

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-002341- -00003-0000

Fecha: 2008-09-23 15:08:42 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 18

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y CO

E.

S.

D.

REF:

Expediente 08-002-341

TÍTULO SOLICITADO:

SALES METALICAS DE 2'-(1H-TETRAZOL-5-IL)-1,1'-
BIFENIL-4-CARBOXALDEHÍDO.

PUBLICACIÓN:

Gaceta 590 de 31 de Marzo de 2008, N° de
publicación 191.

PRIORIDAD:

GB 0514206.2 de 11/07/2005

SOLICITANTE:

NOVARTIS AG

APODERADO:

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TRÁMITE:

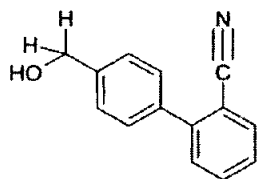
SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada con antelación, en los siguientes términos:

I. RATIFICACIÓN

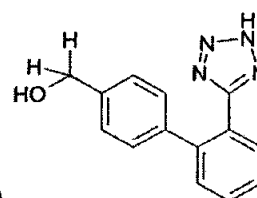
Comedidamente me permito insistir en los argumentos planteados en la oposición respetiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

1. Si tenemos en cuenta que en forma muy general, el proceso de obtención de Valsartan descrito en la solicitud colombiana en trámite, puede resumirse en: Una primera reacción (**que llamaremos reacción A**) entre el compuesto de



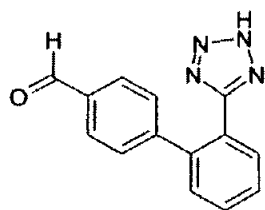
formula (III)

y un compuesto tipo azida de la formula **(R1)(R2)-**

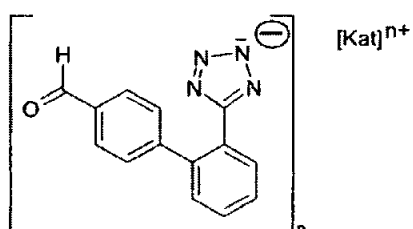


M-N3; que da como resultado un compuesto de fórmula (II)

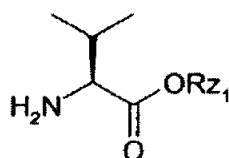
posteriormente se oxida (**Reacción B**) a un compuesto de formula (I)



del cual se forma la sal de la formula (IA)

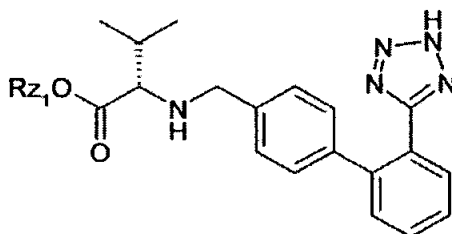


(**Reacción C**); para después reaccionar con el



compuesto de formula (IV)

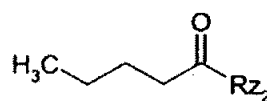
(**Reacción D**) para obtener así el



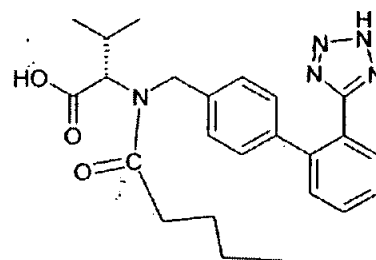
compuesto de formula (V)

que posteriormente

reacciona con el compuesto de fórmula (VI)



(**Reacción E**);



Para finalmente obtener el compuesto de formula (VII)

(Valsartan); se puede afirmar que todas estas reacciones, son reacciones sencillas, descritas en el estado de la técnica y reconocidas por cualquier persona versada en la materia.

Por ejemplo la **reacción A** es un común y reconocido método de reacción de cicloadición [2 + 3] entre un compuesto orgánico de azida ($R-N_3$) y un compuesto orgánico de nitrilo ($R-CN$) (o compuesto III en el caso que nos ocupa). Las características fundamentales, tales como las condiciones óptimas de reacción, los mecanismos de reacción y las variantes, como la estereoquímica resultante y los posibles isómeros que pueden resultar de la reacción entre los diversos compuestos azídicos y nitrílicos para formar tetrazoles se encuentran ampliamente descritos en publicaciones de carácter científico tales como "Novel Synthesis of 5-Substituted-Tetrazoles¹"; "Why Is Tetrazole Formation by Addition of Azide to Organic Nitriles Catalyzed by Zinc(II) Salts²?" y "Mechanisms of Tetrazole Formation by Addition of Azide to Nitriles³".

La **reacción B** es una simple y común reacción de oxidación de alcoholes, que como cualquier persona medianamente versada en la materia sabe, implica la pérdida de uno o más hidrógenos del carbono que sustenta el grupo hidroxilo. Este tipo de reacciones de oxidación, se encuentran ampliamente descritas en publicaciones de carácter científico tales como "Fast and Selective Oxidation of Primary Alcohols to Aldehydes or to Carboxylic Acids and of Secondary Alcohols to Ketones Mediated by Oxoammonium Salts under Two-Phase Conditions⁴" y "Readily Accessible 12-14' Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones⁵".

¹ KOGURO K. ; OGA T. ; MITSUI S. ; ORITA R. ; Synthesis ISSN 0039-7881 CODEN SYNTBF; 1998, no6, pp. 910-914 [5 page(s) (article)] INIST-CNRS, Cote INIST : 14694, 35400007661649.0210.

² Fahmi Himo, Zachary P. Demko, Louis Noodleman, and K. Barry Sharpless. J. AM. CHEM. SOC. 2003, 125, 9983-9987.

³ Fahmi Himo, Zachary P. Demko, Louis Noodleman, and K. Barry Sharpless. J. AM. CHEM. SOC. 2002, 124, 12210-12216.

⁴ Pier Lucio Anelli, Carlo Biffi, Fernando Montanari, and Silvio Quici. J. Org. Chem. 1987, 52, 2559-2562.

