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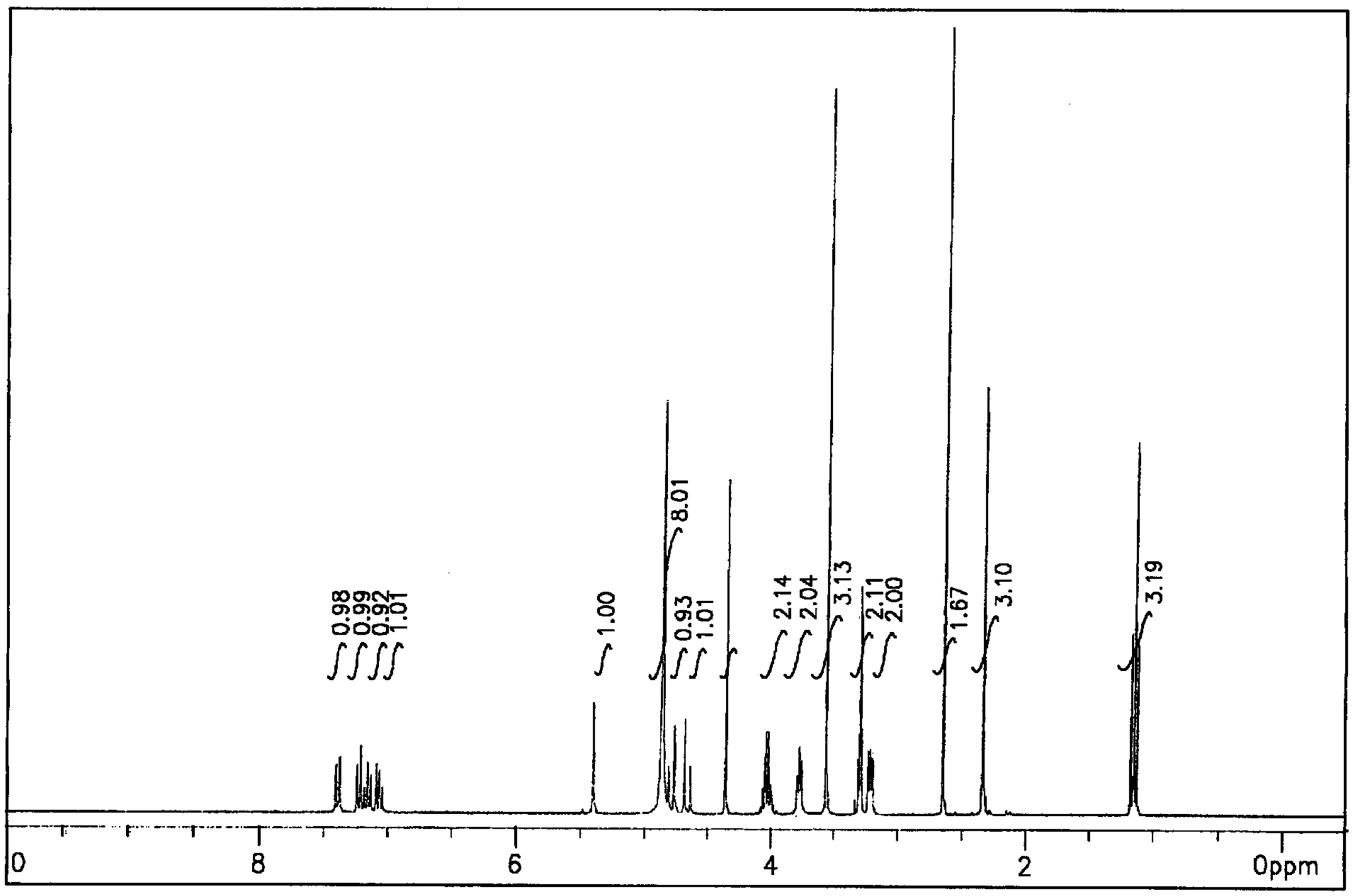
(54) Titre : MODES DE PREPARATION DE S-(-)-AMLODIPINE
(54) Title: PROCESSES FOR THE PREPARATION OF S-(-)-AMLODIPINE



(57) Abrégé/Abstract:
The present invention provides a process for the preparation of S-(-)-amlodipine from (R,S)-amlodipine in industrial-scale using L-(+)-tartaric acid, which is much cheaper than D-(-)-tartaric acid.

