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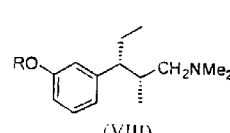
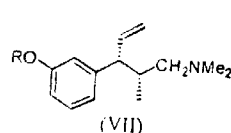
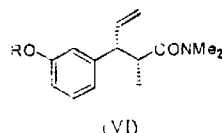
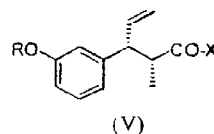
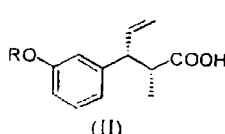
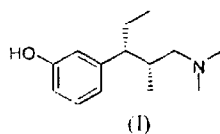
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(54) Title: O-SUBSTITUTED (2R,3R)-3-(3-HYDROXYPHENYL)-2-METHYL-4-PENTENOIC ACIDS AND A METHOD OF OBTAINING THE SAME



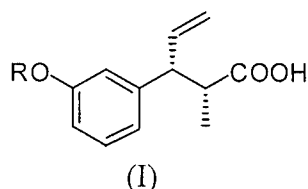
(57) Abstract: The compounds of general formula II are new and represent important intermediates in the synthesis of tapentadol. In the synthesis of tapentadol of formula I and its pharmaceutically acceptable salts, O-protected (2R,3R)-acids of general formula II, in step A, are reacted in an inert organic solvent with an activating agent, optionally in presence of a catalyst or a base; in step B, the obtained compounds of general formula V, wherein R has the above mentioned meaning and X stands for chlorine or alkoxy-carbonyloxy group O-CO-OR¹ or pivaloyloxy O-CO-t-Bu group, wherein R¹ is methyl or ethyl, are reacted with dimethylamine or its salts optionally in presence of a base; in step C, the obtained N, N-dimethylamides of general formula VI, wherein R has the above mentioned meaning, are reduced by means of hydride agents in a suitable solvent; in step D, the produced alkeneamines of general formula VII, wherein R has the above mentioned meaning, are hydrogenated on a metal catalysts in a suitable solvent; and, finally, in step E, the produced alkaneamines of general formula VIII, wherein R has the above mentioned meaning, are O-dealkylated by means of dealkylating agents, and, if required, the obtained tapentadol is converted by the action of a pharmaceutically acceptable acid to respective salts, e.g. hydrochloride.

O-Substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids and a method of obtaining the same

Technical Field

5

This invention relates to a method of producing *O*-substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula I.



10 The compounds of general formula I are new and represent important intermediates in the synthesis of tapentadol.

Background Art

15 Tapentadol (I), chemically (2*R*,3*R*)-*N,N*-dimethyl-3-(3-hydroxyphenyl)-2-methylpentyl amine, acts as an agonist of μ -opioid receptors and an inhibitor of noradrenaline reuptake. It has been developed in the form of hydrochloride of (2*R*,3*R*)-enantiomer by the firm Johnson & Johnson based on development of the firm Gruenenthal, as a general analgetic.

According to the original method disclosed in document EP 0 693 475 (CZ 286441;
20 Gruenenthal GmbH), tapentadol is produced from (2*S*,3*S*)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentane-3-ol (A), which is obtained by two methods by means of the Grignard addition to a ketone, e.g. by addition of 2-methoxyphenylmagnesium bromide to 1-dimethylamino-2-methyl-3-pentanone. The reaction is non-stereo-selective and obtaining of the (2*R*,3*R*)-stereo-isomer requires separation on a chiral HPLC column. Compound A is then
25 converted to a chloride by means of thionyl chloride and the obtained chloro-derivative is converted by reduction, e.g. by means of NaBH₄/ZnCl₂, to (2*R*,3*R*)-*N,N*-dimethyl-3-(3-methoxyphenyl)-2-methylpentylamine (B), which is finally demethylated by hydrobromic acid. The method is inherently disadvantageous because of demanding HPLC separation of stereo-isomers on a chiral column.

30 According to a process patent, WO 2004/108658 (Gruenenthal GmbH), the compound (2*S*,3*S*)-A is converted, by the action of acidic agents, such as concentrated hydrochloric acid,

to alkene B, which is subjected to diastereoselective hydrogenation with formation of (2*R*,3*R*)-C, accompanied by a (2*R*,3*S*)-C epimer as a by-product. Disadvantages involve formation of diastereoisomeric mixtures and the necessity of stereo-chemical purification of products at the end of the synthesis.

5 A similar method, i.e. acidic dehydration of A followed by hydrogenation of alkene B, is also claimed in WO 2005/000788 and WO 2007/051576 (Gruenenthal GmbH).

Alternatively, the same tertiary amine C is produced according to WO 2008/012047 (Gruenenthal GmbH) by resolving 1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-1-propanone (D), obtained by the Mannich reaction from 3'-methoxypropiophenone, by means
10 of (*R,R*)-dibenzoyltartaric acid, and reacting its (*S*)-enantiomer with ethylmagnesium bromide with formation of the (2*S*,3*S*)-stereo-isomer of compound A as a predominating stereo-isomer. In a subsequent method, similar to that mentioned above, compound A is subjected to acidic dehydration; the subsequent hydrogenation of alkene B provides predominantly amine (2*R*,3*R*)-C, which is demethylated to finally produce tapentadol. The disadvantages are similar
15 to those of the previous methods.

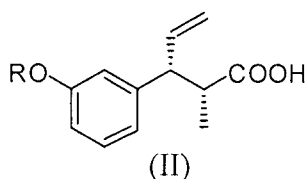
The initial steps of a further method according to WO 2008/012283 (Janssen Pharmaceutica) are similar to those of the previous method; here, compound (*S*)-D is finally converted by the Grignard reaction to predominating (2*R*,3*S*)-A. The claimed deoxygenation is carried out by a method in which *O*-trifluoroacetylation is first carried out by means of
20 trifluoroacetic anhydride; followed by hydrogenolysis with hydrogen on Pd/C, leading to (2*R*,3*R*)-C with ee 92.6%. The deoxygenation method specifically relates to methyl as a protecting group for the phenolic hydroxyl.

The same deoxygenation method, with utilization of hydrogenolysis of trifluoroacetyl derivatives, is also claimed in WO 2008/012046 (Gruenenthal GmbH); however, it relates to
25 phenolic hydroxyl protecting groups other than the methyl group. Deprotection, and optionally formation of salts, is also claimed. A disadvantage of both methods involves the problem of ensuring stereo-chemical homogeneity of the whole process.

Disclosure of Invention

30 The present invention provides production of optically pure or enriched *O*-substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula II

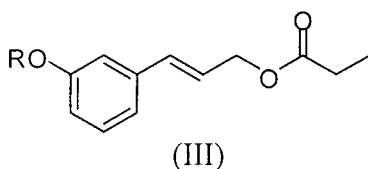
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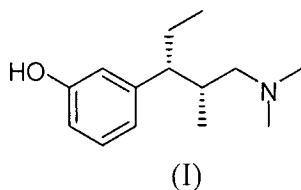
wherein R stands for H, an alkyl group with 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group,

5 the key intermediates in the synthesis of tapentadol,

which is based on diastereoselective skeletal rearrangement of enolates of cinnamyl propanoates of general formula III



10 In another aspect, the invention provides a new effective method of producing tapentadol of formula I



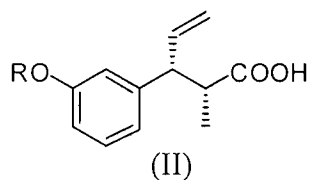
and its pharmaceutically acceptable salts.

15

O-Substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula II are new compounds, representing key intermediates in the synthesis of pure tapentadol. This statement is based on the experimental finding that the acids of general formula II are available in a highly diastereoselective process, followed by resolving, during
20 which final diastereoisomeric purification takes also place.

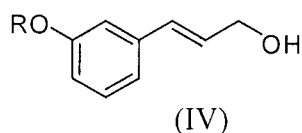
A method of producing *O*-substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids, optically pure or optically enriched, of general formula II

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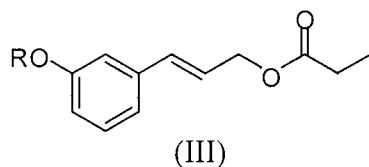
wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group,

5 in which *O*-protected cinnamyl alcohols of general formula IV

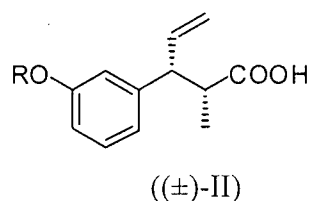


wherein R stands for the same as above,

- 10 a) are propionylated by means of propionylating agents without solvents or in an inert organic solvent, optionally in presence of catalysts, to compounds of general formula III;
b) the obtained cinnamyl propanoates of general formula III



- 15 wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group,
are rearranged by means of strong bases to racemic acids of general formula (±)-II;
c) and, finally, the produced racemic acids of general formula (±)-II



20

wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group,

are resolved by crystallization of the salt of compound ($\pm$)-II with a chiral base in suitable solvents, selected from the group of C1 to C4 lower alcohols, acetone, methyl ethyl ketone, diethyl ether, tert-butyl methyl ether, ethyl acetate, dichloromethane and water, or their mixtures.

5

The present method of producing *O*-substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2- methyl-4-pentenoic acids of general formula II, optically pure or optically enriched, comprises the following steps:

- 1) Propionylation of *O*-protected cinnamyl alcohols of general formula IV, wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group, is carried out by means of propionylating agents, such as propionic anhydride or propionyl chloride. The reaction is carried out in presence or absence of catalysts, such as Lewis bases or Lewis acids, e.g. dimethylaminopyridine, tributylphosphine, lithium perchlorate, trimethylsilyl triflate, scandium or indium triflate, or tetrabromomethane. Propionylation is performed in inert organic solvents, such as dichloromethane, chloroform, toluene, or under solvent-free conditions in temperature range of from 10 to 100°C.

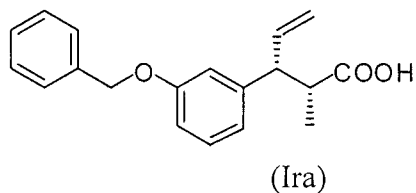
Preferably, the process is performed by heating alcohols of general formula IV, wherein R has the above mentioned meaning, with propionic anhydride without a solvent, in presence or absence of catalytic tetrabromomethane, to a temperature of from 30 to 100°C. According to another preferable embodiment, acylation of alcohols of general formula IV is carried out by the action of propionyl chloride in inert solvents.

- 2) A key step of the whole process includes rearrangement of cinnamyl propanoates of general formula III, wherein R stands for an alkyl group with 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group; it comprises enolisation of the compounds of formula III by the action of a strong base of the type of metal amides in presence of a tertiary amine at low temperatures; the enolates generated then, during heating to higher temperatures, undergo rearrangement to expected ($\pm$)-acids of general formula II. The enolisation is carried out in excess of both metal amide, e.g. lithium hexamethyldisilazide or lithium diisopropylamide, and tertiary amine, e.g. triethylamine, in an amount of at least 2 equivalents, preferably 2.5 to 3 equivalents, in the temperature range of from -40 to -80°C, preferably from -60 to -70°C. The rearrangement

takes place during gradual heating of the reaction mixture to the laboratory temperature. The process is performed in inert organic solvents, preferably in toluene.

The whole process is highly diastereoselective and provides racemic diastereoisomer having the relative configuration shown in formula II with high selectivity.

