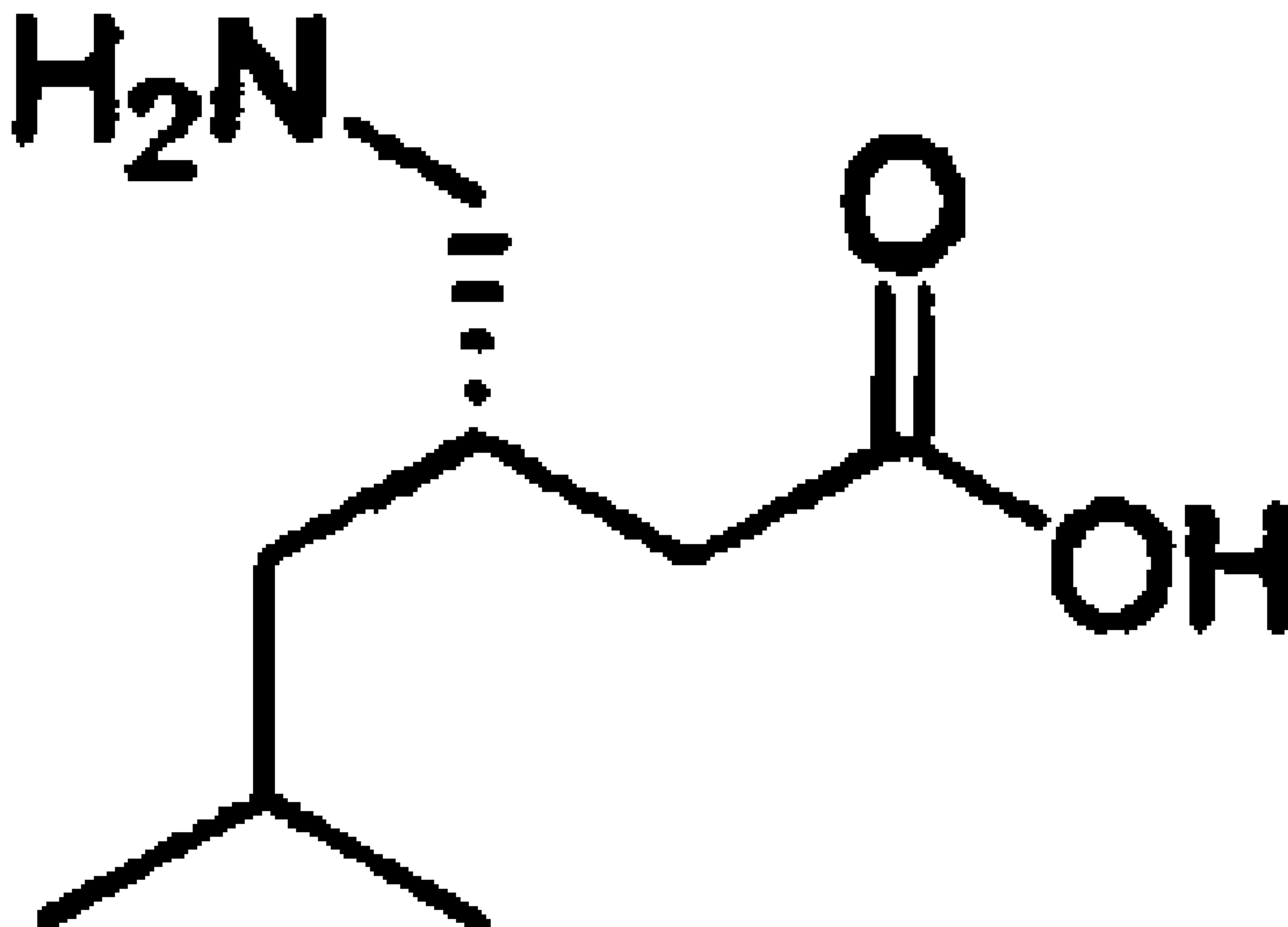




(86) Date de dépôt PCT/PCT Filing Date: 2008/03/24
(87) Date publication PCT/PCT Publication Date: 2008/10/02
(45) Date de délivrance/Issue Date: 2012/09/11
(85) Entrée phase nationale/National Entry: 2009/09/18
(86) N° demande PCT/PCT Application No.: US 2008/003898
(87) N° publication PCT/PCT Publication No.: 2008/118427
(30) Priorités/Priorities: 2007/03/22 (US60/919,575);
2007/05/29 (US60/932,317)

(51) Cl.Int./Int.Cl. *C07C 247/12* (2006.01)
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(54) Titre : SYNTHESE DE L'ACIDE (S)-(+)-3-(AMINOMETHYL)-5-METHYLHEXANOIQUE
(54) Title: SYNTHESIS OF (S)-(+)-3-(AMINOMETHYL)-5-METHYL HEXANOIC ACID



(57) **Abrégé/Abstract:**

Provided are syntheses of (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid, (S)- Pregabalin via a chiral intermediate of the following formula (4) wherein Ar is a C₆-C₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, and R₁ is a straight or branched C₁-C₅ alkyl, aralkyl, or substituted aralkyl.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
2 October 2008 (02.10.2008)

PCT

(10) International Publication Number
WO 2008/118427 A9(51) International Patent Classification:
C07C 247/12 (2006.01)(74) Agents: BIRDE, Patrick, J. et al.; Kenyon & Kenyon
LLP, One Broadway, New York, NY 10004-1050 (US).(21) International Application Number:
PCT/US2008/003898(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 24 March 2008 (24.03.2008)

(25) Filing Language: English

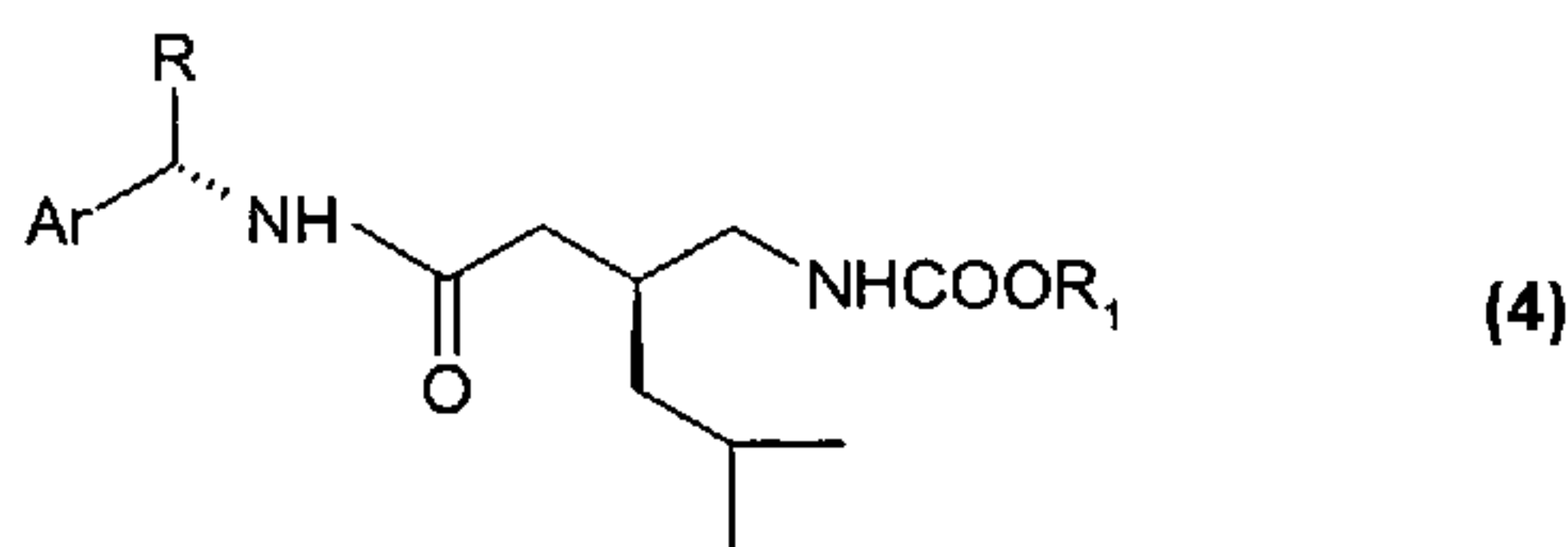
(26) Publication Language: English

(30) Priority Data:
60/919,575 22 March 2007 (22.03.2007) US
60/932,317 29 May 2007 (29.05.2007) US(71) Applicant (*for all designated States except BB, US*):
TEVA PHARMACEUTICAL INDUSTRIES LTD.
[IL/IL]; 5 Basel Street, P.o. Box 3190, 49131 Petah Tiqva (IL).(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).(71) Applicant (*for BB only*): **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.o. Box 1090, North Wales, PA 19454-1090 (US).Published:
— *with international search report*

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18 December 2008(48) Date of publication of this corrected version:
5 February 2009(15) Information about Correction:
see Notice of 5 February 2009

(54) Title: SYNTHESIS OF (S)-(+)-3-(AMINOMETHYL)-5-METHYL HEXANOIC ACID



(4)

(57) Abstract: Provided are syntheses of (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid, (S)- Pregabalin via a chiral intermediate of the following formula (4) wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, and R₁ is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl.

WO 2008/118427 A9

SYNTHESIS OF (S)-(+)-3-(AMINOMETHYL)-5-METHYL HEXANOIC ACID

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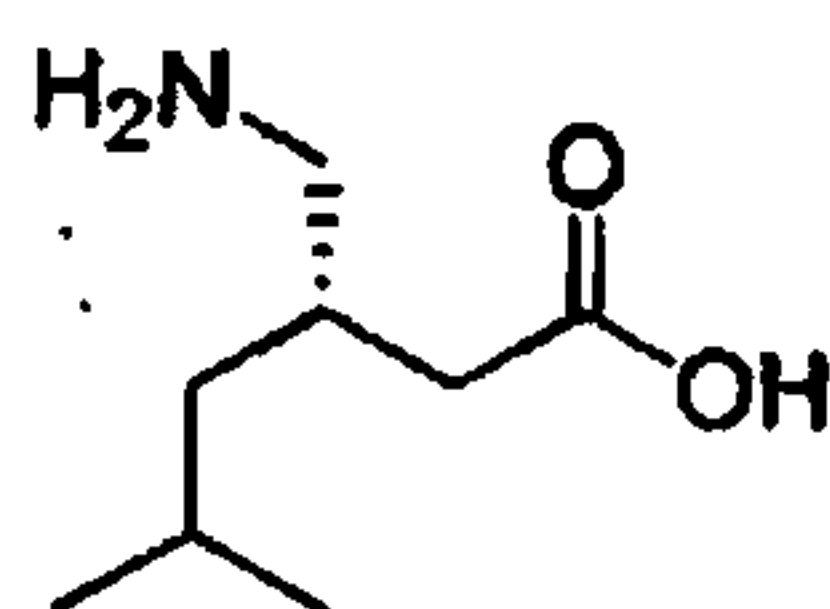
FIELD OF THE INVENTION

The invention encompasses syntheses of (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid, (S)-Pregabalin.

BACKGROUND OF THE INVENTION

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(S)-Pregabalin, (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid, a compound having the chemical structure,



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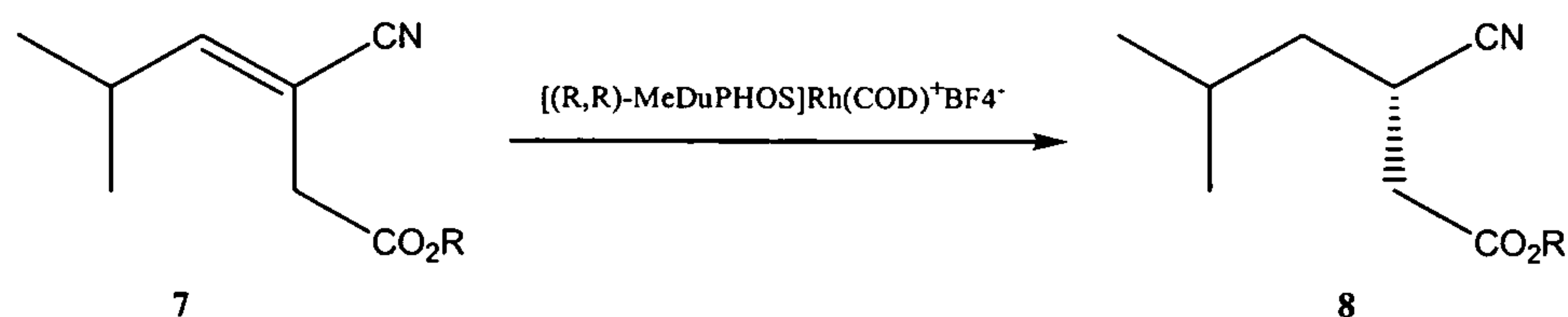
is also known as γ -amino butyric acid or (S)-3-isobutyl GABA. (S)-Pregabalin, marketed under the name LYRICA®, has been found to activate GAD (L-glutamic acid decarboxylase). (S)-Pregabalin has a dose dependent protective effect on seizure, and is a CNS-active compound. (S)-Pregabalin is useful in anticonvulsant therapy, due to its activation of GAD, promoting the production of GABA, one of the brain's major inhibitory neurotransmitters, which is released at 30 percent of the brains synapses. (S)-Pregabalin has analgesic, anticonvulsant, and anxiolytic activity.

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Several processes for the synthesis of (S)-Pregabalin are known. For example, U.S. Patent No. 5,599,973 ("973 patent") discloses the preparation of (S)-Pregabalin using a stoichiometric amount of (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone as a chiral auxiliary that may be recycled. See, e.g., '973 patent, col. 14, l. 29 to col. 18, l. 23 (example 1). In general, however, the route disclosed in the '973 patent is of limited use on an

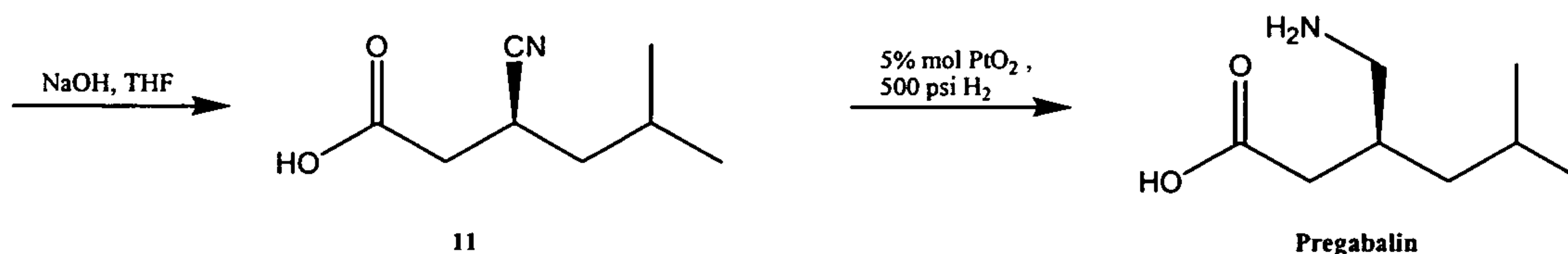
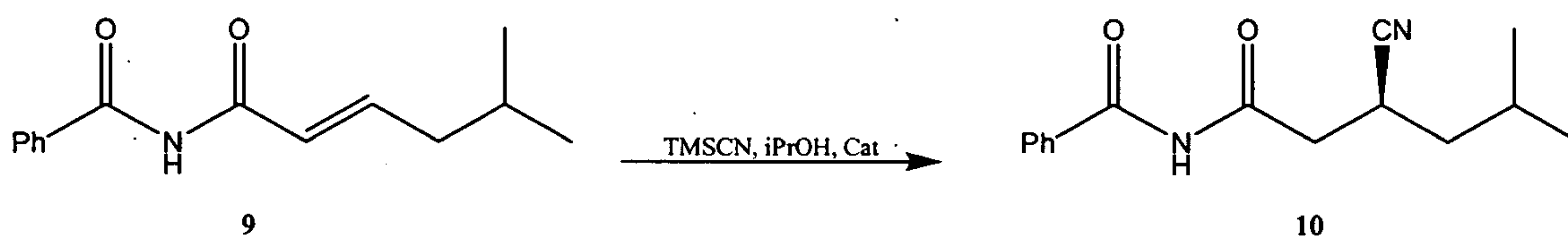
industrial scale, principally due to the low temperature required for the reaction (*e.g.*, -78°C), the use of pyrophoric reagent (*e.g.*, butyl lithium), and a low overall yield (*e.g.*, 59%, 65%).

U.S. Publication No. 2003/0212290 ("290 publication") discloses the synthesis of (S)-Pregabalin by an asymmetric hydrogenation of a cyano-substituted olefin of formula 7, to produce a cyano precursor of (S)-3-(aminomethyl)-5-methyl hexanoic acid of formula 8, which is further reduced to obtain (S)-Pregabalin, as described in the following scheme.



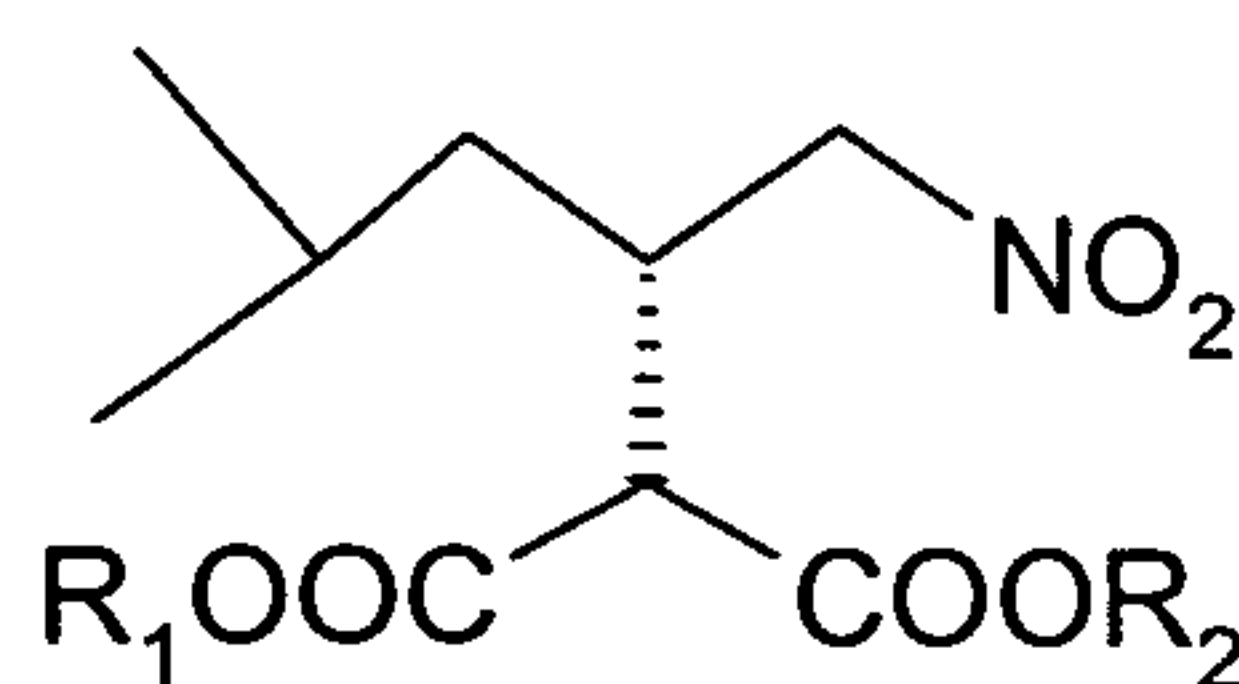
However, the disclosed method requires the use of carbon monoxide under high pressure, raising serious problems in adapting this process for production scale.

Another process is disclosed by G.M. Sammis, et al., *J. Am. Chem. Soc.*, 125(15): 4442-43 (2003), in which an aluminum salen catalyst is used in the conjugate addition of hydrogen cyanide to α , β -unsaturated imides.



This process is also not practical for large scale production due to the use of highly poisonous reagents. In addition, the last reduction step requires high hydrogen pressure, which only adds to the difficulties required for adapting this process for use on an industrial scale.