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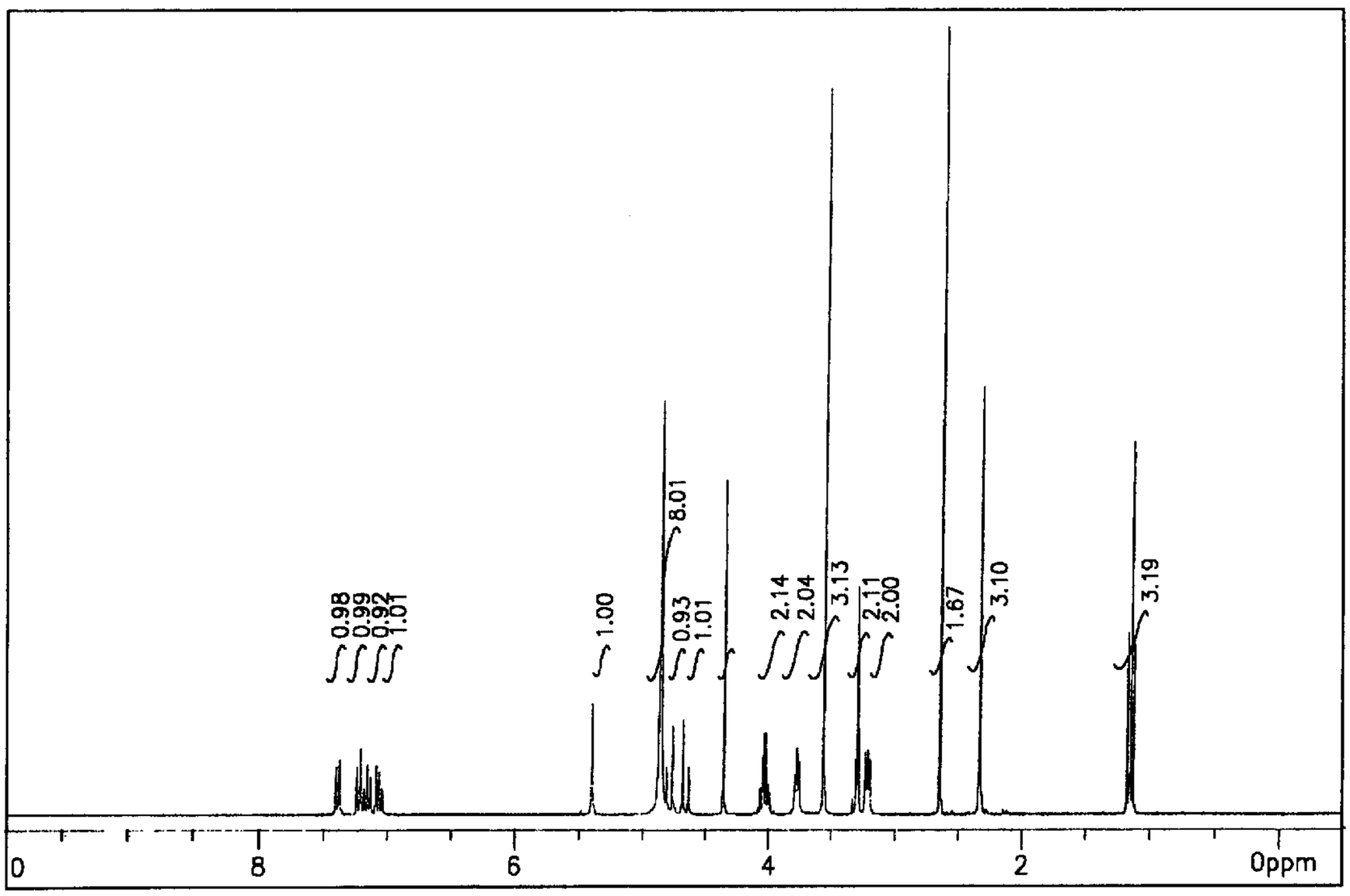
(54) Title: PROCESSES FOR THE PREPARATION OF S-(-)-AMLODIPINE



(57) Abstract: The present invention provides a process for the preparation of S-(-)-amlodipine from (R,S)-amlodipine in industrial-scale using L-(+)-tartaric acid, which is much cheaper than D-(-)-tartaric acid.

WO 2004/024689 A1

PROCESSES FOR THE PREPARATION OF S-(-)-AMLODIPINE

Technical Field

The present invention relates to a process for the preparation of S-(-)-amlodipine, more specifically, to a process for the preparation of S-(-)-amlodipine from (R,S)-amlodipine in industrial-scale using L-(+)-tartaric acid, which is much cheaper than D-(-)-tartaric acid.

