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

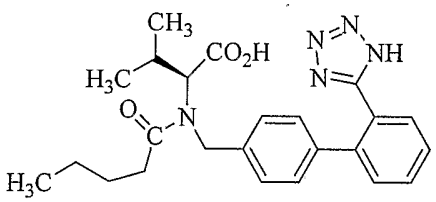
(57) Abstract: The patent relates to a new process of synthesis of an antihypertensive agent, *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (1), also known under the generic name of valsartan, by selective reaction of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl) [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]-4yl]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'-(2N-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.

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

Technical field to which the patent relates:

International class C 07 F

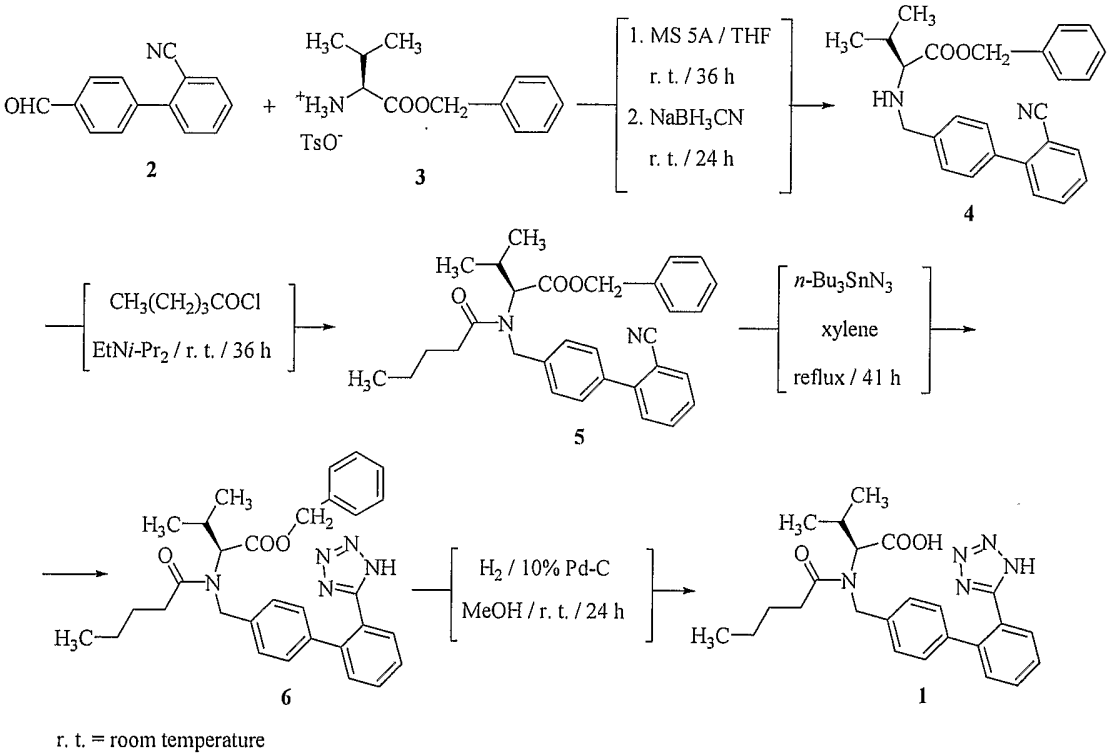
The patent relates to a method of production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**). Known under the generic name of valsartan, this compound is one of the most important agents used in antihypertensive therapy today [Criscione et al., *Brit. J.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



1

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

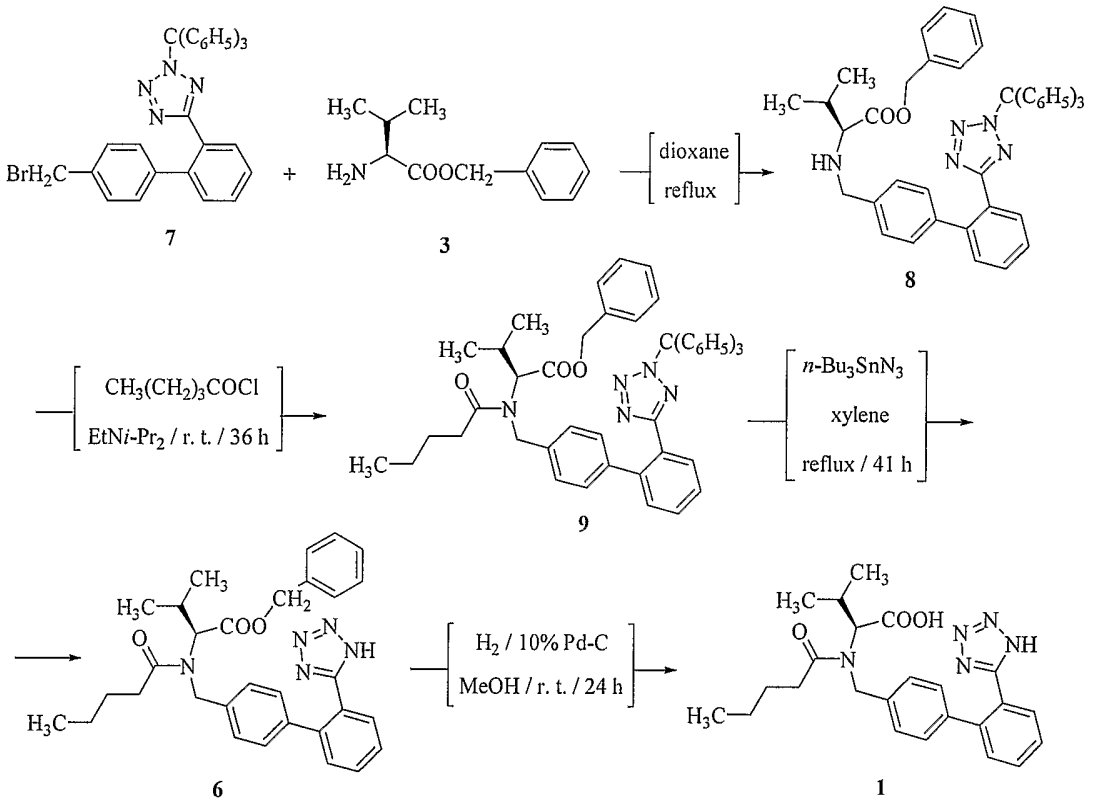
compound **5** cyano-group is converted into tetrazole ring and the compound **6** is produced. Removal of the protecting benzyl-ester function of the compound **6** by hydrogenolytic debenzylation with molecular hydrogen and in the presence of palladium on carbon as the catalyst, results in the production 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