⁵ Pier Lucio Anelli, Carlo Biffi, Fernando Montanari, and Silvio Quici. J. Org. Chem. 1983, 48, 4155-4156

La **reacción C** es una reacción común del tipo ácido-base, en donde el compuesto de formula (I) responde como donador de un protón frente a la adición de una sal básica lo suficientemente fuerte como para desprotonar el nitrógeno correspondiente al anillo de tetrazol de dicho compuesto de formula (I). Esto resume la selección de las sales mencionadas por la solicitud en trámite a la verificación de sus correspondientes valores de pKa que aseguren que el equilibrio ácido-base se desplace hacia la forma desprotonada del anillo de tetrazol del compuesto de formula (IA), como cualquier persona medianamente versada en la materia lo haría.

La **reacción D** corresponde a su vez a una reacción reconocida en el estado de la técnica denominada Aminación Reductiva en donde o a través de ella, muchos aldehídos (RCHO) y cetonas (R₂CO) se convierten en aminas por aminación reductiva, que es en si una reducción en presencia de amoniaco o aminas y que se logra catalíticamente empleando cianoborohidruro. Como se observa, las características fundamentales de este tipo de reacciones, tales como el mecanismo de acción, tipo de reactivos, tipos de productos, condiciones de reacción, aplicaciones y demás, se encuentran ampliamente descritas en publicaciones de carácter científico tales como "Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxymethylborohydride. Studies on Direct and Indirect Reductive Amination Procedures"⁶; "Sodium borohydride on wet clay: Solvent-free reductive amination of carbonyl compounds using microwaves"⁷ e "Improved Procedures For The Conjugation Of Oligosaccharides To Protein By Reductive Amination"⁸.

Por ultimo, la **reacción E** corresponde a una reacción de acilación convencional entre un grupo amino secundario y un compuesto con un "grupo activador" nucleófilo como pueden ser los haluros de ácido, en donde, como cualquier persona medianamente versada en la materia reconoce, las aminas primarias y secundarias reaccionan con estos haluros de ácido para formar amidas. La amida

⁶ Ahmed F. Abdel-Magid,* Kenneth G. Carson, Bruce D. Harris, Cynthia A. Maryanoff, and Rekha D. Shah. J. Org. Chem. 1996, 61, 3849-3862.

⁷ Rajender S. Varma, a and Rajender Dahiyab. Tetrahedron Volume 54, Issue 23, 4 June 1998, Pages 6293-6298.

⁸ Roy R, Katzenellenbogen E, Jennings HJ. Can J Biochem Cell Biol. 1984 May;62(5):270-5.

que se produce en esta reacción generalmente no experimenta acilación posterior y se estabilizan por resonancia.

Con lo anteriormente expuesto, se puede apreciar que cada uno de los pasos que componen el proceso de síntesis reivindicado por la solicitud colombiana en trámite corresponden a reacciones sencillas, reconocidas por cualquier persona medianamente versada en la materia y ampliamente descritas en el estado de la técnica; con lo cual queda evidentemente desvirtuado el nivel inventivo de dicha solicitud.

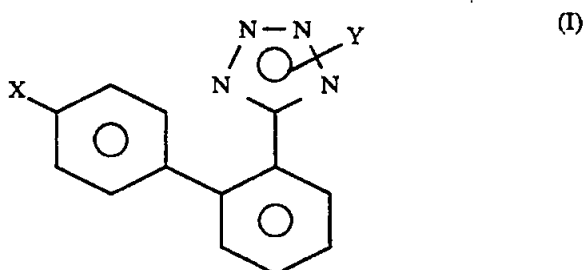
2. Por su parte, la publicación internacional WO 2004/026847 titulada "PROCESS FOR THE MANUFACTURE OF VALSARTAN" revela claramente los mismos intermediarios utilizados por la solicitud colombiana en trámite para la obtención de Valsartan, así mismo, se ven involucrados los mismos tipos de reacciones, diversas condiciones de reacción y diferentes reactivos. Esta evidencia, desvirtúa de manera irrefutable, al menos el nivel inventivo del proceso de síntesis consignado en el capítulo reivindicatorio de dicha solicitud colombiana en discusión.

3. Finalmente, la publicación internacional WO 2005/014602, titulada "PROCESS FOR THE PREPARATION OF TETRAZOLE DERIVATIVES FROM ORGANO BORON AND ORGANO ALUMINIUM AZIDES" revela de manera muy clara la obtención de los mismos intermediarios del proceso de síntesis de la solicitud colombiana, específicamente en lo que se refiere al intermediario de fórmula (I), el intermediario de fórmula (II) y la reacción tipo cicloadición [2+3] entre los compuestos de fórmula (III) y una azida de fórmula (R1)(R2)-M-N₃; con lo cual, no solo se desvirtúa la novedad en el empleo de dichos intermediarios en la obtención de compuestos relacionados a Valsartan, sino que además se desvirtúa el nivel inventivo si se tiene en cuenta que se mencionan los mismos tipos de reacción entre dichos intermediarios, específicamente en lo que se refiere a la oxidación de un alcohol primario del mismo tipo que el del compuesto de fórmula (III) y la obtención del anillo de tetrazol a partir de un compuesto de nitrilo y una azida.

