 H each, CH$_2$-N), 6.96-7.86 (m, 23 H, H-Ar) ppm. Major rotamer $\delta$ 0.71 and 0.99 (2 d, 3 H each, $J = 6.6$ Hz, 2 CH$_3$ (iPr)), 0.83 (t, 3 H, $J = 7.2$ Hz, CH$_3$ (pentanoyl)), 1.07 (t, 9 H, $J = 7.4$ Hz, (CH$_3$)$_3$), 1.39 (m, 2 H, CH$_2$Me), 1.72 (m,
2 H, CH₂Et), 2.21 (m, 2 H, CH₂CO), 2.49 (m, 1 H, CH(iPr)), 2.81 (q, 6 H, J = 7.3 Hz, (CH₂)₃), 3.91 (d, 1 H, J = 10.4 Hz, CHN), 4.68 (bs, 2 H, CH₂-N), 6.96-7.86 (m, 23 H, H-Ar) ppm. ¹³C-NMR (100 MHz, CDCl₃): Mixture of two rotamers δ 8.34 (CH₃Et₃N), 13.8 and 13.9 (CH₃), 19.2 and 19.4 (CH₂), 20.0 and 20.2 (CH₂), 22.3 and 22.6 (CH₂), 27.4 and 27.6 (CH₂), 28.0 and 28.6 (CH), 33.7 and 33.9 (CH₂), 44.6 (CH₂Et₃N), 45.9 (CH₂-Ph), 69.5 (C), 82.8 (CPh₃), 126.1-142.4 (CH- and C-ipso-Ar), 164.2 and 164.4 (C=N), 173.5, 174.6, 175.3 and 175.8 (CO) ppm. IR (υ): 3452 (NH), 1722 (CO-carboxylate), 1641 (CO-amide) cm⁻¹. Mp (toluene): 61-62 °C.

Example 16: Preparation of Thethylammonium N-pentanoyl-N-r[2'-H-(triphenylmethyl)-i H-tetrazol-5-ylH ,1'-biphenyl-4-yl)methyll-L-valinate]

A mixture of benzyl N-pentanoyl-N-{[2'-[1-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valinate (10 g, ee 99%) and triethylamine (3.65 ml) in toluene (48 ml) and MeOH (12 ml) containing 5% palladium on activated Charcoal (44.5% Pd/C, 1.12 g) was hydrogenated at room temperature for 4 h. The resulting crude product was filtered through a Celite® pad and the solvent was evaporated to dryness to furnish the desired product (9.93 g, quantitative, ee 98%).

Example 17: Preparation of Thethylammonium N-pentanoyl-N-r[2'-H-(triphenylmethyl)-i H-tetrazol-5-yl-1 ,1'-biphenyl-4-yl)methyll-L-valinate]

A mixture of benzyl N-pentanoyl-N-{[2'-[1 -(triphenylmethyl)-i H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valinate (0.3 g) and triethylamine (0.11 ml) in AcOEt (3 ml) containing 5% palladium on activated Charcoal (Pd/C 44.5%, 34 mg) was hydrogenated at room temperature overnight and then at 60 °C one day. The resulting crude product was filtered through a Celite® pad and the solvent was evaporated to dryness to furnish the desired product (200 mg, 66%).

Example 18: Preparation of Thethylammonium N-pentanoyl-N-r[2'-H-(triphenylmethyl)-i H-tetrazol-5-ylH ,1'-biphenyl-4-yl)methyll-L-valinate]

To a mixture of Valsartan (0.5 g) in dry THF (4 ml) and Et₃N (0.18 ml) at room temperature under inert atmosphere, was added dropwise a solution of TrCl (0.35 g) in THF (1 ml). The reaction mixture was stirred for 5 h and then was filtered under vacuum. The solid was washed with THF (2 ml). The
solvent of the filtrate was removed under reduced pressure to yield the desired product (0.89 g, quantitative).