Background Art

Amlodipine, with a chemical name of 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate, is a potent and long-acting calcium channel blocker useful as an anti-ischaemic and anti-hypertensive agent. It is known that two types of enantiomers of amlodipine have different pharmacological profiles. S-(-)-isomer is a more potent calcium channel blocker than R-(+)-isomer, while the R-(+)-isomer also exhibits an activity in the treatment or prevention of atherosclerosis.

J. Med. Chem. (1986) 29 1696 discloses a process for the preparation of the two enantiomers of amlodipine via separation of the diastereomeric azide esters, and EP 331,315 A1 discloses the use of cinchonidine salts for the resolution of intermediates to eventually give enantiomerically pure amlodipine isomers. *J. Med. Chem.* (1992) 35 3341 discloses a chromatographic separation of diastereomeric amide isomers.

Further, WO 95/25722 discloses a method for the separation of the (R)-(+)- and (S)-(-)-isomers of amlodipine from mixtures thereof, which comprises reacting the mixture of isomers with either L-(+)- or D-(-)-tartaric acid in dimethyl sulfoxide (DMSO) for the preparation of, respectively, a DMSO solvate of an L-tartrate salt of (R)-(+)-amlodipine, or a DMSO solvate of a D-tartrate salt of (S)-(-)-amlodipine.

In order to manufacture (S)-(-)-amlodipine, having a more potent calcium channel blocking activity, the process according to WO 95/25722 employs D-tartaric acid. However, the fact that D-(-)-tartaric acid is very expensive compared to L-(+)-tartaric acid is unfavorable for industrial-scale mass production of (S)-(-)-amlodipine.

Therefore, a method of industrial-scale mass production of (S)-(-)-amlodipine has been in demand.

Disclosure of the Invention

The present invention provides a process for the preparation of S-(-)-amlodipine from (R,S)-amlodipine in industrial-scale using L-(+)-tartaric acid, which is much cheaper than D-(-)-tartaric acid.

Further, the present invention provides synthetic intermediates for the preparation of S-(-)-amlodipine.

In one aspect of the present invention, there is provided a process for the preparation of S-(-)-amlodipine, which comprises (i) reacting (R,S)-amlodipine with L-(+)-tartaric acid in dimethyl sulfoxide (DMSO); (ii) filtering off the resulting precipitate of step (i); (iii) precipitating (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate by adding methylene chloride to the filtrate of step (ii); (iv) optionally forming (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate by adding an alcohol to (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate obtained in step (iii); and (v) treating with a base (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate obtained in step (iii) or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate obtained in step (iv).

In another aspect of the present invention, there is provided (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate, each being useful for the preparation of S-(-)-amlodipine.

Brief Description of the Drawings

The above and other features and advantages of the present invention will become more apparent by describing in detail illustrative, non-limiting embodiments thereof with reference to the attached drawings, in which:

FIG. 1 shows a ^{1}H-NMR chart of (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate; and