International Publication WO 2006/110783 reports several processes for preparing (S)-Pregabalin via the following intermediate and its analogues



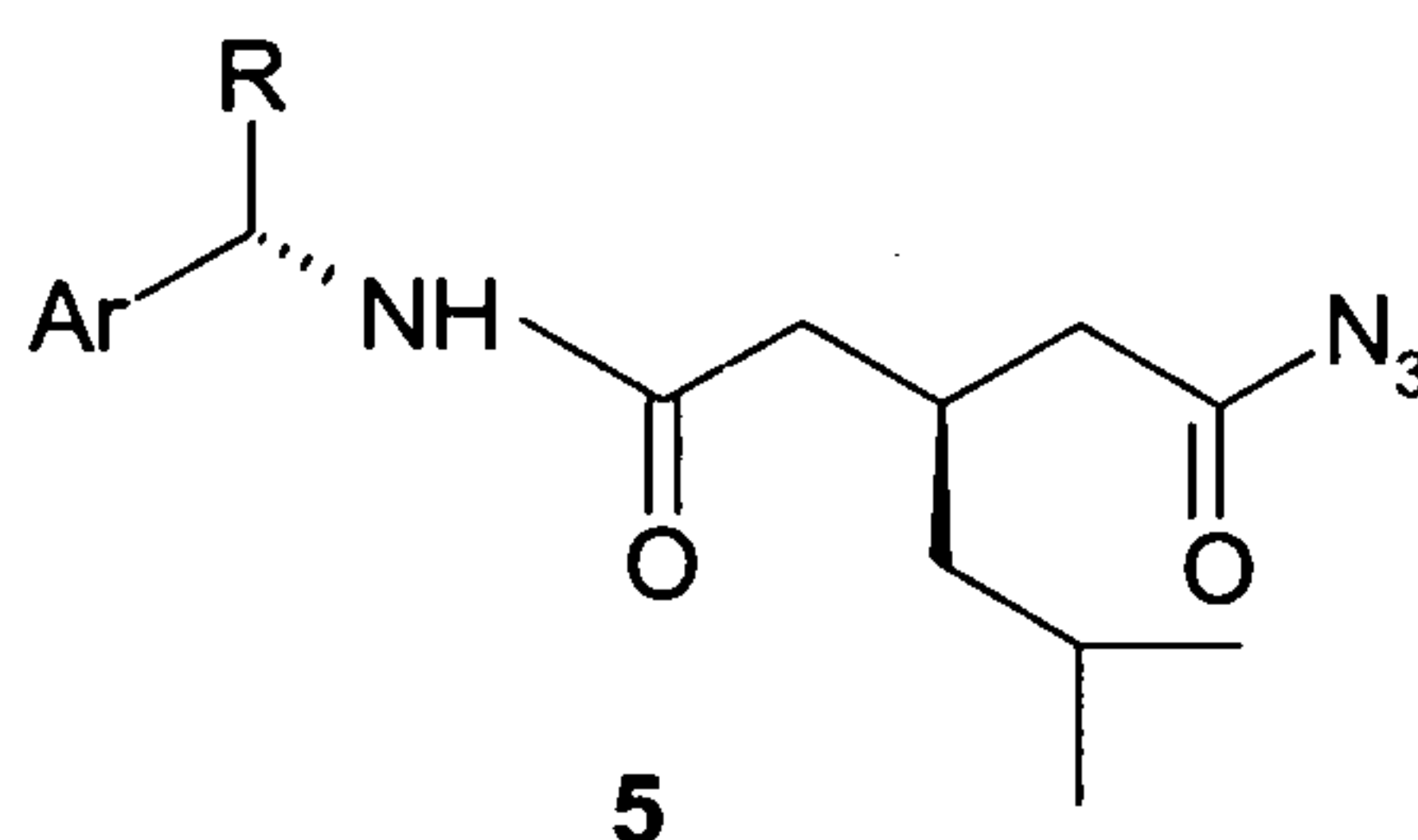
wherein R_1 and R_2 are independently H, a straight or branched C_{1-10} alkyl, C_{6-10} aryl, or C_{3-6} allyl.

U.S. Publication Nos. 2007/0191636 and 2007/0197827 also disclose processes for preparing (S)-Pregabalin.

Thus, there is a need in the art for additional process for the preparation of (S)-Pregabalin that provide (S)-Pregabalin in high quality, and that can be adapted to large (industrial) scale production.

SUMMARY OF THE INVENTION

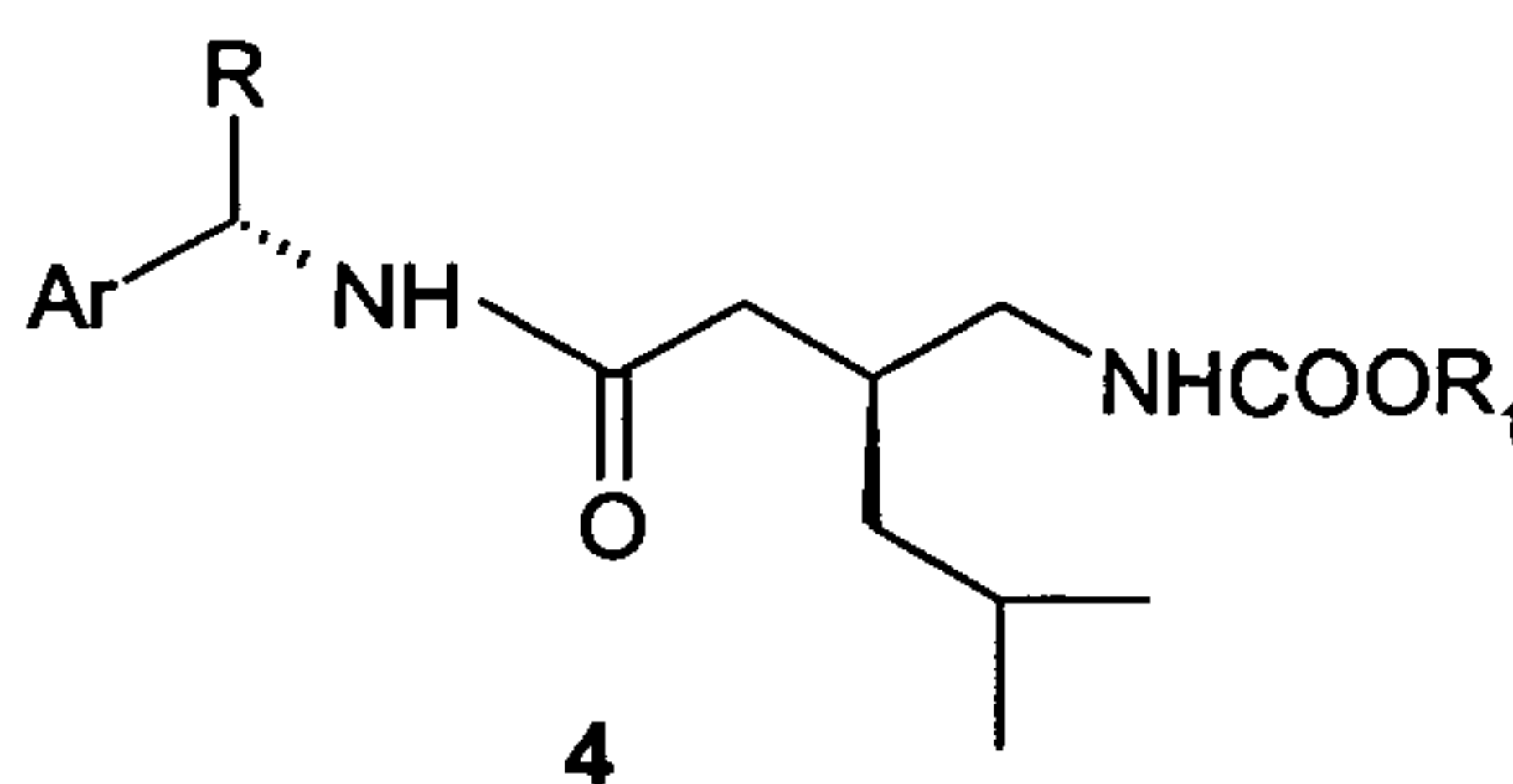
In one embodiment, the invention encompasses a compound of the following formula



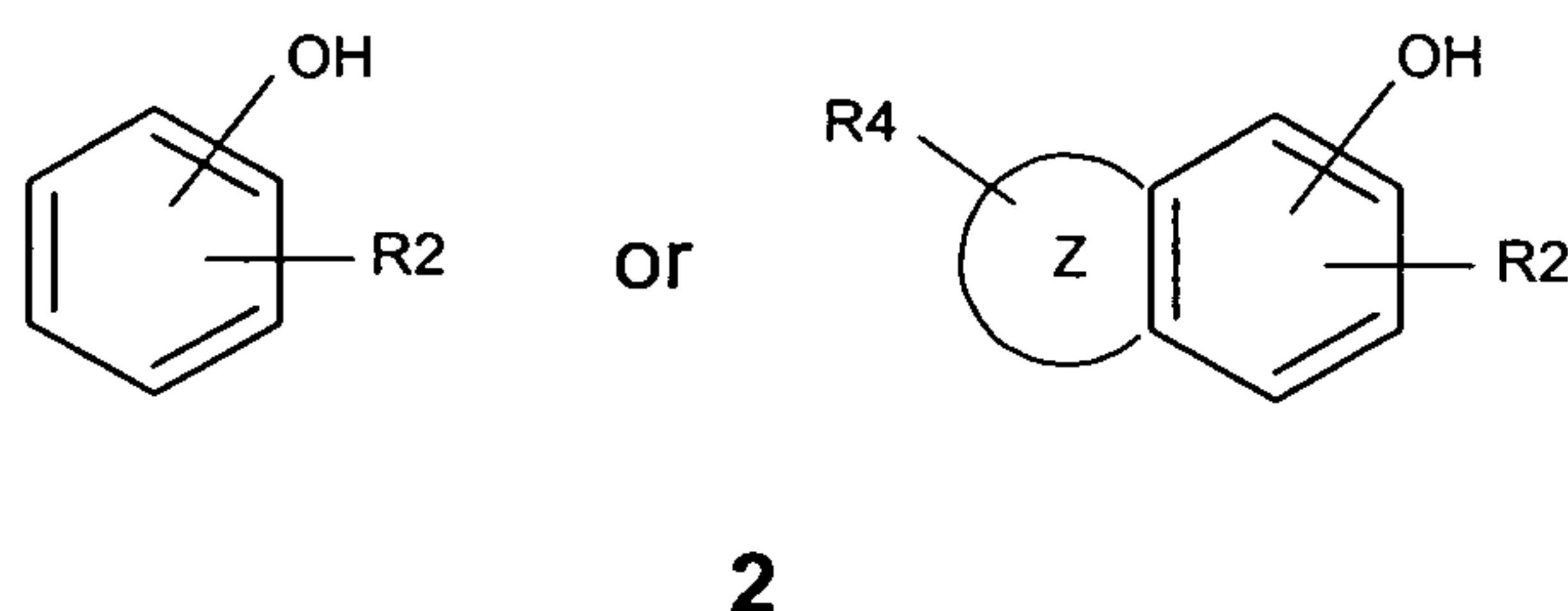
wherein Ar is a C_{6-10} aromatic group, and R is a straight or branched C_{1-4} alkyl, ester, or carboxylic acid.

In another embodiment, the invention encompasses a process for preparing (S)-Pregabalin via the compound of claim 1.

In another embodiment, the invention encompasses a process for preparing (S)-Pregabalin comprising: (a) combining a compound of the following formula 4

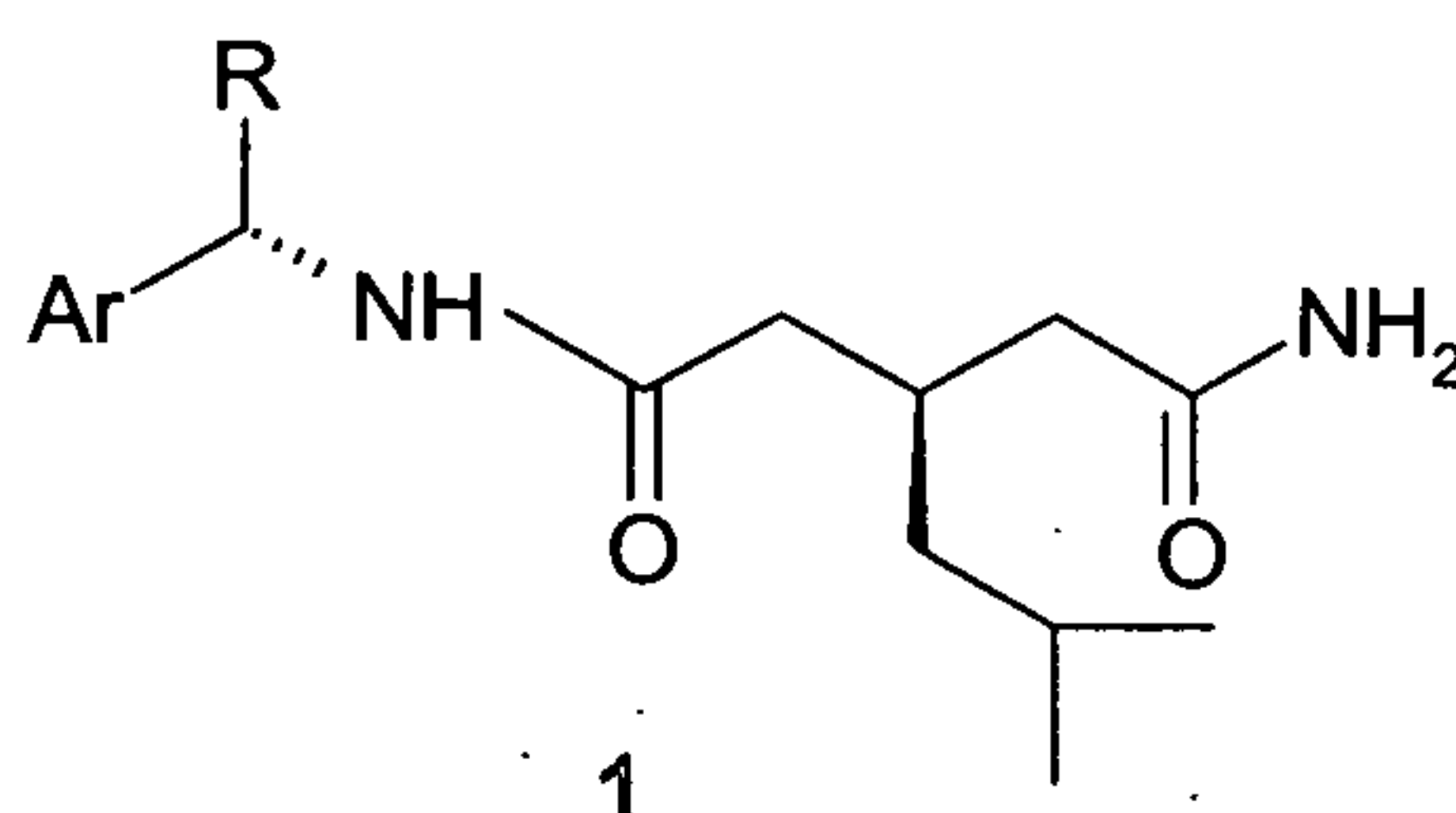


with an acid and a phenol of formula 2;



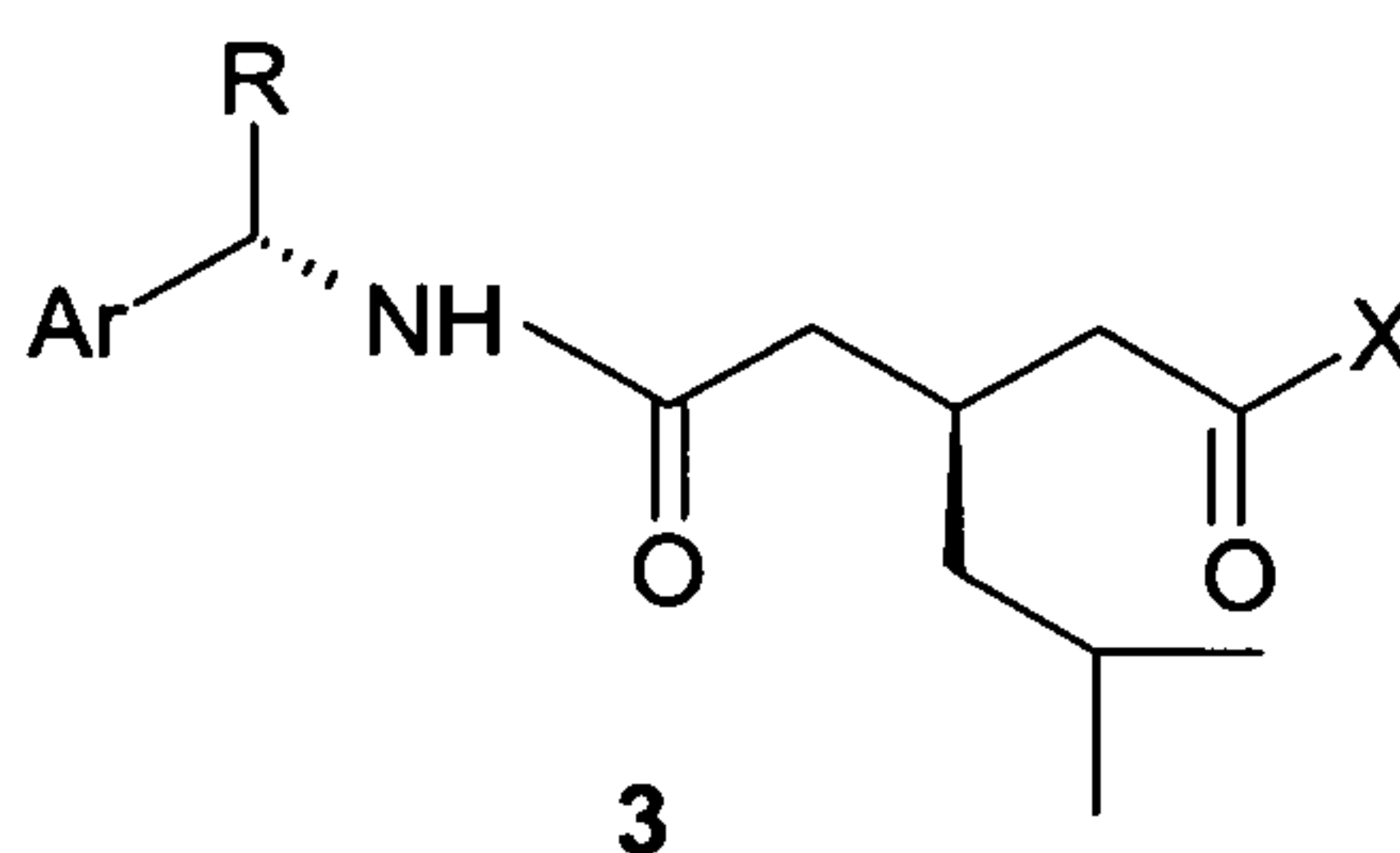
; and (b) recovering (S)-Pregabalin, wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, R₁ is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl, R₂ is H, alkyl, alkoxy, halogen, or mercapto, R₄ is H, alkyl or halogen, and the ring Z is a 5-8-membered ring containing carbon and optionally at least one nitrogen, sulfur or oxygen.

The compound of formula 4 may be prepared by a process comprising combining a compound of formula 1

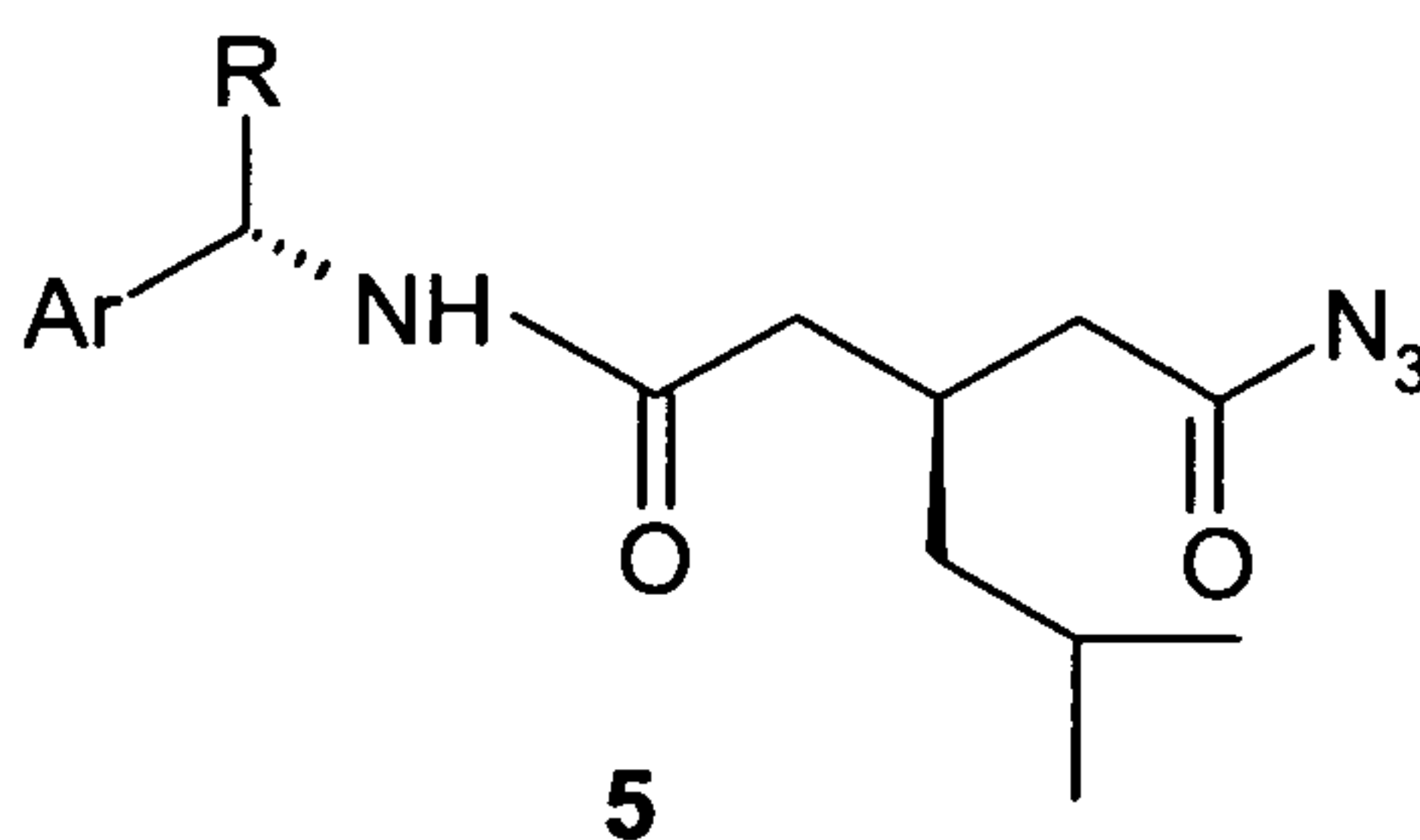


with bromine and a base in a straight or branched alkyl alcohol.