Diastereoselectivity of the rearrangement is only slightly influenced by the temperature during metalation; this procedure provides the compound of formula II with an *erythro* : *threo* ratio of diastereoisomers 25 : 1 to 35 : 1. However, the temperature at which the enolisation is carried out is of key importance for reaching high chemical yield. For instance, if enolisation and rearrangement of the compound of general formula III, wherein R is benzyl, are carried out at -70 to -75°C, a crude racemic acid of general formula II, wherein R is benzyl (formula IIa)



is obtained with a yield of at least 95% (*erythro* : *threo* ratio 31 : 1); with enolisation at -50°C the chemical yield is 72% (*erythro* : *threo* 33 : 1), while at -35°C the yield drops down to 50% (*erythro* : *threo* 25 : 1).

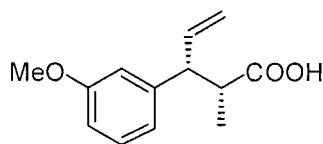
A great advantage of protecting groups R consists in that the produced (2*R*,3*R*)-acids of general formula II are generally crystalline substances. This particularly relates to acids in which R is phenylmethyl group, substituted or non-substituted in the benzene ring, e.g. benzyl or 4-methoxybenzyl, benzhydryl or trityl group. For instance, the racemic acid of general formula II, wherein R is benzyl group (formula IIa), is a well crystallizing substance with a melting point = 98.5-102.5°C, which is prepared in crude state with an *erythro* : *threo* diastereoisomeric purity of 30 : 1 to 35 : 1. A product of an *erythro* : *threo* diastereoisomeric purity higher than 99 : 1 is then prepared in high yield of more than 85% by crystallization of the crude acid IIa from suitable solvents, such as hexane, heptane, toluene, petroleum ether, or their mixtures with diethyl ether, tert-butyl methyl ether.

For practical reasons (process economy), this purification can be omitted in all cases having the objective to obtain optically active products of general formula I, as explained in the following step.

In case of the acids in which R is an alkyl group, e.g. methyl or ethyl, diastereoselectivity of the process is maintained; e.g. at -65°C crude acid IIb (general formula

II: R = methyl (Me)) with an erythro : threo diastereoisomeric purity 32:1 is formed with the yield of 78%.

The oily form of these products is not a defect as possible diastereoisomeric final purification is performed along with the subsequent resolving.



(II)

Me-methyl

Step C. The produced racemic *O*-substituted (2*RS*,3*RS*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula II, wherein R stands for an alkyl group with 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group, is resolved using basic resolving agents, such as 1-phenylethylamine or 1-(4-nitrophenyl)-2-amino-1,3-propanediol. The process is performed in suitable solvents, such as lower alcohols with 1 to 4 carbon atoms, e.g. methanol, ethanol, 2-propanol, tert-butanol, or ketones, e.g. acetone or methyl ethyl ketone, or ethyl acetate, or dichloromethane, or their mixtures. Mixtures of the said solvents with ethers, e.g. diethyl ether or tert-butyl methyl ether, can also be used. Preferably, the resolving is carried out in mixtures of the said solvents with water. During resolving, effective diastereoselective purification of acids of general formula II also takes place. Therefore, crude racemic acids from step 2 can be used in this step without problems.

The isolated salt with the above mentioned basic resolving agents is optically purified by recrystallization from the said solvents or their mixtures. Effectiveness of the procedure is illustrated by data in the following table (for R= benzyl).

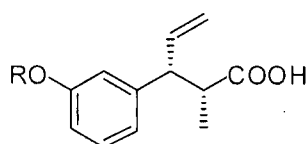
	R,R : S,S	$[\alpha]_D$ (c=2, MeOH)	Melting point (°C)	Yield to racemate (%)
Crude salt	93.3 : 6.7	48.8	138 - 144	45
1 st crystallization	99.5 : 0,5	59.5	144 - 149	36

A considerable purifying effect can also be attained by stirring the isolated salt with a suitable solvent, such as dichloromethane or methyl tert-butyl ether. For instance, stirring of

the salt in dichloromethane results in increasing the content of the R,R enantiomer in the mixture from 93.6% to 98.7%.

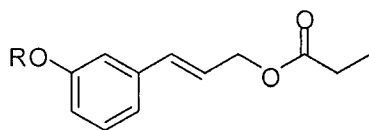
Finally, the acid of general formula II is isolated from the resolved salt by standard procedures, e.g. acidification followed by aspiration (in case of solid acids), or usual extraction
5 in other cases.

The method according to this invention includes, as a key step, production of racemic *O*-substituted (2*RS*,3*RS*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula (±)-II



((±)-II)

wherein R stands for an alkyl group with 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group, in which cinnamyl propionates of general formula III



(III)

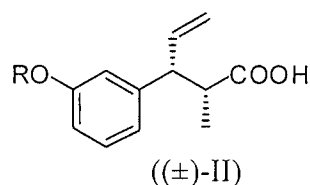
wherein R has the above mentioned meaning,
are rearranged by means of strong bases.

The method of producing (±)-acids of general formula II, wherein R stands for an alkyl group with 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl group, or phenylmethyl group, substituted or non-substituted in the benzene ring, e.g. benzyl or 4-methoxybenzyl, benzhydryl or trityl group, comprises enolisation of the esters of general formula III, wherein R has the above mentioned meaning, by the action of a strong base of the type of metal amides in presence of a tertiary amine at low temperatures; then the enolates generated undergo, during heating to higher temperatures, rearrangement to the expected racemic acids of general formula II. The enolisation is carried out by means of an excess of
25 both the metal amide, e.g. lithium hexamethyldisilazide or lithium diisopropylamide, and

tertiary amine, e.g. triethylamine, in the amount of at least 2 equivalents, preferably 2.5 to 3 equivalents, in the temperature range of from -40 to -80°C, preferably from -60 to -70°C. The rearrangement takes place during gradual heating of the reaction mixture to the laboratory temperature. The process is performed in inert organic solvents, preferably in toluene. The whole process is highly diastereoselective and provides a racemic diastereoisomer with high selectivity. Using this procedure, compounds of general formula (±)-II are obtained with an *erythro* : *threo* ratio of diastereoisomers of 25 : 1 to 35 : 1.

It is highly preferable to use the benzyl group as a protecting group R because the racemic acid IIa (general formula II: R = benzyl) is a crystalline substance that is prepared with an *erythro* : *threo* diastereoisomeric purity of 30 : 1 to 35 : 1. Crystallization of the crude acid IIa (R = benzyl) from suitable solvents, such as hexane, heptane, toluene, petroleum ether, or their mixtures with diethyl ether, tert-butyl methyl ether, then provides a product with an *erythro* : *threo* diastereoisomeric purity higher than 99 : 1, in a high yield of more than 85%.

The method according to this invention also includes production of *O*-substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids, optically pure or optically enriched, of general formula II, wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group, in which racemic *O*-substituted (2*RS*,3*RS*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula (±)-II



wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group, are resolved by means of basic resolving agents.

The produced racemic *O*-substituted (2*RS*,3*RS*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula (±)-II, wherein R stands for an alkyl group with 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl group, or benzyl or 4-methoxybenzyl, benzhydryl or trityl group, are resolved by means of basic resolving agents, such as optically active 1-phenylethylamine or 1-(4-nitrophenyl)-2-amino-1,3-propanediol. The method is

carried out in organic solvents, using, e.g., lower alcohols with 1 to 4 carbon atoms, e.g. methanol, ethanol, 2-propanol, tert-butanol; further, ketones, e.g. acetone or methyl ethyl ketone, or ethyl acetate, or their mixtures, are used. Mixtures of the said solvents with ethers, e.g. diethyl ether or tert-butyl methyl ether, can also be used. Preferably, the resolving is
5 carried out in mixtures of the said solvents with water, wherein diastereoselective purification also takes place.

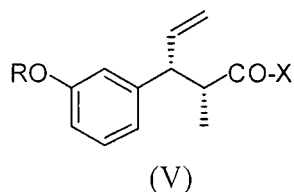
The isolated salt with the above said basic resolving agents is optically purified by recrystallization from the said solvents or their mixtures. Preferably, this can be carried by stirring the isolated salt with a chlorinated hydrocarbon, such as dichloromethane.

Another aspect of the present invention comprises synthesis of tapentadol, which uses compounds of formula II, which,

for R, which stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group,

are, in step A, reacted with an activating agent, such as thionyl chloride, oxalyl chloride, or an alkyl chloroformate Cl-COOR^1 , wherein R^1 stands for methyl or ethyl, or pivalic acid chloride $t\text{-Bu-CO-Cl}$;

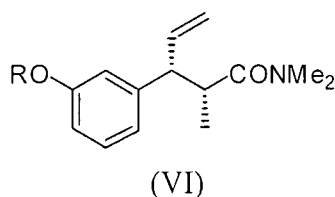
in step B, the obtained compounds of general formula V



wherein both R and R^1 have the above mentioned meaning and X stands for chloro or an alkoxy carbonyloxyl group O-CO-OR^1 or pivaloyloxyl group $\text{O-CO-}t\text{-Bu}$,

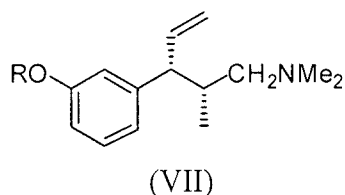
are reacted with dimethylamine or its salts, optionally in presence of a base;

in step C, the obtained *N,N*-dimethylamides of general formula VI



wherein R has the above mentioned meaning,
are reduced by means of hydride agents in a suitable solvent;

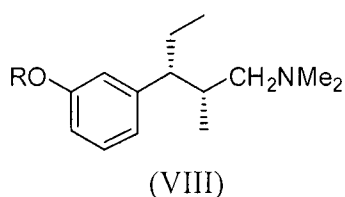
5 in step D, the produced alkeneamines of general formula VII



wherein R has the above mentioned meaning,

10 are hydrogenated on metal catalysts in a suitable solvent;

and, finally, in step E, the produced alkaneamines of general formula VIII



15

wherein R has the above mentioned meaning,

are *O*-dealkylated by means of dealkylating agents;

and, if desired, the obtained tapentadol is converted by the action of pharmaceutically acceptable acids to respective salts.

20

The method of producing tapentadol from the acids of general formula II, wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group comprises the following synthetic steps:

25

Step A. The conversion of optically pure or optically enriched *O*-protected (2*R*,3*R*)-acids of general formula II to the activated compounds of general formula V, wherein X stands for chloro or an alkoxycarbonyloxyl group O-CO-OR¹, wherein R¹ stands for methyl or ethyl, or pivaloyloxyl group O-CO-*t*-Bu, is carried out by means of activating agents: The activating

agents used are, for instance, chlorides of inorganic acids, e.g. thionyl chloride, phosphoryl chloride or phosphorus pentachloride, or chlorides of organic acids, e.g. oxalyl chloride. The reaction is preferably carried out in presence of a catalytic amount of dimethylformamide. The reaction is carried out in presence or absence of an inert organic solvent, e.g. in chloroform, dichloromethane or toluene, in a temperature range of from 10°C to the boiling temperature of the mixture, preferably from 25°C to the boiling temperature of the mixture.

According to a preferable embodiment, thionyl chloride and a catalytic amount of dimethylformamide in dichloromethane, chloroform or toluene in the temperature range of from 25 to 100°C is used.