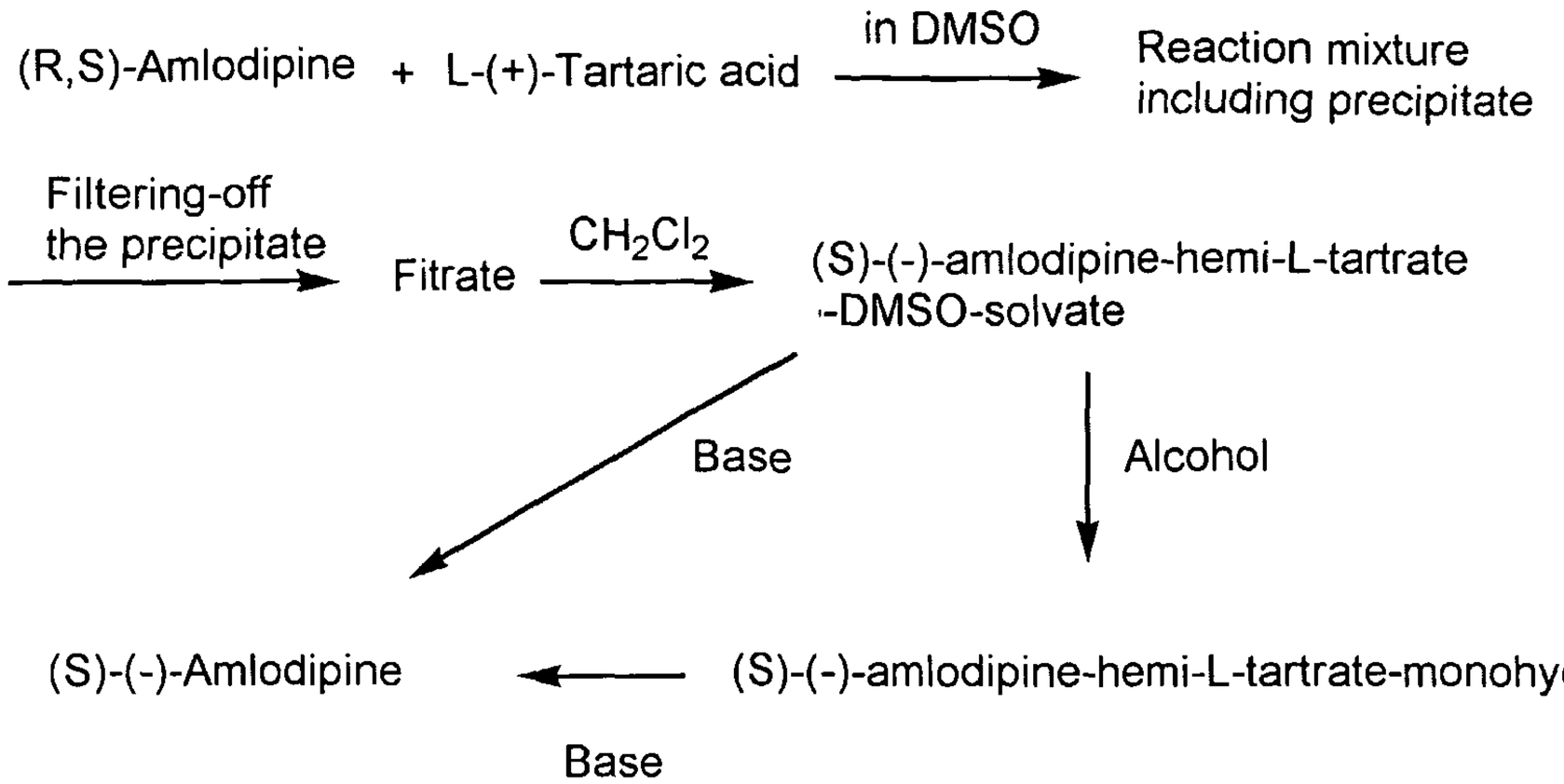
FIG. 2 shows shows a ^{1}H-NMR chart of (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate.

Best mode for carrying out the Invention

The present invention provides an economic process for preparing S-(-)-amlodipine in high yield and enantiomeric purity. According to the process of the present invention, (R,S)-amlodipine is reacted with L-(+)-tartaric acid in dimethyl sulfoxide (DMSO) and the resulting precipitate is filtered off. The resultant filtrate is added with methylene chloride to precipitate (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate. Optionally, (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate is added with an alcohol to form (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate. (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate is treated with a base.

The following reaction scheme illustrates the process of the present invention.

Reaction Scheme :



L-(+)-tartaric acid is much cheaper than D-(-)-tartaric acid, and greatly downs the production cost, which is very favorable for industrial-scale mass production of S-(-)-amlodipine. Preferably, the amount of L-(+)-tartaric acid is about 0.5~0.55 eq. to 1 eq. of (R,S)-amlodipine.

In one embodiment, (R,S)-Amlodipine is reacted with L-(+)-tartaric acid in dimethyl sulfoxide (DMSO) to give a precipitate, (R)-(+)-amlodipine-hemi-L-tartrate-DMSO-solvate, which is then filtered off. The amount of DMSO is about 4 – 6 times, preferably about 5 times, in volume (ml) to 1 gram of the racemic mixture, i.e., (R,S)-amlodipine. In case an excess of DMSO is used (e.g., about 10 ml of DMSO to 1 gram of (R,S)-amlodipine), about 10 % of (R)-(+)-amlodipine-hemi-L-tartrate-DMSO-solvate may exist in DMSO, which unfavorably causes lowering the optical purity of the final product, i.e., (S)-amlodipine.

In filtering-off (R)-(+)-amlodipine-hemi-L-tartrate-DMSO-solvate, any conventional filtration methods can be used, preferably under a reduced pressure. For example, conventional centrifugation methods can be used. In this case, a supernatant obtained by the centrifugation is used as the filtrate in the subsequent step. Therefore, the filtering-off process according to the present invention should be construed to include any applicable conventional methods for removing a precipitate.

Addition of methylene chloride to the filtrate gives a precipitate, i.e., (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate. The amount of methylene chloride may be about 100 – 200 % by volume based on the volume of DMSO used in the step (i).

The process of the present invention may further comprise a recrystallization step for forming (S)-(-)-amlodipine L-(+)-tartrate free from DMSO, i.e., (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate. The optical purity of (S)-amlodipine may be increased by further performing the recrystallization step. The recrystallization may be performed using an alcohol, including methanol.