Alternatively, the compound of formula 4 may be prepared by a process comprising:
(i) combining a compound of formula 3



with an azide nucleophile to obtain a compound of formula 5,



and (ii) combining the compound of formula 5 with an alcohol to obtain the compound of formula 4, wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, and X is a leaving group.

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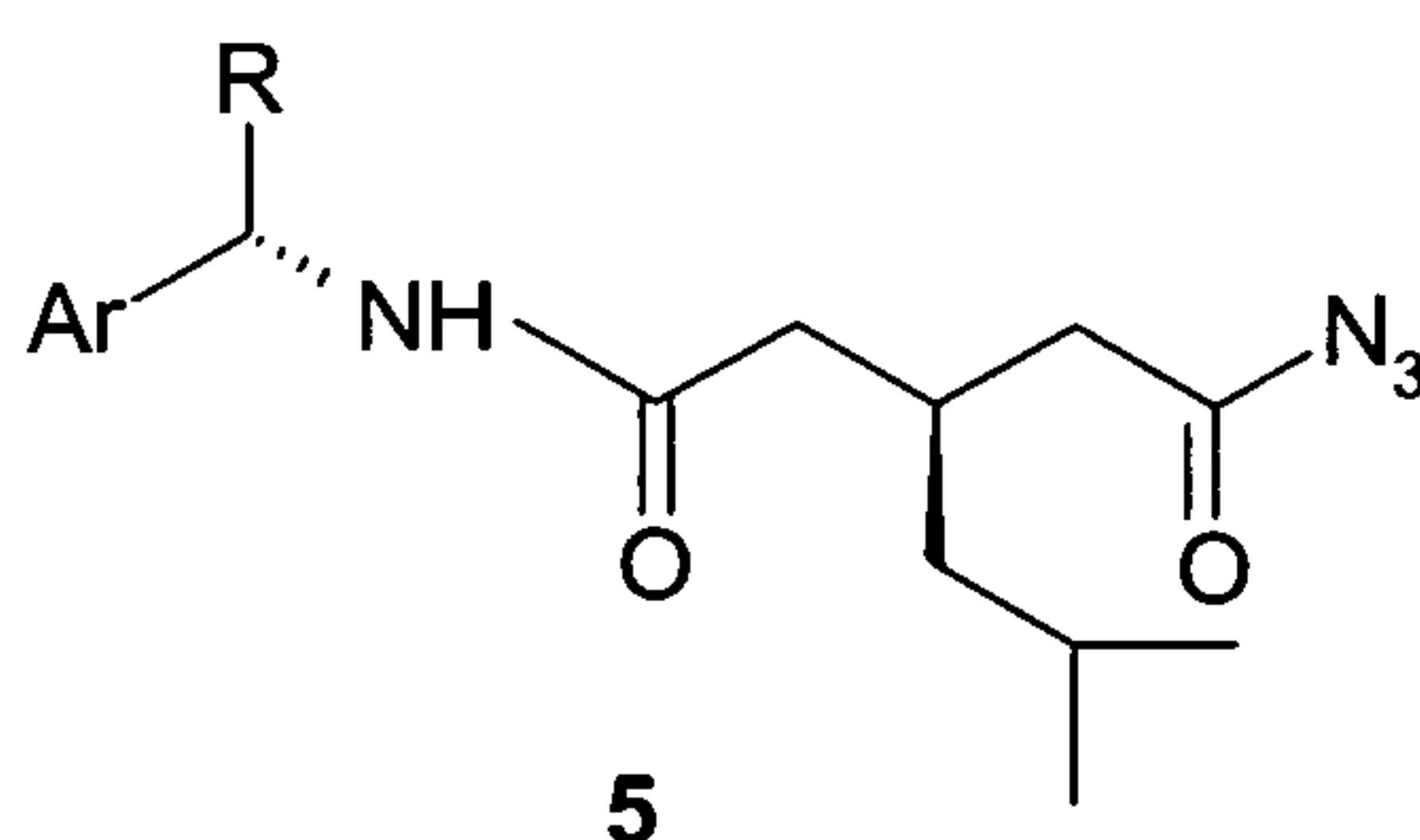
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates an infrared spectrum of the compound of formula 5, wherein Ar is phenyl and R is ethyl.

DETAILED DESCRIPTION OF THE INVENTION

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In one embodiment, the invention encompasses an azide of the following formula 5

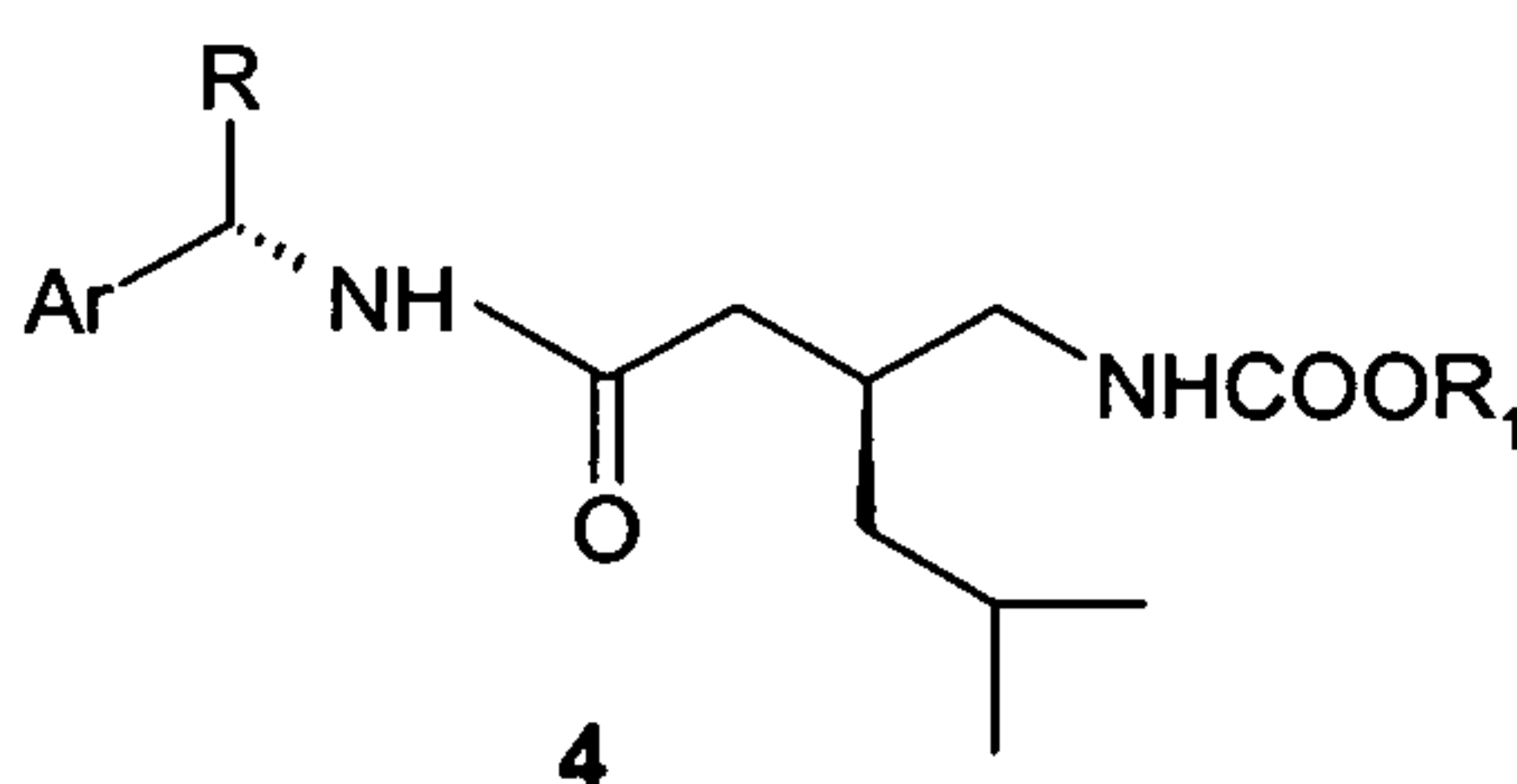


wherein Ar is a C₆₋₁₀ aromatic group, and R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid. Preferably, Ar is phenyl and R is ethyl.

15

The azide of formula 5 is used as an intermediate in the synthesis of (S)-Pregabalin as will be demonstrated below.

The invention also encompasses asymmetric syntheses of (S)-Pregabalin via a chiral intermediate of the following formula 4



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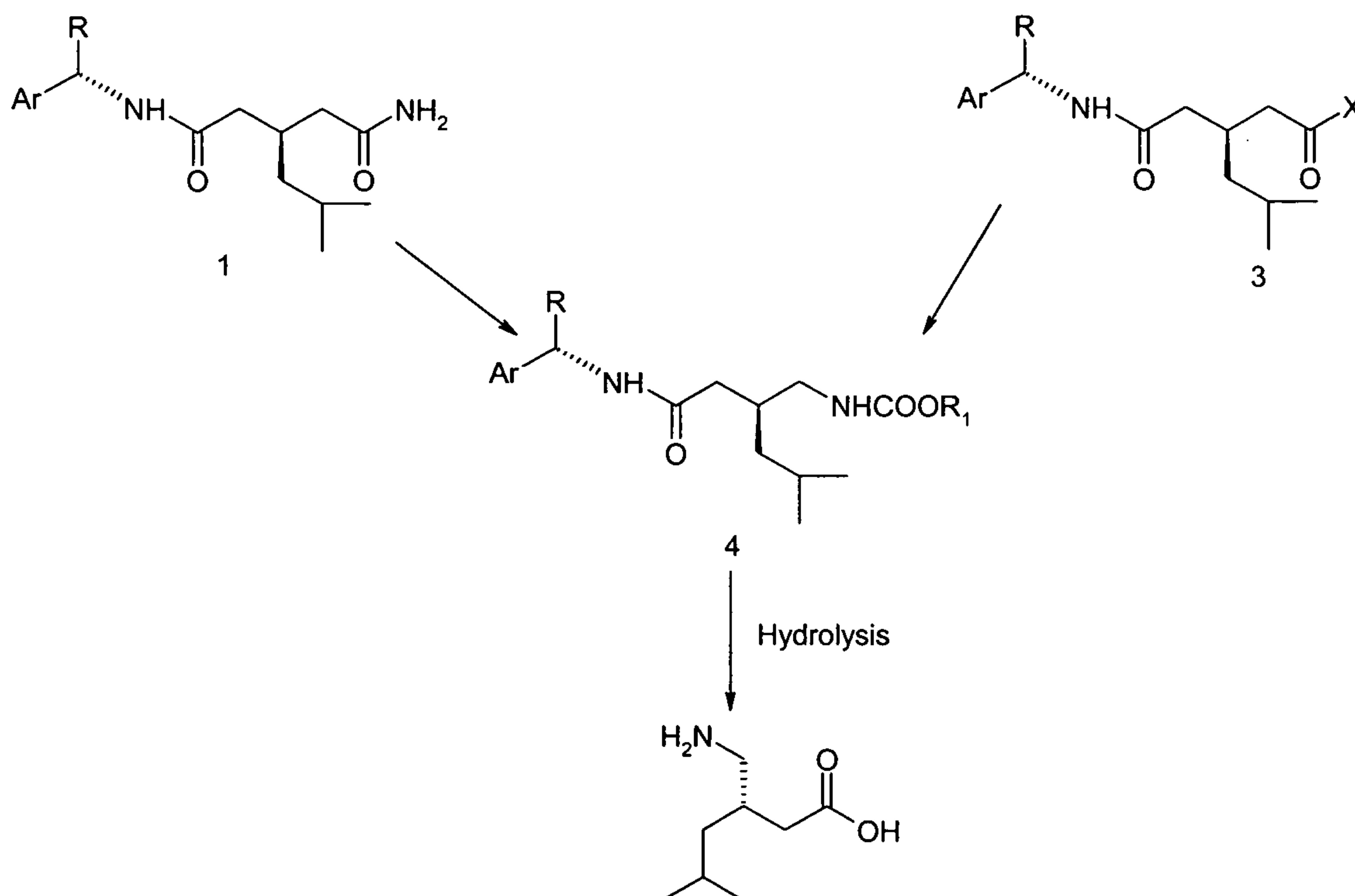
wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, and R₁ is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl.

These asymmetric syntheses produce (S)-Pregabalin with relatively high enantiomeric and chemical purity, while avoiding an optical resolution step. These asymmetric syntheses are also economical and easy to conduct, and thus suitable for large scale production. These

25

asymmetric syntheses can be illustrated by the following Scheme 1.

Scheme 1.



wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or
 5 carboxylic acid, R₁ is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl, and X is
 a leaving group.

Preferably, the C₆₋₁₀ aromatic group is naphthyl, phenyl, substituted phenyl, or
 substituted naphthyl, more preferably phenyl. Preferably, the substituted phenyl is a phenyl
 group substituted with at least one of alkoxy, halogen, alkyl, carboxylic acid, or ester. A
 10 preferred alkoxy phenyl is methoxyphenyl. Preferred halogenated phenyls are
 chlorobenzene, bromobenzene, and fluorobenzene. Preferred alkylated phenyls are either
 toluene or ethylbenzene. Preferably, the carboxylic acid substituent is -COOH, -CH₂COOH, -
 CH(CH₃)COOH or -C(CH₃)₂COOH. Preferably the ester substituent is a methylester,
 ethylester, isopropylester, n-butylester, isobutyl, or t-butyl derivative of one of the above-
 15 listed carboxylic acid substituents. The most preferred C₆₋₁₀ aromatic group is phenyl.

Preferably, the C₁₋₄ alkyl is methyl, ethyl, isopropyl, n-butyl, isobutyl or t-butyl, and
 more preferably methyl.

Preferably, the ester is a C₂₋₄ ester.

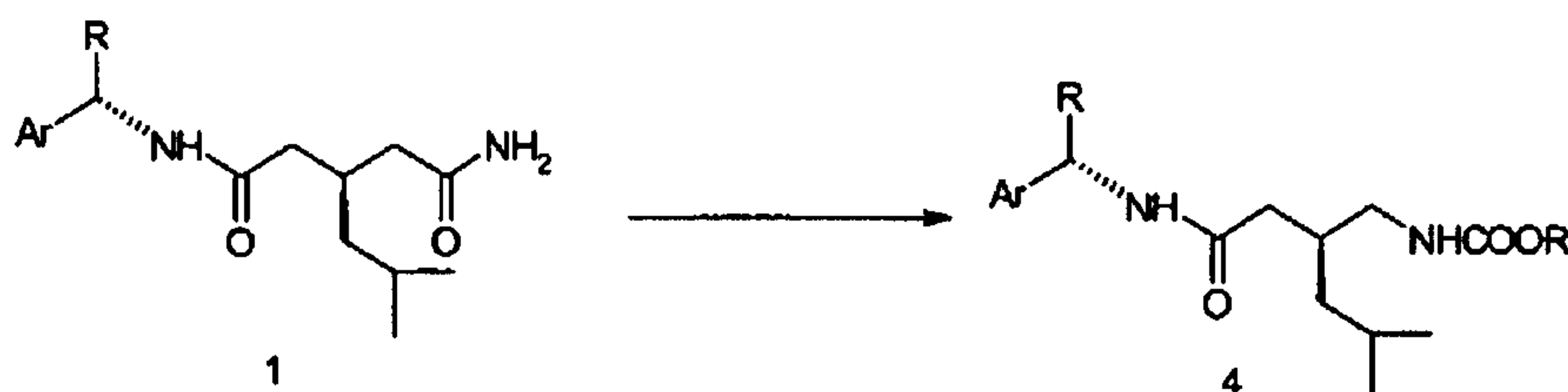
Preferably, the carboxylic acid is a C₁₋₂ carboxylic acid.

Preferably, the straight or branched C₁₋₅ alkyl is methyl.

Preferably, the aralkyl is a C₇₋₁₀ aralkyl, and more preferably benzyl.

Typically, the leaving group is derived from an acid activating agent. The term "acid activating agent" refers to a substance containing a group that activates a carbonyl group, *i.e.*, makes the carbonyl group more susceptible to nucleophilic attack, when attached to it. Preferably, the leaving group is a halogen or a mixed anhydride. Preferably, the halogen is either Cl or Br. Preferably, the mixed anhydride is $-\text{OCOR}_3$, wherein $-\text{OCOR}_3$ is derived from a haloformate, an acid halide, or an anhydride, such as acetic anhydride, di-*t*-butyl dicarbonate (" $(\text{BOC})_2\text{O}$ "), and the like. Preferably, R_3 is an alkyl group.

One synthetic path follows the conversion of compound of formula 1 to the compound of formula 4 by a Hoffman reaction as depicted below



wherein Ar is a C_{6-10} aromatic group, R is a straight or branched C_{1-4} alkyl, ester, or carboxylic acid, and R_1 is a straight or branched C_{1-5} alkyl, aralkyl, or substituted aralkyl.

The compound of formula 1 can be prepared, for example, according to the process disclosed in U.S. Publication No. 2007/0197827 and its international counterpart International Publication No. WO 2007/035890.

The Hoffman reaction comprises combining the compound of formula 1 with bromine and a base in a straight or branched alkyl alcohol, aralkyl alcohol, or substituted aralkyl alcohol to obtain a mixture, and heating the mixture to obtain the compound of formula 4.

Typically, the compound of formula 1 and the alcohol are initially combined to obtain a solution. Preferably, the aralkyl alcohol is a C_{7-10} aralkyl alcohol, and more preferably benzyl alcohol. Preferably, the alcohol is a straight or branched alkyl alcohol. Preferably, the straight or branched alkyl alcohol is methyl, ethyl, isopropyl, *n*-butyl, isobutyl, or *t*-butyl alcohol, and more preferably methanol or ethanol.

Then, the solution is preferably cooled prior to the addition of the base. Preferably, the cooling is to a temperature of about 10°C to about -30°C , and more preferably to about 5°C to about 0°C .

Preferably, the base is either a metal alkoxide or a metal hydroxide. Preferably, the metal alkoxide is a C_{1-4} alkoxide, and more preferably is selected from the group consisting of sodium ethoxide, sodium methoxide, potassium methoxide, potassium ethoxide, and

potassium tert butoxide. Preferably, the metal hydroxide is selected from the group consisting of lithium hydroxide, sodium hydroxide and potassium hydroxide. The more preferred base is either sodium hydroxide or potassium hydroxide

Typically, the addition of the base provides a first mixture. Typically, this mixture is cooled prior to the addition of the bromine because the addition of the bromine causes an exothermic reaction. Preferably, the mixture is cooled to a temperature of about 10°C to about -30°C, and more preferably to about 15°C to about -25°C.

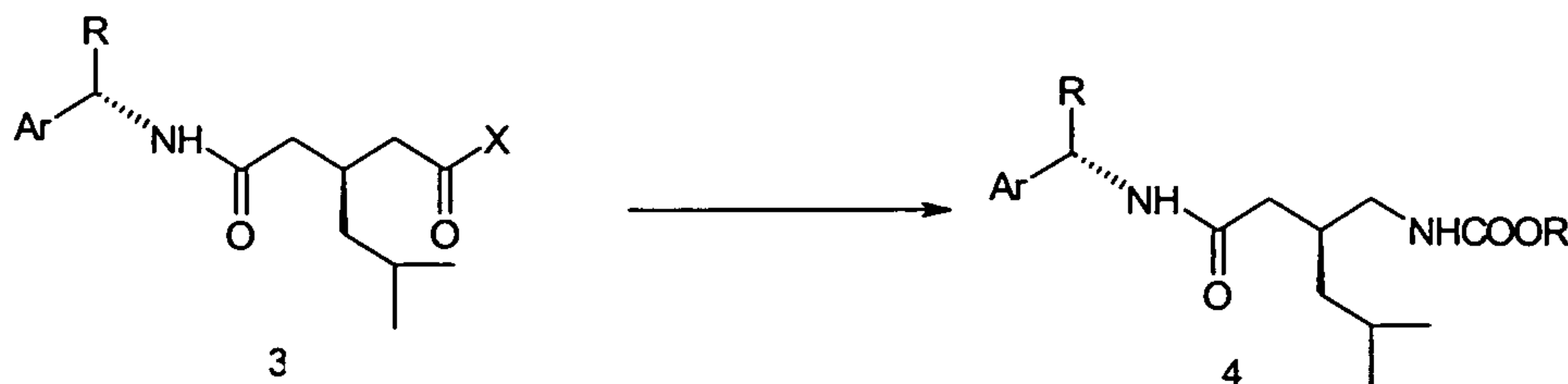
Typically, the addition of the bromine provides a second mixture, which is maintained while cooling as described above before being heated. Preferably, the second mixture is maintained with cooling for about 0.5 hour to about 4 hours, and more preferably for about 1 to about 2 hours.