II. COMPLEMENTO DE INFORMACIÓN

Por si no fuesen suficientes los argumentos presentados en el respectivo escrito de oposición, la patente americana US 5,371,233 publicada el 06 de Diciembre de 1994 y titulada "2-(TETRAZOL-5-YL)-1,1'-BIPHENYL DERIVATIVES, THEIR PREPARATION AND THEIR USE AS SYNTHETIC INTERMEDIATES" revela:

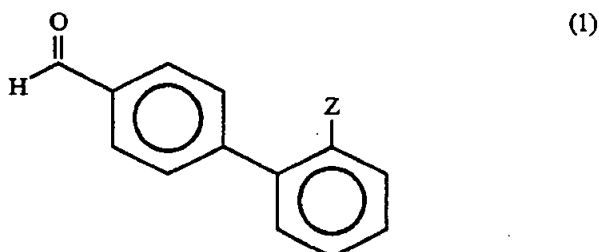
Compounds corresponding to the formula (I)



in which X represents dibromomethyl, formyl, (C₁₋₄)alkyl, or a group CH(OR₅)₂ or CH(OH)OR₅, wherein the or each R₅ is hydrogen (C₁₋₃)alkyl or the two R₅'s in the case of CH(OR₅)₂ are linked to provide a 1,3-dioxolane or 1,3-dioxane ring, and Y represents hydrogen, 1,1-dimethylethyl, triphenylmethyl, trimethylstannyl, tributylstannyl, (1,1-dimethylethyl)dimethylsilyl, (1,1-dimethylethyl)diphenylsilyl, 2-cyanoethyl, or a group CH₂OR₆ wherein R₆ is methyl, phenylmethyl, 1,1-dimethylethyl, 2,2,2-trichloroethyl, benzyloxycarbonyl or 2,2,2-trichloroethyloxycarbonyl, Y being in position 1 or 2 on the tetrazole ring. The compounds of formula (I) are useful as intermediates in the synthesis of compounds possessing therapeutic activity.

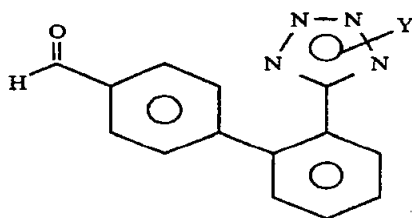
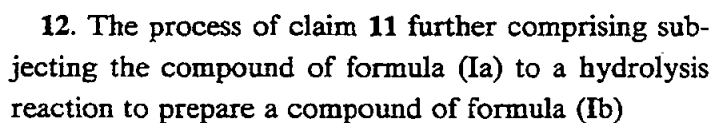
(...)

1,1'-Biphenyl-4-carboxaldehyde derivatives, corresponding to the formula (1)



in which Z is either a cyano group, or a nitro group or an alkoxycarbonyl group, are mentioned in EP-A-0449699.

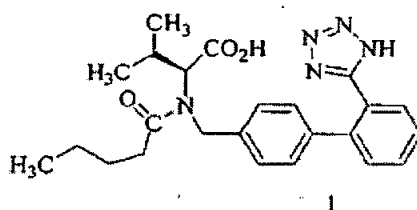
(...)

O=Cc1ccc(cc1)-c2ccccc2C3=NN=NN3

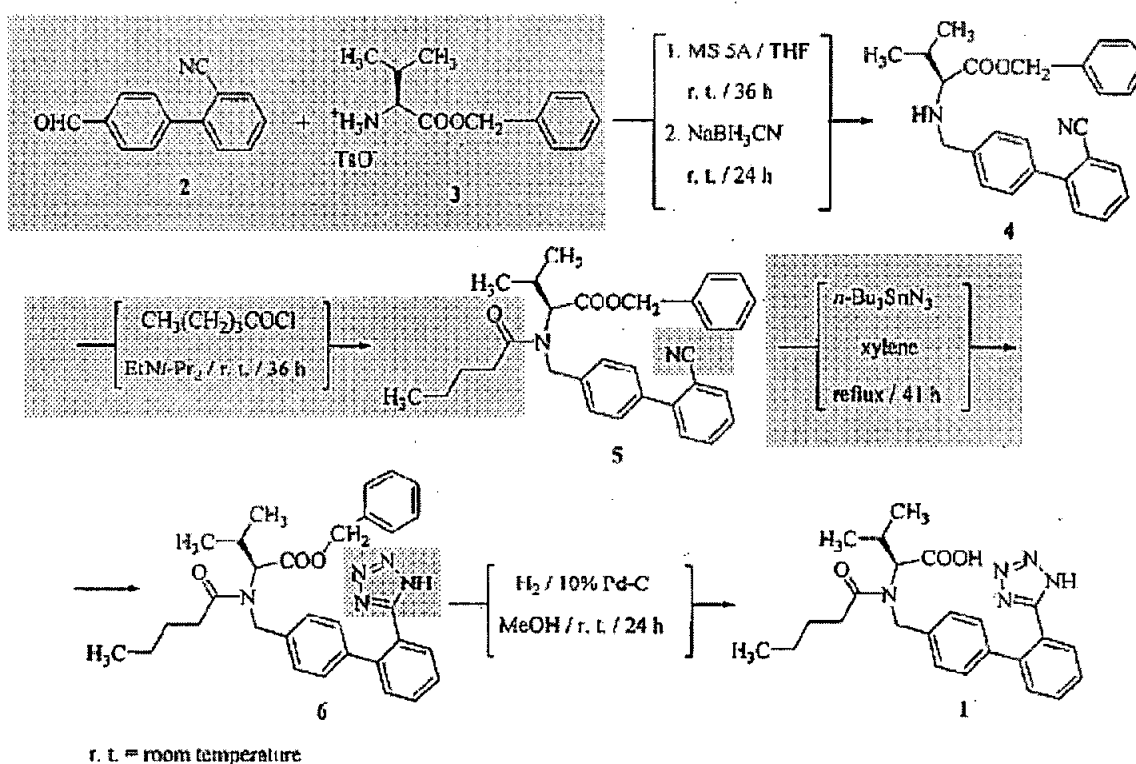
(I) y que como ya se mencionó anteriormente, se hace a través de una simple reacción ácido-base convencional. En otras palabras, lo expuesto por esta anterioridad desvirtúa la novedad de dicho intermediario reivindicado por la solicitud colombiana en trámite.

Por su parte la publicación internacional WO 2005/049586 publicada el 02 de Junio de 2005 y titulada "PROCESS FOR PRODUCTION OF (S)-N-[[2'-(1H-TETRAZOLE-5YL)METHYL]-L-VALINE" revela:

The patent relates to a method of production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (1). Known under the generic name of valsartan, this compound is one of the most important agents used in antihypertensive therapy today [Criscione et al., *Brit. J. Pharmacol.*, **110** (1993) 761].