Besides the toxic azide component that has no alternative, the above-mentioned azide also contains organotin residue that is extremely dangerous to human health. The use of organotin or other heavy metal compounds in syntheses of pharmaceutically active substances is very dangerous because traces of heavy metals almost regularly remain in the final product. According to the international guidelines that specify permitted levels of heavy metals in pharmaceutically active substances, such low concentrations of residual heavy metals are very difficult to achieve when they are used in stoichiometric quantities in the industrial production. Furthermore, conversion of nitrile **5** into tetrazole **6** requires for the reaction to take place at the xylene boiling point (136 °C) over 2 days, which is an awkward and drastic procedure. The described procedure requires a high energy expenditure and reactor overload: 48 hours at 136 °C. An additional problem in valsartan production according to this procedure is hydrogenolytic debenzylation of the compound **6**, which must take place in the hydrogenation reactor. This is a standard procedure in organic synthesis but it presupposes working with potentially explosive hydrogen. The same patent mentions alternative procedures for valsartan (**1**) production. One procedure starts with 4'-bromomethyl-2-(2*N*-trityl-tetrazole-5-yl)biphenyl (**7**), which is by alkylation with *L*-valine benzyl-ester (**3**) converted into the compound **8**. Acylation of the compound **8** with valeroyl chloride results in the compound **9**, valsartan, the ester group of which is protected with benzyl group, and the tetrazole group with triphenylmethyl (trityl) group. Removal of protecting groups from the compound **9** to produce valsartan (**1**) is conducted in two reaction steps. In the first step, the compound **9** is treated with a hydrogen chloride solution in 1,3-dioxane to remove

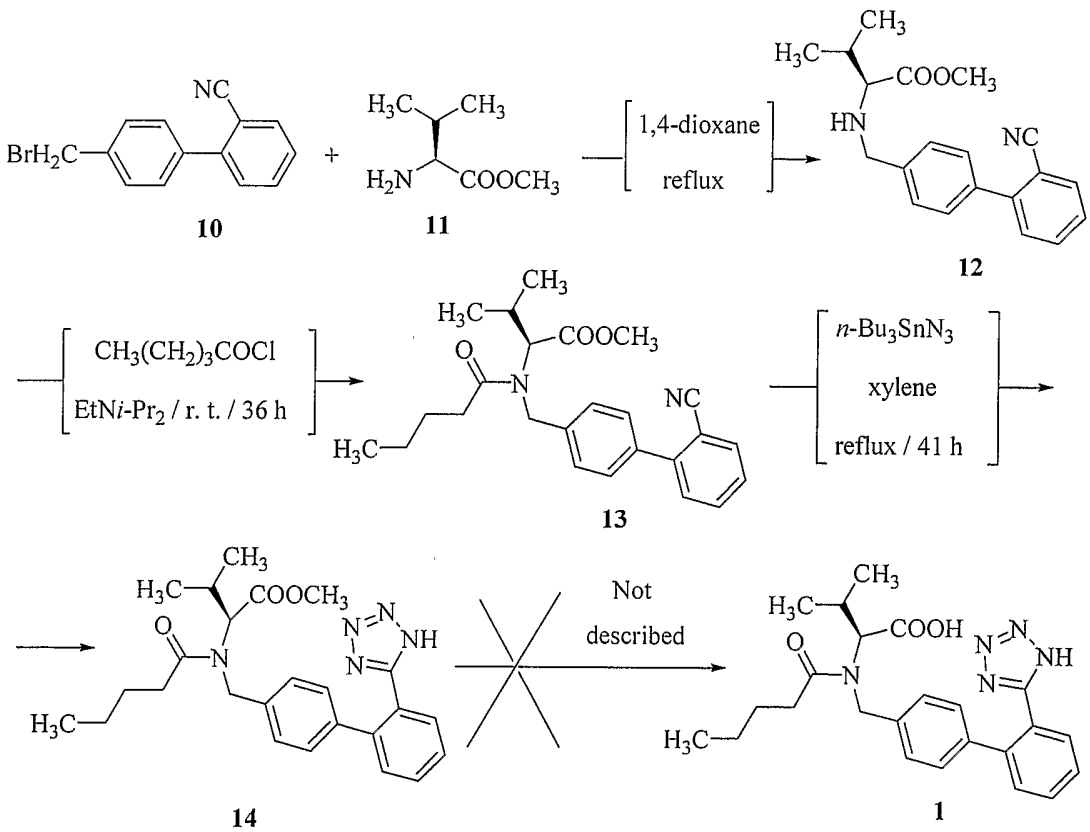
trityl group from tetrazole. Benzyl protecting group is then removed with the previously described hydrogenolytic debenzylation of the compound **6**, Scheme 2.



Scheme 2

The described synthesis has a number of advantages over the previously explained procedure because it eliminates the need to use toxic and expensive sodium cyanoborohydride. However, the last step of the synthesis, hydrogenolytic debenzylation of the compound **6** into valsartan (**1**), remains the same and involves working with explosive hydrogen. The same authors have also described an analogous method of synthesis that starts from alkylation of 4'-bromomethylbiphenyl-2-carbonitrile (**10**) with *L*-valine methyl-ester (**11**) and results in the compound **12**.

Acylation of the compound **12** with valeroyl chloride produces the compound **13**. Its nitrile group is then, by way of reaction with tri-*n*-butyltin azide converted, to *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**), also known as valsartan methyl-ester **14**. The described procedure is thus completely analogous to the synthesis depicted in the Scheme 1, and shares the same disadvantages. The only difference between the two described syntheses (Scheme 1 and Scheme 3) is in the type of ester group, that is the protecting group of valsartan carboxyl-group. In the first synthesis (Scheme 1), the protecting group in use was benzyl ester group, in the third synthesis (Scheme 3), it was methyl ester functionality.



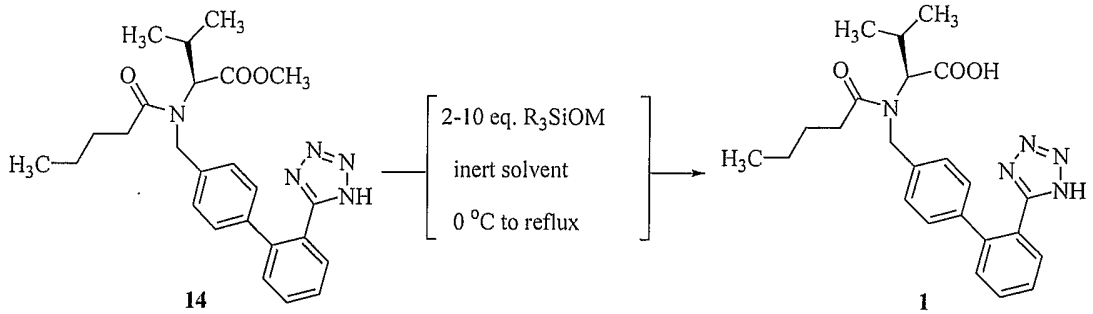
Scheme 3

However, Bühlmayer and coworkers have not described the removal of methyl ester functionality from the compound **14** to valsartan (**1**). Thus the described method of synthesis (Scheme 3) has not been tested to produce valsartan (**1**).