The activating agents used can also include alkyl chloroformates Cl-COOR^1 , wherein R^1 has the above mentioned meaning, or the pivalic acid chloride $t\text{-Bu-CO-Cl}$. These reactions are carried out in presence of a base, e.g. triethylamine, in an inert organic solvent, in the temperature range of from 0°C to 50°C, preferably from 0 to 30°C.

According to a preferable embodiment, the compounds of general formula V are not isolated or purified, but directly reacted with dimethylamine.

Step B. The synthesis of *N,N*-dimethylamides of general formula VI from activated compounds of general formula V, wherein X stands for chloro or an alkoxycarbonyloxyl group O-CO-OR^1 , wherein R^1 stands for methyl or ethyl, or pivaloyloxyl group $\text{O-CO-}t\text{-Bu}$, is carried out by the reaction with dimethylamine in an inert organic solvent, in the temperature range of from 0°C to 40°C, preferably from 10 to 25°C. Here, dimethylamine is used in the gaseous form or in the form of an aqueous solution, or in the form of a salt, e.g. of hydrochloride, in presence of a base, such as triethylamine, or an aqueous solution of an inorganic base, such as sodium or potassium carbonate or hydrogencarbonate.

Step C. The reduction of *N,N*-dimethylamides of general formula VI to amines of general formula VII is carried out by means of hydride agents based on aluminium, such as lithium hydrido aluminate or sodium bis(2-methoxyethoxy)hydrido aluminate, in an inert organic solvent, such as ethers, e.g. tetrahydrofuran, 2-methyltetrahydrofuran, diethyl ether, or toluene, in a temperature range of from 20°C to the boiling temperature of the mixture, preferably from 20 to 100°C.

Preferably, the reduction of a compound of general formula VI is carried out by means of sodium bis(2-methoxyethoxy)hydrido aluminate in toluene at a temperature of from 25°C to the boiling temperature of the mixture, preferably from 60 to 10 °C.

5 Step D. The saturation of the terminal double bond in the compound of general formula VII is carried out by reduction with hydrogen on metal catalysts, such as e.g. palladium or platinum. The hydrogenation is carried out in an inert organic solvent, such as lower alcohols, e.g. methanol, ethanol or isopropyl alcohol, or cyclic ethers, such as tetrahydrofuran or 1,4-dioxane, or ethyl acetate, or their mixtures, at a pressure of from 0.1 to 5 MPa in a temperature
10 range of from 10 to 60°C.

 According to a preferable embodiment, for instance, hydrogen on Pd/C in the environment of an alcohol, such as methanol or ethanol, at a pressure of from 0.1 to 2 MPa, is used.

15 Step E. The removal of *O*-protective group R in the compounds of general formula VIII, wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, is carried out by means of dealkylation agents, such as e.g. hydrobromic acid, boron tribromide, or trimethylsilyl iodide.

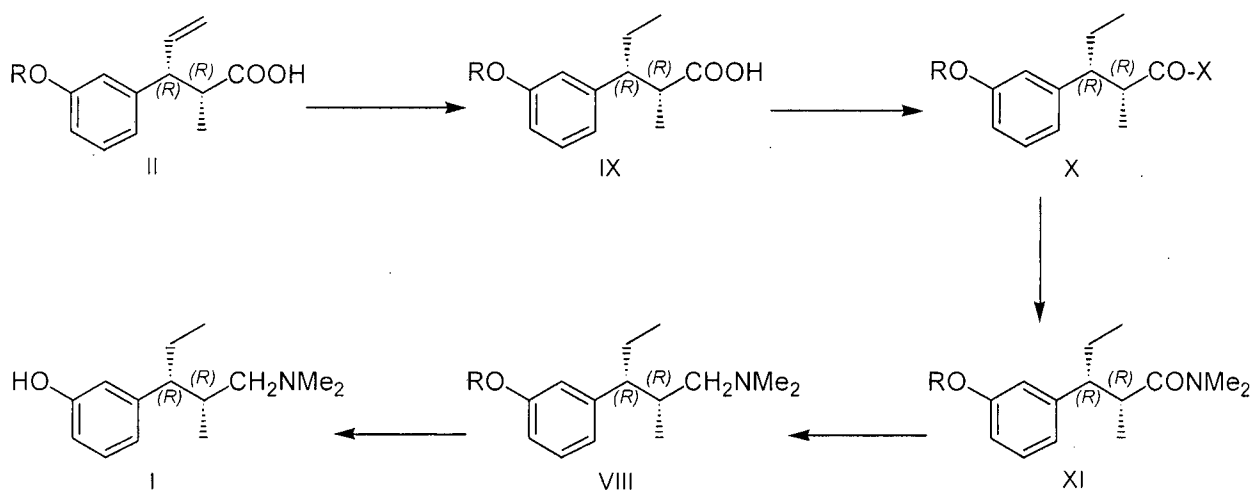
20 The obtained compound of formula I (tapentadol) is, if desired, finally converted, by the action of pharmaceutically acceptable acids, to a corresponding salt and purified by crystallization from a suitable organic solvent or a mixture of solvents, such as ethyl acetate, 2-propanol or methanol, or their combinations with water.

25 Alternatively, it is also possible to proceed by using, as the starting materials, racemic acids of general formula II, which are transformed, by the above said procedures, via racemic activated compounds of general formula V, wherein R has the above mentioned meaning, X stands for chloro or an alkoxycarbonyloxyl group O-CO-OR¹, wherein R¹ stands for methyl or ethyl, or pivaloyloxyl group O-CO-*t*-Bu, to racemic *N,N*-dimethylamides of general formula
30 VI, wherein R has the above mentioned meaning, and further to racemic alkeneamines of general formula VII, wherein R stands for the same as above. Their hydrogenation provides racemic alkaneamines of general formula VIII, wherein R stands for the same as above, and

their *O*-deprotection provides racemic tapentadol of formula I, which is subsequently resolved by means of resolving acids of the type of carboxyl or sulphonic acids.

Alternatively, it is also possible to proceed by carrying the resolution out by means of acidic resolving agents in the stage of racemic alkaneamines of general formula VIII, wherein
 5 R stands for the same as above, or racemic alkeneamines of general formula VII.

Another alternative procedure includes the variant shown in Scheme 1, in which the *O*-protected (2*R*,3*R*)-acids of general formula II, wherein R stands for an alkyl group with 1 to 4 carbon atoms, such as methyl, ethyl, isopropyl or tert-butyl group, optically pure or optically
 10 enriched, or racemic,



Scheme 1: Alternative production of tapentadol from acids of general formula II

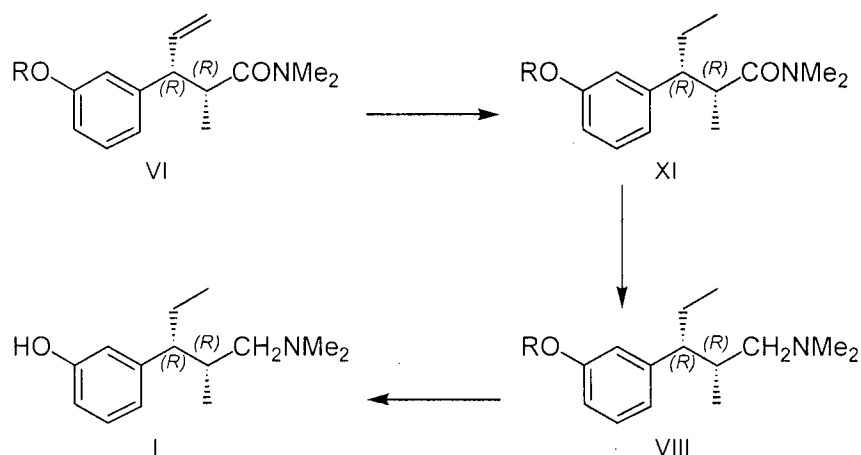
are first hydrogenated on metal catalysts to form *O*-protected (2*R*,3*R*)-acids of general formula IX, which are further transformed by the above mentioned procedures via activated derivatives of acids of general formula X to saturated *O*-protected (2*R*,3*R*)-amides of general formula XI. Their reduction provides the above described *O*-protected (2*R*,3*R*)-amines of general formula VIII, and, finally, the deprotection by means of demethylation agents provides tapentadol,
 20 and/or its salts by means of pharmaceutically acceptable acids.

Using the procedure according to the variant shown in Scheme 2, the *O*-protected (2*R*,3*R*)-amides of general formula VI, wherein R stands for an alkyl group with 1 to 4 carbon

atoms, such as methyl, ethyl, isopropyl or tert-butyl group, optically pure or optically enriched, or racemic,

are first hydrogenated on metal catalysts;

and the obtained *O*-protected (2*R*,3*R*)-amides of general formula XI are then converted to
5 tapentadol and its salts by the above described methods.



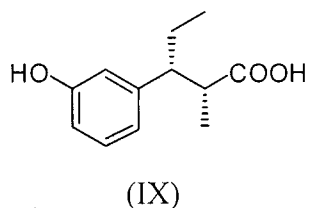
Scheme 2: Alternative production of tapentadol from amides of general formula VI

Another alternative method for the synthesis of Tapentadol includes a procedure, which uses,
10 as starting materials, compounds of formula II, wherein R stands for a phenylmethyl group, substituted or unsubstituted in the benzene ring, e.g. benzyl or 4-methoxybenzyl, the benzhydryl or trityl group,

wherein *O*-protected (2*R*,3*R*)-acids of general formula II, optically pure, optically enriched, or racemic,

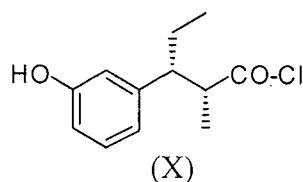
15 are hydrogenated on metallic catalysts in a suitable solvent;

the obtained (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methylpentanoic acid of formula IX



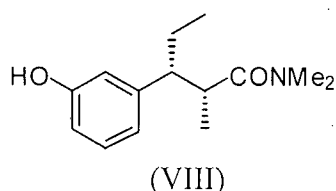
wherein R = H, is reacted with an activating agent such as thionyl chloride or oxalyl chloride,
20 in an inert organic solvent, optionally in the presence of a catalyst or a base;
the resulting compound of formula X (R = H)

16



is reacted with dimethylamine or its salts, optionally in the presence of a base;
the obtained *N,N*-dimethylamide of formula XI (*R* = H)

5



, Me denotes the methyl group

is reduced by means of hydride agents in a suitable solvent;
and, if desired, the obtained tapentadol is converted to the respective salts by the action of
pharmaceutically acceptable acids, e.g. to the hydrochloride.

10

Simultaneous saturation of the terminal double bond and removal of *O*-protecting group *R* in the compound of general formula II, wherein *R* stands for a phenylmethyl group, substituted or unsubstituted in the benzene ring, e.g. benzyl or 4-methoxybenzyl, the benzhydryl or trityl group,

15

optically pure, optically enriched, or racemic, is carried out by reduction with hydrogen on metallic catalysts, such as palladium on carbon or platinum. The hydrogenation is performed in an inert organic solvent such as in C1 to C3 lower alcohols, e.g. in methanol, ethanol or isopropyl alcohol, or in cyclic ethers, such as tetrahydrofuran, 2-methyl tetrahydrofuran or 1,4-dioxane, or in ethyl acetate, or in their mixtures, at a pressure of 0.1 to 5 MPa in the temperature range of from 10 to 60°C, preferably 20 to 40°C. The reduction can be conducted in the presence or absence of strong acids, such as hydrochloric or sulphuric acid.