The method of valsartan (1) synthesis described in the patent literature [Bühlmayer et al., U.S. Pat. 5,399,578 (1995)] starts with reductive alkylation of 2-cyanobiphenyl-4'-carboxaldehyde (2) with *L*-valine benzyl-ester (3) in the form of tosylate, which is then converted into *N*-[2'-cyanobiphenyl-4-yl-methyl]-*L*-valine benzyl-ester (4). Acylation of the compound 4 with valeroyl chloride results in *N*-pentanoyl derivate 5. In reaction of the compound 5 with tri-*n*-butyltin azide in boiling xylene at a high temperature, the compound 5 cyano-group is converted into tetrazole ring and the compound 6 is produced. Removal of the protecting benzyl-ester function of the compound 6 by hydrogenolytic debenzylation with molecular hydrogen and in the presence of palladium on carbon as the catalyst, results in the production of valsartan (1), Scheme 1. The described synthesis involves working with highly toxic and expensive sodium cyanoborohydride in the phase of reductive alkylation of the compound 3 with the compound 2, as well as with toxic tri-*n*-butyltin azide (see also Wittenberger et al., *J. Org. Chem.*, **58** (1993) 4139).



Scheme 1

Como se puede apreciar claramente, en esta anterioridad se hace mención de algunas reacciones del mismo tipo que se utilizan en el proceso de obtención de Valsartan en la solicitud colombiana en trámite, específicamente se exponen la adición de un grupo amino sobre un carbonilo (aminación reductiva); la adición de un haluro de ácido sobre un grupo amino para formar una amida; así como una reacción de cicloadición [2 + 3] entre un compuesto orgánico de azida (R-N₃) y un compuesto orgánico de nitrilo (R-CN).

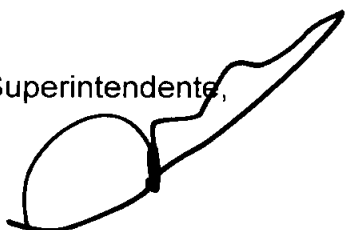
Si bien es cierto que algunas de las condiciones e intermediarios utilizados o el orden en esta anterioridad no son idénticos a los mencionados por la solicitud colombiana en trámite, el hecho de involucrar las mismas clases de reacciones afecta de manera relevante el nivel inventivo de la misma.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS.

- ❖ La patente americana US 5,371,233 publicada el 06 de Diciembre de 1994 y titulada "2-(TETRAZOL-5-YL)-1,1'-BIPHENYL DERIVATIVES, THEIR PREPARATION AND THEIR USE AS SYNTHETIC INTERMEDIATES" columnas 1 a 3 y capítulo reivindicatorio.
- ❖ La publicación internacional WO 2005/049586 publicada el 02 de Junio de 2005 y titulada "PROCESS FOR PRODUCTION OF (S)-N-[[2'-(1H-TETRAZOLE-5YL) METHYL]-L-VALINE" paginas 1 y 2.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.



US005371233A

United States Patent [19]

Daumas et al.

[11] Patent Number: 5,371,233

[45] Date of Patent: Dec. 6, 1994

[54] 2-(TETRAZOL-5-YL)-1,1'-BIPHENYL
DERIVATIVES, THEIR PREPARATION AND
THEIR USE AS SYNTHETIC
INTERMEDIATES

[75] Inventors: Marc Daumas; Christian Hoornaert,
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Jolie; Guy Rossey,
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Greciet, Val de Reuil, all of France

[73] Assignee: Synthelabo, Le Plessis Robinson,
France

[21] Appl. No.: 998,055

[22] Filed: Dec. 29, 1992

[30] Foreign Application Priority Data

Dec. 30, 1991 [FR] France 91 16290
Mar. 16, 1992 [FR] France 92 03113

[51] Int. Cl.⁵ C07D 257/04; C07D 403/10

[52] U.S. Cl. 548/250; 548/252;
548/253

[58] Field of Search 548/252, 253, 250

[56] References Cited

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4,820,843 4/1989 Aldrich et al. 548/252
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4,874,867 10/1989 Aldrich et al. 548/101
5,039,814 8/1991 Shuman et al. 548/250
5,128,355 7/1992 Carini et al. 514/381
5,130,439 7/1992 Lo et al. 548/110

FOREIGN PATENT DOCUMENTS

0106140 4/1984 European Pat. Off. .
0449699 10/1991 European Pat. Off. .

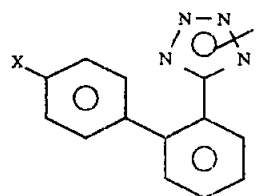
OTHER PUBLICATIONS

Journal of the Chemical Society, Perkin Transaction
No. 2, No. 12, 1979, London, pp. 1670-1674.

Primary Examiner—David B. Springer
Attorney, Agent, or Firm—Jacobson, Price, Holman &
Stern

[57] ABSTRACT

Compounds corresponding to the formula (I)



(I)

in which X represents dibromomethyl, formyl, (C₁₋₄)alkyl, or a group CH(OR₅)₂ or CH(OH)OR₅, wherein the or each R₅ is hydrogen (C₁₋₃)alkyl or the two R₅'s in the case of CH(OR₅)₂ are linked to provide a 1,3-dioxolane or 1,3-dioxane ring, and Y represents hydrogen, 1,1-dimethylethyl, triphenylmethyl, trimethylstannyl, tributylstannyl, (1,1-dimethylethyl)dimethylsilyl, (1,1-dimethylethyl)diphenylsilyl, 2-cyanoethyl, or a group CH₂OR₆ wherein R₆ is methyl, phenylmethyl, 1,1-dimethylethyl, 2,2,2-trichloroethyl, benzyloxycarbonyl or 2,2,2-trichloroethyloxycarbonyl, Y being in position 1 or 2 on the tetrazole ring. The compounds of formula (I) are useful as intermediates in the synthesis of compounds possessing therapeutic activity.

