Improved synthesis scheme for lacosamide

The present invention is concerned with an improved method of producing (R)-2-acetamido-N-benzyl-3-methoxypropionamide (lacosamide) comprising the O-methylation of a compound of formula I to produce a compound of formula II in a single step reaction.
Description

[0001] (R)-2-acetamido-N-benzyl-3-methoxypropionamide (recommended INN: lacosamide) is an anticonvulsant drug useful for treating epilepsy and pain. Two methods for producing this compound are disclosed in US 6,048,899.

[0002] Scheme 2 of US 6,048,899 comprises the benzylamide formation prior to the O-methylation. However, this reaction scheme results in various impurities which must be removed by chromatography which is impractical on an industrial scale. Also, the yield of the individual steps is only between 80 and 85%.

[0003] Scheme 1 of US 6,048,899 involves the O-methylation of an N-protected D-serine prior to benzylamide formation, N-deprotection and N-acetylation. Although, this production scheme is a more promising starting point for upscaling it suffers from major deficiencies. Most importantly, the O-methylation of N-protected D-serine using silver (I) oxide and methyl iodide is impractical and expensive and results in partial racemisation (about 15%) which reduces the yield of this step to 79%. Also, the removal of the S-enantiomer during production of (R)-2-acetamido-N-benzyl-3-methoxypropionamide is extremely difficult.

[0004] It has now been detected, surprisingly, that the racemisation can be avoided by using alternative O-methylation methods, such as e.g. O-methylation using phase transfer catalysis or O-methylation using organolithium and a suitable methylation agent, such as dimethyl sulfate.

[0005] Also, the present invention provides an improved lacosamide synthesis route, wherein the O-methylation method is selective for the alcoholic hydroxy group of the N-protected D-serine. Accordingly, compared to the unspecified methylation suggested in scheme 1 of US 6,048,899, which also leads to the esterification of the carboxylic group, the present invention results in a shortened, more effective synthesis, wherein the subsequent step of hydrolysing the methyl ester group of an intermediate is avoided.

[0006] Accordingly, the present invention relates to an improved method of producing (R)-2-acetamido-N-benzyl-3-methoxypropionamide comprising the O-methylation of a compound of formula I

![formula I]

\[
\text{formula I}
\]

to produce a compound of formula II

![formula II]

\[
\text{formula II}
\]

wherein Rx is an N-protecting group, characterised in that the O-methylation is being carried out in a one-step reaction and wherein racemisation is avoided such that the compound of formula II is obtained as an R-enantiomer of at least 88%, preferably at least 90% and even more preferred of at least 95, 96, 97, 98 or 99 % enantiomeric purity.

[0007] The language "one-step reaction" as used in this patent application means that when transforming a compound of formula I to a compound of formula II no significant amount (i.e. an amount of 5 Mol% or more) of ester of the carboxyl group from is formed that needs to be hydrolysed in a separate step. Usually, even less than 1 Mol% of ester is formed which is then removed during the further processing to lacosamide as described further below without the need for any additional hydrolysis step.

[0008] The inventive O-methylation can be achieved by adding to a compound of formula I, such as e.g. to N-Boc-D-serine, a methylation agent in the presence of an organo lithium compound. Suitable methylation agents are e.g. dimethyl sulphate, trimethyl phosphate or methyl iodide with dimethyl sulphate being particularly preferred. The organo lithium compound is preferably an alkyl lithium compound, such as butyllithium, methyllithium or hexyllithium. More preferable the organo lithium compound is t-butyllithium or n-butyllithium. THF/2-methoxyethyl ether mixtures, diethoxymethane or, preferably, THF may be used as solvent. The reaction is usually allowed to proceed for at least 5 hours at 0-10°C, and preferably for 7-24 hours at 0-10 °C, most preferably for 9-18
hours at 0-5°C. Also, the reaction may be performed at higher or lower temperatures such as any temperature between -10 and +25°C if the reaction time is adopted accordingly.

If the N-protecting group Rx of the compound of formula I is N-Boc a typical reaction can be illustrated by the following scheme (step 1-A)

\[ \text{BocHN} \xrightarrow{(i) \text{ Butyllithium}} \xrightarrow{(ii) \text{CH}_3\text{SO}_4} \text{OH} \]

\[ \text{N-Boc-D-serine} \]

\[ \text{OH} \]

\[ \xrightarrow{\text{THF}} \]

\[ \text{O} \]

\[ \text{Me} \]

\[ \text{Butane + CH}_3\text{LiSO}_4 \cdot \text{CH}_3\text{SO}_4 \]

\[ (R)-2-\text{((t-butoxy)carbonylamino)-3-methoxypropanoic acid} \]

Surprisingly, this process does not result in methyl ester formation or significant racemisation of the product. The yield is 91%, with the major impurities being N-methylations.

Typically the amount of ester impurity after step 1a is significantly below 1 Mol% and is regularly below the limit of detection.