The process of the present invention comprises treating with a base (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate to give optically pure (S)-(-)-amlodipine. The base includes, but not limited to, a metal hydroxide, an oxide, a carbonate, a bicarbonate, and an amide. Preferably, the base is sodium bicarbonate. Further, the treatment with a base may be performed in an organic solvent, preferably methylene chloride.

The present invention also includes, within its scope, synthetic intermediates for the preparation of S-(-)-amlodipine. That is, the present invention provides (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate, each being useful for the preparation of S-(-)-amlodipine. (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate may be in a form of 1/4-, 1/2-(i.e., hemi-), or mono- DMSO solvate; or in a form of the mixture thereof, e.g., the mixture of 1/4- and 1/2- DMSO solvate. Preferably, (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate is the form of 1/4-DMSO solvate, i.e., (S)-(-)-amlodipine-hemi-L-tartrate-1/4-DMSO-solvate.

Although the present invention may be more detailed explained by reference to the following Examples, the following Examples are not intended to limit the scope of the present invention.

Example 1. Preparation of S-(-)-amlodipine from (R,S)-amlodipine

(1) (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate

The solution of L-(+)-tartaric acid (1.872 g, 0.51 mole equivalents) in dimethyl sulfoxide (25 ml) was added to the solution of (R,S)-amlodipine (10 g, 24.46 mmole) in dimethyl sulfoxide (25 ml) under stirring. Precipitation was observed within 5 minutes after the addition, and the resulting slurry was stirred overnight at room temperature. The resulting solid was filtered off. CH_2Cl_2 (50 ml) was added to the obtained filtrate, which was then stirred at room temperature for 40 hours. The resulting slurry was cooled to 5 ℃, stirred for 2 hours, and then filtered. The resulting solid was dried overnight at 50 ℃ *in vacuo* to give a solid (5.48 g) having the following ^{1}H-NMR data. Fig. 1 shows the ^{1}H-NMR chart of the solid, which means that the solid is (S)-(-)-amlodipine-hemi-L-tartrate-1/4-DMSO-solvate.

^{1}H-NMR (CD_3OD): 7.04-7.41(m, 4H), 5.40(s, 1H), 4.72(gq, 2H), 4.36(s, 1H), 4.02(m, 2H), 3.77(m, 2H), 3.57(s, 3H), 3.28(m, 2H), 2.65(s, DMSO), 2.31(s, 3H), 1.15(t, 3H)

(2) (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate

The (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate (5.48 g) obtained in Step (1) was refluxed in methanol (25 ml) to obtain a solution. The solution was cooled to room temperature. The resulting slurry was stirred overnight at room temperature and filtered to obtain a solid. The solid was dried overnight at 50 ℃ *in vacuo* to give a solid (4.92 g) having the following ^{1}H-NMR data. Fig. 2 shows the ^{1}H-NMR chart of the solid, which means that the solid is (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate.

^{1}H-NMR (CD_3OD): 7.04-7.41(m, 4H), 5.40(s, 1H), 4.72(gq, 2H), 4.34(s, 1H), 4.04(m, 2H), 3.77(m, 2H), 3.57(s, 3H), 3.29(m, 2H), 2.33(s, 3H), 1.15(t, 3H)

(3) S-(-)-amlodipine

2N $NaHCO_3$ (44 ml) was added to the slurry of (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate (4.92 g) obtained in Step (2) in CH_2Cl_2 (44 ml) at 5 ℃. The reaction mixture was stirred for 20 minutes. The resulting organic layer was washed with water twice and concentrated. The solution of the resulting mixture in the mixed solvent of 30 ml of n-hexane and ethyl acetate (2:1, v/v) was cooled to 5 ℃ and filtered. The resulting solid was dried overnight at 50 ℃ *in vacuo* to give S-(-)-amlodipine (3.45 g).

Yield : 69 %

Melting Point : 108-110 ℃

^{1}H-NMR (CD_3OD) 7.03-7.41(m, 4H), 5.39(s, 1H), 4.67(gq, 2H), 3.98-4.06(m, 2H), 3.55-3.58(t, 2H), 3.57(s, 3H), 2.86(m, 2H), 2.33(s, 3H), 1.15(t, 3H)

$[\alpha]_D^{25}$ = -31.2 (c=1, MeOH)

Chiral HPLC : 97.9 %e.e.

Example 2.

The procedure of Step (3) in Example 1 was repeated, except that (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate (3 g) prepared in accordance with Step (1) of Example 1 was used instead of (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate, to obtain 2.1 g of S-(-)-amlodipine.