20

In a preferred embodiment, for instance, hydrogen on Pd/C in the environment of an alcohol such as methanol or ethanol, or their mixtures with water, at a pressure of 0.1 to 2 MPa, is used.

25

The conversion of an optically pure, optically enriched, or racemic (2*R*,3*R*)-acid of formula IX (*R* = H) to the activated compound of formula X (*R* = H) is carried out by means

of activating agents: Activating agents used include, e.g., chlorides of inorganic acids, e.g. thionyl chloride, phosphoryl chloride or phosphorus pentachloride, or chlorides of organic acids, e.g. oxalyl chloride. The reaction is preferably performed in the presence of a catalytic amount of dimethylformamide. The process is carried out in the presence or absence of an inert organic solvent, such as chloroform, dichloromethane or toluene, in the temperature range of from 10°C to the boiling point of the mixture, preferably from 25°C to the boiling point of the mixture.

In a preferred embodiment, thionyl chloride and a catalytic amount of dimethylformamide in dichloromethane, chloroform or toluene, in the temperature range of from 25 to 100°C, is used.

In another preferred embodiment the chloride of formula X is not isolated or purified but directly reacted with dimethylamine.

The production of *N,N*-dimethylamide of formula XI from the activated compound of formula X is carried out by reaction with dimethylamine in an inert organic solvent, in the temperature range of 0°C to 40°C, preferably at 10 to 25°C. In the reaction, dimethylamine is used in the gaseous form or the form of an aqueous solution, or a salt, e.g. hydrochloride, in the presence of a base, such as triethylamine, or of an aqueous solution of an inorganic base, e.g. sodium or potassium carbonate or hydrogencarbonate.

The reduction of *N,N*-dimethylamide of formula XI ($R = H$) is carried out by means of hydride agents based on aluminium, such as lithium hydrido aluminate, sodium bis-(2-methoxyethoxy) hydrido aluminate, or diisobutylaluminium hydride, in an inert organic solvent, such as ethers, e.g. tetrahydrofuran, 2-methyltetrahydrofuran, diethyl ether, or toluene, in the temperature range of from 20°C to the boiling point of the mixture, preferably 20 to 100°C.

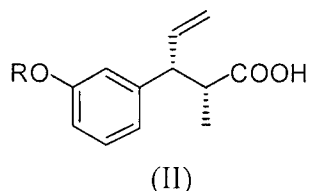
Preferably, the reduction of the compound of general formula XI ($R = H$) is carried out by means of sodium bis-(2-methoxyethoxy)hydrido aluminate in toluene at a temperature of from 25°C to the boiling point of the mixtures, preferably at 60 to 100°C.

The method can also be conducted by using, in the above mentioned procedure, racemic acids of general formula II, wherein R has the above mentioned meaning, and

carrying out the resolution at the stage of the (2*R*,3*R*)-acid of formula IX (R = H) by means of basic resolving agents, such as 1-phenylethylamine.

It is also possible to carry the synthesis out in the racemic version until the stage of racemic tapentadol, which is resolved by means of acidic resolving agents, such as camphorsulfonic or mandelic acid.

The method in accordance with the invention includes, as an important step, production of an optically pure or optically enriched (2*R*,3*R*)-acid of formula IX (R = H), in which the *O*-protected (2*R*,3*R*)-acids of general formula II



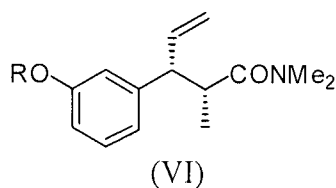
wherein R stands for a phenylmethyl group, substituted or unsubstituted in the benzene ring, e.g. benzyl or 4-methoxybenzyl, the benzhydryl or trityl group, optically pure or optically enriched, are hydrogenated on a metallic catalyst.

Simultaneous saturation of the vinylic double bond and deprotection of *O*-protecting group R, which has the same meaning as above, in the compound of general formula II is achieved by reduction with hydrogen on metallic catalysts, e.g. palladium or platinum on carbon. The hydrogenation is carried out in an inert organic solvent, such as in lower alcohols, e.g. in methanol, ethanol or isopropyl alcohol, or in cyclic ethers, such as tetrahydrofuran or 1,4-dioxane, or in ethyl acetate, or in their mixtures, at a pressure of 0.1 to 5 MPa in the temperature range of 10 to 60°C, preferably 20 to 40°C. The reduction can be carried out in the presence or absence of strong acids, e.g. hydrochloric or sulphuric acid.

In a preferable embodiment, for instance, hydrogen on Pd/C in the environment of an alcohol, e.g. methanol or ethanol, or their mixtures with water, at a pressure of 0.1 to 2 MPa, is used.

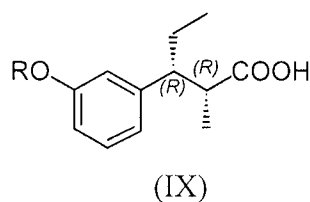
O-Protected (2*R*,3*R*)-3-(3-hydroxyphenyl)-*N,N*,2-trimethylpent-4-eneamides of general formula VI

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wherein R stands for an alkyl group having 1 to 4 carbon atoms, such as the methyl, ethyl, isopropyl or tert-butyl group, in the optically pure, optically enriched, or racemic, form, are new and represent valuable intermediates in the synthesis of tapentadol.

(2*R*,3*R*)-3-(3-Hydroxyphenyl)-2-methylpentanoic acid of formula IX



wherein R = H,

optically pure, optically enriched, or racemic, is a new compound and represents a key intermediate in the production of tapentadol.

The resulting compound of formula I (tapentadol) is finally converted, by the action of pharmaceutically acceptable acids, to a corresponding salt a purified by crystallization from a suitable organic solvent, such as ethyl acetate, 2-propanol or methanol, or mixtures of such solvents with water.

Tapentadol, or (2*R*,3*R*)-*N,N*-dimethyl-3-(3-hydroxyphenyl)-2-methylpentylamine by its chemical name, and its salts are prepared by the above described procedures in a chemical and/or optical purity higher than 99.5%.

The following working examples illustrate, but do not limit in any way, the generality of the method of production according to this invention.

Working Examples

Example 1

a) Preparation of (2*RS*,3*RS*)-3-(3-benzyloxyphenyl)-2-methylpent-4-enoic acid (general formula (±)-II: R = CH₂Ph)

120 ml of triethylamine (2.9 eq.) is added to a 0.95 M solution of lithium hexamethyldisilazide in toluene (800 ml; 0.76 mol, 2.6 eq.), cooled down to - 65°C, under N₂ and then a the solution of 85.0 g (0.29 mol) of (2*E*)-3-(3-benzyloxyphenyl)prop-2-en-1-yl-propionate (general formula III: R = CH₂Ph) in 510 ml of toluene is added dropwise within 45 min. The mixture is stirred at - 65°C for 2.5 h and then left to heat up spontaneously (within about 3 h) to the laboratory temperature. The reaction mixture is poured into 1270 ml of 5 % sodium hydroxide (the mixture spontaneously heats up to ca. 30 °C), stirred for 10 min, and diluted with 200 ml of methyl tert-butyl ether (MTBE) and 200 ml of water. The aqueous phase is separated, shaken with 1x 150 ml of MTBE, cooled in an ice bath, and acidified by dropwise adding of 95 ml of concentrated hydrochloric acid (pH = 1 - 2). The product is extracted with 1x 500 ml and 2x 250 ml of MTBE. The combined organic extracts are dried with Na₂SO₄, and, after filtration, evaporated in a rotating vacuum evaporator. A crude product of general formula (±)-I (R = CH₂Ph) is obtained with the yield of 94% (79.85 g) as a solid slightly yellowish evaporation residue with a melting point of 95 – 101°C. The *erythro* : *threo* ratio of diastereoisomers 30 : 1.

The product is subjected to final diastereoisomeric purification by crystallization from the mixture of hexane : MTBE (1:1); 90% (70.76 g) of white crystals are obtained with a melting point = 98.5-102.5°C. The *erythro* : *threo* ratio of diastereoisomers >99:1.

The crude product can also be obtained by direct aspiration from the acidified aqueous phase – by stirring in an ice bath the separated oil is solidified. In this way, 91% of a product is obtained with a melting point = 93 to 100.5°C and an *erythro* : *threo* ratio of diastereoisomers 35:1.

b) Resolving of (2*RS*,3*RS*)-3-(3-benzyloxyphenyl)-2-methylpent-4-enoic acid (general formula (±)-II: R = CH₂Ph)

33 ml (1 equiv.) of (*R*)-1-phenylethylamine is added to a solution of the racemic acid 72.94 g (0.25 mol) in ethanol (1760 ml) at 40 °C within 5 min. Hexane or heptane (440 ml;

ratio of ethanol/hexane 4:1) is added to the mixture, from which crystals separate. Then, the reaction mixture is heated up to the boil, kept at this temperature for 15 min, and left to cool down to the laboratory temperature overnight. The separated crystals are aspirated, washed with a mixture ethanol/hexane (100 ml), and dried in a vacuum drier at $t = 50^{\circ}\text{C}$. 46.33 g (45 %)
5 of a salt with a melting point = $138 - 144^{\circ}\text{C}$, $[\alpha]_{\text{D}} = +48.8$ ($c = 2$, MeOH), (2R,3R : 2S,3S) = 93.3:6.7, is obtained.

The obtained salt (45.58 g) is re-crystallized from a mixture ethanol/hexane (1400 ml) in the same way as described above. 37.42 g (36 %) of a salt with a melting point = $143.5 - 149^{\circ}\text{C}$, $[\alpha]_{\text{D}} = +59.5$ ($c = 2$; MeOH), (2R,3R : 2S,3S) = 99.5 : 0.5, is obtained.

10 c) Releasing of (2R,3R)-3-(3-benzyloxyphenyl)-2-methylpent-4-enoic acid of general formula II ($\text{R} = \text{CH}_2\text{Ph}$) from the salt with (R)-1-phenylethylamine.

The salt of (2R,3R)-3-(3-benzyloxyphenyl)-2-methylpent-4-enoic acid of general formula I ($\text{R} = \text{CH}_2\text{Ph}$) with (R)-1-phenylethylamine (37.04 g, 89 mmol) is suspended in 740
15 ml of methyl tert-butyl ether (MTBE), and 110 ml of 1M hydrochloric acid is added dropwise under stirring. The mixture is stirred at the laboratory temperature for 15 min, the layers are separated, and the aqueous portion is extracted with another 1x 50 ml MTBE. The combined organic portions are dried with Na_2SO_4 , filtered, and evaporated in a rotating vacuum evaporator. 26.43 g (100%) of an optically active acid of general formula I ($\text{R} = \text{CH}_2\text{Ph}$) is
20 obtained in the form of a yellowish oil, $[\alpha]_{\text{D}} = +65.7$ ($c = 2$, MeOH), (2R,3R : 2S,3S = 99.5 : 0.5).

$^1\text{H-NMR}$ (CDCl_3) δ 1.22 (3H, d, $J = 7.0$ Hz), 2.84 (1H, dq, $J = 7.0, 9.3$ Hz), 3.51 (1H, t, $J = 9.3$ Hz), 5.03 (2H, s), 5.06-5.16 (2H, m), 5.89 (1H, dt, $J = 9.3, 19.4$ Hz), 6.80-6.83 (3H, m), 7.16-7.42 (6H, m).