13 Claims, No Drawings

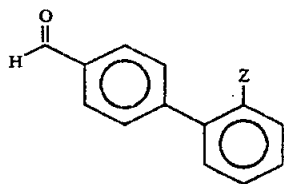
2-(TETRAZOL-5-YL)-1,1'-BIPHENYL DERIVATIVES, THEIR PREPARATION AND THEIR USE AS SYNTHETIC INTERMEDIATES

FIELD OF THE INVENTION

The present invention relates to 2-(tetrazol-5-yl)-1,1'-biphenyl derivatives, their preparation and their use as intermediates in the preparation of 3-pyrazolane and 4-pyrimidinone derivatives.

BACKGROUND OF THE INVENTION

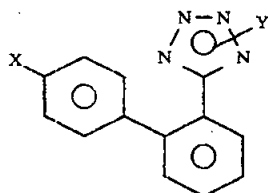
1,1'-Biphenyl-4-carboxaldehyde derivatives, corresponding to the formula (I)



in which Z is either a cyano group, or a nitro group or an alkoxycarbonyl group, are mentioned in EP-A-0449699.

SUMMARY OF THE INVENTION

The invention provides a compound of the general formula (I)



in which X represents a group selected from dibromomethyl, formyl, (C₁₋₄)alkyl, a group CH(OR₅)₂ and a

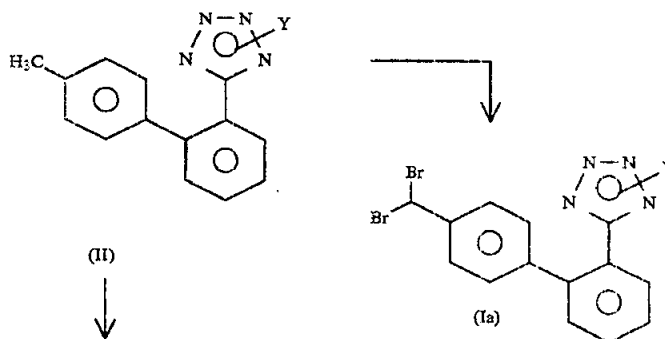
group CH(OH)OR₅, wherein the or each R₅ is selected from hydrogen and (C₁₋₃)alkyl or the two R₅'s in the case of CH(OR₅)₂ are linked to provide a heterocyclic ring selected from 1,3-dioxolane and 1,3-dioxane, and Y represents an atom or group and selected from hydrogen, 1,1-dimethylethyl, triphenylmethyl, trimethylstannyl, tributylstannyl, (1,1-dimethylethyl)dimethylsilyl, (1,1-dimethylethyl)diphenylsilyl, 2-cyanoethyl and a group CH₂OR₆, wherein R₆ is a group selected from methyl, phenylmethyl, 1,1-dimethylethyl, 2,2,2-trichloroethyl, benzyloxycarbonyl and 2,2,2-trichloroethyloxycarbonyl, Y being in position 1 or 2 on the tetrazole ring.

DETAILED DESCRIPTION OF THE INVENTION

Preferred compounds of the invention are those wherein X represents a group selected from dibromomethyl, formyl, dimethoxymethyl, 1,3-dioxolan-2-yl and 1,3-dioxan-2-yl, and Y represents an atom or group selected from hydrogen, 1,1-dimethylethyl, triphenylmethyl and methoxymethyl. More preferred compounds of the invention are those wherein X represents a group selected from dibromomethyl and formyl and Y represents an atom or group selected from hydrogen, 1,1-dimethylethyl and triphenylmethyl. Examples of compounds of the invention include 5-(4'-dibromomethyl-1,1'-biphenyl-2-yl)-2-triphenylmethyl-2H-tetrazole, 5-(4'-dibromomethyl-1,1'-biphenyl-2-yl)-2-(1,1-dimethylethyl)-2H-tetrazole, 2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-carboxaldehyde, 2'-[2'-(1,1-dimethylethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-carboxaldehyde, 5-(4'-dimethoxymethyl-1,1'-biphenyl-2-yl)-2-triphenylmethyl-2H-tetrazole, 5-(4'-dimethoxymethyl-1,1'-biphenyl-2-yl)-2-(1,1-dimethylethyl)-2H-tetrazole and 2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-carboxaldehyde.

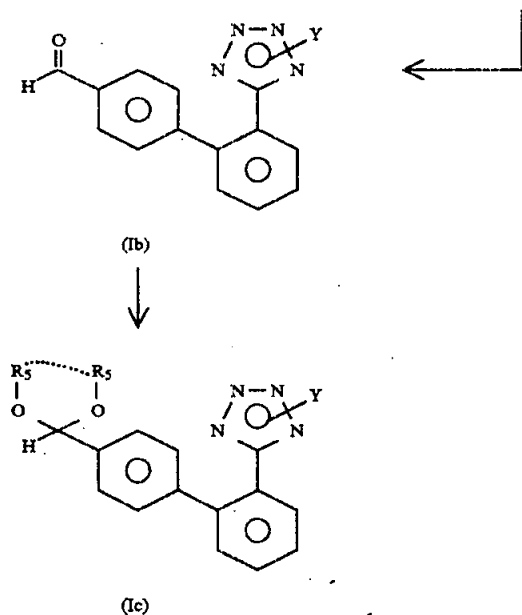
The compounds of the invention can be prepared according to various methods which are well known in organic chemistry. Thus, the aldehydes of formula (Ib) can be synthesised, according to Scheme 1, following one or the other of the reaction sequences, depending on the nature of the substituent Y:

Scheme 1



-continued

Scheme 1



In a first method, a derivative of formula (II) is 30 treated with an oxidising agent, such as, for example, ceric ammonium nitrate or potassium permanganate. Examples of the use of this method will be found in *Synthesis*, 1989, 293 and in *Can. J. Chem.*, 1976, 54, 411. The derivatives of formula (II) in which Y is either a 35 hydrogen atom, or a group SnR_3 where R is a (C_{1-6}) alkyl group or a phenyl group or a cyclohexyl group, or a triphenylmethyl group, or a 2-cyanoethyl group or a (4-nitrophenyl)methyl group are described in European Patent Application EP 0291969.