$[\alpha]_D^{25}$ = -26.4 (c=1, MeOH)

CLAIMS

1. A process for the preparation of S-(-)-amlodipine, which comprises:

(i) reacting (R,S)-amlodipine with L-(+)-tartaric acid in dimethyl sulfoxide (DMSO);

(ii) filtering off the resulting precipitate of the step (i);

(iii) precipitating (S)-(-)-amlodipine-hemi-L-tartrate-1/4DMSO-solvate by adding methylene chloride to the filtrate of the step (ii);

(iv) optionally forming (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate by adding an alcohol to (S)-(-)-amlodipine-hemi-L-tartrate-1/4DMSO-solvate obtained in the step (iii); and

(v) treating with a base (S)-(-)-amlodipine-hemi-L-tartrate-1/4DMSO-solvate obtained in the step (iii) or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate obtained in the step (iv).

2. The process of claim 1, wherein the amount of L-(+)-tartaric acid is about 0.5~about 0.55 eq. to 1 eq. of (R,S)-amlodipine.

3. The process of claim 1, wherein the amount of DMSO is about 4-6 times in volume (ml) to 1 gram of (R,S)-amlodipine.

4. The process of claim 1, wherein the amount of methylene chloride in the step (iii) is about 100-200% by volume based on the volume of DMSO used in the step (i).

5. The process of claim 1, wherein the alcohol is methanol.

6. The process of claim 1, wherein the base is a metal hydroxide, an oxide, a carbonate, a bicarbonate, or an amide.

7. The process of claim 6, wherein the base is sodium bicarbonate.

8. The process of claim 1, wherein the step (v) is performed in an organic solvent.

9. The process of claim 8, wherein the organic solvent is methylene chloride.

10. (S)-(-)-amlodipine-hemi-L-tartrate-1/4DMSO-solvate.

11. (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate.