Preferably, the second mixture is heated to a temperature of about 50°C to about 70°C, and more preferably to a temperature of about 55°C to about 65°C. Usually, the heated mixture is maintained for a period of time, during which the formation of the compound of formula 4 is expected to occur. Preferably, the heated mixture is maintained for about 0.5 hour to about 4 hours, and more preferably for about 1 hour to about 4 hours.

The compound 4 thus obtained may be recovered prior to being hydrolyzed to obtain (S)-Pregabalin. The compound of formula 4 may be recovered, for example, by evaporating the solvent; extracting with a solvent selected from a group consisting of dichloromethane, ethylacetate and toluene; and evaporating the solvent.

The recovered compound of formula 4 may have a purity of at least about 80% area by HPLC, preferably about 90% to about 100% area by HPLC, and more preferably about 92% to about 100% area by HPLC.

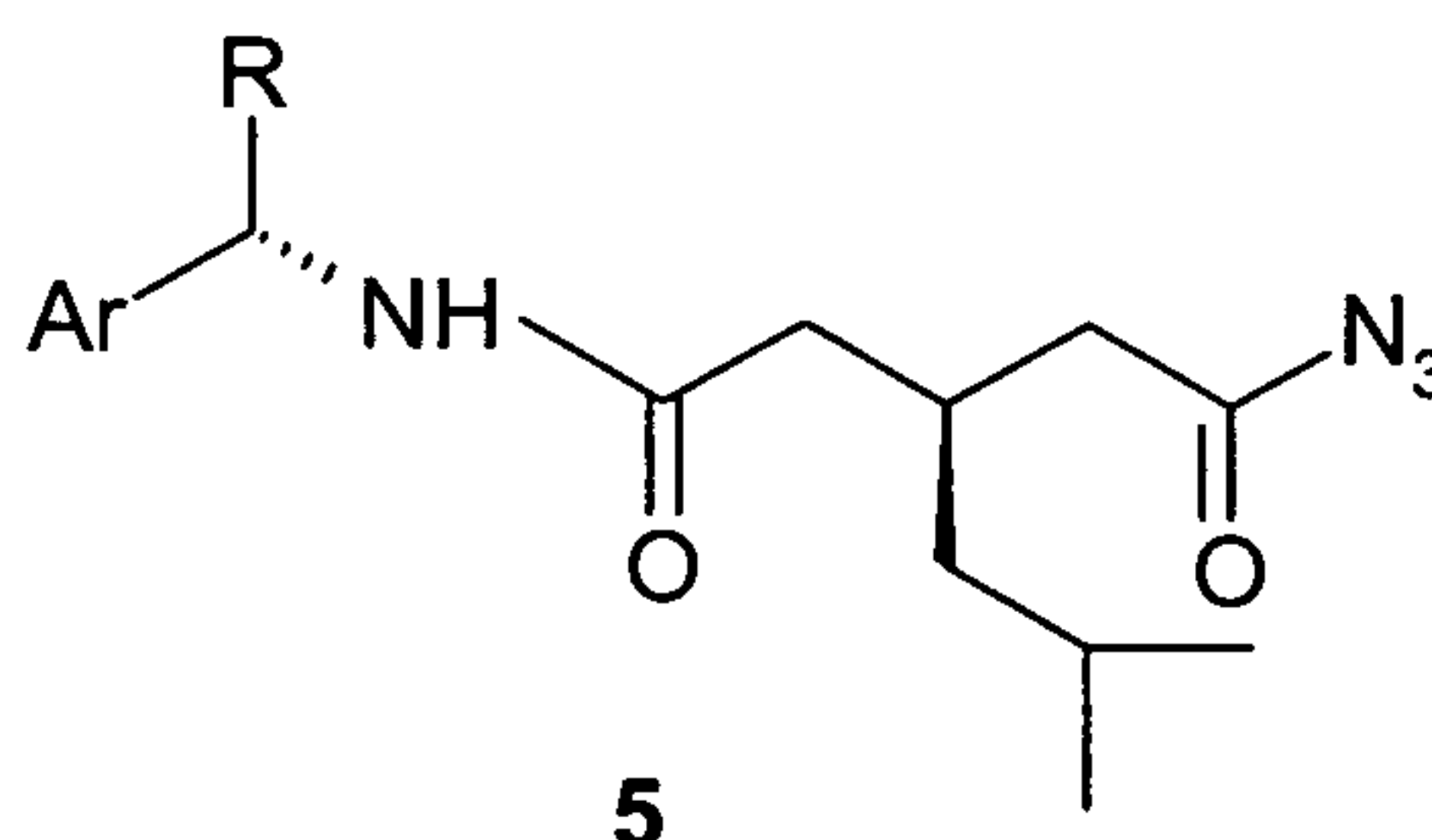
The second synthetic path follows the conversion of compound of formula 3 to the compound of formula 4:



wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, R₁ is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl, and X is a leaving group as described above.

The compound of formula 3 can be prepared, for example, according to the process disclosed in U.S. Publication No. 2007/0197827 and its international counterpart International Publication No. WO 2007/035890. The compound of formula 3 can be recovered prior to being converted to the compound of formula 4 or can be converted in-situ to the compound of formula 4.

The conversion comprises combining the compound of formula 3 with an azide nucleophile to obtain the compound of formula 5,



and combining the compound of formula 5 with an alcohol to obtain the compound of formula 4.

Typically, the azide nucleophile is a substance containing a nucleophilic "N₃" group. Examples of such substances include, but are not limited to, NaN₃, diphenylphosphoryl azide, trialkyl silyl azide, trialkyl tin azide, and like metal azides. More preferably, the azide nucleophile is NaN₃.

The azide nucleophile can be provided in the form of a solid or in an aqueous or organic solution. Typically, the compound of formula 3 is combined with the azide nucleophile at a low temperature. Preferably, the compound of formula 3 is combined with the azide nucleophile at a temperature of about 30°C to about -30°C, and more preferably at about -10°C to about -20°C.

The reaction between the azide nucleophile and the compound of formula 3 typically leads to a slurry. The slurry, usually, further comprises an organic solvent. This organic solvent is either the solvent from the reaction used to produce the compound of formula 3 when the reaction is one-pot, or a new solvent used to dissolve the compound of formula 3 when the reaction begins with a recovered compound of formula 3.

Preferably, the organic solvent is selected from the group consisting of aromatic hydrocarbons, aliphatic hydrocarbons, ethers and ketones. Preferably, the aromatic hydrocarbon is a C₆₋₁₀ aromatic hydrocarbon, and more preferably toluene, xylene or ethyl benzene. Preferably, the aliphatic hydrocarbon is a C₆₋₁₀ aliphatic hydrocarbon, and more preferably either hexane or heptane. Preferably, the ether is a C₃₋₉ ether, and more preferably

diethylether, diisopropylether or t-butylmethyl ether. Preferably, the ketone is a C₃₋₆ ketone, and more preferably acetone, methylethyl ketone or methylisobutyl ketone. The more preferred solvent is acetone or toluene.

5 The above slurry is typically maintained for a sufficient time to provide the compound of formula 5. Preferably, the slurry is maintained for about 0.5 hour to about 4 hours, more preferably for about 0.5 hour to about 2 hours, and most preferably for about 1 hour to about 2 hours.

The slurry of the compound of formula 5 may be used to synthesize the compound of formula 4 directly, without isolation of the compound of formula 5 from the slurry.

10 Alternatively, the compound of formula 5 is separated from the slurry by addition of water and an organic solvent prior to its use in the synthesis of the compound of formula 4. Preferably, the organic solvent is the same as described above. The water dissolves the inorganic salts while the compound of formula 5 is transferred into the organic phase. Optionally, the aqueous phase can be further extracted with the organic solvent to increase
15 the yield of the compound of formula 5.

The compound of formula 5 can be characterized by an infrared spectrum having an azide peak at 2134 cm⁻¹. An infrared spectrum for a representative compound of formula 5, wherein Ar is phenyl and R is ethyl, is illustrated in Figure 1.

20 The organic phase having the compound of formula 5 is then combined with an alcohol to obtain the compound of formula 4. Preferably, the organic phase is added slowly to the alcohol, more preferably the organic phase is added over a period of about 0.5 to about 10 hours, and most preferably over a period of about 0.5 hour to about 4 hours. Preferably, the combination is done while heating the alcohol, more preferably while heating the alcohol to a temperature of about 50°C to about 110°C, and most preferably while heating the alcohol
25 to a temperature of about 50°C to about 70°C. Preferably, the alcohol is in the form of a solution of the alcohol in an organic solvent. Preferably, the solvent is the same as mentioned above. Preferably, the alcohol is a C₁₋₅ alcohol, and more preferably methanol, ethanol, isopropanol, t-butanol, n-butanol, isobutanol, or neopentylalcohol. More preferably, the alcohol is either methanol or ethanol. The heated combination is then maintained, preferably,
30 for about 0.5 to about 6 hours to provide the compound of formula 4. More preferably, the heated combination is maintained for about 0.5 to about 4 hours, and most preferably for about 2 to about 4 hours, to provide the compound of formula 4.

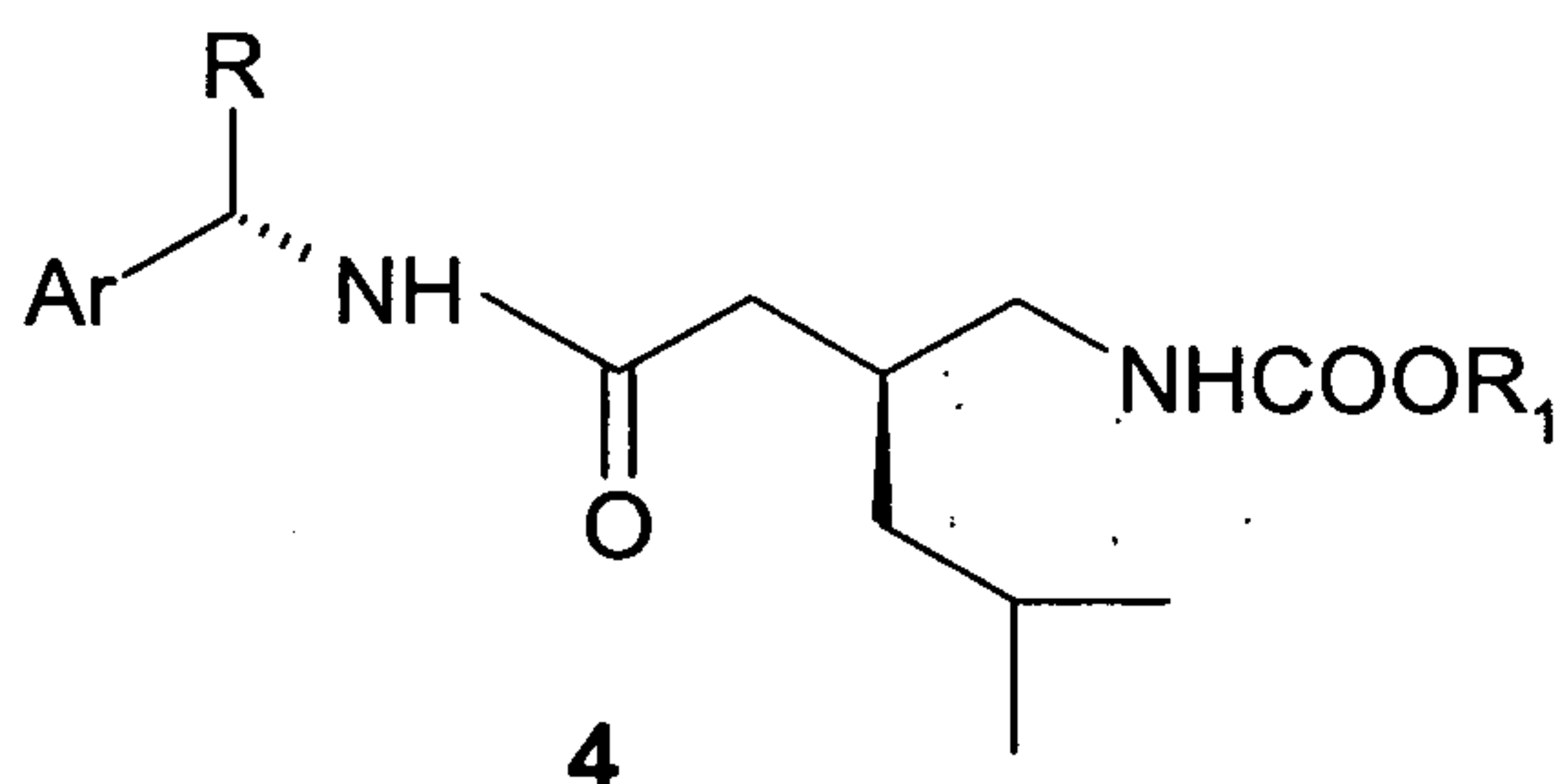
The compound of formula 4 may be recovered prior to being hydrolyzed to obtain (S)-Pregabalin. The compound of formula 4 may be recovered, for example, by evaporating the solvents.

The recovered compound of formula 4 may have a purity of at least about 85% area by HPLC, preferably about 92% to about 100% area by HPLC, and more preferably about 95% to about 100% area by HPLC.

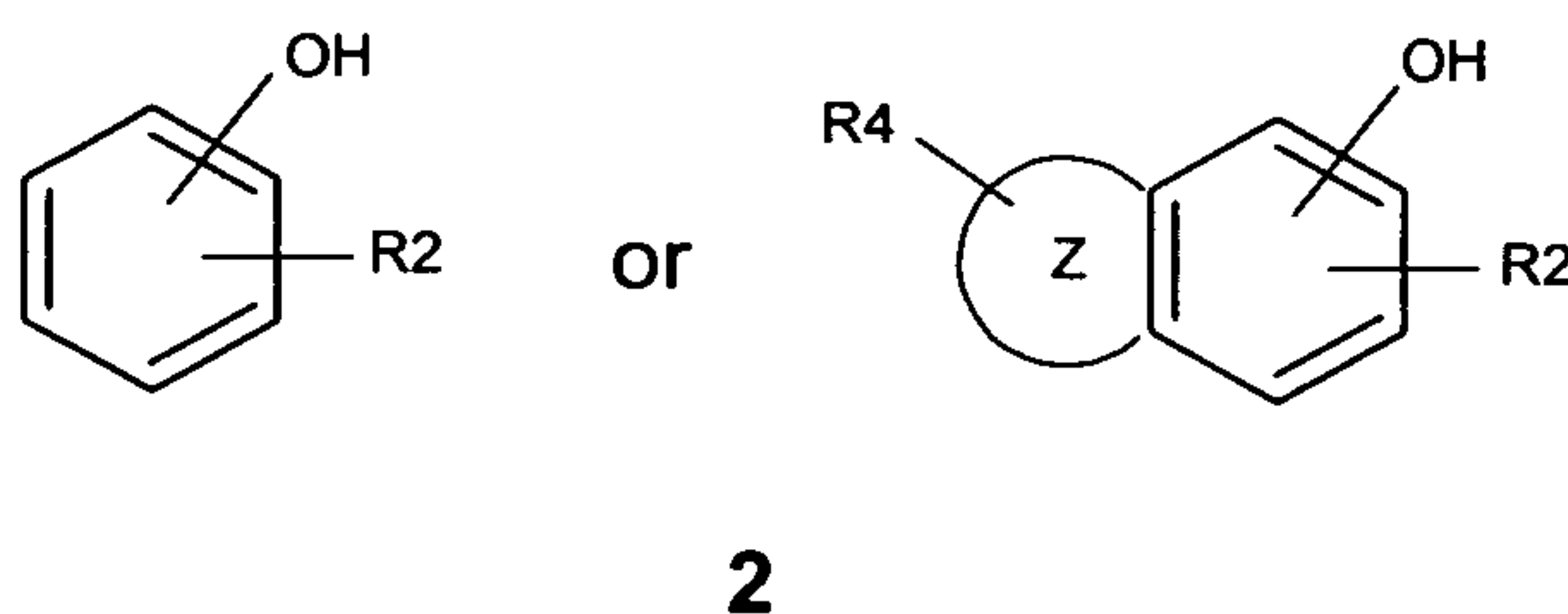
The compound of formula 4 can then be converted to (S)-Pregabalin, for example, by the process disclosed in U.S. Publication No. 2007/0197827 and its international counterpart International Publication No. WO 2007/035890.

Typically, the conversion of the compound of formula 4 to (S)-Pregabalin is done by hydrolyzing the amide and amine group. The hydrolysis of the compound of formula 4 to give (S)-pregabalin can be done without isolating the compound of formula 4, *i.e.*, a one-pot process.

The hydrolysis comprises combining the compound of formula 4,



with an acid and a phenol of formula 2;



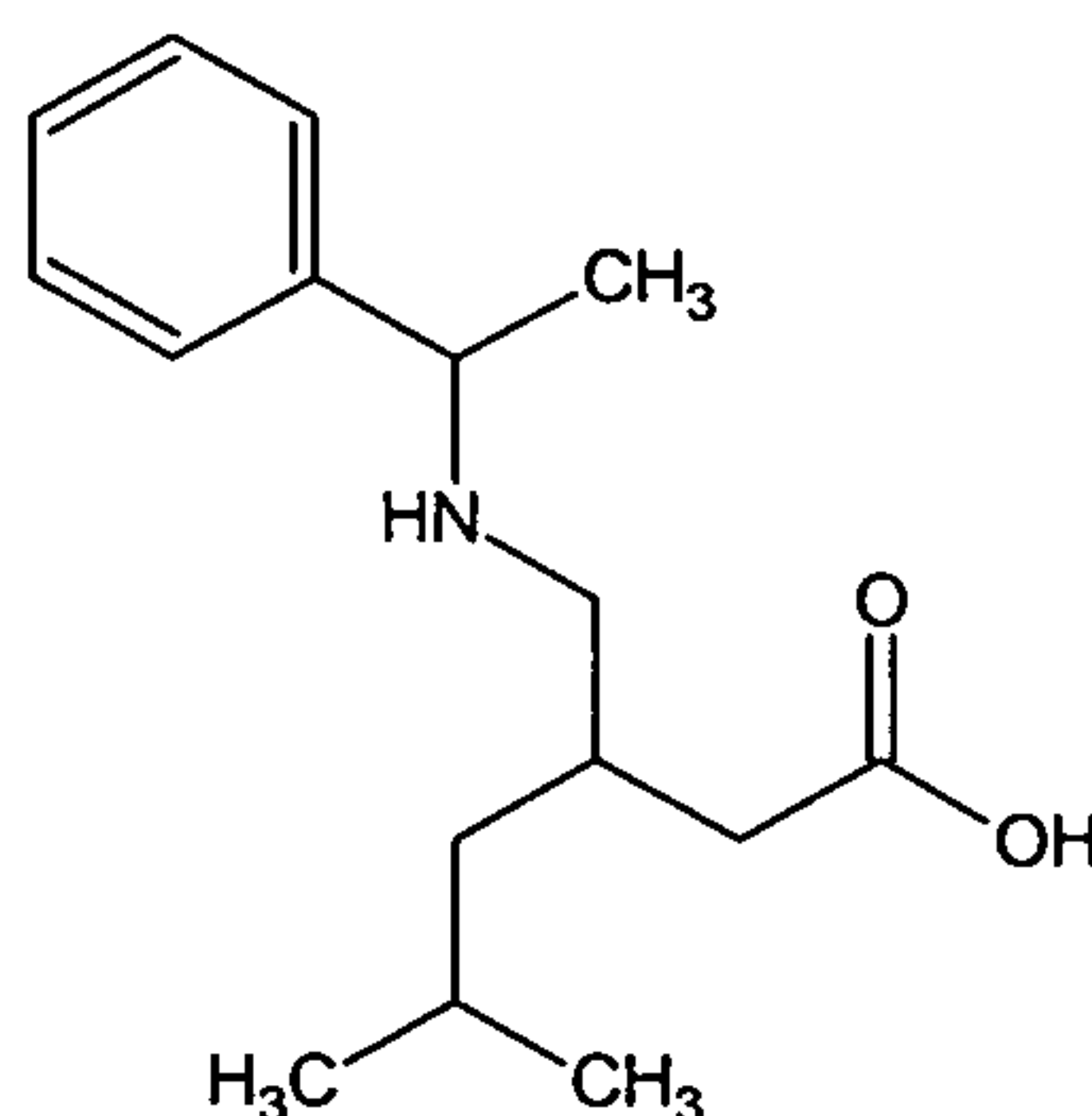
; and recovering the (S)-Pregabalin thus obtained, wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, R₁ is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl, R₂ is H, alkyl, alkoxy, halogen, or mercapto, R₄ is H, alkyl or halogen, and the ring Z is a 5-8-membered ring containing carbon and optionally at least one nitrogen, sulfur or oxygen.

The preferred alkyl group is methyl or ethyl. The preferred halogen is either Cl or Br. The most preferred phenol is unsubstituted phenol, *i.e.*, C₆H₅OH.

Preferably, R₂ is alkyl, alkoxy, or halogen. Preferably, the alkyl is methyl, ethyl, or propyl. Preferably, the alkoxy is methoxy, or ethoxy. Preferably, the halogen is chlorine, bromine, or iodine.

When the hydrolysis is done in one-pot, the phenol and the acid are mixed with a mixture having the compound of formula 4. Optionally, the mixture having the compound of formula 4 can be cooled prior to the addition of the acid and phenol. Preferably, the mixture is cooled to a temperature of about 50°C to about 0°C, and more preferably to about 30°C to about 25°C.