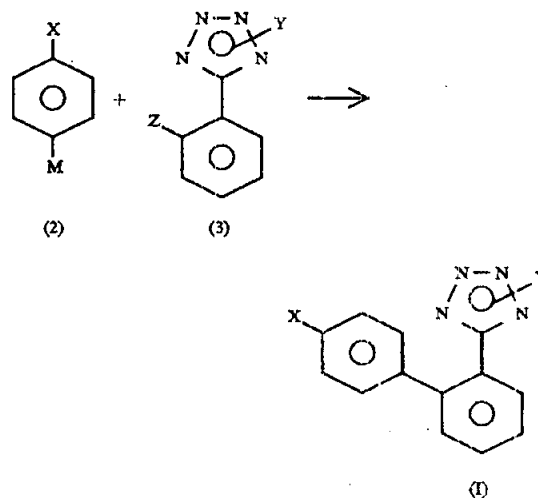
In a second method, the derivatives of formula (II) are converted to derivatives of formula (Ia), for example by making them react with N-bromosuccinimide, in a solvent such as carbon tetrachloride, in the presence of an initiator such as benzoyl peroxide or α, α' -45 azoisobutyronitrile, at reflux temperature. The derivatives of formula (Ia) are converted to aldehydes of formula (Ib). This conversion can be carried out either by reacting with an amine such as pyridine, hydroxylamine, hydrazine or morpholine and by hydrolysing, or by a hydrolysis catalysed by an organic or inorganic base 50 or acid, or by a hydrolysis catalysed by silver salts, or by a solvolysis in an aliphatic diol or alcohol. Examples of these types of conversions will be found in *J. Labelled Comp.*, 1972, 8, 397; *Syn. Comm.*, 1987, 17, 1695; *Org. Synth.*, 1954, 34, 82; *Tetrahedron Lett.*, 1984, 25, 3099.

The aldehyde functional group of the compounds of formula (Ib) can be protected, for example, in the form of an aliphatic or alicyclic acetal, to give compounds of formula (Ic), in particular 1,3-dioxolanes or 1,3-dioxanes, by using techniques which are well established in organic chemistry and which are described, for example, by T. W. Greene in *Protective Groups in Organic Synthesis*, 1981, Wiley-Interscience.

U.S. Pat. No. 5,039,814 describes a process for the 65 preparation of analogous derivatives, from organolithium compounds, which includes an intermediate stage of transmetalation in the presence of a catalyst.

Another process of the invention makes it possible to carry out a direct aryl-aryl coupling in the presence of a catalyst, according to Scheme 2 below:

Scheme 2



For the compounds of formula (I) in which X does not represent the dibromomethyl group, a coupling between a compound of formula (2), in which M represents a metal chosen from aluminium, boron, cadmium, copper, magnesium and zinc, and a compound of formula (3), in which Y is as defined above and Z represents a bromine or iodine atom, is carried out in the presence of a catalytic quantity of palladium or activated nickel, if necessary, with a Grignard reagent or an aluminium hydride.

The compounds of formula (Ib) can be obtained by hydrolysis of the compounds of formula (I) in which X represents either a group $\text{CH}(\text{OR}_5)_2$ or a group

French Patent Application FR 91 02031 and in European Patent Application EP 0500409. These compounds are reacted, either with hydrazines of formula (V) or with amidines of formula (VI), in order to prepare 3-pyrazolone derivatives of formula (VII) or 4-pyrimidinone derivatives of formula (VIII), respectively, as is described in French Patent Application FR 91 02031 and European Patent Application EP 0500409.

The example below illustrates the synthesis of a compound of formula (IV), a compound converted to a compound of formula (VII) or (VIII) according to Scheme 3 on the previous page.

Synthesis of methyl 3-oxo-2-[[2'-(2-(1,1-dimethylethyl)-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]heptanoate.

3.6 g (12 mmol) of the compound described in Example 4 are dissolved in 25 ml of toluene. 1.96 g (12 mmol) of methyl 3-oxoheptanoate, 175 mg (3 mmol) of acetic acid and 50 mg (0.5 mmol) of piperidine are added. The mixture is brought to reflux with azeotropic separation for 2 hours. 5 ml of solvent are removed and the mixture is put back on reflux for 5 hours. 1 ml of a solution containing 1.2 g (20 mmol) of acetic acid and 0.35 g (4 mmol) of piperidine in 5 ml of toluene is added and the mixture is brought to reflux for 5 hours. The solvent is evaporated and the crude reaction product is taken up in 80 ml of ether. This solution is washed with 40 ml of hydrochloric acid, then with 2×40 ml of 1M sodium carbonate and with 40 ml of water. The organic phase is dried over magnesium sulphate. After evaporating the solvent, 4.9 g of product are obtained in the form of a yellow oil. The oil obtained is taken up in 80 ml of methanol, 350 mg of palladium-on-charcoal are added and the mixture is hydrogenated on a Parr apparatus for 3 hours. The catalyst is filtered off and the solvent is evaporated. The crude reaction product is purified by chromatography on a column of silica gel by eluting with an ethyl acetate and heptane gradient. 3.6 g of a pale-yellow oil are obtained.

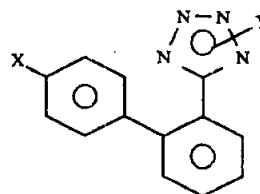
Yield = 69% ¹H NMR (CDCl₃, δ in ppm with respect to TMS): 8.00–7.92, m, 1H, aromatic; 7.64–7.43, m, 3H, aromatic; 7.15, s, 4H, aromatic; 3.79, t, 1H, 7.7 Hz, >CH—; 3.69, s, 3H, OMe; 3.15, d, 2H, 7.7 Hz, CH₂—Ar; 2.64–2.25, m, 2H, CH₂—C(O); 1.59, s, 9H, (CH₃)₃; 1.62–1.41, m, 2H, CH₂; 1.36–1.15, m, 2H, CH₂; 0.87, t, 3H, CH₃. IR (NaCl, film): 1750, 1720 cm⁻¹.