25 Example 2

a) Preparation of (2RS,3RS)-3-(3-methoxyphenyl)-2-methylpent-4-enoic acid (general formula ($\pm$)-II: $\text{R} = \text{Me}$)

48 ml (2.6 eq.) of triethylamine and 130 ml of toluene are added to 342 ml of a 1 M
30 solution of lithium hexamethyldisilazide under N_2 , and, after cooling down to -60°C , a solution of 28.51 g (130 mmol) of (2E)-3-(3-methoxyphenyl)prop-2-en-1-yl-propanoate (general formula III: $\text{R} = \text{Me}$) in 50 ml toluene is added dropwise within 20 min. The mixture is stirred under cooling to -60°C for 2.5 h, and then left to spontaneously heat up (ca. 3 h) to

the laboratory temperature. The reaction mixture is poured into 570 ml of 5 % sodium hydroxide, stirred for 10 min, and the phases are separated. The aqueous phase is shaken with 2x 100 ml of methyl tert-butyl ether (MTBE), cooled in an ice bath, and acidified by dropwise adding of 95 ml of concentrated hydrochloric acid. The product is extracted with 2x 150 ml MTBE. The combined extracts are dried with Na₂SO₄, filtered, and evaporated in a rotating vacuum evaporator. A crude product of general formula III: R = Me) is obtained in the form of a yellow oil. Yield 19.24 g (67 %), *erythro* : *threo* ratio of diastereoisomers >20 : 1.

b) Resolving of (2*RS*,3*RS*)-3-(3-methoxyphenyl)-2-methylpent-4-enoic acid (general formula (±)-II: R = Me)

11.9 ml of (*R*)-1-phenylethylamine is added dropwise to a solution of 19.21 g (87 mmol) of the racemic acid (±)-I (R = Me) in 160 ml of ethanol within 5 min. The product separates already during stirring. The mixture is diluted with 100 ml of methyl tert-butyl ether (MTBE) (or diethyl ether), and left to stand at 10°C for 2 h. The salt is aspirated, washed with a mixture of ethanol/methyl tert-butyl ether (MTBE) (or diethyl ether) (30 ml), and dried in the air to a constant weight. 14.82 g (50 %) of salt is obtained, (2*R*,3*R* : 2*S*,3*S*) = 93:7.

The salt (14.82 g) is dissolved in 75 ml of boiling ethanol, and left to cool down to the laboratory temperature. The suspension is diluted with MTBE or diethyl ether and treated as mentioned above. After two subsequent recrystallizations, 28% of a salt with optical purity > 99 %, melting point = 136–148°C, [α]_D = +66.6 (c= 2, MeOH), (2*R*,3*R* : 2*S*,3*S*) = 99.4 : 0.6), is obtained.

c) Releasing of (2*R*,3*R*)-3-(3-methoxyphenyl)-2-methylpent-4-enoic acid of general formula II (R = Me) from the salt with (*R*)-1-phenylethylamine

8.1 g (23.7 mmol) of the salt of (2*R*,3*R*)-acid of general formula II (R = Me) with (*R*)-phenylethylamine is suspended in 80 ml of ethyl acetate, and 27 ml of 1M hydrochloric acid is added dropwise under stirring. The mixture is stirred at laboratory temperature for 15 min, the layers are separated, and the aqueous portion is extracted with 1x 10 ml of ethyl acetate. The combined organic portions are dried with Na₂SO₄, filtered, and evaporated in a rotating vacuum evaporator. 4.99 g (95%) of the optically active acid of general formula II (R = Me) is obtained.

$^1\text{H-NMR}$ (CDCl_3) δ 1.21 (3H, d, $J = 7.0$ Hz), 2.83 (1H, dq, $J = 7.0, 9.3$ Hz), 3.50 (1H, t, $J = 9.3$ Hz), 3.77 (3H, s), 5.08-5.16 (2H, m), 5.90 (1H, dt, $J = 9.8, 16.9$ Hz), 6.71-6.80 (3H, m), 7.19 (1H, t, $J = 7.6$ Hz).

5 Example 3

Preparation of (2*E*)-3-(3-benzyloxyphenyl)prop-2-en-1-yl-propionate (general formula III: $\text{R} = \text{CH}_2\text{Ph}$)

Propionic anhydride (49.2 ml, 0.384 mol) is added to 83.06 g (0.346 mol) of (2*E*)-3-(3-benzyloxyphenyl)prop-2-en-1-ol (general formula II: $\text{R} = \text{CH}_2\text{Ph}$) preheated in a bath under Ar to 62°C, and, after 10 min, tetrabromomethane (5.74 g, 5 mol %) is added. Within 20 min of stirring, a homogeneous solution is formed, which is heated in a bath at 62°C for 10 h. The mixture is cooled down, diluted with toluene (420 ml), and washed with a 20% solution of potassium carbonate (200 ml +27 g of solid potassium carbonate). The separated organic phase is then shaken with 1N sodium hydroxide (200 ml) for 3 min, washed with water (100 ml) and brine (75 ml), and, after filtration, evaporated in a rotating vacuum evaporator. A crude product is obtained, which is stirred with hexane or petroleum ether (125 ml), and optionally inoculated. After 3 h, the crystals are aspirated, washed with the same solvent (75 ml), and dried out freely. 98.04 g (95.7%) of the ester is obtained, melting point = 61.6 to 62.8°C.

$^1\text{H-NMR}$ (CDCl_3) δ 1.17 (3H, t, $J = 7.6$ Hz), 2.38 (2H, q, $J = 7.6$ Hz), 4.73 (2H, d, $J = 6.4$ Hz), 5.07 (2H, s), 6.27 (1H, dt, $J = 6.4, 15.9$ Hz), 6.32 (1H, d, $J = 15.9$ Hz), 6.89 (1H, dd, $J = 2.5, 8.3$ Hz), 6.98-7.01 (2H, m), 7.20-7.39 (6H, m).

Example 4

Preparation of (2*E*)-3-(3-methoxyphenyl)prop-2-en-1-yl-propanoate (general formula III: $\text{R} = \text{Me}$)

2.99 g (5 mol %) of tetrabromomethane is added to a mixture of 29.3 g (0.24 mol) of (2*E*)-3-(3-methoxyphenyl) prop-2-en-1-ol (general formula II: $\text{R} = \text{Me}$) and 26 ml (0.264 mol, 1.1 eq.) of propionic anhydride, and the obtained solution is heated in a 60°C bath for 10 h. The reaction mixture is separated between 200 ml of water and 200 ml of methyl tert-butyl ether (MTBE), and the separated aqueous phase is shaken with 2x 50 ml of MTBE. The combined organic portions are washed with 50 ml of 1M sodium hydroxide and 50 ml of

brine, dried with Na₂SO₄, and evaporated in a rotating vacuum evaporator. The evaporation residue is vacuum-distilled: boiling point = 138 to 142 °C/200 Pa, yield 28.6 g (81 %).

¹H-NMR (CDCl₃) δ 1.17 (3H, t, J = 7.6 Hz), 2.38 (2H, q, J = 7.6 Hz), 3.81 (3H, s), 4.74 (2H, d, J = 6.4 Hz), 6.28 (1H, dt, J = 6.4, 15.9 Hz), 6.22 (1H, d, J = 15.9 Hz), 6.82 (1H, dd, J = 3.4, 7.9 Hz), 7.23 (1H, t, J = 7.9 Hz).

Example 5

Preparation of (2*E*)-3-(3-benzyloxyphenyl)prop-2-en-1-ol (general formula IV: R = CH₂Ph)

A solution of 103.1 g (0.365 mol) of ethyl-3'-benzyloxy-*E* cinnamate in dry toluene (730 ml) is cooled in an ice bath (ice + salt) under argon atmosphere to -10°C, and then, a 1M solution of diisobutylalane in toluene is added dropwise (temperature range -5 to 0°C) within 50 min. The yellowish solution is stirred at about -3°C for 2.5 h; the course of the reaction is checked using TLC, the cooling is switched off, and slow stirring continues overnight.

The reaction mixture cooled in an ice bath to 5°C is added gradually under stirring to 500 ml of a cooled saturated solution of ammonium chloride. Then, 1 N hydrochloric acid (500 ml) and, thereafter, concentrated hydrochloric acid (145 ml) are added. Methyl tert-butyl ether (MTBE; 400 ml) is added and the mixture is stirred for another 30 minutes. The aqueous phase is separated and shaken with MTBE (400 ml, 150 ml). The combined organic portions are washed with 0.5 N sodium hydroxide (380 ml), water (380 ml), and brine (350 ml). After filtration, the solution is evaporated in a rotating vacuum evaporator, during which a product crystallizes. 86.17 g (98.2 %) of the alcohol of general formula II: R = CH₂Ph) is obtained, sufficiently pure for using in the following step, melting point = 60.2 – 63.7°C.

¹H-NMR (CDCl₃) δ 1.40 (1H, bs), 4.32 (2H, d, J = 5.6 Hz), 5.08 (2H, s), 6.35 (1H, dt, J = 5.6, 15.9 Hz), 6.59 (1H, d, J = 15.9 Hz), 6.88 (1H, dd, J = 2.5, 8.3 Hz), 6.98-7.01 (2H, m), 7.20-7.39 (6H, m).

Example 6

Preparation of (2*E*)-3-(3-methoxyphenyl)prop-2-en-1-ol (general formula IV: R = Me)

A suspension of 15 g (84 mmol) of 3-methoxycinnamic acid in 200 ml of dried toluene is cooled down in an ice bath under nitrogen atmosphere, and a 1 M solution of diisobutylalane in toluene (280 ml, 280 mmol) is then added dropwise within 30 min with the temperature kept within the range of -15 to 0°C. The formed yellow solution is stirred in an ice bath for 20 min and at the laboratory temperature overnight. The reaction mixture is cooled

down in an ice bath, 12 ml of methanol is added dropwise, and then 200 ml of 2 M hydrochloric acid is added within 40 min. The two-phase mixture is stirred at the laboratory temperature for 1 h and diluted with 150 ml of water. The separated aqueous phase is additionally extracted with ethyl acetate (2x 100 ml). The combined organic portions are washed with 2x 100 ml of 2 M sodium hydroxide and 100 ml of brine, dried with Na₂SO₄, and evaporated in a rotating vacuum evaporator. 12.22 g (88 %) of alcohol of general formula II: R = Me) is obtained as a yellow oil.

¹H-NMR (CDCl₃) δ 1.74 (1H, s), 3.79 (3H, s), 4.30 (2H, d, J = 5.6 Hz), 6.34 (1H, dt, J = 5.6, 15.9 Hz), 6.58 (1H, d, J = 15.9 Hz), 6.80 (1H, dd, J = 2.5, 7.9 Hz), 6.91-6.98 (2H, m), 7.22 (1H, t, J = 7.9 Hz).

Example 7

Preparation of ethyl-(*E*)-3'-benzyloxy cinnamate

Benzyl triethylammonium chloride (2.14 g; 9.4 mmol), potassium carbonate (162.4 g; 1.175 mol), and dimethylformamide (470 ml) are added to 90.36 g (0.47 mol) of ethyl-(*E*)-3'-hydroxy cinnamate under N₂ and the mixture is stirred at 25°C until most of the substance is dissolved. Then, 101 ml of benzyl bromide is added and the mixture is heated to 80°C (bath). The residual amount of benzyl bromide (38.8 ml; total of 1.175 mol, 2.5 eq.) is added after two hours and the mixture is stirred at the same temperature for 20 h.