The combination of the compound of formula 4, the phenol, and the acid provides a second mixture, wherein the phenol preferably plays the role of a scavenger of impurities such as N-benzylated pregabalin of the following formula.



Preferably, the acid is a strong mineral acid, and more preferably hydrochloric acid, sulfuric acid, or poly phosphoric acid. As used herein, unless otherwise defined, a “strong” mineral acid is one that, when dissolved in aqueous media, produces a pH of less than about 1.5.

The second mixture also comprises an inorganic salt, such as sodium chloride, potassium chloride, magnesium sulfate, and sodium sulfate. The use of such a salt allows one to heat the second mixture to high temperatures, leading to a shorter reaction time. Preferably, second mixture is heated to a temperature of about 60°C to about 130°C, and more preferably about 80°C to about 110°C.

Typically, the second mixture is heated for a period of time sufficient to obtain an (S)-pregabalin salt. Preferably, the mixture is heated for about 5 to about 24 hours.

The reaction time is also related to the kind of mineral acid that is used. Preferably, the mixture is heated for about 18 to about 24 hours when the mineral acid is hydrochloric acid and for about 5 to about 10 hours when the mineral acid is sulfuric acid.

Typically, the acid protonates the amine group of (S)-Pregabalin, thus providing an acid salt of (S)-Pregabalin, from which free (S)-Pregabalin is recovered by extractions and reaction with a base. The recovery typically comprises: adding an inorganic base to the second mixture; extracting the acid salt of (S)-Pregabalin from the mixture with a C₄₋₈ alcohol; adjusting the pH of the extract to about 4 to about 7 and thereby precipitate (S)-Pregabalin. The precipitated (S)-Pregabalin is then collected. Preferably, the inorganic base is added to the second mixture in an amount sufficient to adjust the pH of the combination to about 1 to about 3. Preferably, the inorganic base is sodium hydroxide. Preferably, the pH of the extract is adjusted to about 4 to about 7 by adding a base. Preferably, the base is an organic base and more preferably tributylamine. Preferably, the C₄₋₈ alcohol is iso-butanol.

The (S)-Pregabalin obtained by the above-described process has a purity of at least about 80% area by HPLC, preferably at least about 98% area by HPLC, and more preferably about 99% to about 100% area by HPLC. The (S)-Pregabalin obtained by the above-described process also has less than 0.15%, preferably, less than 0.1%, more preferably less than 0.06%, even more preferably less than 0.02% and most preferably less than 0.01% area by HPLC of the N-benzylated pregabalin impurity.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

Infrared Spectroscopy:

Infrared spectroscopy of the compound of formula 5 was performed with a Nicolet Avatar 370 DTGS system over a range of 4000-400 cm⁻¹, using KBR pellets.

Example 1: Preparation of (3S)-5-methyl-3-(2-oxo-2-[(1S)-1-phenylethyl]amino) ethyl) hexanoic acid (the precursor to compound 1)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with toluene (400 ml), (S) (-)-phenylethylamine (142.35 g, 1.1764 mole), and 4-dimethylaminopyridine (0.7176 g, 0.0059 mole). The mixture was cooled to a temperature of -10°C to -15°C, followed by addition of a solution of 3-isobutyl glutaric anhydride (100 g, 0.59 mole) in toluene (100 ml), over a period of 45-60

minutes, and stirring for additional 1.5-2 hours, at a temperature of -10°C to -15°C . The mixture was then extracted with 10% aqueous solution of NaOH (500 ml), and the aqueous phase was washed with toluene (1x250 ml). The pH of the aqueous phase was adjusted to 2-2.5 by adding a solution of hydrochloric acid (1-12N). The aqueous phase was further
5 extracted with toluene (1x 800 ml) at a temperature of 70-80°C. The toluene layer was washed with 10% sodium chloride solution {700ml) at a temperature of 70-80°C followed by crystallization to obtain 125 g (73.0% yield) of a white solid of (3S)-5-methyl-3-(2-oxo-2-
{[(1S)-1-phenylethyl]amino}ethyl) hexanoic acid with an optical purity of 99.75% area, as measured by chiral HPLC.

10

Example 2: Preparation of (3S)-5-methyl-3-(2-oxo-2 {[(1S)-1-phenylethyl]amino} ethyl) hexanoic acid (the precursor to compound 1)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with toluene (800 ml), (S) (-)-phenylethylamine
15 (284.7 g, 2.353 mole), and 4-dimethylaminopyridine (1.435 g, 0.0118mole). The mixture was cooled to a temperature of -10°C to -15°C, followed by addition of a solution of 3-isobutyl glutaric anhydride (200 g, 1.176 mole) in toluene (200 ml), over a period of 45-60 minutes, and stirring for additional 1.5-2 hours, at a temperature of -10°C to -15°C . The mixture was then extracted with 10% aqueous solution of NaOH (1000 ml), and the aqueous phase was
20 washed with toluene (1x500 ml). The pH of the aqueous phase was adjusted to 2-2.5 by adding a solution of hydrochloric acid (1-12N). The aqueous phase was further extracted with toluene (1x 1600 ml) at a temperature of 70-80°C. The toluene layer was washed with 10% sodium chloride solution {1400ml) at a temperature of 70-80°C followed by crystallization to get 257 g (75.0% yield) of a white solid of (3S)-5-methyl-3-(2-oxo-2-
25 {[(1S)-1-phenylethyl]amino}ethyl) hexanoic acid with an optical purity of 99.8% area , as measured by chiral HPLC.

Example 3: Preparation of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl)amide (compound 3)

30 A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methylene dichloride (1000 ml), (3S)-5-methyl-3-(2-oxo-2 {[(1S)-1-phenylethyl]amino} ethyl) hexanoic acid (200 g, 0.687 mole), and with triethylamine (7.65g, 0.756 mole), and cooled to 0°-5°C followed by addition of ethyl chloroformate (90 g, 0.825 mole). The mixture was stirred for 1-2 hours at a

temperature of 20°C to 25°C, followed by quenching with 25% aqueous ammonia (1000 ml). The resulted slurry was filtered and washed with water and dried to get 140 g (70.0% yield) of a white solid of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl)amide of formula 3, with a purity of 95% area, as measured by HPLC.

5

Example 4: Preparation of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl)amide (compound 1)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methylene dichloride (500 ml), (3S)-5-methyl-3-(2-oxo-2{[(1S)-1-phenylethyl]amino} ethyl)hexanoic acid (100 g, 0.343 mole), and with triethylamine (41.67g, 0.412mole), and cooled to -15°C to -20°C followed by addition of ethyl chloroformate (39.1 g, 0.36 mole). The mixture was stirred for 1-2 hours at a temperature of -15°C to -20°C, followed by quenching over a solution of 20% aqueous ammonia (280ml). The dichloromethane was distilled out from the mass followed by filtering the resulted slurry, washed with water and dried to get 87 g (87% yield) of a white solid of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl)amide of formula 1, with a purity of 98% area, as measured by HPLC.

Example 5: Preparation of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl) amide (compound 1)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methylene dichloride (125 ml), (3S)-5-methyl-3-(2-oxo-2{[(1S)-1-phenylethyl]amino} ethyl) hexanoic acid (25 g, 0.086 mole), triethyl amine (10.43 g, 0.129 mole), and cooled to 0°-5°C followed by addition of pivaloyl chloride (12.43 g, 0.103 mole). The mixture was stirred for 1-2 hours at a temperature of 20°C to 25°C, followed by quenching with 20% aqueous ammonia (250 ml). The resulted slurry was filtered and washed with water and dried to get 15.2 g (61% yield) of a white solid of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl)amide of formula 1, with a purity of 95% area, as measured by HPLC.

30

Example 6: Preparation of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl) amide (compound 1)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with acetone (125 ml), (3S)-5-methyl-3-(2-oxo-

2 {[(1S)-1-phenylethyl]amino}ethyl) hexanoic acid (25 g, 0.086 mole), triethyl amine (10.43 g, 0.129 mole), and cooled to 0-5°C followed by addition of pivaloyl chloride (12.43 g, 0.103 mole). The mixture was stirred for 1-2 hours at a temperature of 20°C to 25°C, followed by quenching with 20% aqueous ammonia (250 ml). The resulted slurry was
5 filtered and washed with water and dried to get 10.68 g (43.4% yield) of a white solid of (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylethyl)amide of formula 1, with a purity of 95.4% area, as measured by HPLC.

Example 7: Preparation of {(S)-4-methyl-2-[(S)-1-phenylethylcarbamoyl]-methyl]pentyl} carbamic acid methyl ester (compound 4)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (2000 ml), (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (200g, 0.689 mole) and cooled to 0° to 5°C followed by addition of sodium methoxide (149 g, 2.758 mole). The reaction mass was cooled to -15 to -25°C followed by addition of bromine (165.5 g, 1.034 mole) and stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours. The solvent was then stripped off and water was added to the mass. The resulted slurry was further extracted with toluene, toluene layer washed with brine followed by stripping off the
20 solvent results in 215 g (97% yield) of {(S)-4-methyl-2-[(S)-1-phenylethylcarbamoyl]-methyl]pentyl} carbamic acid methyl ester (4) with a purity of 90.9% area, as measured by HPLC.

Example 8: Preparation of {(S)-4-methyl-2-[(S)-1-phenylethylcarbamoyl]-methyl]pentyl} carbamic acid methyl ester (compound 4)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (1000ml), (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (50g, 0.1724 mole) and cooled to 0° to 5°C followed by addition of sodium hydroxide (27.58 g, 0.6896 mole). The reaction mass was cooled to -15 to -25°C followed by addition of bromine (41.38 g, 0.2586 mole) and stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours. The solvent was then stripped off and water was added to the mass. The resulted slurry was further extracted with toluene, toluene layer washed with brine followed by stripping off the

solvent results in 53 g (96% yield) of {(S)-4-methyl-2-[(S)-1-phenylethylcarbamoyl]-methyl]pentyl}carbamic acid methyl ester (4) with a purity of 92.89% area, as measured by HPLC.

5 Example 9: Preparation of {(S)-4-methyl-2-[(S)-1-phenylethylcarbamoyl]-methyl]pentyl}carbamic acid methyl ester (compound 4)

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with acetone (25 ml), (3S)-5-methyl-3-(2-oxo-2{[(1S)-1-phenylethyl]amino} ethyl) hexanoic acid (5 g, 0.0172 mole), and with
10 triethylamine (2.17g, 0.0215 mole), and cooled to -10° to -20°C followed by addition of solution of ethyl chloroformate (2.05 g, 0.0189 mole in 5 ml acetone). The mixture was stirred for 1 hour at a temperature of -10° to -20°C, followed by addition of solution of sodium azide (2.8g, 0.0429 mole in water). The resulted slurry was maintained for 1 hour at -10° to -20°C, quenched over ice water followed by extracting the mass with sufficient
15 amount of toluene. The toluene layer was slowly added over a refluxing mixture of toluene and methyl alcohol, followed by stirring for 2 to 4 hours. The stripping off the solvent results in 4.95 g (89.7% yield) of {(S)-4-methyl-2-[(S)-1-phenylethylcarbamoyl]-methyl]pentylcarbamic acid methyl ester (120) with a purity of 97.4% area, as measured by HPLC.

20

Example 10: Preparation of (S)-Pregabalin

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (2000 ml), (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (200g,
25 0.689 mole) and cooled to 0° to 5°C followed by addition of sodium methoxide (149 g, 2.758 mole). The reaction mass was cooled to -15 to -25°C followed by addition of bromine (165.5 g, 1.034 mole) and stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours. The solvent was then stripped off and water was added to the mass. The resulted slurry was
30 further extracted with toluene, toluene layer washed with brine followed by stripping off the solvent. 4N hydrochloric acid (2580 ml), phenol (10.72 g, 0.114 mole), sodium chloride (78.15 g, 1.342 mole) was added to the mass and was heated to 105°-110°C for 15-24 hours, and then cooled to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was

then extracted with 600ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount sufficient to provide a pH of 4. The (S)-Pregabalin was precipitated, filtered, and washed with 100ml of iso-butanol which on crystallization from isobutanol water mixture results in (S)-Pregabalin as white crystals in a 56% yield. Purity: 99.85% area
5 by HPLC. N-benzylated pregabalin: 0.01% area by HPLC.

Example 11: Preparation of (S)-Pregabalin

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (500 ml), (R)-3-
10 isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (25g, 0.086 mole) and cooled to 0° to 5°C followed by addition of sodium hydroxide (13.79 g, 0.3448 mole). The reaction mass was cooled to -15 to -25°C followed by addition of bromine (20.69 g, 0.129 mole) and stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours.
15 The solvent was then stripped off and water was added to the mass. The resulted slurry was further extracted with toluene, toluene layer washed with brine followed by stripping off the solvent. 4N hydrochloric acid (300 ml), phenol (1.1 g, 0.0117 mole), sodium chloride (16.04 g, 0.2741 mole) was added to the mass and was heated to 105°-110°C for 15-24 hours, and then cooled to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium
20 hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 600ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount sufficient to provide a pH of 4. The (S)-Pregabalin was precipitated, filtered, and washed with 100ml of iso-butanol which on crystallization from isobutanol water mixture results in (S)-Pregabalin as white crystals in 52.7% yield. Purity: 99.95% area
25 by HPLC. N-benzylated pregabalin: 0.02% area by HPLC.

Example 12: Preparation of (S)-Pregabalin

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (500 ml), (R)-3-
30 isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (25g, 0.086 mole) and cooled to 0° to 5°C followed by addition of sodium hydroxide (13.79 g, 0.3448 mole). The reaction mass was cooled to -15 to -25°C followed by addition of bromine (20.69 g, 0.129 mole) and stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours.

The solvent was then stripped off followed by addition of 4N hydrochloric acid (300 ml), phenol (1.83 g, 0.0194 mole), sodium chloride (16.04 g, 0.2741 mole) and was heated to 105°-115°C for 15-24 hours, and then cooled to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 150ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount sufficient to provide a pH of 4. The (S)-Pregabalin was precipitated, filtered, and washed with 100ml of iso-butanol which on crystallization from isobutanol water mixture results into (S)-Pregabalin as white crystals in a 53.86% yield. Purity: 99.94% area by HPLC. N-benzylated pregabalin: 0.01% area by HPLC.

Example 13: Preparation of (S)-Pregabalin

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (2000 ml), (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (200g, 0.689 mole) and cooled to 0° to 5°C, followed by addition of sodium methoxide (149 g, 2.758 mole). The reaction mass was cooled to -15 to -25°C, followed by addition of bromine (165.5 g, 1.034 mole) and was stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours. The solvent was stripped off and then 4N hydrochloric acid (2580 ml), phenol (10.72 g, 0.114 mole), and sodium chloride (78.15 g, 1.342 mole) were added to the mass, followed by heating to 105°-110°C for 15-24 hours, and then cooling to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 600ml of iso-butanol, and the organic layer was separated. Bu₃N was added in an amount sufficient to provide a pH of 4. The crude (S)-Pregabalin was precipitated, filtered, and washed with 100ml of iso-butanol providing (S)-Pregabalin with purity of 95.87% area by HPLC.

Example 14: Preparation of (S)-Pregabalin

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with acetone (200 ml), (3S)-5-methyl-3-(2-oxo-2-[(1S)-1-phenylethyl]amino} ethyl) hexanoic acid compound (50 g, 0.172 mole), and with triethylamine (21.7g, 0.215 mole), and cooled to -10° to -20°C followed by addition of solution of methyl chloroformate (18.67 g, 0.196 mole in 50 ml acetone). The mixture was

stirred for 1 hour at a temperature of -10° to -20°C, followed by addition of solution of sodium azide (27.92g, 0.429 mole in water). The resulted slurry was maintained for 1 hour at -10° to -20°C, quenched over ice water followed by extracting the mass with sufficient amount of toluene.. The toluene layer was slowly added over a refluxing mixture of toluene and methyl alcohol, followed by stirring for 2 to 4 hours followed by stripping of solvents results into an oily mass. 4N hydrochloric acid (600 ml), phenol (2.42 g, 0.0257 mole), sodium chloride (40.2 g, 0.687 mole) was added to the oily mass and was heated to 105°-110°C for 15-24 hours, and then cooled to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 150 ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount sufficient to provide a pH of 4-4.5. The (S)-Pregabalin was precipitated, filtered, and washed with 25ml of iso-butanol which on crystallization from isobutanol water mixture resulted in (S)-Pregabalin as white crystals in a 67% yield. Purity: 99.9% area by HPLC.

Example 15: Preparation of (S)-Pregabalin

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with acetone (200 ml), (3S)-5-methyl-3-(2-oxo-2-[(1S)-1-phenylethyl]amino} ethyl) hexanoic acid (50 g, 0.172 mole), and with triethylamine (21.7g, 0.215 mole), and cooled to -10° to -20°C followed by addition of solution of methyl chloroformate (18.67 g, 0.196 mole in 50 ml acetone). The mixture was stirred for 1 hour at a temperature of -10° to -20°C, followed by addition of solution of sodium azide (27.92 g, 0.429 mole in water). The resulting slurry was maintained for 1 hour at -10° to -20°C, quenched over ice water followed by extracting the mass with sufficient amount of toluene.. The toluene layer was slowly added over a refluxing mixture of toluene and methyl alcohol, followed by stirring for 2 to 4 hours followed addition of 4N hydrochloric acid (600 ml), phenol (2.42 g, 0.0257 mole), sodium chloride (40.2 g, 0.687 mole) was added to the mass and was heated to 105°-110°C for 15-24 hours, and then cooled to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 150 ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount sufficient to provide a pH of 4-4.5. The (S)-Pregabalin was precipitated, filtered, and washed with 25ml of iso-butanol which on crystallization from isobutanol water

mixture results in (S)-Pregabalin as white crystals in a 65% yield. Purity: 99.98% area by HPLC, N-benzylated pregabalin: 0.01% area by HPLC.

Example 16: One pot Preparation of (S)-Pregabalin from (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide

5 A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (2000 ml), (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (50g, 0.172 mole) and cooled to 0° to 5°C followed by addition of sodium methoxide (37.25 g, 10 0.689 mole). The reaction mass was cooled to -15 to -25°C followed by addition of bromine (41.4 g, 0.258 mole) and stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours. The reaction was cooled to 25-30°C followed by addition of 4N hydrochloric acid (600 ml), phenol (2.42 g, 0.026 mole), sodium chloride (10.1g, 0.1724 mole). The mass was heated to 15 105°-110°C for 15-24 hours, and then cooled to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 300 ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount sufficient to provide a pH of -4-5. The (S)-Pregabalin was precipitated, filtered, and washed with 100ml of iso-butanol which on 20 crystallization from isobutanol water mixture results in (S)-Pregabalin as white crystals in a 46% yield. Purity: 100% area by HPLC.

Example 17: One pot Preparation of (S)-Pregabalin from (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide

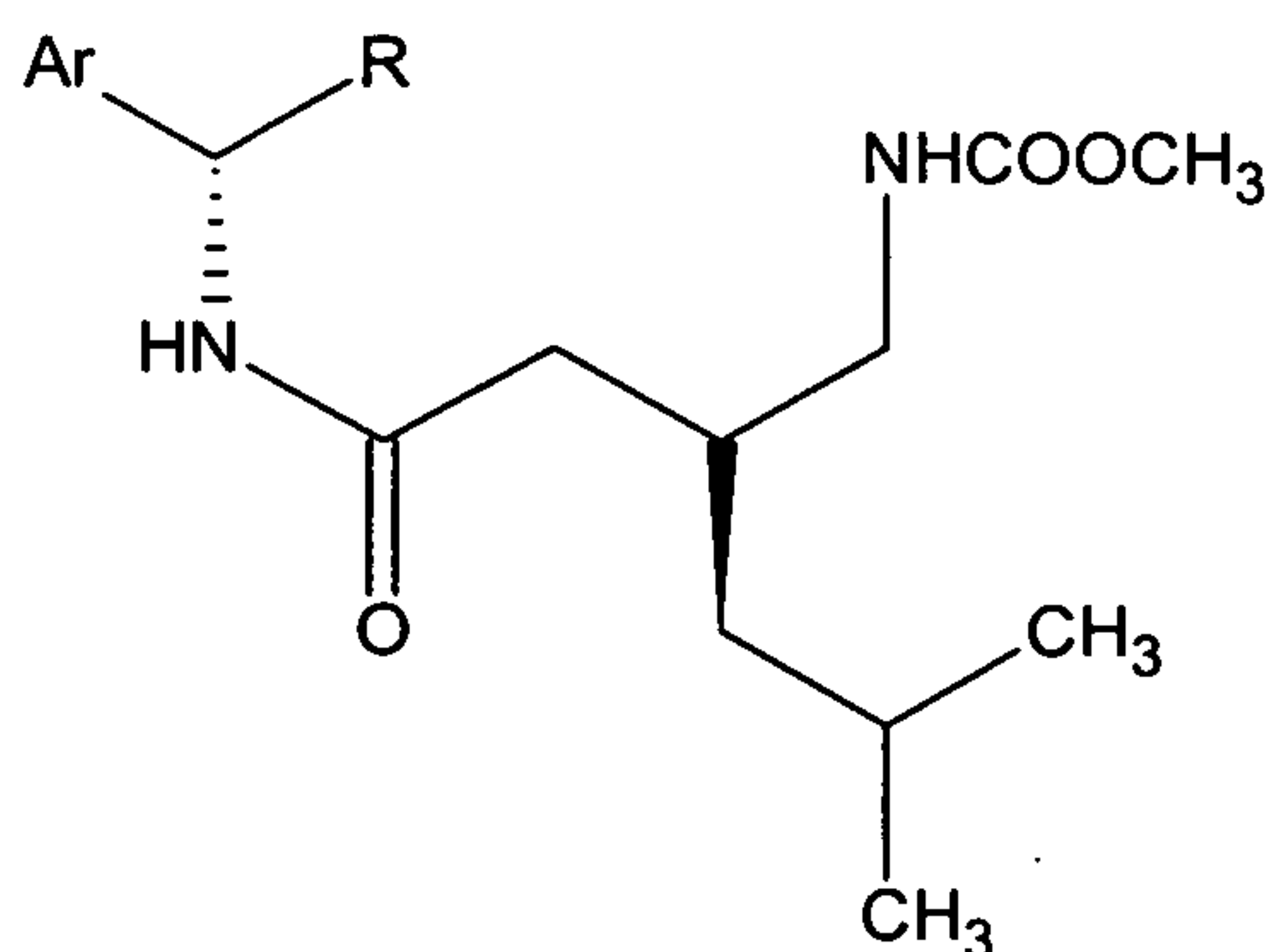
25 A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (1000 ml), (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (50g, 0.172 mole) and cooled to 0° to 5°C followed by addition of sodium hydroxide (27.52 g, 0.688 mole). The reaction mass was cooled to -15 to -25°C followed by addition of bromine 30 (41.38 g, 0.258mole) and stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours. The reaction was cooled to 25-30°C followed by addition of 4N hydrochloric acid (600 ml), phenol (2.42 g, 0.026 mole), sodium chloride (10.1g, 0.1724 mole). The mass was heated to 105°-110°C for 15-24 hours, and then cooled to room temperature, i.e., about 20° to about

25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 300ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount sufficient to provide a pH of 4-5. The (S)-Pregabalin was precipitated, filtered, and washed with 100ml of iso-butanol which on
 5 crystallization from isobutanol water mixture results in (S)-Pregabalin as white crystals in a 59.5% yield. Purity: 99.44% area by HPLC. N-benzylated pregabalin: 0.06% area by HPLC.