Example 19: Preparation of Diethylammonium N-pentanoyl-N-[(2'-H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-L-valinate

A mixture of N-pentanoyl-N-[(2'-[1-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valine (1 g) in toluene (2.5 ml) was stirred at room temperature. Then diethylamine (0.3 ml) was added and the solid was dissolved. The mixture was stirred at room temperature for 2 h. The formed solid was filtered under vacuum and dried (40 °C) to give diethylammonium N-pentanoyl-N-[(2'-[1 -(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valinate (0.7 g, 63 %). ¹H-NMR (400 MHz, CDCl₃): Mixture of two rotamers δ 0.7-1.2 (m, 15 H, 2 CH₃ (iPr), CH₃ (pentanoyl), 2 CH₃ (NEt)), 1A-2.2 (m, 6 H, CH₂Me, CH₂Et, CH₂CO), 2.4-2.6 (m, 1 H, CH(iPr)), 2.7 (m, 4 H, 2 CH₂ (NEt)), 3.9 and 4.45 (2 d, J = 10.8 Hz, J = 17.2 Hz, 1 H, CHN), 4.5-4.8 (m, 2 H, CH₂N), 6.96-7.83 (m, 23 H, H-Ar) ppm. ¹³C-NMR (100 MHz, CDCl₃): Mixture of two rotamers δ 11.4 (CH₃), 13.8 and 13.9 (CH₃), 19.1, 19.4, 20.3 and 20.4 (CH₃), 22.3 and 22.6 (CH₂), 27.5 and 27.6 (CH₂), 28.3 and 28.6 (CH), 33.8 and 33.9 (CH₂), 41.8 (CH₂), 46.1 and 48.2 (CH₂), 66.1 and 70.3 (CH), 82.8 and 82.9 (C), 125.2-142.1 (CH- and C-ipso-Ar), 164.2 and 164.4 (CN), 174.6, 175.0, 175.3 and 175.6 (CO) ppm. IR (υ): 3446 (broad band, NH), 1641 (broad band, CO-carboxylate and amide) cm⁻¹. Mp (toluene): 129-131 °C.

Example 20: Preparation of Diethylammonium N-pentanoyl-N-[(2'-H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-L-valinate

A mixture of benzyl N-pentanoyl-N-[(2'-[1-(triphenylmethyl)-1 H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl]-L-valine (2 g) and diethylamine (0.54 ml) in toluene (10 ml) and MeOH (2.5 ml) containing 5% palladium on activated Charcoal (44.5% Pd/C, 224 mg) was hydrogenated at room temperature at pressure of 5 bars overnight. The resulting crude product was filtered through a Celite® pad and the solvent was evaporated to dryness to furnish the desired product (1.4 g, 72%).
Example 21: Preparation of N-pentanoyl-N-[r2'-(1 H-tetrazol-5-yl)-1','1'-biphenyl-4-yllmethyl]-L-valine

The residue obtained in Example 16 (4 g, ee 98%) was partitioned between toluene (20 ml) and 1 M KOH (20 ml). The mixture was heated until a clear solution was obtained and then cooled slowly to room temperature. The mixture was further cooled to 0-5 °C for 1 h, filtered under vacuum, washed with cold toluene (2 ml) and dried at 40 °C to give potassium N-pentanoyl-N-[r2'-(1-(triphenylmethyl)-1 H-tetrazol-5-yl]-1',1'-biphenyl-4-yllmethyl]-L-valinate (1.94 g, 50%). The resulting crude (0.3 g) in MeOH (3 ml) was heated under reflux for 3 h. The solvent of the resulting solution was distilled under reduced pressure. The residue was treated with saturated aqueous NaHCO₃ (3 ml) and washed with toluene (2 x 3 ml). The organic solvent of the aqueous layer was removed by distillation. The resulting aqueous phase was acidified with 1 M HCl (4 ml) and stirred for 1 h at room temperature. The solid formed was filtered under vacuum, washed with cold water (1 ml) and dried under vacuum to give Valsartan (130 mg, 73%, ee 98%).

Example 22: Preparation of N-pentanoyl-N-[r2'-(1 H-tetrazol-5-yl)-1',1'-biphenyl-4-yllmethyl]-L-valine

A mixture of sodium N-pentanoyl-N-[r2'-(1-(triphenylmethyl)-1 H-tetrazol-5-yl]-1',1'-biphenyl-4-yllmethyl]-L-valinate (167 mg, ee 74%) in MeOH (1 ml) was heated under reflux overnight. The solvent of the resulting solution was distilled under reduced pressure. The residue was dissolved in AcOEt (5 ml) and washed with saturated aqueous NaHCO₃ (2 ml). The aqueous layer was acidified with 2 M HCl (2 ml) and extracted with AcOEt (5 ml x 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure to give Valsartan (85 mg, 82%, ee 74%).