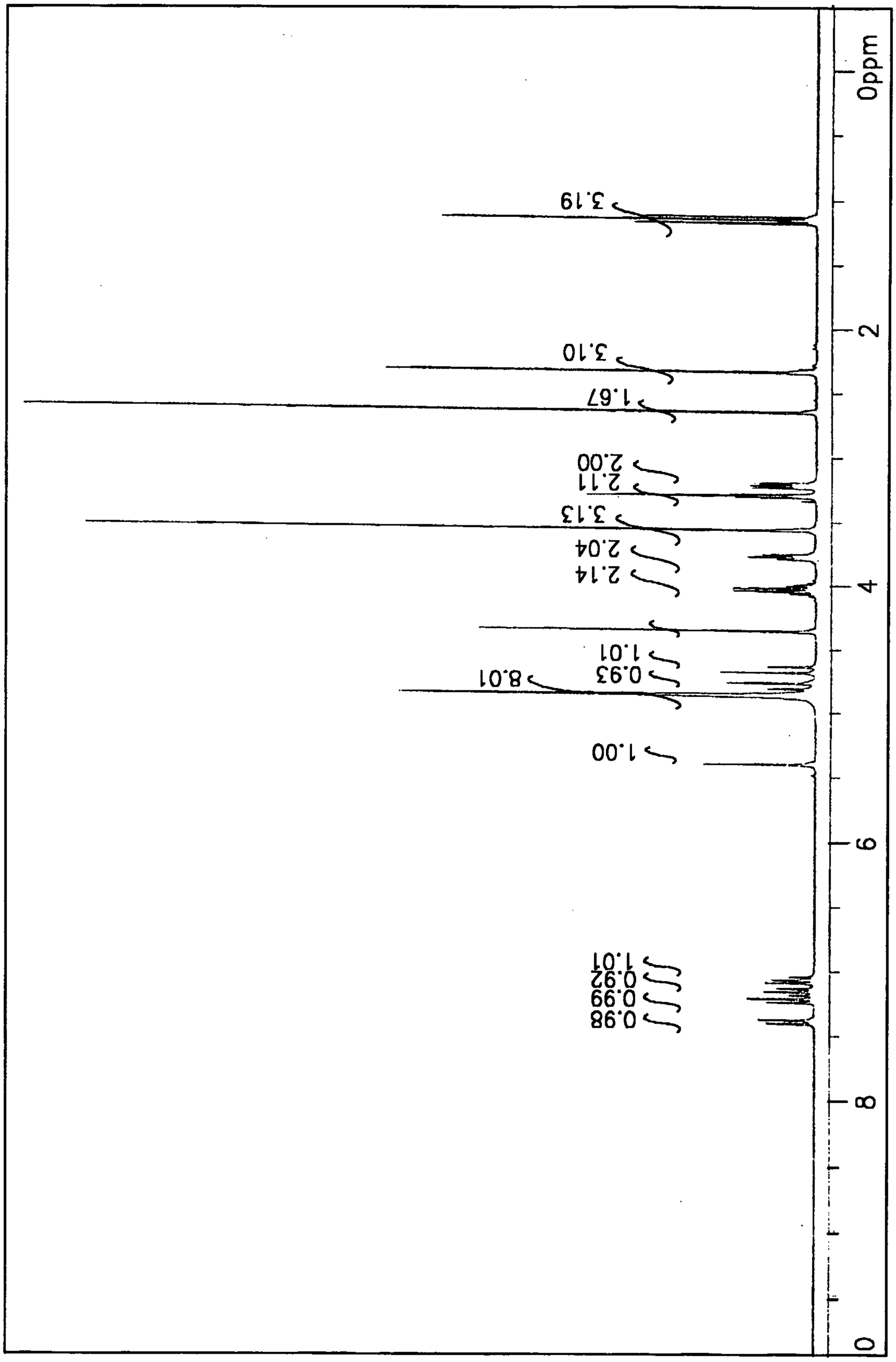

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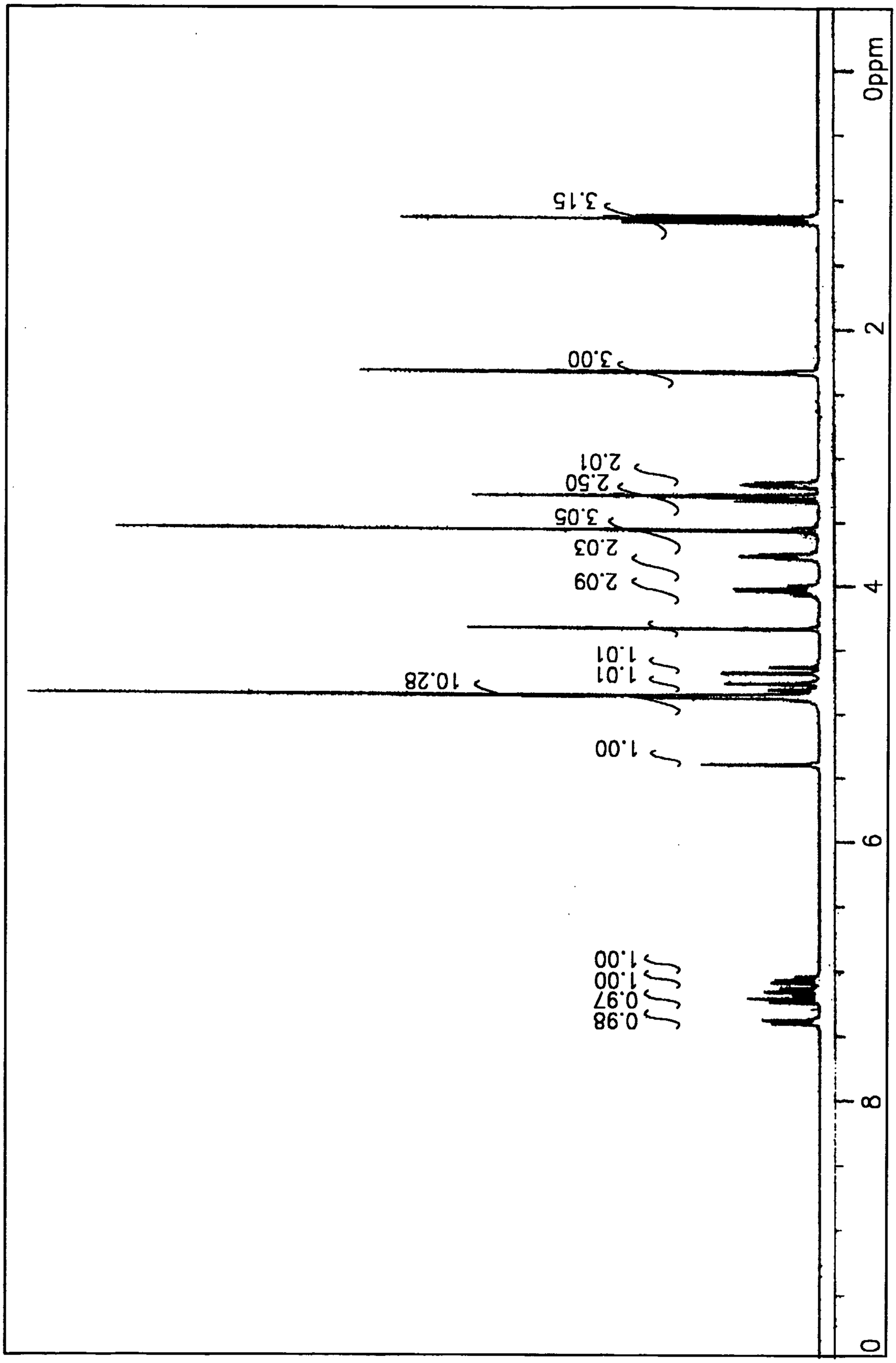
FIG. 1