A study of different procedures for valsartan synthesis has discovered that classical methods of ester saponification, for instance with sodium or potassium hydroxide in lower alcohols or mixtures of water an lower alcohols at various temperatures, does not result in selective hydrolysis of the compound **14** to valsartan because hydrolysis of valeroyl (amide) group occurs in parallel.

This patent relates to a new and efficient valsartan, *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), production method by way of chemoselective reaction of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl] methyl]-*L*-valine methyl-ester (**14**) with salts of trimethylsilanol or similar low molecular weight silanolates of the general formula R_3SiOM where R= methyl, ethyl or other lower alkyls (up to C10 straight or branched chains), M= metallic cation such as Li, Na, K, Rb, Cs, R_4N: R= straight or branched chain lower alkyl in inert solvents from the classes of ethers, nitriles, aromatic hydrocarbons, chlorinated hydrocarbons, esters of lower aliphatic alcohols with lower aliphatic acids, such as tetrahydrofuran, diethylether, diisopropylether, 1,4-dioxane, dimethoxyethane, diethoxyethane, diethyleneglycol dimethylether, diethyleneglycol diethylether, triethyleneglycol dimethylether, triethyleneglycol diethylether, acetonitrile, propionitrile, benzene, toluene, xylene, tetrachlormethane, chloroform, dichloromethane, 1,2-dichloroethane, trichloroethylene, methylformate, ethylformate, methylacetate, ethylacetate, ethylpropionate, 1-propylacetate, 2-propylacetate, butylacetate, *N*,*N*-dimethyl

formamide, *N*-methylpyrrolidinone, *N*,*N*-dimethylacetamide, acetone, methylethyl ketone, cyclohexanone, dimethylsulfoxide, hexamethylphosphoramide, or similar inert solvents and their mixtures in different ratios and at temperatures from 0 °C to the solvent reflux temperature, usually most effective in the temperature range from room temperature to circa 50 °C. Valsartan methyl-ester, which is the common name of the compound **14**, produces valsartan (**1**) in practically 100% yield under very mild reaction conditions. For example, with three equivalents of sodium trimethylsilanolate in tetrahydrofuran as solvent, the reaction is completed within 2 hours at room temperature. At higher temperatures, reactions proceed at increased rate so sodium trimethylsilanolate in the quantity of 5 or more equivalents to the compound **14** produces valsartan (**1**) in quantitative yield after only 10 minutes. Since one equivalent of metallic trialkylsilanolate is used for neutralization of the free tetrazole group that reacts as an acid, the necessary quantity of metallic silanolate is at least 2 equivalents to the compound **14**. In terms of practical use, 2-10 equivalents of metallic silanolate can be empoyed to 1 equivalent to the compound **14**, Scheme 4.



14 **1**

R = alkyl, C1-C10

M = Li, Na, K, Rb, Cs, R_4N: R = alkyls, C1-C20

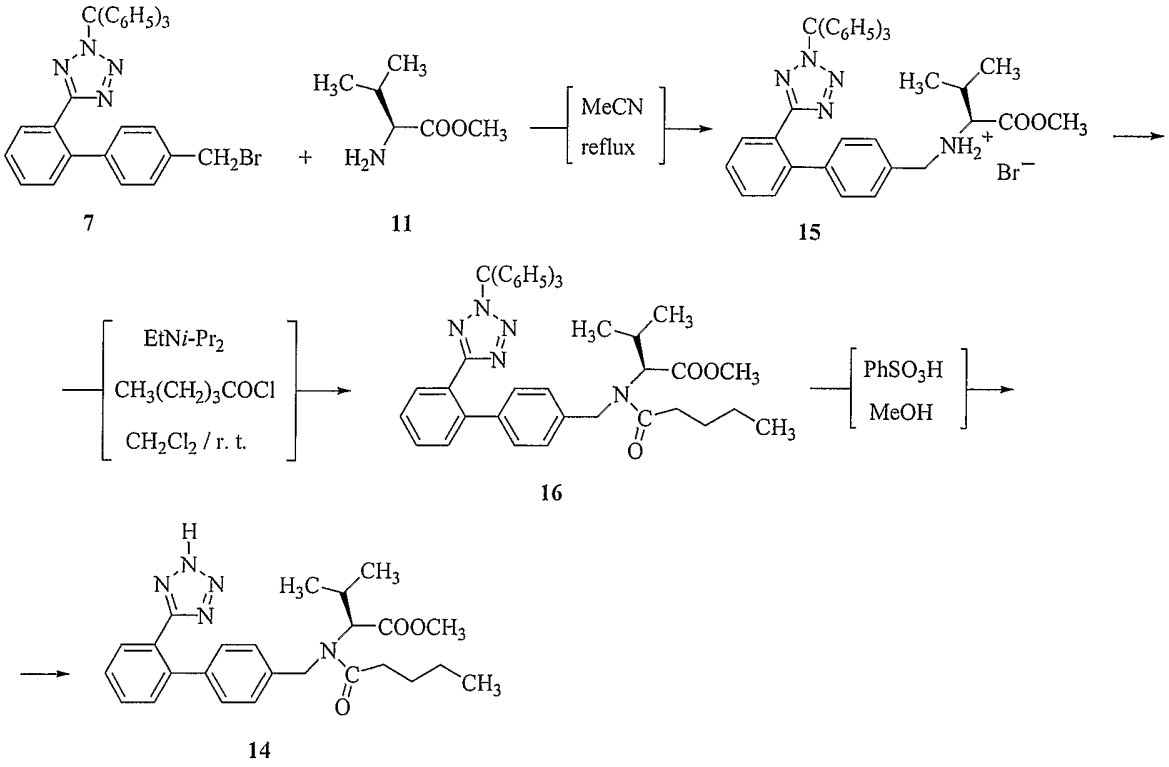
inert solvent = diethylether, tetrahydrofuran, dioxan, dichloromethane, toluene, etc.

Scheme 4

According to this patent, the key intermediate, *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl) [1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) is synthesized from 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl)tetrazole (7) and *L*-valine methyl-ester (**11**), via *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**15**) and *N*-pentanoyl-*N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**16**). Alkylation of *L*-valine methyl-ester (**11**) with the compound 7 produces the compound **15**. Acylation of the compound **15** with valeroyl chloride or valeric acid anhydride in the presence of tertiary amines results in the compound **16** in very high yield. Removal of the protecting triphenymethyl (trityl) group under acid conditions produces valsartan methyl-ester **14**. All of the three above-mentioned chemical reactions are highly selective and high-yielding so the procedure may be carried out in one-pot manner without isolation of the intermediates, compounds **15** i **16**. Namely, because conditions for acylation of the compound **15** are fully compatible with the reaction medium in which the previous reaction step took place, acylation of the compound **15** with valeric acid anhydride or valeroyl chloride immediately follows the synthesis of the compound **15** and takes place in the same reaction vessel. Moreover, the efficient procedure and the chemoselective course of both of the reactions enable that even the third step – removal of the protecting triphenylmethyl (trityl) group - is performed without isolation of the pure compound **16**.