Example 23: Preparation of N-pentanoyl-N-[r2'-(1 H-tetrazol-5-yl)-1',1'-biphenyl-4-yllmethyl]-L-valine

A mixture of potassium N-pentanoyl-N-[r2'-(1-(triphenylmethyl)-1 H-tetrazol-5-yl]-1',1'-biphenyl-4-yllmethyl]-L-valinate (200 mg, ee 74%) in MeOH (4 ml) was heated under reflux for 3 h. The solvent of the resulting solution was
distilled under reduced pressure. The residue was dissolved in AcOEt (3 ml) and washed with saturated aqueous NaHCO₃ (3 ml). The aqueous layer was extracted with AcOEt (2 ml), acidified with 1 M HCl (4.5 ml) and extracted with AcOEt (5 ml x 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure to give Valsartan (110 mg, 89%, ee 74%).

Example 24: Preparation of N-pentanoyl-N\{-r²'-(1 H-tetrazol-5-yl)-1',1'-biphenyl-4-yllmethyl\}-L-valine

To a mixture of Valsartan (0.5 g, ee 99.4%) in MIK (3 ml) and NaOH (100 mg) at room temperature under inert atmosphere, was added TrCl (0.35 g). The reaction mixture was stirred for 4 h and then H₂O (3 ml) was added. The mixture was then heated until a clear solution was obtained (more solvent was needed, 0.3 ml). The mixture was cooled to room temperature and stirred overnight. The solid formed was filtered under vacuum, washed with cold MIK (1 ml) and cold H₂O (1 ml) and dried to give sodium N-pentanoyl-N-[\{2'-(1)-(triphenylmethyl)-i H-tetrazol-5-yl]-1 ',1'-biphenyl-4-yllmethyl\}-L-valinate (400 mg, 50%). The crude salt obtained (200 mg) in MeOH (4 ml) was heated under reflux overnight. The solvent of the resulting solution was distilled under reduced pressure. The residue was dissolved in AcOEt (3 ml) and washed with saturated aqueous NaHCO₃ (3 ml). The aqueous layer was extracted with AcOEt (2 ml), acidified with 1 M HCl (4.5 ml) and extracted with AcOEt (5 ml x 3). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure to give Valsartan (79 mg, 70%, ee 99.3%).
CLAIMS

1. A salt of a compound of formula (H)-P.

(N)-P

wherein P is an amino protective group.

2. The salt compound according to claim 1, which is an inorganic or organic salt selected from the group consisting of an alkaline metal salt, a alkaline earth metal salt and a quaternary ammonium salt.

3. The salt compound according to claim 2, which is selected from sodium salt and potassium salt

4. The salt compound according to claim 2, which is selected from diethylammonium salt and triethylammonium salt.

5. The compound according to any of the claims 1-5, wherein the amino protective group P is trityl.

6. A preparation process of a salt of the compound of formula (H)-P as defined in any of the claims 1-5, which comprises coupling a compound of formula (III) or a salt thereof,
wherein:

$Y_1$ and $Y_2$ are each independently selected from the group consisting of hydroxy, ($C_4$-$C_4$)-alkoxy and phenoxy, the latter optionally substituted by a ($C_4$-$C_4$)-alkoxy, ($C_4$-$C_4$)-alkyl or an halogen group; or alternatively $Y_1$ and $Y_2$ are taken together with the boron atom to form a cyclic structure selected from the following ones,

[Diagram of cyclic structure]

wherein $Z$ is selected from the group consisting of ($CH_2)_n$, ($CH_2)rCR_uR_v(CH_2)s$ and $CR_uR_v(CH_2)tCR_uR_v$; $n$ is an integer from 2 to 4; $r$ and $s$ are integers from 0 to 4 with the condition that $r$ and $s$ are not both 0; $t$ is an integer from 0 to 1, and $R_u$ and $R_v$ are each independently selected from the group consisting of $H$, ($C_4_4$)-alkyl, phenyl and mono- or di-substituted phenyl, the substituents being halogen, ($d-C_4$)-alkyl and ($d-C_4$)-alkoxy;

with a compound of formula (IV),
wherein Y is a leaving group and P is a protective group;
in an appropriate solvent system and in the presence of a metallic compound and a base; and optionally carrying out a further step which comprises crystallizing the salt obtained in an appropriate solvent system.