Example 18: Conversion of the Compound of Formula 4 to (S)-Pregabalin: Example 14 of International Publication No. WO 2007/035890

10 A 0.2 l reactor was loaded with 70% sulfuric acid (200 g) containing compound 26 (10 g, 0.031 mole), and was heated to 115-120°C for 5-10 hours, and then cooled to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 35 ml of iso-butanol, the organic layer was separated, and Bu₃N was added in an amount
 15 sufficient to provide a pH of 4. The (S) Pregabalin was precipitated, filtered, and washed with 10 ml of iso-butanol. After drying at 55°C under vacuum, (S)-Pregabalin was obtained as white crystals in a 40.4% yield. Purity: 99.95% area by HPLC.

Compound 26 has the following chemical structure:



20 wherein Ar is a C₆₋₁₀ aromatic group, and R is a straight or branched C₁₋₄ alkyl, ester or carboxylic acid.

Example 19: Conversion of the Compound of Formula 4 to (S)-Pregabalin: Example 16 of International Publication No. WO 2007/035890

25 A flask was loaded with 47% HBr (12 ml), water (6 ml), and compound 26 (6 g), and then was heated to reflux for 3 hours. The solution was cooled to room temperature, and water (12 ml) was added. An aqueous 47% sodium hydroxide solution was added to obtain pH of 3. The solution was then extracted twice with isobutanol (15 ml), the combined

organic layers were evaporated and fresh isobutanol was added (15 ml). Bu₃N (3.8 g) was added. The mixture was cooled to 2°C for 1 hour, then (S)-Pregabalin was filtered, and washed with of iso-butanol (3 ml). After drying at 55°C under vacuum, (S)-Pregabalin was obtained as white crystals in a 90% yield.

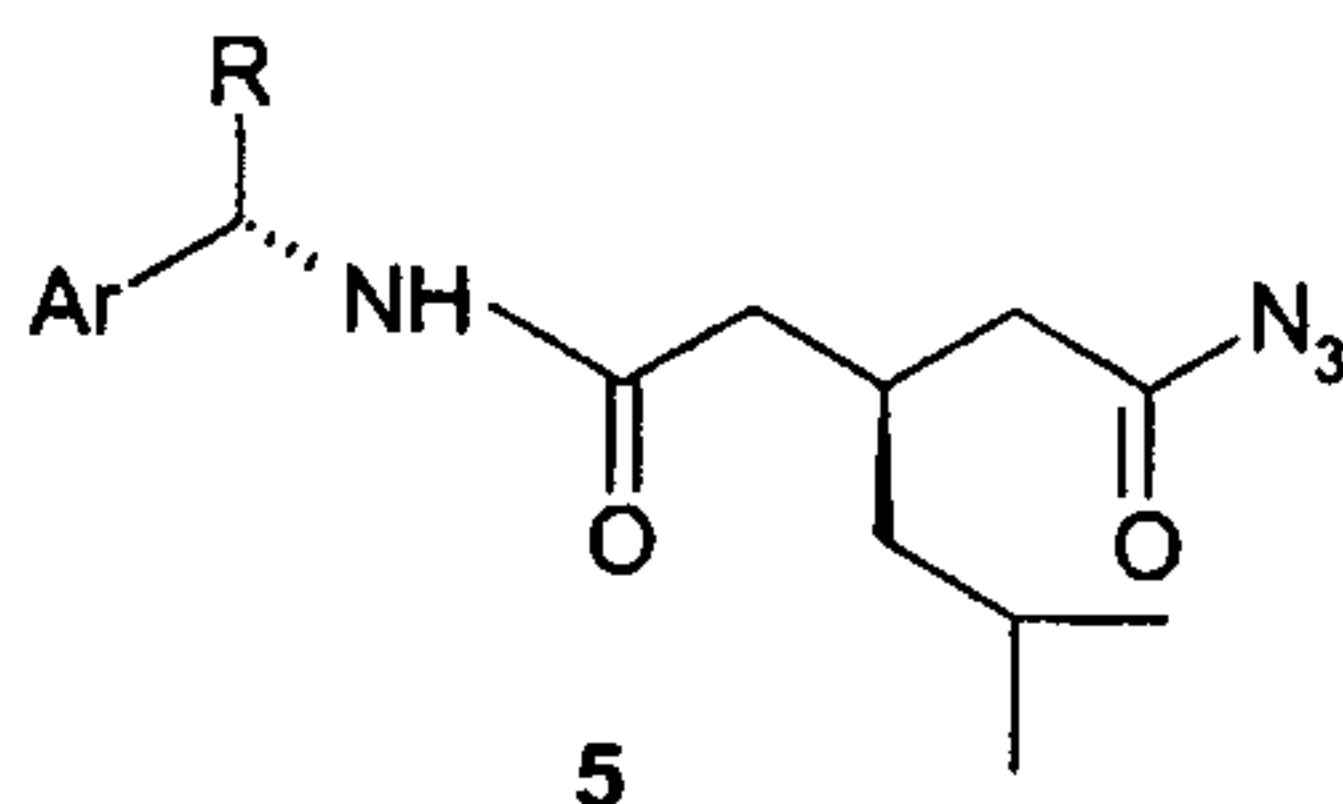
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Example 20: Preparation of (S)-Pregabalin

A three-necked flask equipped with an addition funnel, thermometer pocket, drying tube and a mechanical stirrer, was charged with methanol (2000 ml), (R)-3-isobutylpentanedioic acid amide-((S)-1-phenylmethyl) amide, compound of formula 1 (200g, 0.689 mole) and cooled to 0° to 5°C, followed by addition of sodium methoxide (149 g, 2.758 mole). The reaction mass was cooled to -15 to -25°C, followed by addition of bromine (165.5 g, 1.034 mole) and was stirred for 1-2 h at -15 to -25°C. The mixture was gradually warmed to a temperature of 0°C and then to 55-65°C, followed by stirring for 1 to 2 hours. The solvent was stripped off and then 4N hydrochloric acid (2580 ml), and sodium chloride (78.15 g, 1.342 mole) were added to the mass, followed by heating to 105°-110°C for 15-24 hours, and then cooling to room temperature, i.e., about 20° to about 25°C. An aqueous 40% sodium hydroxide solution was added in an amount sufficient to provide a pH of 1. The solution was then extracted with 600ml of iso-butanol, which on crystallization from isobutanol water mixture resulted in (S)-Pregabalin as white crystals in a 64.9% yield; Purity 99.68% area by HPLC, N-benzylated pregabalin: 0.13% area by HPLC.

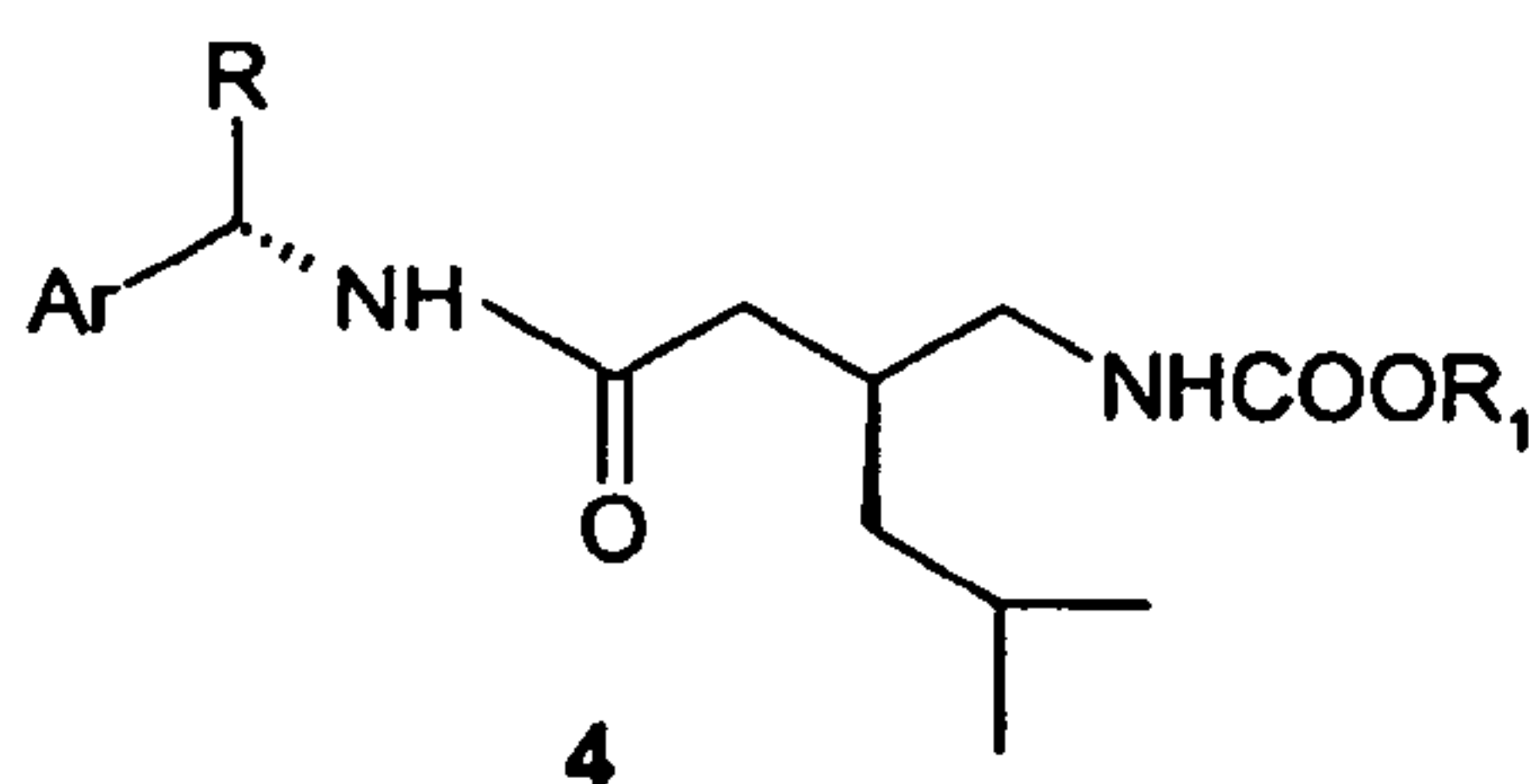
We claim:

1. A compound of the following formula 5

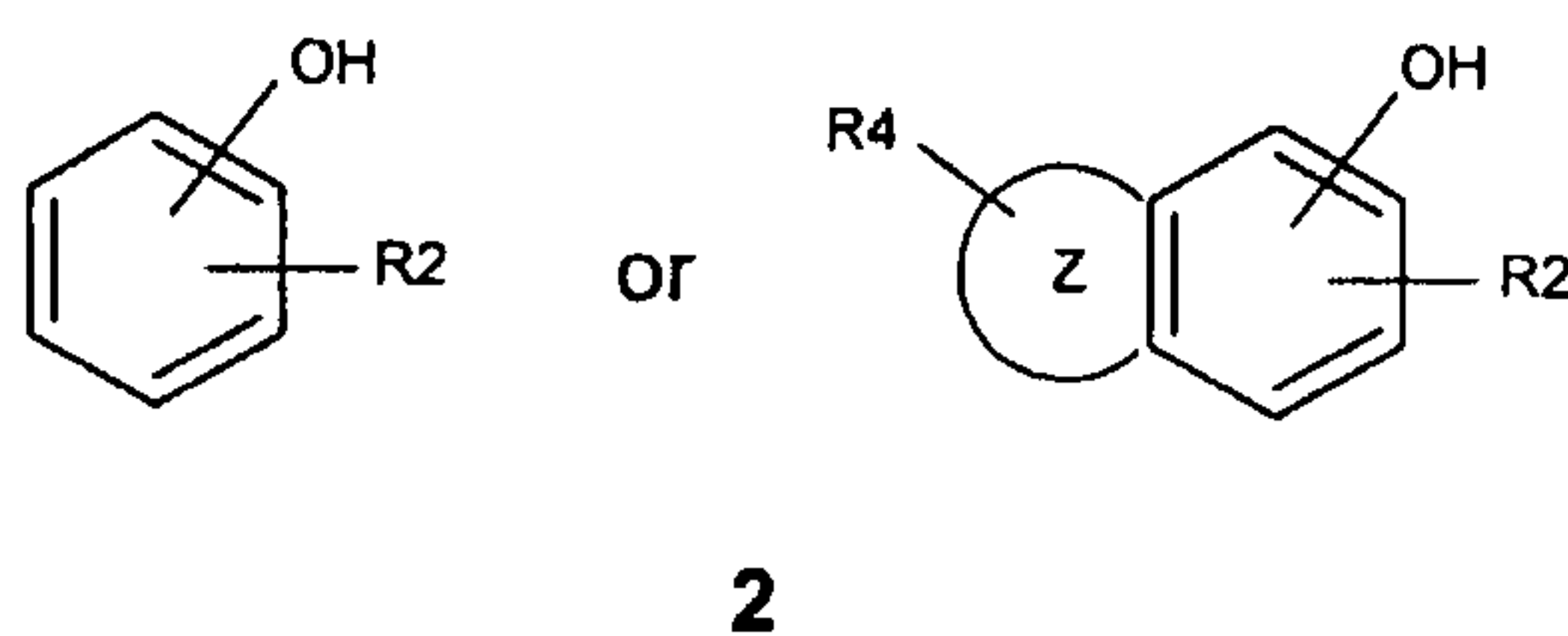


wherein Ar is a C₆₋₁₀ aromatic group, and R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid.

2. The compound of claim 1, wherein the C₆₋₁₀ aromatic group is naphthyl, phenyl, substituted phenyl, or substituted naphthyl.
3. The compound of claim 1 or 2, wherein the C₁₋₄ alkyl is methyl, ethyl, isopropyl, n-butyl, isobutyl, or t-butyl.
4. The compound of claim 1, wherein Ar is phenyl and R is ethyl.
5. A process for preparing (S)-Pregabalin comprising:
a) combining a compound of the following formula 4



with an acid and a phenol of formula 2



; and

b) recovering (S)-Pregabalin,

wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, R1 is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl, R2 is H, alkyl, alkoxy, halogen, or mercapto, R4 is H, alkyl or halogen, and the ring Z is a 5-8- membered ring containing carbon and optionally at least one nitrogen, sulfur or oxygen.

6. The process of claim 5, wherein the C₆₋₁₀ aromatic group is naphthyl, phenyl, substituted phenyl, or substituted naphthyl.

7. The process of claim 5 or 6, wherein the C₁₋₄ alkyl is methyl, ethyl, isopropyl, n-butyl, isobutyl, or t-butyl.

8. The process of any one of claims 5 to 7, wherein the ester is a C₂₋₄ ester.

9. The process of any one of claims 5 to 8, wherein the carboxylic acid is a C₁₋₂ carboxylic acid.

10. The process of any one of claims 5 to 9, wherein the C₁₋₅ alkyl is methyl.

11. The process of any one of claims 5 to 10, wherein the aralkyl is a C₇₋₁₀ aralkyl.

12. The process of any one of claims 5 to 11, wherein the acid is a strong mineral acid.

13. The process of claim 12, wherein the strong mineral acid is hydrochloric acid, sulfuric acid, or polyphosphoric acid.

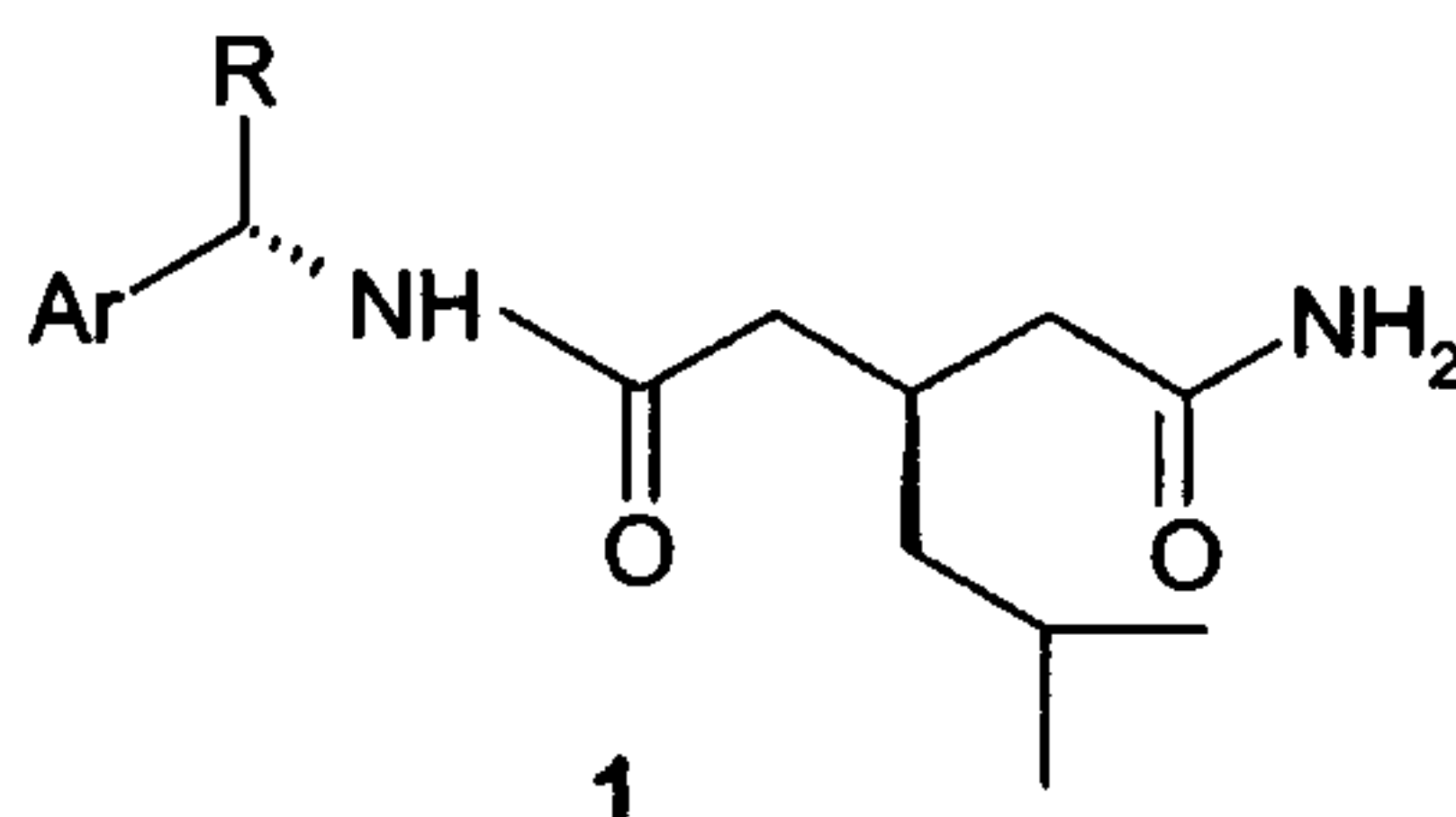
14. The process of any one of claims 5 to 13, wherein the phenol of formula 2 is an unsubstituted phenol.