In the formulae (III) to (VIII), R₁ represents either a straight or branched (C₁₋₇)alkyl group, or a straight or branched (C₃₋₉)alkenyl group or a cyclo(C₃₋₇)alkyl(C₁₋₆)alkyl group, R₂ represents either a hydrogen atom, or a straight or branched (C₁₋₇)alkyl group, or a straight or branched (C₃₋₉)alkenyl group, or a straight or branched (C₃₋₉)alkynyl group, or a straight or branched (C₁₋₇)alkoxy group, or a cyclo(C₃₋₇)alkyl(C₁₋₃)alkyl group, or a cyclo(C₃₋₇)alkoxy group, or a straight or branched (C₁₋₇)alkylthio group, or a cyclo(C₃₋₇)alkylthio group, or an optionally substituted aryl group, or an optionally substituted aryloxy group, or an optionally substituted arylthio group, or an aryl(C₁₋₃)alkyl group optionally substituted on the ring, or an aryloxy(C₁₋₃)alkyl group optionally substituted on the ring, or an arylthio(C₁₋₃)alkyl group optionally substituted on the ring, or a heteroaryl(C₁₋₃)alkyl group optionally substituted on the ring, R₃ represents either a hydrogen atom, or a straight or branched (C₁₋₇)alkyl group, or a straight or branched (C₃₋₉)alkenyl group, or a straight or branched (C₃₋₉)alkynyl group, or an optionally substituted aryl group, or an aryl(C₁₋₃)alkyl group optionally substituted on the ring, or an aryloxy(C₁₋₃)alkyl group optionally substituted on the ring, or an arylthio(C₁₋₃)alkyl

group optionally substituted on the ring, or a cyclo(C₃₋₇)alkyl(C₁₋₃)alkyl group, or a heteroaryl(C₁₋₃)alkyl group optionally substituted on the ring, R₄ represents either a methyl group, or an ethyl group, or a 1,1-dimethylethyl group, or a phenylmethyl group.

We claim:

1. A compound of the general formula (I)



in which X represents a group selected from dibromomethyl, formyl, (C₁₋₄)alkyl, a group CH(OR₅)₂ and a group CH(OH)OR₅, wherein the or each R₅ is selected from hydrogen and (C₁₋₃)alkyl or the two R₅'s in the case of CH(OR₅)₂ are linked to provide a heterocyclic ring selected from 1,3-dioxolane and 1,3-dioxane, and Y represents an atom or group selected from hydrogen, 1,1-dimethylethyl, triphenylmethyl and a group CH₂OR₆, wherein R₆ is a group selected from methyl, phenylmethyl, 1,1-dimethylethyl, 2,2,2-trichloroethyl, benzyloxycarbonyl and 2,2,2-trichloroethyloxycarbonyl, Y being in position 1 or 2 on the tetrazole ring.

2. A compound according to claim 1, wherein X represents a group selected from dibromomethyl, formyl, dimethoxymethyl, 1,3-dioxolan-2-yl and 1,3-dioxan-2-yl, and Y represents an atom or group selected from hydrogen, 1,1-dimethylethyl, triphenylmethyl and methoxymethyl.

3. A compound according to claim 2, wherein X represents a group selected from dibromomethyl and formyl and Y represents an atom or group selected from hydrogen, 1,1-dimethylethyl and triphenylmethyl.

4. 5-(4'-Dibromomethyl-1,1'-biphenyl-2-yl)-2-triphenylmethyl-2H-tetrazole.

5. 5-(4'-Dibromomethyl-1,1'-biphenyl-2-yl)-2-(1,1-dimethylethyl)-2H-tetrazole.

6. 2'-(2-Triphenylmethyl-2H-tetrazol-5-yl)-1,1-biphenyl-4-carboxaldehyde.

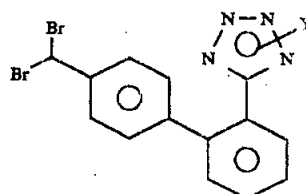
7. 2'-[2'-(1,1-Dimethylethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-carboxaldehyde.

8. 5-(4'-Dimethoxymethyl-1,1'-biphenyl-2-yl)-2-triphenylmethyl-2H-tetrazole.

9. 5-(4'-Dimethoxymethyl-1,1'-biphenyl-2-yl)-2-(1,1-dimethylethyl)-2H-tetrazole.

10. 2'-(1H-Tetrazol-5-yl)-1,1'-biphenyl-4-carboxaldehyde.

11. A process for the preparation of a compound of formula (Ia)

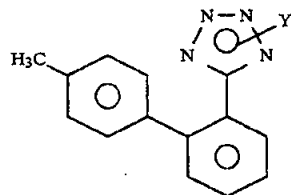


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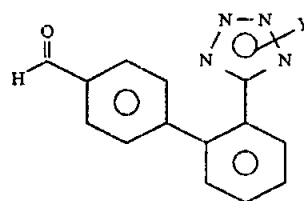
wherein Y is an atom or group selected from hydrogen, 1,1-dimethylethyl, triphenylmethyl and a group CH_2OR_6 , wherein R_6 is a group selected from methyl, phenylmethyl, 1,1-dimethylethyl, 2,2,2-trichloroethyl, benzyloxycarbonyl and 2,2,2-trichloroethyloxycarbonyl, Y being in position 1 or 2 on the tetrazole ring, which process comprises reacting a compound of formula (II)



with N-bromosuccinimide under free-radical reaction conditions.

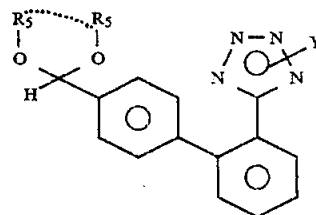
12. The process of claim 11 further comprising subjecting the compound of formula (Ia) to a hydrolysis reaction to prepare a compound of formula (Ib)

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(Ib)

13. The process of claim 12 further comprising protecting the aldehyde functional group of the compound of formula (Ib) in the acetal form to prepare a compound of formula (Ic)



(Ic)

* * * * *

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
2 June 2005 (02.06.2005)

PCT

(10) International Publication Number
WO 2005/049586 A1

(51) International Patent Classification: **C07D 257/04** (74) Agent: BIOCINA, Mirna; I Savica 36, 10000 Zagreb (HR).