The reaction solvent from the acylation phase, such as chloroform, is simply evaporated, the residue is redissolved in methanol, and with addition of a catalytic quantity of a strong acid (for example benzenesulfonic acid), the compound **16**, is

converted into the compound **14**, also known as valsartan methyl-ester in almost 100% yield. Scheme 5.



7 11 15 16 14

Scheme 5

Alkylation of the compound **7** with *L*-valine methyl-ester (**11**) may be effectively performed not only in acetonitrile (as shown in the Scheme 5) but also in other inert solvents such as *N*,*N*-dimethylformamide, *N*-methylpyrrolidinone, propionitrile, butyronitrile, hexamethylphosphoramide, ethylformate, ethylacetate, methylacetate, 1-, 2-propylacetate, 1-, 2-, *iso*-, *tert*-butylacetate, pentylacetates, tetrahydrofuran, 1,4-dioxane, dimethoxyethane, diethyleneglycol dimethylether, diethyleneglycol diethylether, triethyleneglycol dimethylether, triethyleneglycol diethylether,

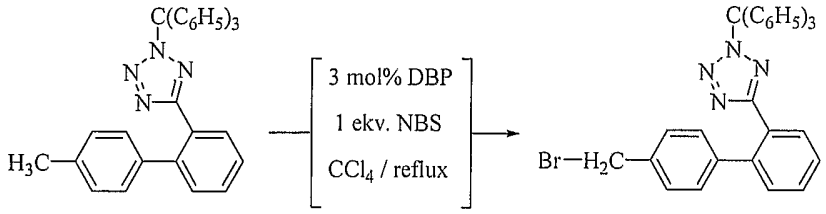
tetrachlormethane, chloroform, dichloromethane, 1,2-dichlorethane, trichlorethylene, toluene, xylene, or similar inert solvents from the class of nitriles, ethers, esters, chlorinated hydrocarbons, aromatic hydrocarbons up to C10 or their mixtures, at temperatures ranging from room temperature to the solvent reflux temperature.

The second phase, acylation of the compound **15** with valeroyl chloride or valeric acid anhydride in the quantity of 1-10 (ideally 2-3) equivalents to the compound **15**, is conducted in inert solvents such as those applicable for the phase 1, and in the presence of tertiary amines such as triethylamine, methyldiethylamine, *N*-methylmorpholine, pyridine, isomeric lutidines, isomeric collidines, ethyldiisopropylamines, diethylisopropylamines, or other related lower aliphatic amines with the general formula $R_1R_2NR_3$, whereby R_1, R_2, i R_3 are straight, branched, benzyl or aromatic hydrocarbon chains with C1-C10 atoms.

Removal of the protecting triphenylmethyl (trityl) group from the compound **16** to obtain valsartan methyl-ester (**14**) is conducted in the presence of strong acids such as hydrochloric, hydrobromic, hydroiodic, methanesulfonic, ethanesulfonic, benzenesulfonic, toluenesulfonic, naphthalenedisulfonic, trifluoroacetic, trifluoromethanesulfonic, trichloroacetic, sulfuric, perchloric, or other strong inorganic or organic acids in the quantity of 1-200 mol% of the compound **16**, most effectively 10-30 mol%, in polar solvents such as methanol, ethanol, isopropanol, other lower aliphatic alcohols, mixtures of lower aliphatic alcohols (C1-C6) or water with organic solvents miscible with alcohols or water such as: 1,4-dioxane, acetonitrile, dimethoxyethane, tetrahydrofuran, *N,N*-dimethylformamide, diethyleneglycol dimethylether, diethyleneglycol diethylether, triethyleneglycol dimethylether,

triethyleneglycol diethylether, and other lower aliphatic nitriles or water-miscible ethers. Removal of the protecting trityl group is conducted at a temperature in the range from -10 °C to the solvent reflux temperature (most conveniently at room temperature), whereby the compound **14** is produced with a quantitative conversion of the compound **16**.

This patent thus describes a simple and efficient method of production of 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl)tetrazole (**7**) by bromination of 2*N*-trityl-5-(4'-methylbiphenyl-2-yl)tetrazole (**17**) with *N*-bromosuccinimide (NBS). The reaction is carried out in boiling tetrachloromethane or in a mixture of tetrachloromethane and a co-solvent such as benzene, cyclohexane or acetonitrile in the presence of a catalytic quantity (1-5 mol%) of diacyl peroxides such as dibenzoyl peroxide (DBP), or azo-compounds such as azo-*bis*-isobutyronitrile (AIBN) or other related free-radical initiators. The reaction temperature ranges from 55 °C to the reflux temperature of tetrachloromethane (or of its mixture with a co-solvent) usually around 70-77 °C. The quantity of NBS is usually around 0.9-1.1 equivalents to the compound **17**, Scheme 6.



17 **7**

Scheme 6

Synthesis of the compound **17** has been also described in the literature [Carini et al., *J. Med. Chem.*, **34** (1991) 2525].

In short, the described patent is a new and efficient method of synthesis of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**, valsartan) from *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**), characterized by a high total yield and pharmaceutical purity of the final product, compound **1**. According to this patent, the compound **14** is efficiently synthesized in 4 reaction steps starting from 2*N*-trityl-5-(4'-methylbiphenyl-2-yl)tetrazole (**17**) and *L*-valine methyl-ester (**11**), the preparation of which is well described in the scientific literature.

Example 1

Preparation of 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl)tetrazole (7)

Dibenzoyl peroxide (3 g, 0.0124 mol, 3 mol%) and *N*-bromosuccinimide (74.3 g, 0.418 mol) are added to a solution of 2*N*-trityl-5-(4'-methylbiphenyl-2-yl)tetrazole (**17**, 200 g, 0.418 mol) in 3000 ml of tetrachloromethane. The reaction mixture was heated at the reflux temperature, around 77 °C, for 20 hours. After that, the reaction mixture was evaporated to circa 1/3 of the initial volume and then stirred at room temperature for 2 hours. The precipitate was filtered and washed out with 3x100 ml of tetrachloromethane. The filtrate was evaporated to dryness and the crude product was then purified by trituration in diisopropylether. The final product was 207.57 grams of pure 2*N*-trityl-5-(4'-bromomethyl biphenyl-2-yl)tetrazole (7) in the form of colorless to pale yellow crystals, m. p. 141.0-142.3 °C, single spot by TLC, R_f= 0.61, with dichloromethane as an eluent.

IR (KBr)ν: 3027, 3051, 1601, 1522, 1510, 1491, 1474, 1443, 1428, 1407, 1354, 1325, 1282, 1224, 1202, 1187, 1154, 1097, 1083, 1029, 1007, 959, 948, 930, 905, 876, 848, 841, 822, 788, 758, 748, 734, 728, 701, 675, 642, 633, 612 cm^{-1}.