15. The process of any one of claims 5 to 14, wherein the compound of formula 4, the acid, and the phenol are combined in the presence of an inorganic salt.
16. The process of claim 15, wherein the inorganic salt is sodium chloride, potassium chloride, magnesium sulfate, or sodium sulfate.
17. The process of any one of claims 5 to 16, wherein the combination of the compound of formula 4, the phenol, and the acid is heated to obtain a salt of (S)- pregabalin.
18. The process of claim 17, wherein the combination is heated to a temperature of about 60°C to about 130°C.
19. The process of claim 17, wherein the (S)-Pregabalin is recovered by a process comprising:
 - i) adding an inorganic base to the combination;
 - ii) extracting the salt of (S)-Pregabalin from the mixture with a C₄₋₈ alcohol;
 - iii) adjusting the pH of the extract to about 4 to about 7 and precipitate (S)- Pregabalin; and
 - iv) collecting the precipitated (S)-Pregabalin.
20. The process of claim 19, wherein the inorganic base in step i) is added in an amount sufficient to adjust the pH of the combination to about 1 to about 3.
21. The process of claim 19 or 20, wherein the inorganic base is sodium hydroxide.
22. The process of any one of claims 19 to 21, wherein the pH is adjusted in step iii) by adding a base.
23. The process of claim 22, wherein the base is an organic base.
24. The process of claim 23, wherein the organic base is tributylamine.

25. The process of any one of claims 19 to 24, wherein the C₄₋₈ alcohol is iso-butanol.

26. The process of any one of claims 5 to 25, wherein the (S)-Pregabalin has less than 0.15% area by HPLC of N-benzylated pregabalin.

27. The process of any one of claims 5 to 26, wherein the compound of formula 4 is prepared by a process comprising combining a compound of formula 1



with bromine and a base in a straight or branched alkyl alcohol.

28. The process of claim 27, wherein the straight or branched alkyl alcohol is methyl, ethyl, isopropyl, n-butyl, isobutyl, or t-butyl alcohol.

29. The process of claim 27 or 28, wherein the base that is combined with the compound of formula 1 and the bromine is a metal alkoxide or a metal hydroxide.

30. The process of claim 29, wherein the metal alkoxide is a C₁₋₄ alkoxide.

31. The process of any one of claims 27 to 30, wherein the base that is combined with the compound of formula 1 and the bromine is sodium hydroxide or potassium hydroxide.

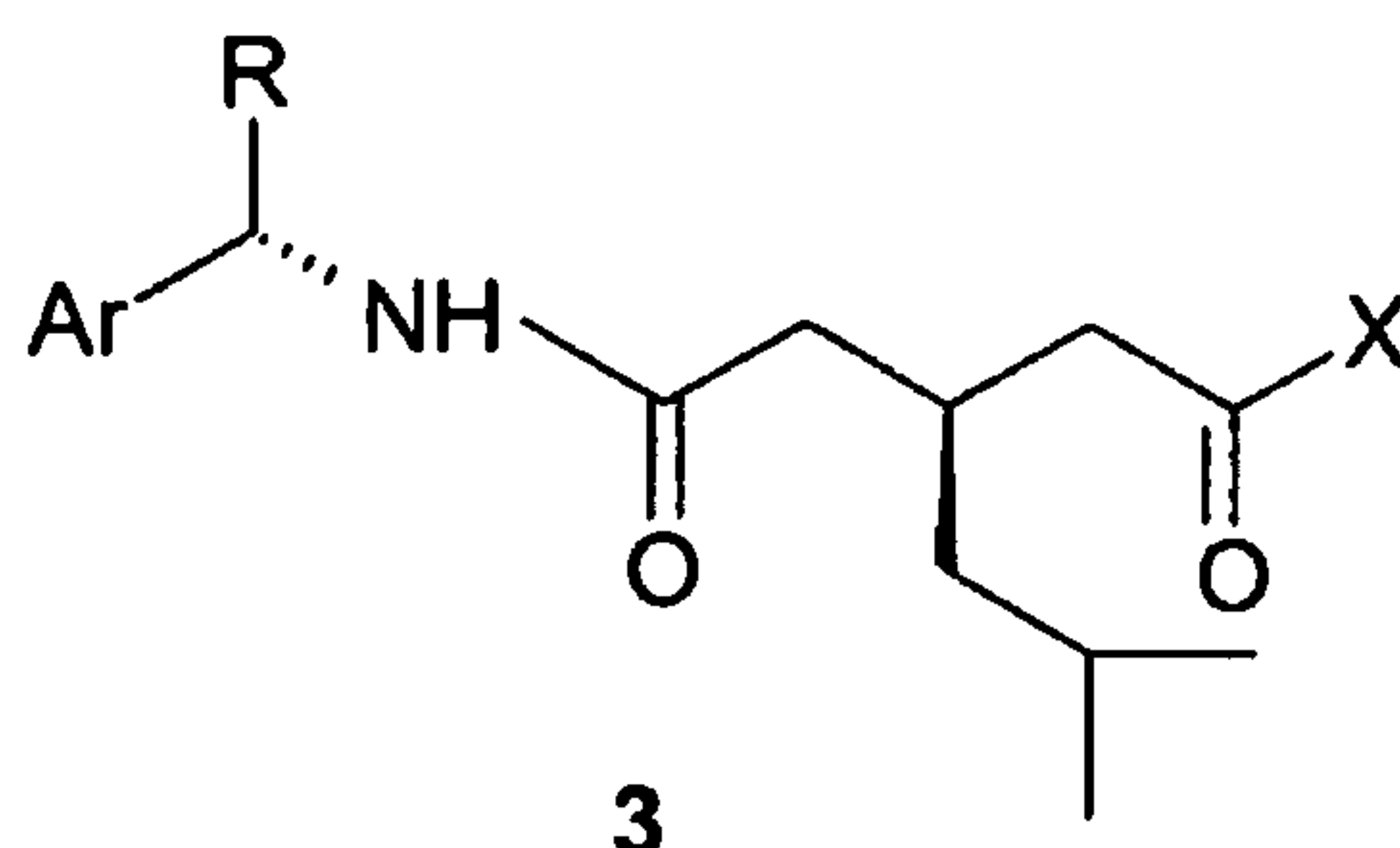
32. The process of any one of claims 27 to 31, wherein the combination of the compound of formula 1, the bromine, the base, and the alcohol is heated to obtain the compound of formula 4.

33. The process of claim 32, wherein the combination of the compound of formula 1, the bromine, the base, and the alcohol is heated to a temperature of about 50°C to about 70°C.

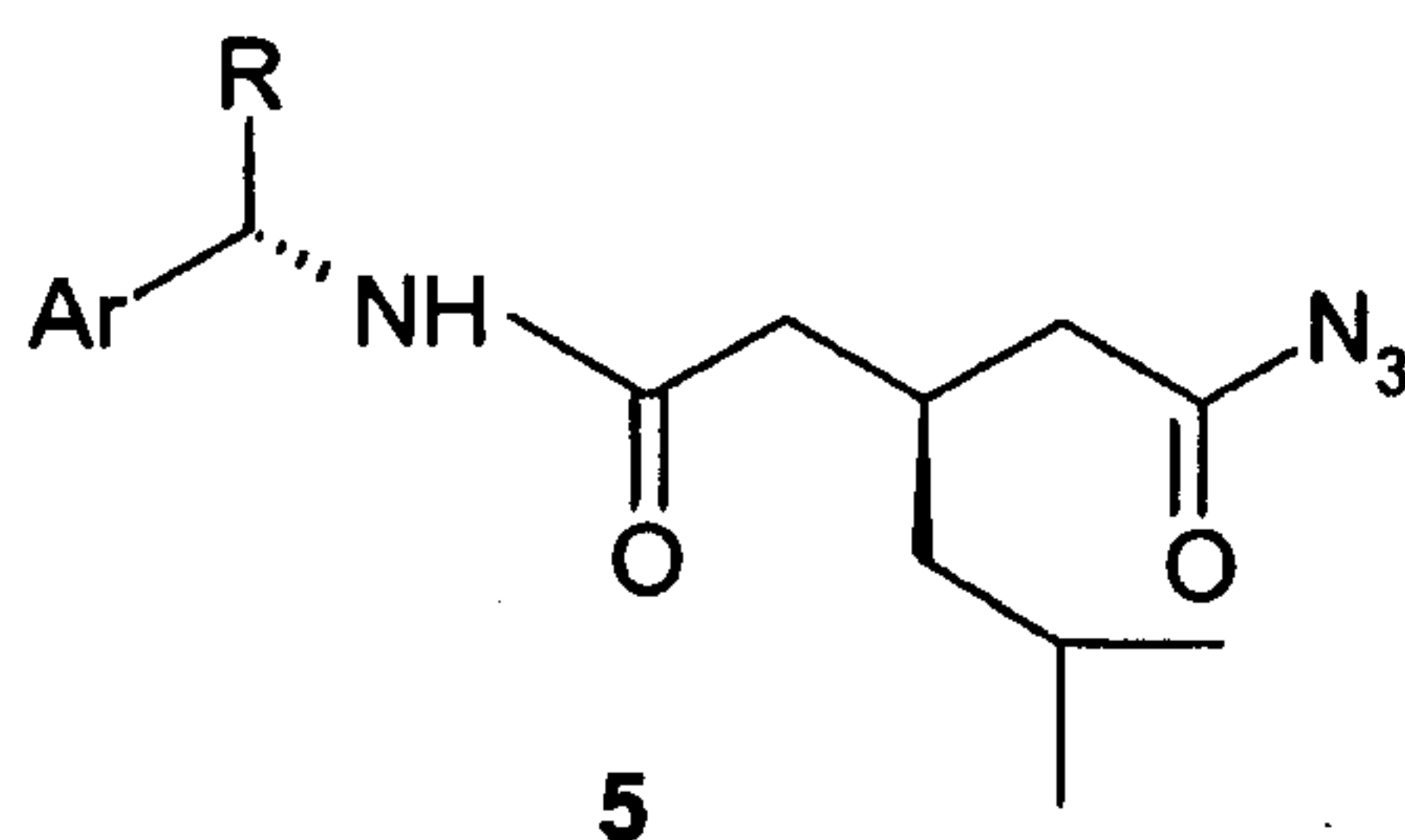
34. The process of any one of claims 27 to 33, wherein the compound of formula 4 is converted to (S)-Pregabalin without isolation.

35. The process of any one of claims 5 to 26, wherein the compound of formula 4 is prepared by a process comprising:

(i) combining a compound of formula 3



with an azide nucleophile to obtain a compound of formula 5,



and (ii) combining the compound of formula 5 with an alcohol to obtain the compound of formula 4, wherein X is a leaving group.

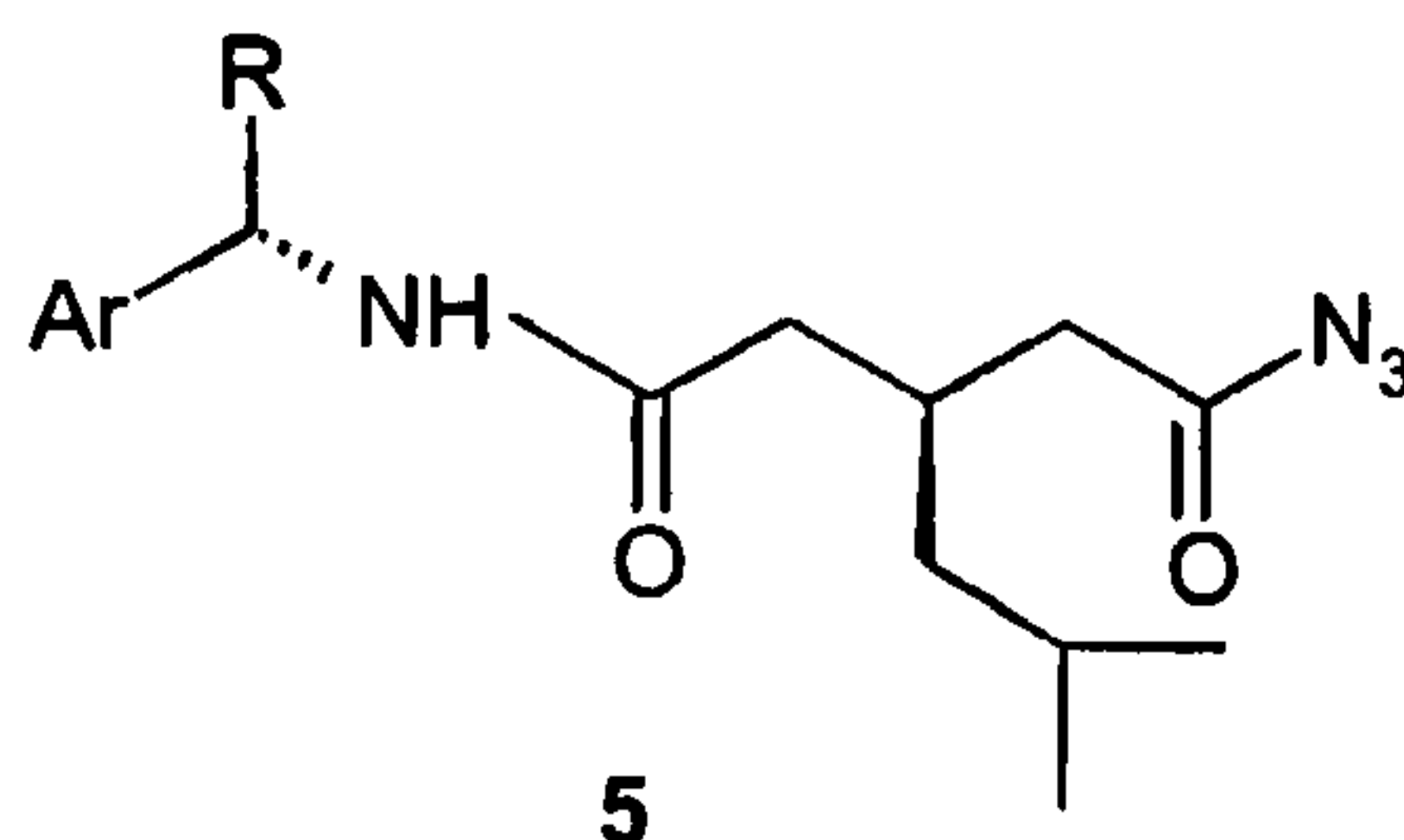
36. The process of claim 35, wherein the leaving group is a halogen or a mixed anhydride.

37. The process of claim 35 or 36, wherein the azide nucleophile is NaN_3 , diphenylphosphoryl azide, trialkyl silyl azide, or trialkyl tin azide.

38. The process of any one of claims 35 to 37, wherein the compound of formula 3 is combined with the azide nucleophile at a temperature of about 30°C to about -30°C .

39. The process of any one of claims 35 to 38, wherein the step (i) comprises combining the compound of formula 3 with the azide nucleophile and an organic solvent.

40. The process of claim 39, wherein the organic solvent is selected from the group consisting of aromatic hydrocarbons, aliphatic hydrocarbons, ethers and ketones.
41. The process of claim 39, wherein the organic solvent is acetone or toluene.
42. The process of any one of claims 35 to 41, wherein the compound of formula 5 is recovered prior to combination with the alcohol.
43. The process of claim 42, wherein the compound of formula 5 is recovered by extraction.
44. The process of any one of claims 35 to 43, wherein the alcohol is a C₁₋₅ alcohol.
45. The process of any one of claims 35 to 44, wherein the alcohol is methanol, ethanol, isopropanol, t-butanol, n-butanol or isobutanol.
46. The process of any one of claims 35 to 45, wherein the compound of formula 5 is added to the alcohol while heating the alcohol.
47. The process of claim 46, wherein the alcohol is heated to a temperature of about 50°C to about 110°C.
48. The process of any one of claims 35 to 47, wherein the compound of formula 4 is converted to (S)-Pregabalin without isolation.
49. The process of any one of claims 5 to 26, wherein the compound of the formula 4 is prepared by a process comprising combining a compound of the following formula 5



with an alcohol to obtain the compound of the formula 4.

50. The process of claim 49, wherein the alcohol of claim 49 is a C₁₋₅ alcohol.

51. The process of claim 49 or 50, wherein the alcohol of claim 49 is methanol, ethanol, isopropanol, t-butanol, n-butanol or isobutanol.

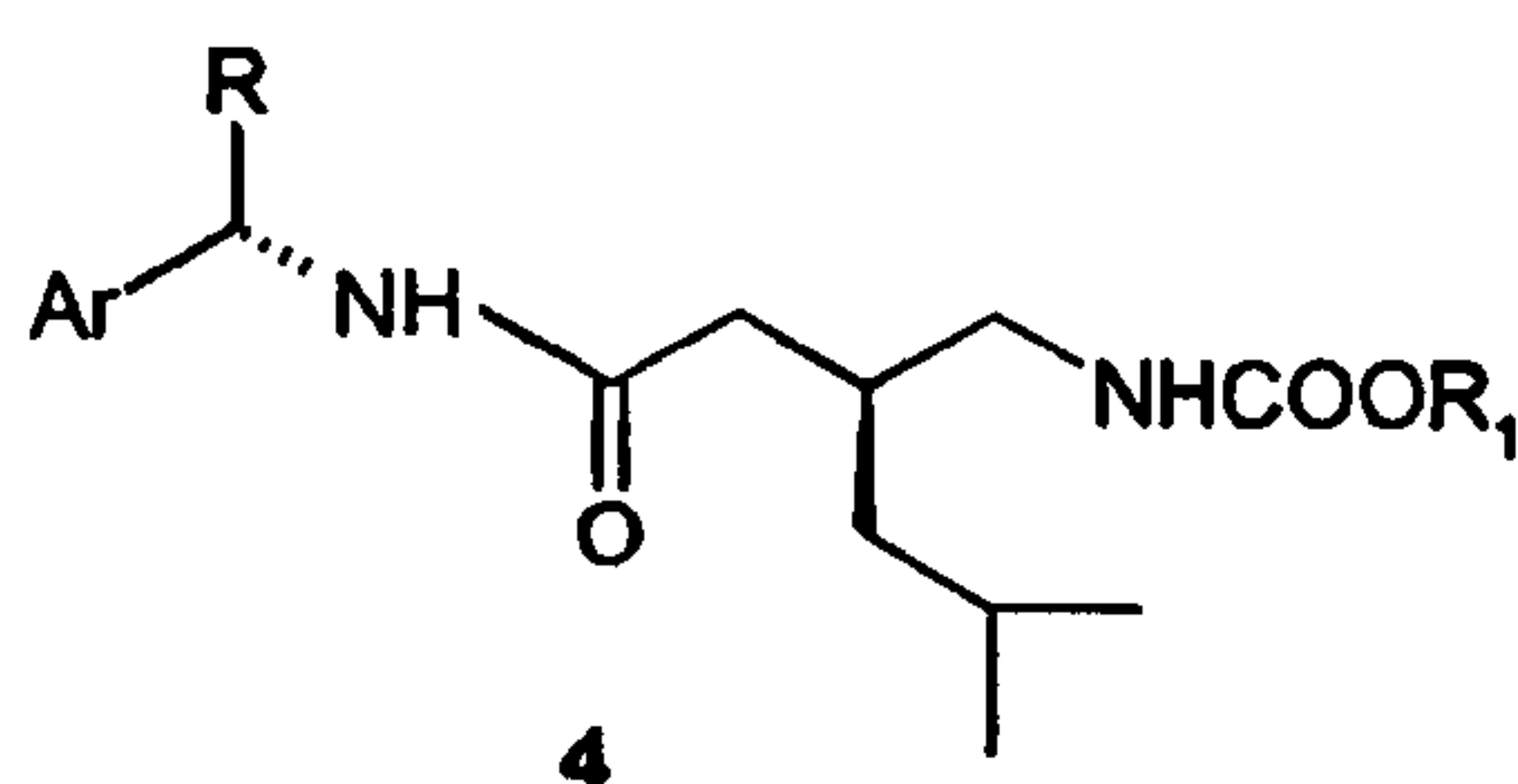
52. The process of any one of claims 49 to 51, wherein the compound of formula 5 is added to the alcohol of claim 49 while heating the alcohol of claim 49.