7. The process according to claim 6, wherein the process is carried out from the sodium salt of the compound of formula (III).

8. The process according to any of the claims 6-7, wherein Y₁ and Y₂ together with the boron atom form a cyclic structure, wherein Z is CH₂C(CH₃)₂CH₂.

9. The preparation process according to any of the claims 6-8, wherein the leaving group Y is Br.

10. The preparation process according to any of the claims 6-9, wherein the protective group P is trityl.

11. The preparation process according to any of the claims 6-10, wherein the metallic compound is selected from palladium, nickel, a metallic salt and a metallic complex.

12. The preparation process according to claim 11, wherein the catalyst is selected from the group consisting of Pd(PPh₃)₄, PdCl₂(dpff), and Pd(OAc)₂/PPh₃.

13. The preparation process according to any of the claims 6-12, wherein the base is selected from the group consisting of an alkaline metal carbonate and an alkaline metal phosphate.
14. The preparation process according to claim 13, wherein the base is selected from potassium carbonate and potassium phosphate.

15. The preparation process according to any of the claims 6-14, wherein the compound of formula (III) is previously prepared by submitting a compound of formula (V)

\[ \text{(V)} \]

wherein $Y_1$ and $Y_2$ have the same meaning mentioned above for the compound (III) and $R_i$ is a group which may be converted into a carboxy group,

to a hydrolysis, acidolysis, thermolysis, or hydrogenolysis reaction, optionally in the presence of a base, and thereafter as necessary converting the compound (III) obtained into a salt form.

16. The preparation process according to claim 15, wherein $R_1$ is a radical of formula $\text{COOR}_2$ wherein $R_2$ is a radical selected from the group consisting of $(\text{C}_1-\text{C}_6)$-alkyl, substituted methyl, 2-substituted ethyl, 2,6-dialkyl-phenyl, benzyl, substituted benzyl and silyl.

17. The preparation process according to claim 6, wherein the solvent of the optional crystallization is selected from the group consisting of methyl isobutyl ketone, toluene and their mixtures with water.

18. A preparation process of a salt of the compound of formula (N)-P as
defined in any of the claims 1-5, which comprises the steps of:

a) coupling a compound of formula (V), wherein $Y_1$, $Y_2$, and $R_1$ have the meaning mentioned in claim 15,

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{R}_1 & \quad \text{B} \\
\text{Y}_1 & \quad \text{Y}_2
\end{align*}
\]

(V)

with a compound of formula (IV), wherein $Y$ and $P$ have the meaning mentioned in claim 6,

\[
\begin{align*}
\text{Y} & \quad \text{N} \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{Y} & \quad \text{P}
\end{align*}
\]

(IV)

in an appropriate solvent system and in the presence of a metallic compound and a base; to yield the compound of formula (VI);

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{R}_1 & \quad \text{N} \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{Y} & \quad \text{Y}
\end{align*}
\]

(VI)
wherein $R_1$ is a group which may be converted into a carboxy group, and $P$ is a protective group;

b) submitting the compound of formula \( \text{(VI)} \) to a hydrolysis, thermolysis, or hydrogenolysis reaction, in the presence of a base, and optionally carrying out a further step which comprises crystallizing the salt obtained in an appropriate solvent system.

19. The preparation process according to claim 18, wherein $R_1$ is a radical of formula \( \text{COOR}_2 \) wherein $R_2$ is a radical selected from the group consisting of (C1-C6)-alkyl, substituted methyl, 2-substituted ethyl, 2,6-dialkyl-phenyl, benzyl, substituted benzyl and silyl.

20. The process according to claim 19, wherein $R_2$ is a benzyl radical.

21. The process according to any of the claims 18-20, wherein $Y_1$ and $Y_2$ together with the boron atom form a cyclic structure, wherein $Z$ is \( \text{CH}_2\text{C(CH}_3)_2\text{CH}_2 \).

22. The preparation process according to any of the claims 18-21, wherein the leaving group $Y$ is Br.

23. The preparation process according to any of the claims 18-22, wherein the protective group $P$ is trityl.

24. The preparation process according to any of the claims 18-23, wherein the metallic compound is selected from palladium, nickel, a metallic salt and a metallic complex.