^{1}H-NMR ($CDCl_3$)δ: 4.37 (s, 2H, $C\underline{H}_2Br$), 6.88-6.91 (m, 7H, arom.), 7.09-7.10 (m, 3H, arom.), 7.24-7.38 (m, 10H, arom.), 7.43-7.51 (m, 2H, arom.), 7.95-7.97 (m, 1H, arom.) ppm.

^{13}C-NMR ($CDCl_3$)δ: 33.06, 82.86, 126.20, 127.44, 127.50, 127.53, 127.60, 127.81, 128.08, 128.13, 128.35, 129.50, 129.82, 130.11, 130.15, 130.21, 130.26, 130.51, 136.07, 140.96, 141.06, 141.18, 141.36, 146.77, 163.70 ppm.

Example 2

Preparation of 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl)tetrazole (**7**)

Dibenzoyl peroxide (3 g, 0.0124 mol, 3 mol%) was added to a solution 2*N*-trityl-5-(4'-methylbiphenyl-2-yl)tetrazole (**17**, 200 g, 0.418 mol) in 1500 ml of tetrachloromethane. The reaction mixture was then heated to the reflux temperature, circa 77 °C. A solution of *N*-bromosuccinimide (74.3 g, 0.418 mol) in 1500 ml of acetonitrile was added dropwise in the boiling solution of the compound **17** over 6 hours. The reaction mixture was then heated under reflux, circa 77 °C, for another 4 hours. After that, the reaction mixture was evaporated to dryness. A volume of 1000 ml of tetrachloromethane was added to the residue and stirred at room temperature for 2 hours. The precipitate was filtered and washed out with 3x100 ml of tetrachloromethane. The filtrate was evaporated to dryness and the crude product was purified by trituration in diisopropylether with stirring at room temperature for 3 hours. After filtration and drying, the product contained 211.98 g of pure 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl)tetrazole (**7**) in the form of almost colorless crystals, m. p. 141.2-143.1 °C, a single

spot on TLC, R_f= 0.61 with dichloromethane as an eluent. The IR and ^{1}H-NMR spectra are identical to the spectra of the product described in the Example 1.

Example 3

Preparation of *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**)

A solution of *L*-valine methyl-ester (**11**, 23.53 g, 0.179 mol, 1 eq.) in 200 ml of acetonitrile was added to a suspension of 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl) tetrazole (**7**, 100.00 g, 0.179 mol) in 800 ml of acetonitrile. The reaction mixture was heated under reflux temperature, 82 °C, for 6 hours. After that, the reaction mixture was evaporated to dryness and the residue was triturated in a small quantity of boiling ethylacetate. The result was 115.28 g of pure *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**) in the form of colorless crystals, m. p. 156.6-158.2 °C, R_f= 0.57 with dichloromethane/isopropanol (9.5:0.5) as an eluent.

IR (KBr) ν: 2926, 1749 (C=O, ester group), 1584, 1559, 1494, 1449, 1440, 1377, 1333, 1284, 1242, 1214, 1137, 1101, 1030, 969, 926, 878, 842, 758, 750, 732, 703, 676, 641, 633, 612 cm^{-1}.

Elemental analysis for $C_{39}H_{38}N_5O_2Br$: Calculated w(C)= 68.02%, w(H)= 5.56%, w(N)= 10.17%; Found w(C)= 68.1%, w(H)= 5.7%, w(N)= 10.1%.

Example 4

Preparation of *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**)

A solution of *L*-valine methyl-ester (**11**, 23.53 g, 0.179 mol, 1 eq.) in 200 ml of ethylacetate was added to a suspension of 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl) tetrazole (**7**, 100.00 g, 0.179 mol) in 800 ml of ethylacetate. The reaction mixture was heated under reflux temperature, 77 °C, for 20 hours. After that, most of ethylacetate was evaporated and the resulting suspension was cooled to the room temperature and stirred at +10 °C for 3 hours. The crystalline product was removed under vacuum and washed out with a small quantity of ethylacetate. The result was 108.91 g of pure *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**) in the form of colorless crystals, m. p. 156.1-157.9 °C, R_f= 0.57 with dichloromethane/isopropanol (9.5:0.5) as an eluent. The melting point and IR spectrum correspond to the product from the Example 3

Example 5

Preparation of *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**)

A solution of *L*-valine methyl-ester (**11**, 23.53 g, 0.179 mol, 1 eq.) in 200 ml of dry *N*,*N*-dimethylformamide was added to a suspension of 2*N*-trityl-5-(4'-bromomethylbiphenyl-2-yl)tetrazole (**7**, 100.00 g, 0.179 mol) in 800 ml of dry *N*,*N*-dimethylformamide. The reaction mixture was heated at 70-80 °C for 5 hours. After that, the reaction solvent, *N*,*N*-dimethylformamide, was evaporated to dryness from the reaction mixture under reduced pressure (around 0.1 mmHg). The residue was triturated in a small quantity of boiling ethylacetate. The result was 102.95 g of pure *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**) in the form of colorless crystals, m. p. 156.9-158.3 °C, R_f= 0.57 with dichloromethane/isopropanol (9.5:0.5) as an eluent. The melting point and IR spectrum corresponded to the product from the Example 3.

Example 6

Preparation of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**)

A solution of triethylamine (43 ml, 31.09 g, 0.307 mol, 2.1 eq.) in 100 ml of dichloromethane was added dropwise for 20 minutes to a suspension of *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**, 100.00 g, 0.1452 mol) in 800 ml of dichloromethane, cooled to -5 °C. After that, a solution of valeroyl chloride (20.00 g, 0.166 mol, 1.14 eq.) in 100 ml of dichloromethane was added dropwise to the reaction mixture. The reaction mixture was

stirred at 0 °C for 2 hours, and then at room temperature for 48 h. After that, the reaction mixture was evaporated to dryness. First a volume of 900 ml of methanol and then a solution of benzenesulfonic acid (4.59 g, 0.029 mol, 20 mol%) in 100 ml of methanol were added to the residue, which contained almost pure *N*-pentanoyl-*N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**16**). The reaction mixture was stirred at room temperature for 5 hours and then evaporated to dryness. A volume of 500 ml of diisopropylether and a solution of sodium hydroxide (50 g) in 500 ml of distilled water were added to the residue. The resulting biphasic system was stirred for 30 minutes at room temperature. Then the organic phase was separated and the aqueous phase extracted with 2x250 ml of diisopropylether. We added 500 ml of dichloromethane to the aqueous phase and, while vigorously stirring, added dropwise concentrated hydrochloric acid until the pH reached 3.0. After separation of the organic phase, the aqueous phase was extracted by stirring in 2x250 ml of dichloromethane at room temperature. The combined organic extract were dried (Na_2SO_4), filtered and evaporated. The result after drying was 64.89 g of crude *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) in the form of orange-reddish thick oil. The crude product was purified by column chromatography, R_f= 0.48, with dichloromethane/methanol/acetic acid (9.5:0.5:0.1) as an eluent to colorless crystals, m. p. 70.9-73.3 °C, or used in the further synthesis without purification because the crude product was sufficiently pure.