FIG. 2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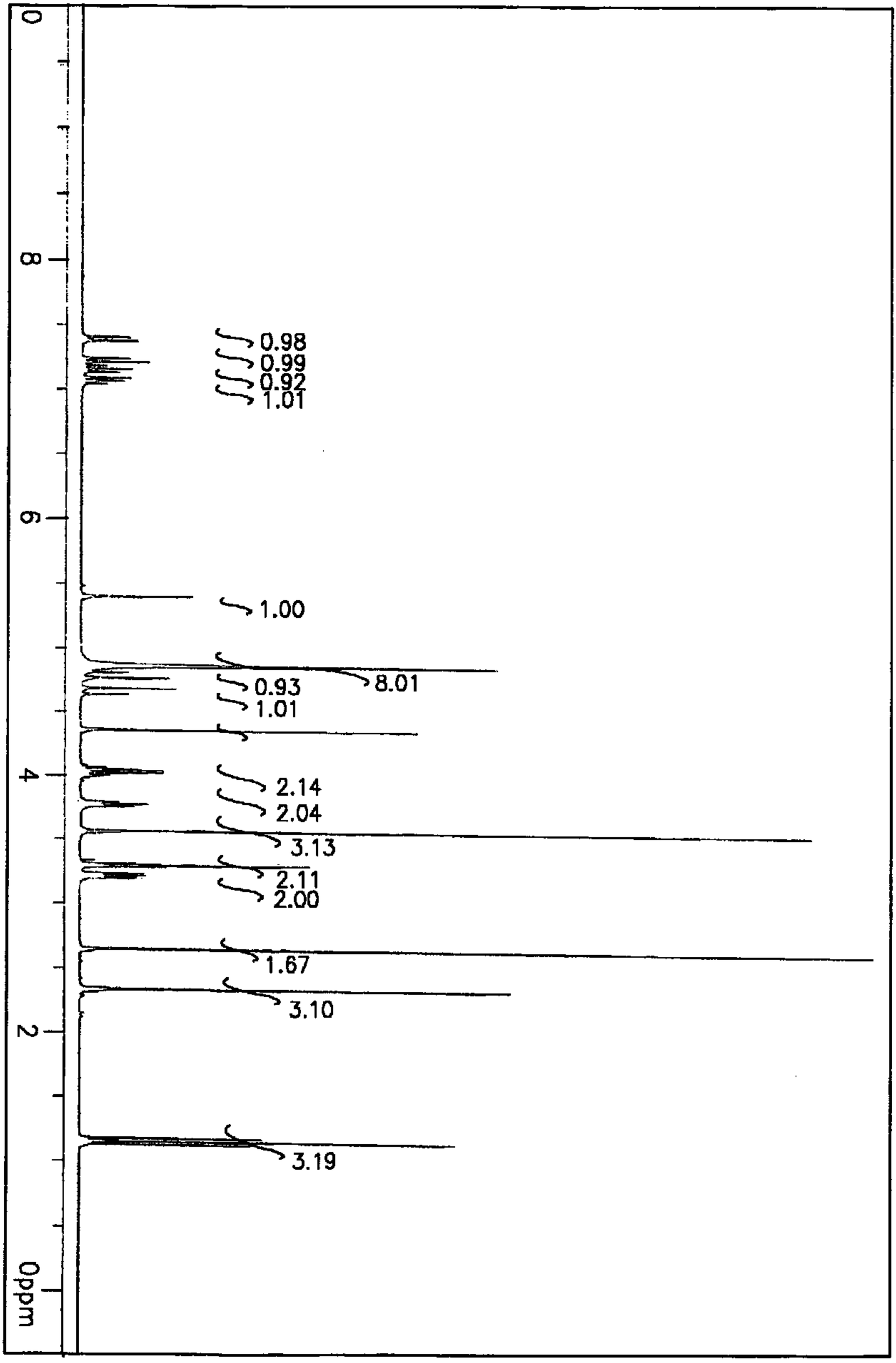
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