25. The preparation process according to claim 24, wherein the catalyst is selected from the group consisting of \( \text{Pd(PPh}_3)_4 \), \( \text{PdCl}_2(\text{dppf}) \), and \( \text{Pd(OAc)}_2(\text{PPh}_3) \).

26. The preparation process according to any of the claims 18-25, wherein the base is selected from the group consisting of an alkaline metal carbonate and an alkaline metal phosphate.
27. The preparation process according to claim 26, wherein the base is selected from potassium carbonate and potassium phosphate.

28. The preparation process according to any of the claims 18-27, wherein the solvent of the optional crystallization is selected from the group consisting of methyl isobutyl ketone, toluene and their mixtures with water.

29. A preparation process of a salt of the compound of formula (H)-P as defined in any of the claims 1-5, which comprises submitting Valsartan to a protection reaction in the presence of a base and an appropriate solvent system, and recovering the salt.

30. A preparation process of a salt of the compound of formula (N)-P as defined in any of the claims 1-5, which comprises reacting a compound of formula (N)-P with a base in an appropriate solvent system and recovering the salt.

31. The process according to any of the claims 29-30 wherein the solvent system comprises an organic solvent selected from the group consisting of methyl isobutyl ketone and toluene and their mixtures with water.

32. The process according to any of the claims 29-31, wherein the base is selected from the group consisting of an alkaline metal hydroxide, an alkaline metal carbonate and an organic base of formula N(Ri)₃, Ri being a radical, same or different, independently selected from the group consisting of H and (Ci-C₄)-alkyl.

33. A preparation process of Valsartan of formula (I), or a pharmaceutically acceptable salt thereof,
which comprises.

a) first converting a salt of the compound of formula (H)-P

into its free acid form by reaction with an acid, and then submitting the compound obtained to a deprotection reaction to remove the protective group P yielding the Valsartan as free acid or in salt form, or alternatively, submitting the salt of the compound of formula (H)-P to a deprotection reaction to remove the protective group P yielding a salt of Valsartan, and if desired, converting the resulting salt of Valsartan into the free acid form of

wherein:

P is an amino protective group;
Valsartan by reaction with an acid; and

c) if desired, converting the resulting free acid form of Valsartan into a salt thereof, or converting a resulting salt of Valsartan into the free acid form of Valsartan, or converting a resulting salt of Valsartan into a different salt.

34. The process according to claim 33, wherein the salt of the compound of formula (N)-P is selected from the sodium salt and the potassium salt.

35. The process according to claim 33, wherein the salt of the compound of formula (H)-P is selected from the diethylammonium salt and the triethylammonium ion salt.

36. A compound of formula (III), or a salt thereof, as well as solvates, including hydrates,

wherein: \( Y_1 \) and \( Y_2 \) are each independently selected from the group consisting of hydroxy, \((\text{CrC}_4)\)-alkoxy and phenoxy, the latter optionally substituted by a \((\text{CrC}_4)\)-alkoxy, \((\text{CrC}_4)\)-alkyl or an halogen group; or alternatively \( Y_1 \) and \( Y_2 \) are taken together with the boron atom to form a cyclic structure selected from the following ones,
wherein Z is selected from the group consisting of \((\text{CH}_2)_n\), \((\text{CH}_2)^r\text{CR}_u\text{R}_v(\text{CH}_2)^s\) and \(\text{CR}_u\text{R}_v(\text{CH}_2)^t\text{CR}_u\text{R}_v\); \(n\) is an integer from 2 to 4; \(r\) and \(s\) are integers from 0 to 4 with the condition that \(r\) and \(s\) are not both 0; \(t\) is an integer from 0 to 1, and \(\text{R}_u\) and \(\text{R}_v\) are each independently selected from the group consisting of \(\text{H}\), \((\text{C}_1-\text{C}_4)-\text{alkyl}\), phenyl and mono- or di- substituted phenyl, the substituents being halogen, \((\text{C}_1-\text{C}_4)-\text{alkyl}\) and \((\text{C}_1-\text{C}_4)-\text{alkoxy}\).
According to International Patent Classification (IPC) or to both national classification and IPG

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F

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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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Further documents are listed in the continuation of Box C. See patent facsimile annex

"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

Date of the actual completion of the international search: 3 May 2007

Date of mailing of the international search report: 11/05/2007

Name and mailing address of the ISA/
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Tel (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer: Von Daacke, Axel
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