(21) International Application Number:
PCT/HR2004/000029

(22) International Filing Date:
24 September 2004 (24.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P20030965A 24 November 2003 (24.11.2003) HR

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- with amended claims

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PRODUCTION OF (S) -N-PENTANOYL-N-[[2'-(1H-TETRAZOLE-5YL) [1,1'-BIPHENYL]-4-YL]METHYL]-L-VALINE

(57) Abstract: The patent relates to a new process of synthesis of an antihypertensive agent, *N*-pentanoyl-*N*-[[2'-(1H-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (1), also known under the generic name of valsartan, by selective reaction of *N*-pentanoyl-*N*-[[2'-(1H-tetrazole-5-yl) [1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (14) with metallic or quaternary ammonium trialkylsilanolates by S_N2 reaction. The compound 14 was produced in four reaction steps starting from 2*N*-trityl-5-(4'-methylbiphenyl-2-yl)tetrazole (17) and *L*-valine methyl-ester (11). Free-radical bromination of the compound 17 with *N*-bromosuccinimide produced 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl)tetrazole (7), which in the reaction with *L*-valine methyl-ester (11) results in *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (15). Acylation of the compound 15 with pentanoyl chloride in the presence of trialkylamine bases results in *N*-pentanoyl-*N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (16). Removal of trityl protecting group by strong acids produces the key intermediary, compound 14.

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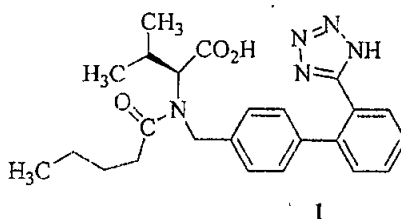
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PROCESS FOR PRODUCTION OF (S)-N-PENTANOYL-N-[[2'-(1H-TETRAZOLE-5-YL)[1,1'-BIPHENYL]-4-YL]METHYL]-L-VALINE

Technical field to which the patent relates:

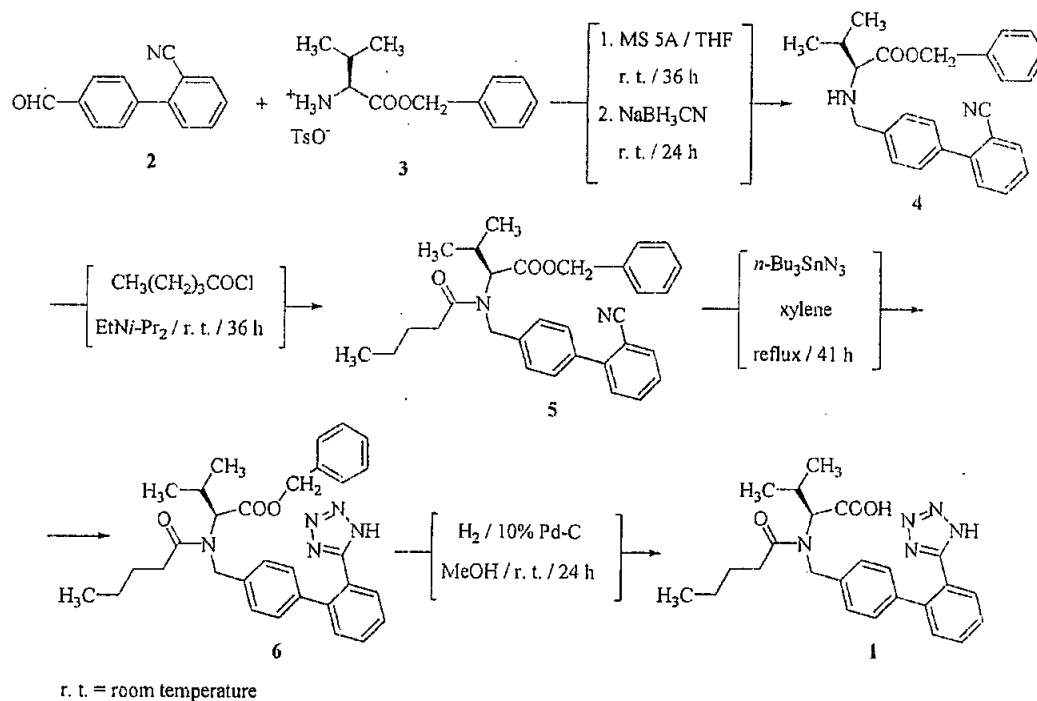
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The patent relates to a method of production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (1). Known under the generic name of valsartan, this compound is one of the most important agents used in antihypertensive therapy today [Criscione et al., *Brit. J. Pharmacol.*, **110** (1993) 761].



The method of valsartan (1) synthesis described in the patent literature [Bühlmayer et al., U.S. Pat. 5,399,578 (1995)] starts with reductive alkylation of 2-cyanobiphenyl-4'-carboxaldehyde (2) with *L*-valine benzyl-ester (3) in the form of tosylate, which is then converted into *N*-[2'-cyanobiphenyl-4'-yl-methyl]-*L*-valine benzyl-ester (4). Acylation of the compound 4 with valeroyl chloride results in *N*-pentanoyl derivate 5. In reaction of the compound 5 with tri-*n*-butyltin azide in boiling xylene at a high temperature, the

compound **5** cyano-group is converted into tetrazole ring and the compound **6** is produced. Removal of the protecting benzyl-ester function of the compound **6** by hydrogenolytic debenzylization with molecular hydrogen and in the presence of palladium on carbon as the catalyst, results in the production of valsartan (**1**), Scheme 1. The described synthesis involves working with highly toxic and expensive sodium cyanoborohydride in the phase of reductive alkylation of the compound **3** with the compound **2**, as well as with toxic tri-*n*-butyltin azide (see also Wittenberger et al., *J. Org. Chem.*, **58** (1993) 4139).



Scheme 1