The reaction mixture is diluted with ice-cold water (825 ml) and extracted three times with ether (500 ml, 300 ml, 150 ml). The combined organic phases are washed with water (200 ml) and brine (150 ml), and, after drying (Na₂SO₄) and filtration, evaporated in a rotating vacuum evaporator. The oily evaporation residue is then connected to an oil vacuum pump and the volatile portion (boiling point 44 to 45°/13 Pa) is distilled off. The distillation residue is cooled, mixed with hexane or light petroleum (about 125 ml), and optionally seeded. After 2 h at the laboratory temperature, the crystals are aspirated and washed with hexane or petroleum ether (75 ml). The crystals are left to dry out freely. Yield 94.9 % (125.9 g). The compound is sufficiently pure for using in the following step.

¹H-NMR (CDCl₃) δ 1.33 (3H, t, J = 7.1 Hz), 4.25 (2H, q, J = 7.1 Hz), 5.08 (2H, s), 6.41 (1H, d, J = 16.0 Hz), 6.99 (1H, ddd, J = 1.1, 2.5, 8.2 Hz), 7.10-7.14 (2H, m), 7.25-7.46 (6H, m), 7.64 (1H, d, J = 16.0 Hz).

Example 8

Preparation of (2*E*)-3-(3-benzyloxyphenyl)prop-2-en-1-ol (general formula IV: R = CH₂Ph)

A 1 M solution of diisobutylalane in toluene (51 ml, 51 mmol) is added dropwise to a solution of 8.0 g (23 mmol) of benzyl-(*E*)-3'-benzyloxy cinnamate in 55 ml of dry toluene at -15°C within 15 min, maintaining the temperature to be < -5°C. At this temperature, the reaction mixture is stirred for 2.5 h; then, the reaction is quenched by the addition of 30 ml of a saturated solution of ammonium chloride and 30 ml of 2M HCl. After addition of 25 ml MTBE, the mixture is separated, the aqueous layer is extracted with 2x 20 ml of MTBE; the combined organic portions are washed with water (10 ml) and brine (10 ml), dried with anhydrous sodium sulphate, and evaporated in a rotating vacuum evaporator. Thus obtained crude product (oil) is mixed with 30 ml of hexane; after aspirating and washing with hexane, 87% (4.85 g) of white crystals is obtained, melting point = 60.2 – 3.7°C.

¹H-NMR (CDCl₃) δ 1.40 (1H, bs), 4.32 (2H, d, J = 5.6 Hz), 5.08 (2H, s), 6.35 (1H, dt, J = 5.6, 15.9 Hz), 6.59 (1H, d, J = 15.9 Hz), 6.88 (1H, dd, J = 2.5, 8.3 Hz), 6.98-7.01 (2H, m), 7.20-7.39 (6H, m).

Example 9

Preparation of benzyl-(*E*)-3'-benzyloxy cinnamate

8.5 g (31.3) mmol of potassium carbonate and 9.7 ml (2.7 eq.) of benzyl bromide are added to a solution of 5.0 g (30.5 mmol) of 3-(hydroxy)cinnamic acid in 100 ml of dried acetone. The reaction mixture is refluxed with exclusion of air humidity for 19 h; after cooling down, the mixture is separated between water (100 ml) and ethyl acetate (50 ml); the aqueous layer is extracted with 1x 50 ml of ethyl acetate; the combined organic portions are washed with 1x 20 ml of brine and evaporated in a rotating vacuum evaporator. The crude product in the form of an oil is mixed with 20 ml of ethanol; the white crystals thus formed are aspirated and washed with 2 ml of ethanol. 8.43 g (80%) of crystals is obtained, melting point = 53 - 56°C.

¹H-NMR (CDCl₃) δ 5.08 (2H, s), 5.25 (2H, s), 6.46 (1H, d, J = 16.0 Hz), 7.00 (1H, dd, J = 2.3, 8.1 Hz), 7.11-7.14 (2H, m), 7.25-7.45 (11H, m), 7.69 (1H, d, J = 16.0 Hz).

Example 10

a) Preparation of 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol (formula I, tapentadol)

A mixture of (2*R*,3*R*)-amine of general formula VIII (R = Me; 3.04 g, 11 mmol) and 75 ml of 48 % hydrobromic acid is heated in a bath at 120°C for 2.5 h. After partial cooling, the mixture is evaporated in a rotating vacuum evaporator at $t = 60^{\circ}\text{C}$. The evaporation residue is mixed with water and the obtained solution is basified with 2M sodium hydroxide (about 15 ml). Brine (5 ml) is added to the mixture for salting out of the product and the mixture is extracted with 2x 30 ml of dichloromethane. The combined extracts are dried with Na_2SO_4 , filtered and evaporated in a rotating vacuum evaporator. Ca. 2.58 g of the free tapentadol base (formula I) is obtained in the form of an oil.

b) Preparation of 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride (formula I hydrochloride, tapentadol hydrochloride)

The evaporation residue of the base is dissolved in 20 ml of methyl ethyl ketone and 5 ml of a solution of hydrogen chloride in Et_2O is added dropwise under stirring. The mixture is stirred at the laboratory temperature for 1 hour and then left standing in a refrigerator overnight. The separated crystals are aspirated, washed with 2 ml of methyl ethyl ketone, and dried. 2.16 g (75%) of beige crystals are obtained (melting point = $187 - 200^{\circ}\text{C}$), $[\alpha]_{\text{D}} = -21.7$ ($c = 2$, MeOH). After crystallization from isopropanol, light beige crystals are obtained of purity 99.6% (HPLC) and optical purity 99.8% R,R (chiral HPLC); melting point = $195 - 202^{\circ}\text{C}$, $[\alpha]_{\text{D}} = -25.6$ ($c = 2$, MeOH).

$^1\text{H-NMR}$ (CDCl_3) δ 0.73 (3H, t, $J = 7.5$ Hz), 1.15 (3H, d, $J = 5.0$ Hz), 1.53-1.66 (1H, m), 1.83-1.93 (1H, m), 2.13-2.32 (2H, m), 2.77 (6H, s), 2.85-2.89 (2H, m), 6.64-6.70 (3H, m), 7.15 (1H, t, $J = 7.8$ Hz).

Example 11

Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-*N,N*,2-trimethylpentane-1-amine (general formula VIII: R = Me)

The alkeneamine of general formula VII (R = Me; 3.78 g, 16 mmol) is dissolved in methanol (40 ml) and, under nitrogen atmosphere, 0.67 g of a 5 % Pd/C catalyst (18 % w/w) is added. The hydrogenation vessel is rinsed with hydrogen three times and then hydrogenated at 450 kPa and the laboratory temperature for 16 hours. After replacing the atmosphere with

nitrogen, the catalyst is filtered off and washed with methanol. The combined filtrate is evaporated in a rotating vacuum evaporator. 95% of the crude product of general formula VIII (R = Me) is obtained as a yellow oil.

¹H-NMR (CDCl₃) δ 0.73 (3H, t, J = 7.6 Hz), 0.95 (3H, d, J = 6.4 Hz), 1.56-1.63 (1H, m), 1.74-1.90 (2H, m), 1.94-2.00 (2H, m), 2.12(6H, s), 2.34-2.48 (1H, m), 3.80 (3H, s), 6.68-6.75 (3H, m), 7.19 (1H, t, J = 7.8 Hz).

The substance can be isolated in the form of a crystalline hydrochloride, which is prepared by adding a solution of hydrogen chloride in Et₂O to a solution of the above described base in isopropyl alcohol.

Example 12

Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-*N,N*,2-trimethylpent-4-en-1-amine (general formula VII: R = Me)

A 70 % w/w solution of Synhydride (Red Al; 12.2 ml) is charged into a flask under the N₂ atmosphere, diluted with 20 ml of toluene; and a solution of 4.80 g of (2*R*,3*R*)-amide of general formula VI (R = Me) in 20 ml of toluene is added, the temperature of the mixture thus increasing to ca. 50°C. The reaction mixture is heated to 100°C (bath temperature) in an inert atmosphere for 1 h; after cooling to laboratory temperature, it is cooled down in an ice bath, and 2.3 ml of water and 2.3 ml of 15 % sodium hydroxide are gradually added dropwise. The mixture is stirred at the laboratory temperature for 1 h, filtered through a layer of diatomaceous earth, and diluted with 10 ml of water and 20 ml of ethyl acetate. Layers are separated and the organic portion is washed with 2x 20 ml of 1M hydrochloric acid. The combined acidic aqueous portions are basified with 30 ml of 2M sodium hydroxide, and extracted with 2x 20 ml of ethyl acetate. The combined extracts are washed with 5 ml of brine, dried with Na₂SO₄ and evaporated in a rotating vacuum evaporator. 3.87 (85%) of the compound of general formula VII (R = Me) is obtained as an orange-red oil.

¹H-NMR (CDCl₃) δ 0.93 (3H, d, J = 6.3 Hz), 1.95-2.09 (3H, m), 2.15 (6H, s), 3.20-3.24 (1H, m), 3.79 (3H, s), 5.03-5.11 (2H, m), 5.93-6.04 (1H, m), 6.71-6.80 (3H, m), 7.21 (1H, t, J = 7.6 Hz).

Example 13

a) Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-2-methylpent-4-enoyl chloride (general formula VI: R = Me)

9.5 ml of thionyl chloride (130 mmol) is added to a solution of 4.8 g (22 mmol) of the
5 (2*R*,3*R*)-acid of general formula II (R = Me) in 60 ml of dried toluene and the mixture is heated in a bath at $t = 90^{\circ}\text{C}$ for 4 h. Then, the mixture is cooled to 50°C and evaporated in a rotating vacuum evaporator (at $t = 60^{\circ}\text{C}$). The crude chloride of general formula III (R = Me, X = Cl) is directly used in the following step.

10 b) Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-*N,N*,2-trimethylpent-4-eneamide (general formula VI: R = Me)

The crude chloride of general formula V (R = Me, X = Cl) is dissolved in 50 ml of dichloromethane, 2.66 g (33 mmol) of dimethylamine hydrochloride is added, and the mixture is cooled down in an ice bath. Then, 8.3 ml (60 mmol) of triethylamine is added dropwise, the
15 mixture is stirred under cooling for another 20 min, and then at the laboratory temperature for 40 min. The reaction mixture is diluted with 15 ml of water and 15 ml of dichloromethane, and layers are separated. The organic phase is washed with 5 ml of water and 10 ml of brine, dried with Na_2SO_4 , and, after filtration, evaporated in a rotating vacuum evaporator. 4.82 g (90 %) of the crude amide of general formula VI (R = Me) is obtained as a red-brown semisolid oil.

20 $^1\text{H-NMR}$ (CDCl_3) δ 1.20 (3H, d, $J = 6.7$ Hz), 2.76 (6H, d, $J = 10.5$ Hz), 3.05-3.11 (1H, m), 3.57 (1H, t, $J = 9.9$ Hz), 3.79 (3H, s), 5.11-5.22 (2H, m), 6.00 (1H, dt, $J = 9.9, 16.9$ Hz), 6.70-6.82 (3H, m), 7.19 (1H, t, $J = 7.9$ Hz).