The compound **14** retention factors with different eluents:

Eluent	R_f
CH_2Cl_2 / 2-PrOH (9.5:0.5)	0.31
CH_2Cl_2 / MeOH / HOAc (9.5:0.5:0.2)	0.48
CH_2Cl_2 / MeOH / HOAc (9:1:0.2)	0.64

The structure of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) was confirmed by IR, ^{1}H-, ^{13}C-NMR and two-dimensional NMR spectra COSY, HETCOR, APT, NOESY, as well as by elemental analysis.

IR (KBr)ν: 3453 (wide band, NH, tetrazole), 2963, 2932, 2873, 2744, 1741 (C=O, ester group), 1654 (C=O, amide group), 1617, 1607, 1567, 1516, 1469, 1435, 1410, 1389, 1370, 1263, 1205, 1166, 1133, 1106, 1064, 1007, 946, 885, 820, 807, 777, 760, 706, 668 cm^{-1}.

^{1}H-NMR (CD_3OD)δ: 0.84-0.87 (m, CH_3), 0.95-1.01 (m, CH_3), 1.23-1.29 (m, CH_2), 1.39-1.43 (m, CH_2), 1.53-1.59 (m, CH_2), 1.67-1.69 (m, CH_2), 2.21-2.26 (m, CH), 2.33-2.42 (m, CH_2), 2.50-2.56 (m, CH), 2.65-2.69 (m, CH), 3.30-3.36 (m, $COOCH_3$), 3.40 (s, $COOCH_3$), 4.21-4.22 (m, CH), 4.28-4.31 (m, CH), 4.66-4.75 (m, CH_2, benzyls), 7.03-7.16 (m, 4H, arom.), 7.51-7.57 (m, 2H, arom.), 7.64-7.69 (m, 2H, arom.) ppm.

^{13}C-NMR (CD_3OD)δ: 14.43, 19.21, 19.39, 20.18, 20.66, 23.63, 23.71, 28.81, 28.87, 29.13, 29.34, 34.52, 46.83, 50.22, 52.60, 52.86, 64.39, 67.47, 124.59, 124.74, 127.72, 128.09, 128.75, 129.13, 129.27, 130.14, 130.65, 131.87,

132.08, 132.13, 132.74, 138.55, 139.17, 139.49, 140.11, 143.38, 143.56, 157.11, 171.83, 172.44, 177.04, 177.19 ppm.

Elementary analysis for $C_{25}H_{31}N_5O_3$: Calculated w(C)= 66.79%, w(H)= 6.95%, w(N)= 15.58%; Found w(C)= 66.6%, w(H)= 6.9%, w(N)= 15.5%.

Example 7

Preparation of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**)

A solution of diisopropylethylamine (55 ml, 40.70 g, 0.315 mol, 2.17 eq.) in 100 ml of toluene was added dropwise for 20 minutes to a suspension of *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**, 100.00 g, 0.1452 mol) in 800 ml of toluene, cooled to -10 °C. Next, a solution of valeroyl chloride (20.00 g, 0.166 mol, 1.14 eq.) in 100 ml of toluene was added dropwise to the reaction mixture. The reaction mixture was stirred at 0 °C for 2 hours, and then at room temperature for 72 hours. Then the reaction mixture was evaporated to dryness. Then a volume of 900 ml of 96% ethanol was added dropwise to the residue, which contained nearly pure *N*-pentanoyl-*N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**16**). While stirring, a solution of *p*-toluenesulfonic acid (5.52 g, 0.029 mol, 20 mol%) in 100 ml of 96% ethanol was added dropwise to the reaction mixture, which was then stirred at room temperature for

6 hours. After that, the reaction mixture was evaporated to dryness. In the next step, a volume of 500 ml diisopropylether and a solution of sodium hydroxide (50 g) in 500 ml of distilled water were added to the residue. The resulting biphasic system was stirred at room temperature for 30 minutes. The organic phase was then separated, and the aqueous phase extracted with 2x250 ml of diisopropylether. After the addition of 500 ml of chloroform, while vigorously stirring, concentrated hydrochloric acid was added dropwise until pH reached 3.0. The organic phase was then separated and the aqueous extracted by mixing with 2x250 ml of chloroform at room temperature. The combined chloroform extracts were dried (Na_2SO_4), filtered and evaporated. The result after drying was 61.04 g of crude *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) in the form of orange-red colored thick oil, which was either purified by column chromatography, R_f= 0.48, with dichloromethane /methanol/acetic acid (9.5:0.5:0.1) as an eluent, or directly used in the further synthesis because the crude product was sufficiently pure. The IR and ^{1}H-NMR spectra of the product, m. p. 70.4-73.0 ^{o}C, isolated by preparative chromatography with the mentioned eluent, are identical to the Example 6 product spectra.

Example 8

Preparation of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**)

A solution of triethylamine (43 ml, 31.09 g, 0.307 mol, 2.1 eq.) in 50 ml of 1,2-dichlorethane was added dropwise for 20 minutes to a suspension of *N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester hydrobromide (**15**, 100.00 g, 0.1452 mol) in 500 ml of 1,2-dichlorethane cooled to 0 °C. Next, a solution of valeroyl chloride (20.00 g, 0.166 mol, 1.14 eq.) in 50 ml of dichloromethane was added to the reaction mixture, which was then stirred at 0 °C for 2 h and then at room temperature for 36 hours. Subsequently, the reaction mixture was evaporated to dryness. A volume of 600 ml of ethanol/water mixture (8:2, V/V) was added to the residue, which contained nearly pure *N*-pentanoyl-*N*-[[2'-(2*N*-trityl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**16**). While stirring, a 48% solution of hydrobromic acid (2.35 g HBr, 0.029 mol, 20 mol%), dissolved in 100 ml of the same mixture, was added dropwise. The reaction mixture was then stirred at room temperature for 6 hours and after that evaporated to dryness. A 500 ml volume of diisopropylether and a solution of lithium hydroxide monohydrate (50 g) in 500 ml of distilled water were then added to the residue. The biphasic system was then stirred at room temperature for 30 minutes. Then the organic phase was separated, and the aqueous phase extracted with 2x250 ml of diisopropylether. A 500 ml volume of dichloromethane and 100 g of finely crushed ice were then added to the aqueous phase, and then, while vigorously stirring, concentrated hydrochloric acid was added dropwise until pH dropped to 3.0. Following the separation of the organic phase, the aqueous phase was extracted by stirring at room temperature with 2x250 ml of dichloromethane. The combined dichloromethane extracts were dried (Na_2SO_4), filtered and evaporated. The result after drying was 63.78 g of crude *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-

yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) in the form of orange-red colored thick oil, which was either purified using column chromatography, R_f= 0.48, with dichloromethane/methanol/acetic acid (9.5:0.5:0.1) as an eluent, or directly used in the further synthesis because even the crude product was sufficiently pure.

The IR i ^{1}H-NMR product spectra, m. p. 70.1-73.2 °C, isolated by preparative chromatography with the mentioned eluent, are identical to the spectra of the Example 6 product.