53. The process of claim 52, wherein the alcohol of claim 49 is heated to a temperature of about 50°C to about 110°C.

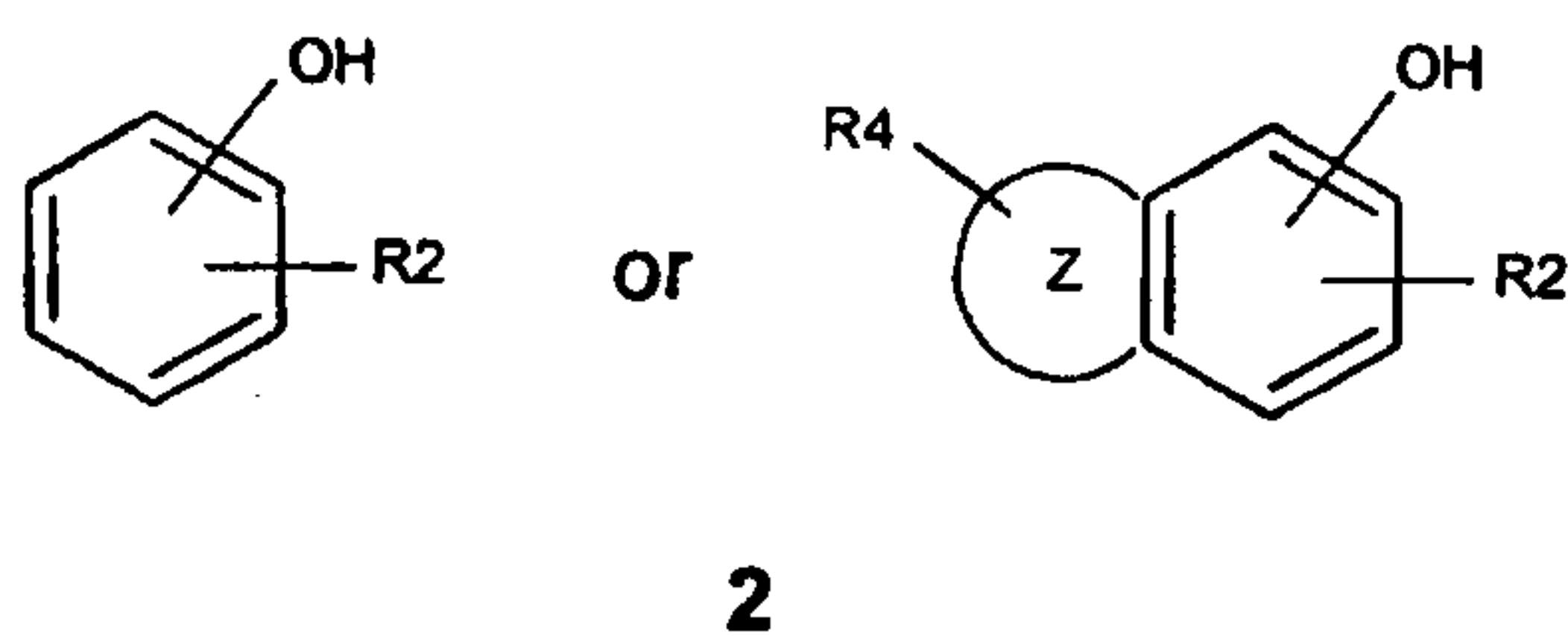
54. The process of any one of claims 49 to 53, wherein the compound of formula 4 is converted to (S)-Pregabalin without isolation.

55. A process for preparing (S)-Pregabalin comprising:

a) combining a compound of the formula 5 according to any one of claims 1 to 4 with an alcohol to obtain a compound of the following formula 4



b) combining the compound of the formula 4 with an acid and a phenol of the following formula 2



and

c) recovering (S)-Pregabalin,

wherein Ar is a C₆₋₁₀ aromatic group, R is a straight or branched C₁₋₄ alkyl, ester, or carboxylic acid, R1 is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl, R2 is H, alkyl, alkoxy, halogen, or mercapto, R4 is H, alkyl or halogen, and the ring Z is a 5-8- membered ring containing carbon and optionally at least one nitrogen, sulfur or oxygen.

56. The process of claim 55, wherein the alcohol is a C₁₋₅ alcohol.

57. The process of claim 55 or 56, wherein the alcohol is methanol, ethanol, isopropanol, t-butanol, n-butanol or isobutanol.

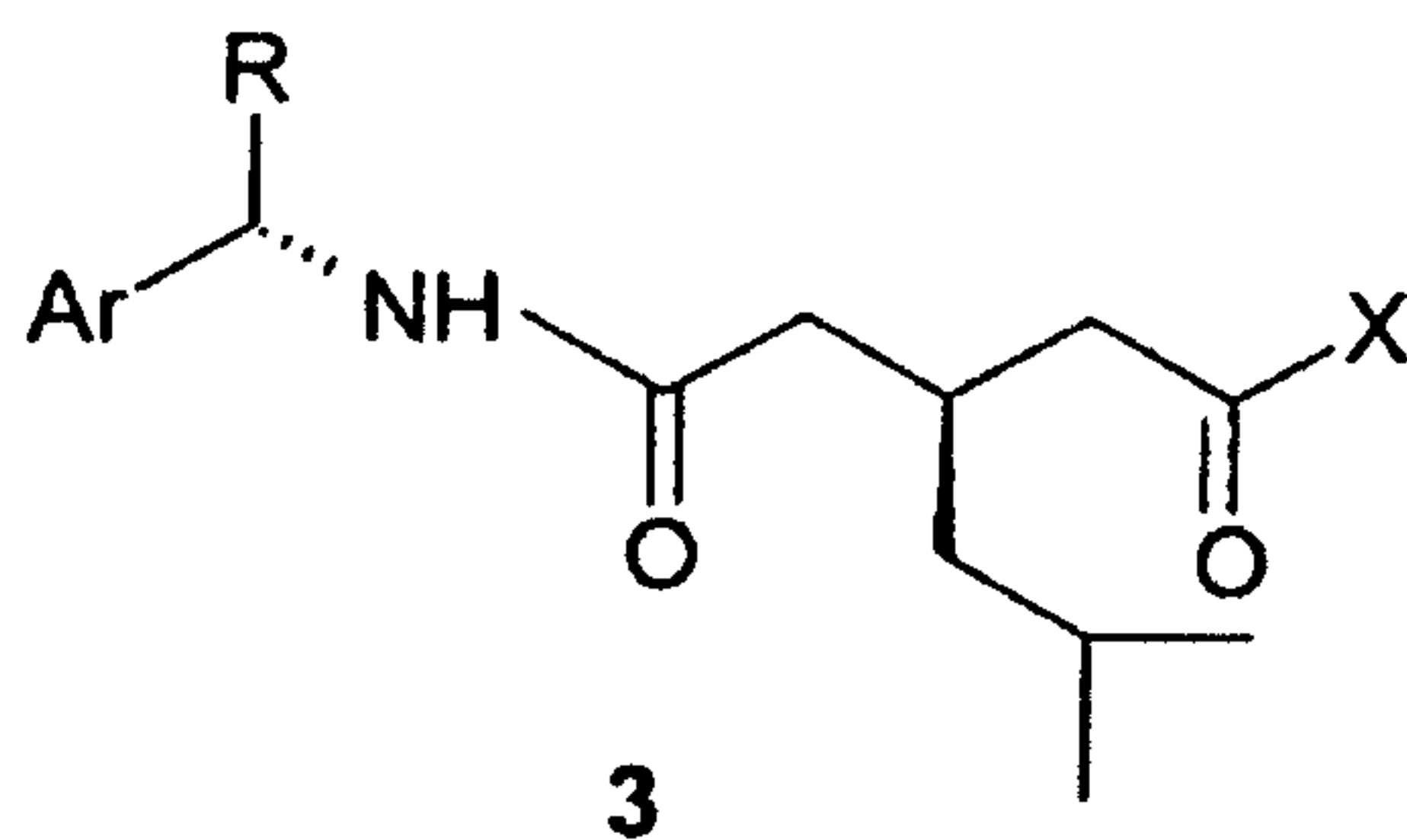
58. The process of any one of claims 55 to 57, wherein the compound of formula 5 is added to the alcohol while heating the alcohol.

59. The process of claim 58, wherein the alcohol is heated to a temperature of about 50°C to about 110°C.

60. The process of any one of claims 55 to 59, wherein the compound of formula 4 is converted to (S)-Pregabalin without isolation.

61. A process for preparing (S)-Pregabalin comprising:

(i) combining a compound of formula 3



with an azide nucleophile to obtain the compound of formula 5 according to any one of Claims 1 to 4, and

(ii) converting the obtained compound of formula 5 to (S)-Pregabalin, wherein X is a leaving group.

62. The process of claim 61, wherein the leaving group is a halogen or a mixed anhydride.

63. The process of claim 61 or 62, wherein the azide nucleophile is NaN_3 , diphenylphosphoryl azide, trialkyl silyl azide, or trialkyl tin azide.

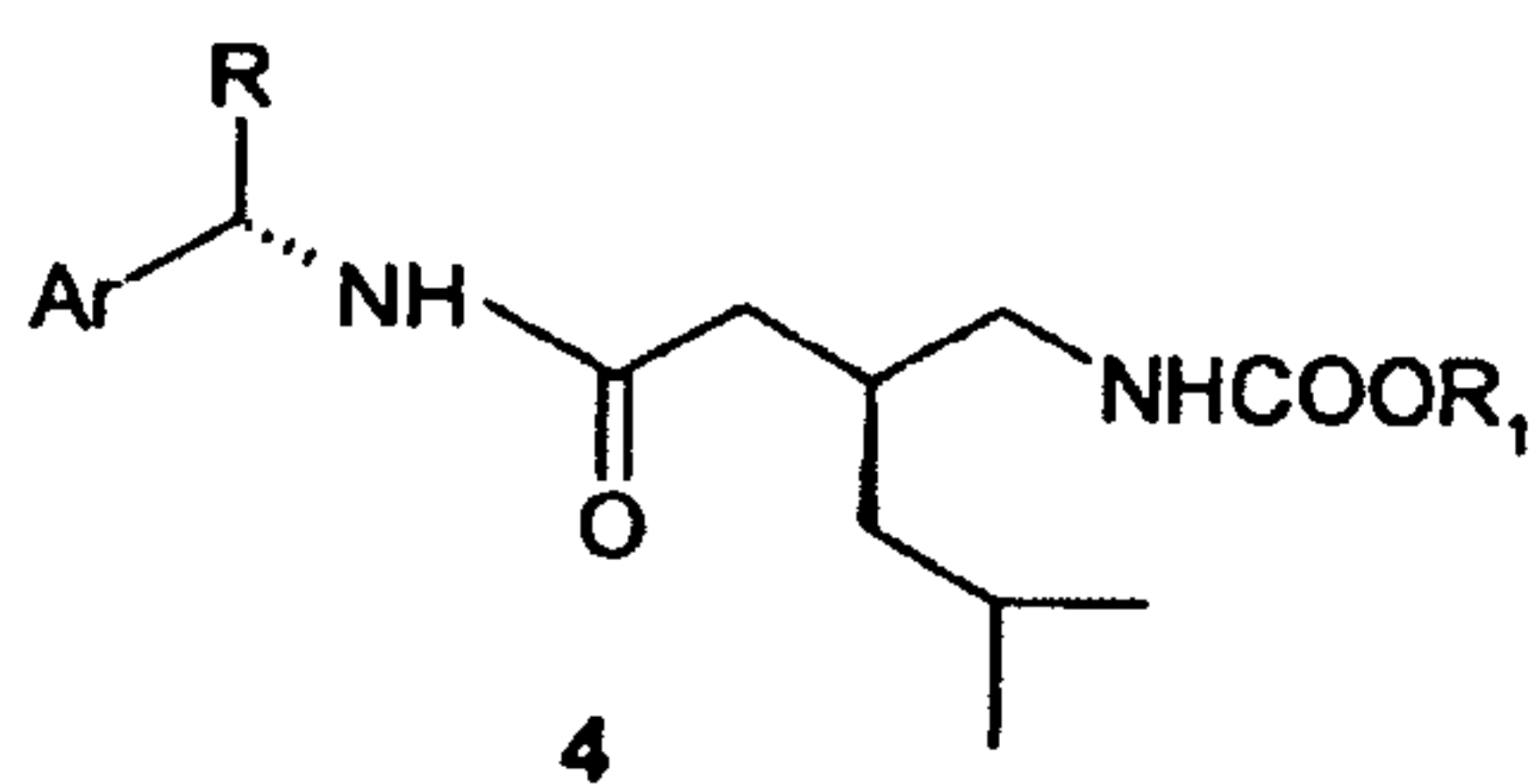
64. The process of any one of claims 61 to 63, wherein the compound of formula 3 is combined with the azide nucleophile at a temperature of about 30°C to about -30°C .

65. The process of any one of claims 61 to 64, wherein the step (i) comprises combining the compound of formula 3 with the azide nucleophile and an organic solvent.

66. The process of claim 65, wherein the organic solvent is selected from the group consisting of aromatic hydrocarbons, aliphatic hydrocarbons, ethers and ketones.

67. The process of claim 65, wherein the organic solvent is acetone or toluene.

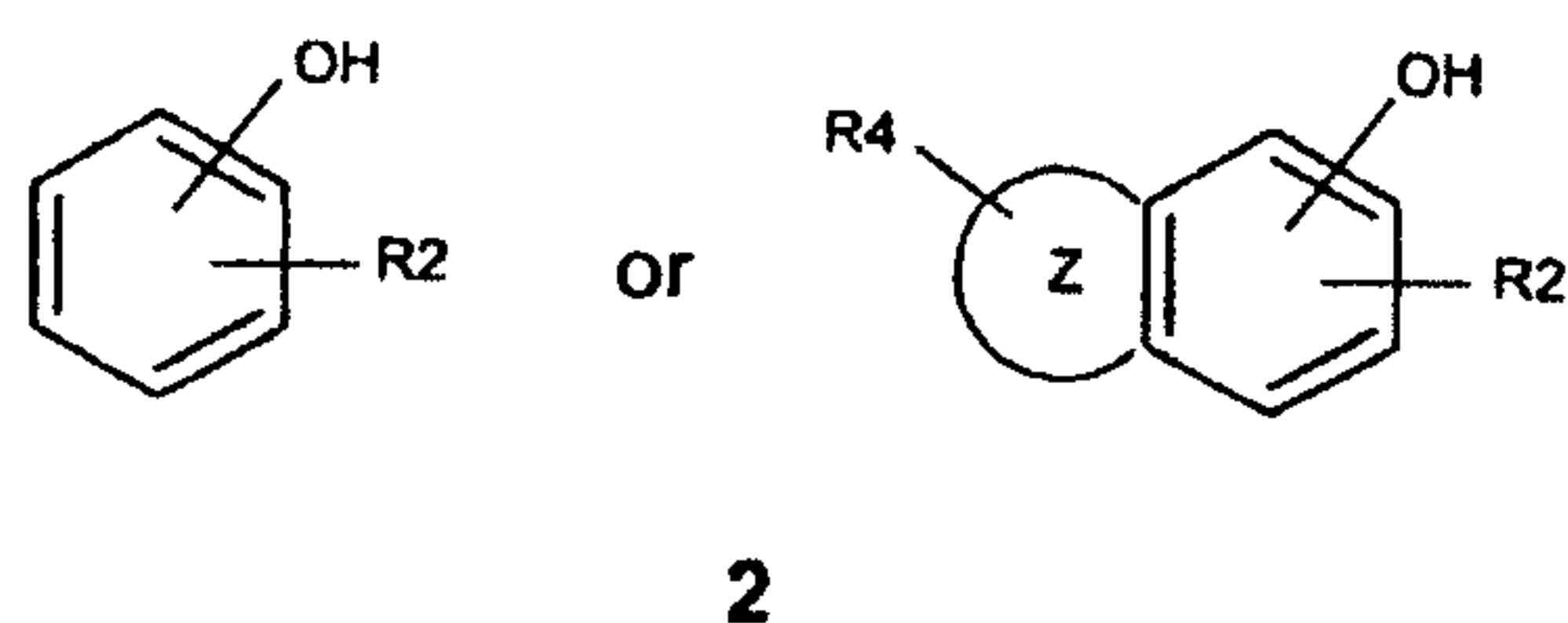
68. The process of any one of claims 61 to 67, wherein the converting the compound of formula 5 to (S)-Pregabalin comprises combining the compound of the formula 5 with an alcohol to obtain a compound of the formula 4



and converting the compound of the formula 4 to the (S)-Pregabalin.

69. The process of claim 68, wherein the compound of formula 5 is recovered prior to combination with the alcohol.

70. The process of claim 69, wherein the compound of formula 5 is recovered by extraction.
71. The process of any one of claims 68 to 70, wherein the alcohol is a C₁₋₅ alcohol.
72. The process of any one of claims 68 to 71, wherein the alcohol is methanol, ethanol, isopropanol, t-butanol, n-butanol or isobutanol.
73. The process of any one of claims 68 to 72, wherein the compound of formula 5 is added to the alcohol while heating the alcohol.
74. The process of claim 73, wherein the alcohol is heated to a temperature of about 50°C to about 110°C.
75. The process of any one of claims 68 to 74, wherein the compound of formula 4 is converted to the (S)-Pregabalin without isolation.
76. The process of any one of claims 68 to 75, wherein the converting the compound of the formula 4 to the (S)-Pregabalin comprises combining the compound of the formula 4 with an acid and a phenol of formula 2



and recovering the (S)-Pregabalin,
 wherein R1 is a straight or branched C₁₋₅ alkyl, aralkyl, or substituted aralkyl, R2 is H, alkyl, alkoxy, halogen, or mercapto, R4 is H, alkyl or halogen, and the ring Z is a 5-8- membered ring containing carbon and optionally at least one nitrogen, sulfur or oxygen.

77. The process of claim 76, wherein the C₁₋₅ alkyl is methyl.

78. The process of claim 76 or 77, wherein the aralkyl is a C₇₋₁₀ aralkyl.
79. The process of any one of claims 76 to 78, wherein the acid is a strong mineral acid.
80. The process of claim 79, wherein the strong mineral acid is hydrochloric acid, sulfuric acid, or polyphosphoric acid.
81. The process of any one of claims 76 to 80, wherein the phenol of formula 2 is an unsubstituted phenol.
82. The process of any one of claims 76 to 81, wherein the compound of formula 4, the acid, and the phenol are combined in the presence of an inorganic salt.
83. The process of claim 82, wherein the inorganic salt is sodium chloride, potassium chloride, magnesium sulfate, or sodium sulfate.
84. The process of any one of claims 76 to 83, wherein the combination of the compound of formula 4, the phenol, and the acid is heated to obtain a salt of (S)- pregabalin.
85. The process of claim 84, wherein the combination is heated to a temperature of about 60°C to about 130°C.
86. The process of claim 84, wherein the (S)-Pregabalin is recovered by a process comprising:
- i) adding an inorganic base to the combination;
 - ii) extracting the salt of (S)-Pregabalin from the mixture with a C₄₋₈ alcohol;
 - iii) adjusting the pH of the extract to about 4 to about 7 and precipitate (S)- Pregabalin;
 - and
 - iv) collecting the precipitated (S)-Pregabalin.

87. The process of claim 86, wherein the inorganic base in step i) is added in an amount sufficient to adjust the pH of the combination to about 1 to about 3.
88. The process of claim 86 or 87, wherein the inorganic base is sodium hydroxide.
89. The process of any one of claims 86 to 88, wherein the pH is adjusted in step iii) by adding a further base.
90. The process of claim 89, wherein the further base is an organic base.
91. The process of claim 90, wherein the organic base is tributylamine.
92. The process of any one of claims 86 to 91, wherein the C₄₋₈ alcohol is iso-butanol.
93. The process of any one of claims 76 to 92, wherein the (S)-Pregabalin has less than 0.15% area by HPLC of N-benzylated pregabalin.

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An infrared spectrum of the compound of formula 5, wherein Ar is phenyl and R is ethyl.

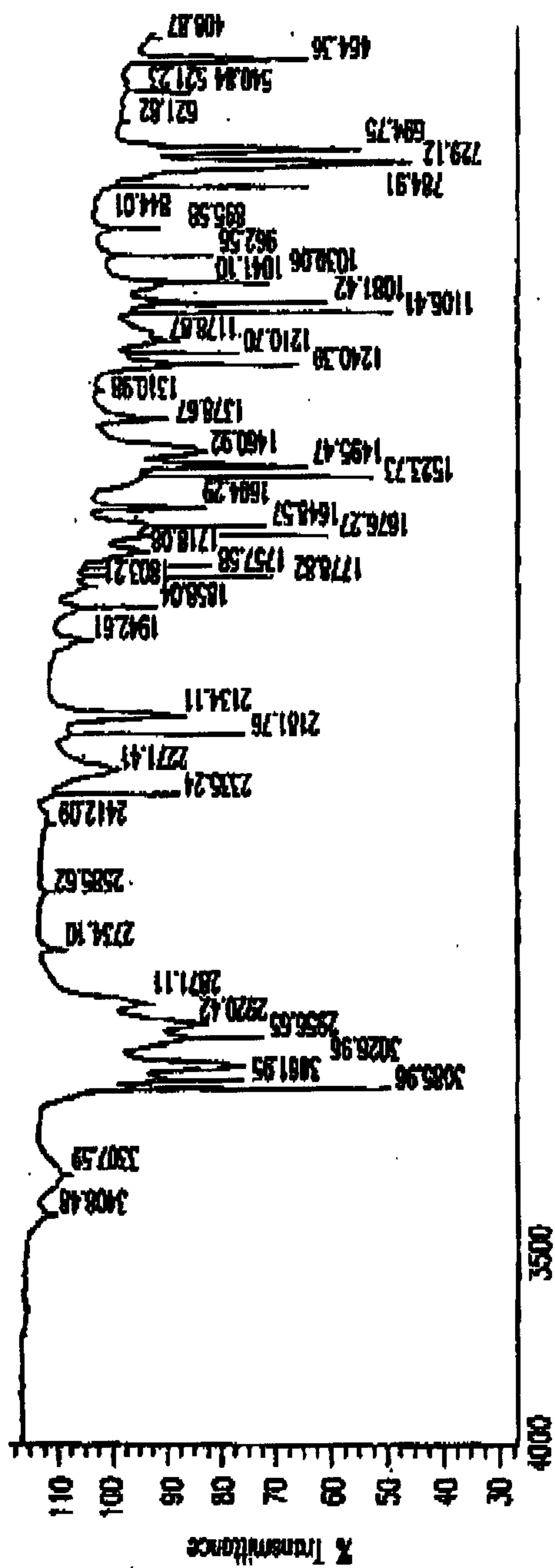


FIG.1