Example 14

25 a) Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-2-methylpentanoic acid (general formula IX: R = Me)

0.25 g of a 5 % Pd/C catalyst is added to a solution of the acid of general formula II (R = Me; *R,R* : *S,S* ratio >98 : 2), released from 2.45 g of its salt with (*R*)-phenylethylamine (7.16 mmol) by means of hydrochloric acid, in methanol (20 ml) under the nitrogen atmosphere.
30 The hydrogenation vessel is rinsed twice with hydrogen and then hydrogenated at 400 kPa at the laboratory temperature under shaking for 18 hours. After the atmosphere has been replaced with nitrogen, the catalyst is filtered off and washed with methanol. The combined filtrate is

evaporated in a rotating vacuum evaporator. 97 % of a crude product of general formula IX (R = Me) is obtained as a colourless oil (1.53 g).

¹H-NMR (CDCl₃) δ 0.74 (3H, t, J = 7.3 Hz), 1.22 (3H, d, J = 6.9 Hz), 1.55-1.65 (1H, m), 1.76-1.83 (1H, m), 2.63-2.81 (2H, m), 3.77 (3H, s), 6.69-6.80 (3H, m), 7.17 (1H, t, J = 7.8 Hz).

b) Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-2-methylpentanoyl chloride (general formula X: R = Me)

9.5 ml of thionyl chloride (130 mmol) is added to a solution of 1.53 g (6.88 mmol) of the (2*R*,3*R*)-acid of general formula IX (R = Me) in 20 ml of dried toluene and the mixture is heated in a bath at t = 90°C for 4 h. Then, the mixture is cooled to 50°C and evaporated in a rotating vacuum evaporator (at t = 60°C). The crude chloride of general formula X (R = Me, X = Cl) is directly used in the following step.

c) Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-*N,N*,2-trimethylpentaneamide (general formula XI: R = Me)

The crude chloride of general formula X (R = Me, X = Cl) is dissolved in 15 ml of dichloromethane, 0.84 g (10.4 mmol) of dimethylamine hydrochloride is added, and the mixture is cooled down in an ice bath. Then, 2.6 ml (18.8 mmol) of triethylamine is added dropwise, the mixture is stirred under cooling for another 20 min, and then at the laboratory temperature for 30 min. The reaction mixture is diluted with 10 ml of water and 15 ml of dichloromethane, and layers are separated. The organic phase is washed with 5 ml of water and 5 ml of brine, dried with Na₂SO₄, and, after filtration, evaporated in a rotating vacuum evaporator. 1.45 g (84%) of the crude amide of general formula XI (R = Me) is obtained as a brown thick oil.

¹H-NMR (CDCl₃) δ 0.72 (3H, t, J = 7.3 Hz), 1.20 (3H, d, J = 6.7 Hz), 1.41-1.56 (1H, m), 1.87-1.96 (1H, m), 2.71 (6H, s), 2.74-2.80 (1H, m), 2.87-2.96 (1H, m), 3.78 (3H, s), 6.68-6.77 (3H, m), 7.16 (1H, t, J = 5.3 Hz).

d) Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-*N,N*,2-trimethylpentane-1-amine (general formula VIII: R = Me)

A 65 % w/w solution of Synhydride (Red Al; 3.82 ml; 2.2 equiv.) is charged into a flask under the N₂ atmosphere, diluted with 6 ml of toluene, and a solution of 1.41 g of

(2*R*,3*R*)-amide of general formula XI (R = Me) in 6 ml of toluene is added. The reaction mixture is heated to the boil and kept at this temperature in an inert atmosphere for 1 h. After cooling to the laboratory temperature, it is cooled down in an ice bath, and 0.65 ml of water and 0.65 ml of 15 % sodium hydroxide are gradually added dropwise. The mixture is stirred at the laboratory temperature for 30 min, filtered through a layer of diatomaceous earth, and the filtration cake is washed with 3 ml of ethyl acetate. The filtrate is extracted with 2x 7 ml of 1M hydrochloric acid. The combined acidic aqueous portions are basified with a 2M solution of sodium hydroxide, and extracted 2x with ethyl acetate. The combined extracts are washed 1x with brine, dried with Na₂SO₄, and evaporated in a rotating vacuum evaporator. 1.11 (84%) of the compound of general formula VIII (R = Me) is obtained as an orange oil.

¹H-NMR (CDCl₃) δ 0.73 (3H, t, J = 7.6 Hz), 0.95 (3H, d, J = 6.4 Hz), 1.56-1.63 (1H, m), 1.74-1.90 (2H, m), 1.94-2.00 (2H, m), 2.12(6H, s), 2.34-2.48 (1H, m), 3.80 (3H, s), 6.68-6.75 (3H, m), 7.19 (1H, t, J = 7.8 Hz).

Example 15

Preparation of (2*R*,3*R*)-3-(3-methoxyphenyl)-*N,N*,2-trimethylpentaneamide (general formula XI: R = Me)

The alkeneamide of general formula VI (R = Me; 3.78 g, 16 mmol) is dissolved in methanol (40 ml) and 0.67 g of a 5 % Pd/C (18 % w/w) catalyst is added under the nitrogen atmosphere. The hydrogenation vessel is rinsed with hydrogen three times and then hydrogenated at 450 kPa at the laboratory temperature for 16 hours. After the atmosphere has been replaced with nitrogen, the catalyst is filtered off and washed with methanol. The combined filtrate is evaporated in a rotating vacuum evaporator. 95% of the crude product of general formula XI (R = Me) is obtained as a yellow oil.

¹H-NMR (CDCl₃) δ 0.72 (3H, t, J = 7.3 Hz), 1.20 (3H, d, J = 6.7 Hz), 1.41-1.56 (1H, m), 1.87-1.96 (1H, m), 2.71 (6H, s), 2.74-2.80 (1H, m), 2.87-2.96 (1H, m), 3.78 (3H, s), 6.68-6.77 (3H, m), 7.16 (1H, t, J = 5.3 Hz).

Example 16

a) Preparation of (1*R*,2*R*)-3-[3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol (compound of formula I, tapentadol)

A 70% (w/w) solution of synhydride (Red Al; 7.1 ml, 23.5 mmol; 2.2 equiv.) is charged into a flask under an inert atmosphere of N₂, 10 ml of toluene is added and then a

solution of 2.50 g (10.7 mmol) of the crude amide of formula XI (R = H) in 10 ml of toluene is added, the temperature thus spontaneously rising to ca. 50°C. The dripping funnel is rinsed with another 5 ml of toluene and the reaction mixture is heated at 100°C (bath) under a reflux condenser in an inert atmosphere for 1 h, left to cool down to the laboratory temperature in 20 minutes and decomposed by gradual dropwise addition of 1.5 ml of water and 2 ml of a 10% sodium hydroxide solution. The mixture is stirred at the laboratory temperature for 15 min, 30 ml of water are added and the mixture is stirred for further 45 minutes. The suspension is filtered over a kieselguhr layer, and the filter is washed with 20 ml of ethyl acetate. The filtrate is extracted with 3x 20 ml of 1M hydrochloric acid. The combined acidic aqueous fractions are neutralized with a 2M solution of sodium hydroxide (pH ca. 7) and extracted with 1x50 ml and 2x 25 ml of ethyl acetate. The combined extracts are washed with 1x 25 ml of brine, dried with Na₂SO₄, and evaporated in vacuo in a rotatory vacuum evaporator. 2.04 g (85.3 %) of crude tapentadol of formula I are obtained.

b) Preparation of 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride (hydrochloride of the compound of formula I, tapentadol hydrochloride)

1.33 g of the crude compound of formula I are dissolved in 10 ml of methylethylketone and 2 ml of a solution of hydrogen chloride in diethyl ether are added dropwise. The mixture is stirred under cooling with an ice bath for 2 h; the separated crystals are aspirated. 1.02 g of tapentadol hydrochloride is obtained (71%), melt. point 183-202°C. Re-crystallization from 2-propanol provides a substance with the purity of 99.7%; 2*R*,3*R* : 2*S*,3*S* = 99.6: 0.4; melt. point = 200 – 206°C, [α]_D = - 29,5 (c= 2, MeOH).

¹H-NMR (CDCl₃) δ 0.73 (3H, t, J=7.5 Hz), 1.15 (3H, d, J=5 Hz), 1.53-1.66 (1H, m), 1.83-1.93 (1H, m), 2.13-2.32 (2H, m), 2.77 (6H, s), 2.85-2.89 (2H, m), 6.64-6.70 (3H, m), 7.15 (1H, t, J= 7.5 Hz).

Example 17

a) Preparation of (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methylpentanoic acid chloride (general formula X: R = H)

5.22 ml of thionyl chloride (72.5 mmol; 6 equiv.) are added to a solution of 2.5 g of the (2*R*,3*R*)-acid of formula III in 36 ml of dried toluene under the nitrogen atmosphere, a drop of dimethylformamide is added and the mixture is heated in a bath at 88°C for 3.5 h. The mixture is cooled and then evaporated in a rotatory vacuum evaporator (at t = 60°C). 20 ml of toluene

are added to the evaporation product, the solution is again evaporated in a rotatory vacuum evaporator; this procedure is repeated once again. The produced crude chloride of general formula X (R = H) is directly used in the next step.

- 5 b) Preparation of (2*R*,3*R*)-3-(3-hydroxyphenyl)-*N,N*,2-trimethylpentanamide (formula XI; R = H)

1.46 g of dimethylamine hydrochloride (17.8 mmol; ca. 1.5 equiv.) are added to a solution of the crude chloride of general formula X (R = H) in 32 ml of dry dichloromethane, the mixture is cooled to 0°C in an ice bath and 4.6 ml of triethylamine are added dropwise
10 during 5 min. The reaction mixture is stirred under cooling for another 15 min, then the cooling is stopped and the mixture is stirred at the laboratory temperature for further 60 min. The reaction mixture is diluted with 20 ml of water and 20 ml of dichloromethane. The organic phase is separated, washed with 1x 20 ml of water, 1x 20 ml of brine, dried with Na₂SO₄ and evaporated in a rotatory vacuum evaporator. 91.8 % of crude (2*R*,3*R*)-amide of
15 formula XI are obtained (calculated with relation to the acid of formula IX; R = H) as partially solidified brown oil.

¹H-NMR (CDCl₃) δ 0.70 (3H, t, J=7.3 Hz), 0.96 (3H, d, J=6.0 Hz), 1.49-1.85 (3H, m), 2.16 (6H, s), 2.26-2.37 (1H, m), 6.58-6.68 (3H, m), 7.12 (1H, t, J=7.8 Hz)

20 Example 18

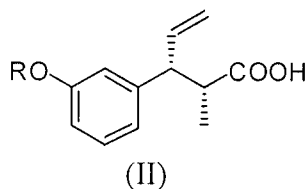
Preparation of (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methylpentanoic acid (formula IX; R = H)

5% Pd/C (0.395 g) is added to a solution of 3.36 g (11.34 mmol) of the (2*R*,3*R*)-acid of general formula II (R = Bn) in methanol (40 ml) in an inert nitrogen atmosphere. The hydrogenation vessel is rinsed with hydrogen three times and then hydrogenated under slight
25 overpressure and at the laboratory temperature for 15 hours. After replacement of the atmosphere with nitrogen the catalyst is removed by filtration, washed with methanol and the solvent is evaporated in a rotatory vacuum evaporator. The (2*R*,3*R*)-acid of formula IX (R = H) is obtained in the yield of 100%.

¹H-NMR (CDCl₃) δ 0.73 (3H, t, J=7.3 Hz), 1.19 (3H, d, J=6.4 Hz), 1.50-1.58 (1H, m),
30 1.75-1.82 (1H, m), 2.63-2.69 (2H, m), 6.63-6.72 (3H, m), 7.1 (1H, t, J=7.7 Hz).