Example 9

Preparation of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), valsartan

Sodium trimethylsilanolate (32.00 g, 0.285 mol, 2.57 eq.) was added to the solution of purified or crude *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**, 50.00 g, 0.111 mol) in 250 ml of diethylether. The reaction mixture was stirred at room temperature for 3 hours. After that, the reaction mixture was evaporated to dryness. A volume of 250 ml of distilled water and of 300 ml of dichloromethane were added to the residue. Concentrated hydrochloric acid was added dropwise into the resulting biphasic system until the pH reached 3.0. Then the organic phase was separated and the aqueous extracted using 2x100 ml of dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. After drying in high vacuum at 50 °C for 5 h, the result was 47.13 g of crude valsartan (**1**) in the form

of light brown to orange-brown thick to semi-solid mass. Purification by recrystallization from ethylacetate and/or a mixture of ethylacetate and diisopropylether resulted in 23.48 g of pure valsartan in the form of colorless crystals, m. p. 115.9-116.7 °C, $[\alpha]_D^{20}$ -65.1° (1% u MeOH), single spot by TLC, with the following retention factors:

Eluent	R_f
CH_2Cl_2 / EtOAc / HOAc (8:2:0.2)	0.20
CH_2Cl_2 / MeOH/ HOAc (9.5:0.5:0.2)	0.42
CH_2Cl_2 / MeOH (7:3)	0.77

The structure of the final product, valsartan (**1**), was confirmed by classic ^{1}H- and ^{13}C-NMR spectra, two-dimensional APT, HETCOR, COSY and NOESY spectra, and elemental analysis.

IR (KBr)ν: 3437, 3118, 2964, 2932, 2874, 2746, 2725, 2619, 1735 (C=O, carboxyl group), 1646 (C=O, amide group), 1602, 1513, 1471, 1458, 1410, 1391, 1372, 1355, 1329, 1274, 1241, 1206, 1161, 1130, 1106, 1065, 1052, 1025, 1006, 996, 978, 938, 885, 857, 811, 778, 761, 684, 670, 623 cm^{-1}.

^{1}H-NMR (CD_3OD)δ: 0.74-0.90 (m, CH_3), 0.92-0.99 (m, CH_3), 1.00-1.12 (m, CH_3), 1.22-1.31 (m, CH_2), 1.36-1.43 (m, CH_2), 1.46-1.61 (m, CH_2), 1.62-1.70 (m, CH_2), 2.18-2.39 (m), 2.49-2.54 (m), 2.63-2.68 (m), 3.30-3.32 (m), 4.15-4.16 (m), 4.58-4.80 (m), 7.02-7.30 (m, 4H, arom.), 7.52-7.62 (m, 2H, arom.), 7.64-7.73 (m, 2H, arom.) ppm.

^{13}C-NMR (CD_3OD)δ: 14.31, 19.44, 19.59, 20.18, 20.74, 23.48, 23.55, 28.60, 28.71, 29.34, 29.39, 34.54, 34.65, 47.54, 50.78, 65.15, 68.11, 124.34, 124.52, 127.94, 128.82, 128.98, 129.12, 129.96, 130.48, 131.75, 131.78, 131.93, 132.62, 138.89, 139.08, 139.63, 139.85, 143.26, 143.39, 156.77, 156.89, 173.08, 173.71, 177.11, 177.32 ppm.

Elemental analysis for $C_{24}H_{29}N_5O_3$: Calculated: w(C)= 66.19%, w(H)= 6.71%, w(N)= 16.08%; Found: w(C)= 66.1%, w(H)= 6.7%, w(N)= 15.9%.

Example 10

Preparation of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), valsartan

Sodium trimethylsilanolate (32.00 g, 0.285 mol, 2.57 eq.) was added to a solution of crude or purified *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**, 50.00 g, 0.111 mol) in 250 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 2 hours and then evaporated to dryness. A volume of 250 ml of distilled water and 300 ml of chloroform were added to the residue. Concentrated hydrochloric acid was added dropwise to the resulting biphasic system until pH dropped to 3.0. Next the organic phase was separated, and the aqueous phase extracted with 2x100 ml of chloroform. The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The result after drying in high vacuum at 50 °C for 2 hours was 45.07 g of crude valsartan (**1**) in the form of light brown to orange

brown thick to semi-solid mass. Recrystallization from ethylacetate and/or a mixture of ethylacetate and diisopropylether resulted in 26.38 g of pure valsartan in the form of colorless crystals, m. p. 116.1-117.1 °C, $[\alpha]_D^{20}$ -65.8° (1% in MeOH), single spot by TLC, R_f= 0.42 with dichloromethane/methanol/acetic acid (9.5:0.5:0.2) as an eluent. The IR i ^{1}H-NMR spectra were identical to the Example 9 product spectra.

Example 11

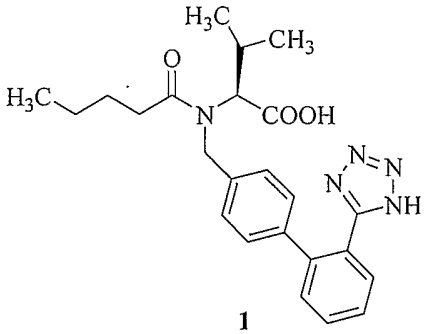
Preparation of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), valsartan

Potassium trimethylsilanolate (42.72 g, 0.333 mol, 3 eq.) was added to a solution of purified or crude *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methylester (**14**, 50.00 g, 0.111 mol) in 250 ml of 1,4-dioxane. The reaction mixture was stirred at room temperature for 5 hours, and then evaporated to dryness under high vacuum at a temperature below 50 °C. Distilled water (250 ml) and 100 g of finely crushed ice were added to the residue, and, following that, concentrated hydrochloric acid was added dropwise until pH dropped to 3.0. The mixture was extracted by stirring at room temperature with 3x200 ml ethylacetate. The combined ethylacetate extracts were dried (Na_2SO_4), filtered and evaporated. The result following drying under high vacuum at 50 °C for 3 h was a mass of 46.98 g of crude valsartan (**1**) in the form of light brown to orange-brown thick to semi-solid mass. Recrystallization from ethylacetate and/or a mixture of ethylacetate and diisopropylether produced a mass

of 29.07 g of pure valsartan in the form of colorless crystals, m. p. 115.6-116.9 °C, $[\alpha]_D^{20}$ -65.0° (1% u MeOH), single spot by TLC, R_f= 0.42 with dichloromethane/methanol/acetic acid (9.5:0.5:0.2) as an eluent. The IR i ^{1}H-NMR spectra were identical to the Example 9 product spectra.

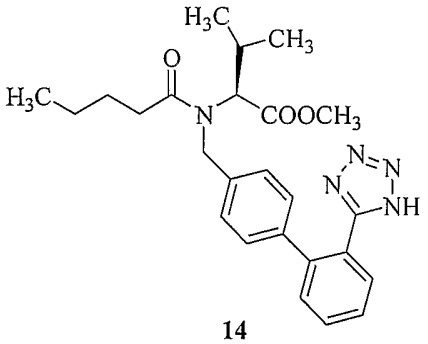
PATENT CLAIMS:

1. A process for production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**),



1

in which *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**),



14

in a reaction with reagents, metallic salts of trialkylsilanol of the general formula R_3SiOM, where R= lower straight or branched alkyl hydrocarbon chain (C1- C6); M= Li, Na, K, Rb, Cs , or R'_4N, where R'= straight or branched aliphatic or aromatic hydrocarbon chain of C1-C20 atoms, in the quantity of 2-10 molar equivalents to the compound **14**, in inert solvents at temperatures ranging from 0 °C to the inert solvent reflux temperature over the period from 10 minutes to 72 h, is converted to valsartan (**1**).

2. A process for production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), as claimed in Claim 1, in which for conversion of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) to the compound **1** the reagents used are metallic- or tetraalkylammonium-salts of trialkylsilanol such as lithium-, sodium-, potassium-, rubidium-, cesium-, tetramethylammonium-, tetraethylammonium-, tetrapropylammonium-, tetra-*n*-butyl ammonium-, didecyldimethylammonium-, hexadecyltrimethylammonium-, benzalkonium-benzyltrimethylammonium-, benzyltriethylammonium-, -trimethyl silanolate, -triethylsilanolate, -tripropylsilanolate, -tributylsilanolate, -tribenzyl silanolate or similar trialkylsilanolates.

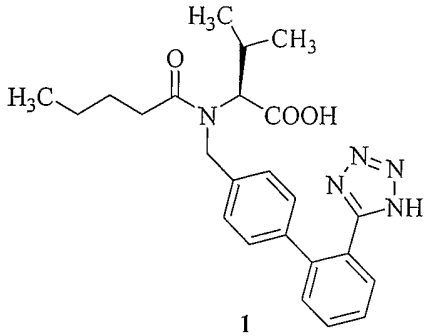
3. A process for production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), as claimed in Claims 1 and 2, in which for conversion of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) into the compound **1**, the following compounds are used as inert solvents: lower aliphatic ethers, nitriles esters, chlorinated lower aromatic hydrocarbons or

liquid aromatic hydrocarbons or ketones such as diethylether, tetrahydrofuran, 1,4-dioxane, dimethoxyethane, diethoxyethane, diethyleneglycol dimethylether, diethyleneglycol diethylether, triethyleneglycol dimethylether, triethyleneglycol diethylether, acetonitrile, propionitrile, methylformate, ethylformate, propylformate, methylacetate, ethylacetate, ethylpropionate, 1-propylacetate, 2-propylacetate, butylacetate, tetrachloromethane, chloroform, dichloromethane, 1,2-dichloretane, trichloroethylene, benzene, toluene, xylene, *N*,*N*-dimethylformamide, *N*-methylpyrrolidinone, *N*,*N*-dimethylacetamide, acetone, ethylmethylketone, cyclohexanone, dimethylsulfoxide, hexamethyl phosphoramide, or their mixtures at temperatures from 0 °C to the solvent reflux temperature.

AMENDED CLAIMS

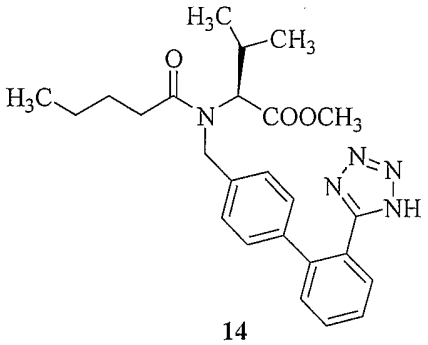
[Received by the International Bureau on 02 March 2005 (02.03.2005): original claims 1-3 replaced by amended claims 1-3]

1. A process for production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**),



1

in which *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**),



14

in a reaction with reagent, salt of trialkylsilanol of the general formula R_3SiOM, where R= lower straight or branched hydrocarbon chain (C1- C6); M= Li, Na, K, Rb, Cs, or R'_4N, where R'= straight or branched aliphatic or aromatic hydrocarbon chain of C1-C20 atoms, in the quantity of 2-10 molar equivalents to the compound

14, in inert solvents at temperatures ranging from 0 °C to the inert solvent reflux temperature over the period from 10 minutes to 72 h, is converted to valsartan (**1**).

2. A process for production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), as claimed in Claim 1, in which for conversion of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) to the compound **1** where the reagent is selected from metallic- or tetraalkylammonium- salts of trialkylsilanol such as lithium-, sodium-, potassium-, rubidium-, cesium-, tetramethylammonium-, tetraethylammonium-, tetrapropylammonium-, tetra-*n*-butyl ammonium-, didecyldimethylammonium-, hexadecyltrimethylammonium-, benzalkonium-benzyltrimethylammonium-, benzyltriethylammonium-, -trimethylsilanolate, -triethylsilanolate, -tripropylsilanolate, -tributylsilanolate, -tribenzylsilanolate or similar trialkylsilanolates.

3. A process for production of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine (**1**), as claimed in Claims 1 and 2, in which for conversion of *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-*L*-valine methyl-ester (**14**) into the compound **1**, the following compounds are used as inert solvent: lower aliphatic ethers, nitriles esters, chlorinated lower aromatic hydrocarbons or liquid aromatic hydrocarbons or ketones such as diethylether, tetrahydrofuran, 1,4-dioxane, dimethoxyethane, diethoxyethane, diethyleneglycol dimethylether, diethyleneglycol diethylether, triethyleneglycol dimethylether, triethyleneglycol

diethylether, acetonitrile, propionitrile, methylformate, ethylformate, propylformate, methylacetate, ethylacetate, ethylpropionate, 1-propylacetate, 2-propylacetate, butylacetate, tetrachloromethane, chloroform, dichloromethane, 1,2-dichloretane, trichloroethylene, benzene, toluene, xylene, *N*,*N*-dimethylformamide, *N*-methylpyrrolidinone, *N*,*N*-dimethylacetamide, acetone, ethylmethylketone, cyclohexanone, dimethylsulfoxide, hexamethyl phosphoramide, or their mixtures, at temperatures from 0 °C to the solvent reflux temperature.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HR2004/000029

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D257/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 399 578 A (SCHMIDLIN TIBUR ET AL) 21 March 1995 (1995-03-21) cited in the application examples 32,37,54	1-3
Y	BUEHLMAYER P ET AL: "VALSARTAN, A POTENT, ORALLY ACTIVE ANGIOTENSIN II ANTAGONIST DEVELOPED FROM THE STRUCTURALLY NEW AMINO ACID SERIES" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 4, no. 1, 1994, pages 29-34, XP002065916 ISSN: 0960-894X pages 30-31	1-3
Y	EP 0 726 288 A (HOPE CITY) 14 August 1996 (1996-08-14) figure 3a	1-3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2005	20/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lauro, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

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