C L A I M S

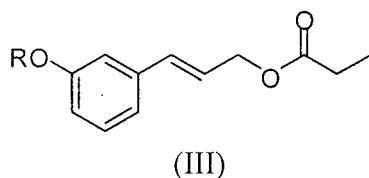
- 1) *O*-Substituted (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methyl-4-pentenoic acids of general formula II



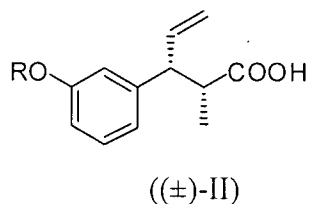
wherein R stands for an alkyl group with 1 to 4 carbon atoms, or the benzyl group, a substituted benzyl group, benzhydryl or trityl group, wherein the acids are optically pure, optically enriched, or racemic.

- 2) *O*-Substituted acids according to claim 1, which contain erythro : threo diastereoisomers in a ratio higher than 25 : 1.

- 3) A method of producing *O*-substituted acids according to claims 1 or 2, characterized in that cinnamyl propanoates of general formula III



wherein R is as defined in claim 1, are rearranged, by means of strong bases, to racemic acids of general formula (±)-II



wherein R is as defined in claim 1, and the produced racemic acids of general formula (±)-II are resolved by crystallization of the salt of compound (±)-II with a chiral base in suitable solvents.

4) The method according to claim 3, characterized in that said strong base is a metal amide selected from lithium hexamethyldisilazide and lithium diisopropylamide, in the presence of a tertiary amine.

5) The method of production according to claims 3 or 4, characterized in that both the metal amide and tertiary amine are used in an amount of at least 2 equivalents.

6) The method according to claims 3-5, characterized in that the rearrangement is carried out in a temperature range of from -40 to -80°C.

7) The method according to claim 3, characterized in that said chiral base is optically active 1-phenylethylamine or 1-(4-nitrophenyl)-2-amino-1,3-propanediol.

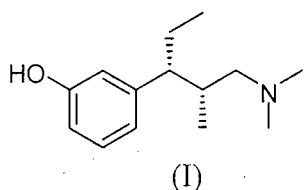
8) The method according to claims 3 or 7, characterized in that the resolving is carried out by crystallization of said salts in suitable solvents, selected from C1 to C4 lower alcohols, acetone, methyl ethyl ketone, diethyl ether, methyl tert-butyl ether, ethyl acetate, dichloromethane, and water, and their mixtures.

9) The method according to claims 3, 7 or 8, characterized in that the salts of acids of general formula (±)-II with 1-phenylethylamine are optically purified by recrystallization.

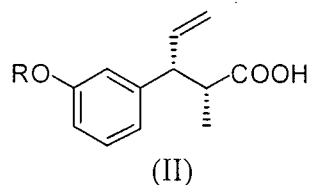
10) The method according to claims 3 and 7, characterized in that the salts of acids of general formula (±)-II with 1-phenylethylamine are optically purified by stirring with dichloromethane or methyl tert-butyl ether.

11) Use of the compounds of claim 1 for the preparation of tapentadol.

12) A method of production of optically pure or optically enriched tapentadol of formula I



and/or its pharmaceutically acceptable salts,
characterized in that *O*-protected (2*R*,3*R*)-acids of general formula II

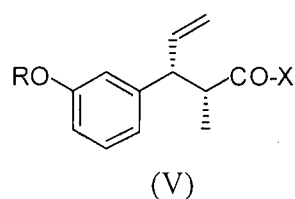


5 wherein R stands for an alkyl group having 1 to 4 carbon atoms,

are, in Step A, reacted with an activating agent selected from chlorides of organic and inorganic acids and chloroformates in an inert organic solvent, optionally in the presence of a catalyst or base;

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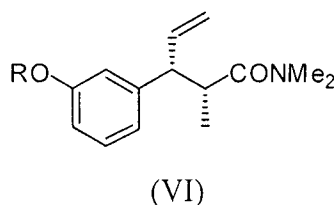
in Step B, the resulting compounds of general formula V



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wherein R is as defined above and X stands for chloro or an alkoxycarbonyloxyl group O-CO-OR¹ or the pivaloyloxyl group O-CO-*t*-Bu, wherein R¹ is methyl or ethyl, are reacted with dimethylamine or its salts, optionally in the presence of a base;

in Step C, the resulting *N,N*-dimethylamides of general formula VI

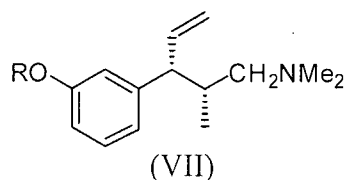


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wherein R is as defined above and, Me is methyl, are reduced by hydride agents based on aluminium in an organic solvent selected from ethers and aromatic hydrocarbons;

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in Step D, the produced alkeneamines of general formula VII

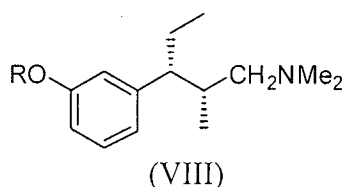


wherein R is as defined above,

are hydrogenated on a metal palladium catalyst in a suitable solvent;

5

in Step E, the resulting alkaneamines of general formula VIII



wherein R is as defined above,

are *O*-dealkylated with dealkylating agents the selection of which depends on the protecting group, and, if desired, the resulting tapentadol is converted to respective salts, for example hydrochloride, by the action of pharmaceutically acceptable acids.

10

- 13) The method according to claim 12, characterized in that thionyl chloride or oxalyl chloride is used as the activating agent in Step A, in the presence of a catalytic amount of dimethylformamide.

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- 14) The method according to claim 12, characterized in that methyl chloroformate, ethyl chloroformate or pivaloyl chloride is used as the activating agent in Step A, in the presence of a base, which is triethylamine, at temperatures of from 0°C to 50°C, preferably from 0 to 30°C.

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- 15) The method according to claims 12-14, characterized in that said inert organic solvent is chloroform, dichloromethane or toluene.

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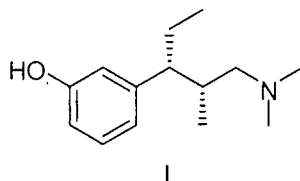
- 16) The method according to claim 12, characterized in that said diethylamine in Step B is used in the gaseous form, or in the form of an aqueous solution, or in the form of a salt, in the presence of a base, which is triethylamine or an aqueous solution of an inorganic base, such as sodium or potassium carbonate or hydrogencarbonate.

- 17) The method according to claim 12, characterized in that said hydride agents based on aluminium of Step C are selected from lithium hydrido aluminate, sodium bis-(2-methoxyethoxy)hydrido aluminate and diisobutylaluminium hydride.

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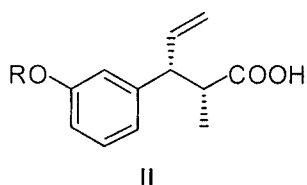
- 18) The method according to claims 12 or 17, characterized in that the reduction in Step C is carried out with sodium bis-(2-methoxyethoxy)hydrido aluminate in toluene, tetrahydrofuran or 2-methyl tetrahydrofuran.

- 10 19) A method of producing optically pure or optically enriched tapentadol of formula I



and/or its pharmaceutically acceptable salts,

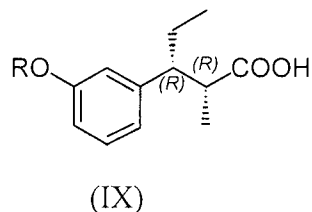
characterized in that *O*-protected (2*R*,3*R*)-acids of general formula II



- 15 wherein R stands for a phenylmethyl group, substituted or unsubstituted in the benzene ring, such as the benzyl or 4-methoxybenzyl, benzhydryl or trityl group,

a) are hydrogenated on a metal catalyst in a suitable solvent for hydrogenation,

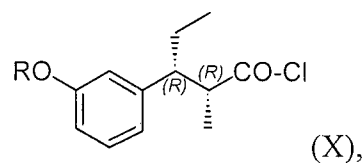
- 20 b) the resulting (2*R*,3*R*)-3-(3-hydroxyphenyl)-2-methylpentanoic acid of formula IX



wherein R is hydrogen,

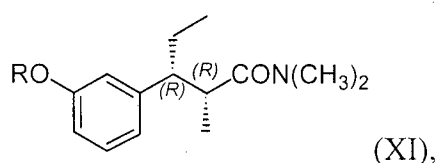
- 25 is reacted with an activating agent, which is a chloride of an organic or inorganic acid, in an inert organic solvent, optionally in the presence of a catalyst or base;

c) the resulting compound of formula X



5 wherein R is hydrogen,
is reacted with dimethylamine or its salts, optionally in the presence of a base;

d) the resulting *N,N*-dimethylamide of formula XI



10 wherein R is hydrogen,
is reduced by hydride agents in a solvent selected from toluene, tetrahydrofuran, 2-methyltetrahydrofuran and their mixtures,
and, if desired, tapentadol is converted to respective salts by the action of
15 pharmaceutically acceptable acids.

20 20) The method according to claim 19, characterized in that said metal catalyst is platinum or palladium on carbon.

20 21) The method according to claims 19 or 20, characterized in that said solvent for hydrogenation is selected from C1 to C3 alcohols such as methanol, ethanol or isopropyl alcohol, cyclic ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran or 1,4-dioxane, and ethyl acetate, and mixtures thereof.

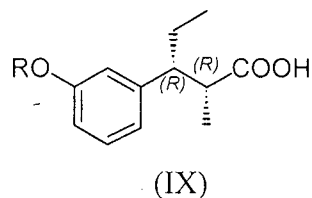
25 22) The method according to claims 19-21, characterized in that thionyl chloride or oxalyl chloride is used as said activating agent, in the presence of a catalytic amount of dimethylformamide.

- 23) The method according to claim 19, characterized in that said dimethylamine is used in the gaseous form or in the form of an aqueous solution or in the form of a salt, in the presence of a base, which is triethylamine or an aqueous solution of an inorganic base such as sodium or potassium carbonate or hydrogencarbonate.

5

- 24) The method according to claim 19, characterized in that said hydride agents are hydride agents based on aluminium selected from lithium hydrido aluminate, sodium bis-(2-methoxyethoxy)hydrido aluminate and diisobutylaluminium hydride.

- 10 25) (2*R*,3*R*)-3-(3-Hydroxyphenyl)-2-methylpentanoic acid of formula IX



wherein R = H.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2011/000128

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C213/02 C07C231/02 C07C51/09 C07C51/377 C07C51/60
C07C59/52 C07C59/64 C07C213/08

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/108658 A1 (GRUENENTHAL GMBH [DE]; HELL WOLFGANG [DE]; KEGEL MARKUS [DE]; AKTERIES) 16 December 2004 (2004-12-16) cited in the application claims; examples	1-25
A	WO 2008/012046 A1 (GRUENENTHAL GMBH [DE]; HELL WOLFGANG [DE]) 31 January 2008 (2008-01-31) cited in the application the whole document	1-25
A	WO 2007/051576 A1 (GRUENENTHAL GMBH [DE]; HELL WOLFGANG [DE]; KEGEL MARKUS [DE]; BUSCHMAN) 10 May 2007 (2007-05-10) cited in the application claims; examples	1-25
	-/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

23 March 2012

Date of mailing of the international search report

04/04/2012

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INTERNATIONAL SEARCH REPORT

International application No

PCT/CZ2011/000128

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No

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Information on patent family members

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