In an alternative route the selective O-methylation of the alcoholic group of N-protected D-serine is performed by phase transfer catalysis ("PTC"). PTC is a method that makes use of heterogeneous two-phase systems - one phase being an aqueous or solid phase and a reservoir of reacting anions or a base for the generation of organic anions, whereas the organic reactants and catalysts are located in the second, organic phase.

Usually, a quaternary ammonium, phosphonium or sulfonium salt, such as e.g. a tetraalkylammonium halide, is used as phase transfer catalyst. Suitable catalysts and PTC reagents can be purchased from many vendors, e.g. from Sigma-Aldrich or Hawks Chemical.

Accordingly, one embodiment of the present invention relates to a method of producing lacosamide, characterized in that a compound of formula I is O-methylated to a compound of formula II by performing the reaction as a phase transfer catalysis.

Typically this method comprises the addition of a methylation reagent, such as dimethylsulfate, methyl iodide or trimethyl phosphate to a phase transfer reaction system comprising the compound of formula I, an aqueous phase, an organic phase and a phase transfer catalyst.

In the PTC of the present invention preferably

(a) the methylation agent is selected from dimethylsulfate, methyl iodide or trimethyl phosphate, wherein dimethylsulfate is particularly preferred;
(b) the first (aqueous) phase is an alkaline aqueous solution, such as aqueous sodium hydroxide, aqueous lithium hydroxide, aqueous potassium hydroxide, aqueous sodium carbonate or aqueous potassium carbonate, wherein aqueous sodium hydroxide is particularly preferred;
(c) the second (organic) phase is selected from toluene, hexane, methylene chloride or methyl t-butyl ether, with toluene being particularly preferred and
(d) the phase transfer catalyst is an ammonium or phosphonium salt of formula IV, a sulfonium salt of formula V or a pyridinium salt of formula VI

\[ \text{formula IV} \]

\[ \text{formula V} \]
wherein R, R', R" and R'" are independently selectable alkyl, aryl or aralkyl groups, Q is a nitrogen or phosphorus and X is a halide, acetate, p-toluenesulfonate, trifluoromethanesulfonate, hexafluoroantimonate, hydroxide, perchlorate, hydrogensulfate, thiocyanate or tetrafluoroborate.

In the PTC of the present inventions suitable concentrations of components (a)-(d) as defined above are as follows:

(a) the amount of methylation agent is 1 to 5 molar equivalents with respect to the compound of formula I;
(b) aqueous alkali is provided as a 5 to 50% w/w solution and in an amount of 1.1 to 10 molar equivalents with respect to the compound of formula I;
(c) the amount of organic solvent with respect to the compound of formula I is preferably between 3-20 volumes;
(d) the amount of phase transfer catalyst is between 0.01 to 0.1 molar equivalents of the compound of formula I.

In formula IV to VI "aryl" comprises unsubstituted phenyl; unsubstituted naphtyl; phenyl or napthyl substituted with one or more substituents selected from e.g. halogen, nitro, C1-6 alkyl, C1-6 alkoxy, amino; substituted or unsubstituted heteroaryls such as pyrroyl; thienyl, indolyl, etc. In formula IV "aryl" is preferably chosen from unsubstituted phenyl or substituted phenyl, e.g. 2,6-difluorophenyl, p-nitrophenyl or p-toluyl. Unsubstituted phenyl is particularly preferred.

In formula IV to VI "alkyl" comprises branched or linear saturated hydrocarbon chains. Preferably "alkyl" is a hydrocarbon with up to 20 carbon atoms. Preferred examples of "alkyl" are cetyl, octyl, heptyl, butyl, propyl, ethyl and methyl.

In formula IV to VI "aralkyl" means a group aryl-alkyl wherein "aryl" and "alkyl" are as defined above. Preferably "aralkyl" is benzyl.

The PTC reaction is usually allowed to proceed at 0-10 °C for at least 30 minutes, e.g. for 0.5 to 24 hours, preferably for at least 45 minutes and even more preferred for at least 1 hour.

A compound of formula I is obtainable from many vendors e.g. from Sima-Aldrich or Lancaster. N-Boc-D-serine can also be produced by reacting D-serine with di-t-butyl dicarbonate to N-Boc-D-serine in a phase transfer catalysis reaction using essentially the conditions (e.g. choice and concentration/amount of alkali, solvent, PCT-catalysts, temperature, reaction time etc) as described above, except that di-t-butyl dicarbonate is used as the reagent instead of a methylation agent.

If the N-protecting group of the compound of formula I is Boc (t-Butoxycarbonyl), a preferred PTC reaction can be illustrated by the following scheme (Step 1-B)
This reaction does not result in any racemisation or esterification of the product. Also, the yield is further improved with impurity levels of only about 1%.

Typically the amount of ester impurity after step 1-B is well below 1 Mol% and usually below the limit of detection.

The process of the current invention further comprises the step of processing the compound of formula II to a compound of formula III (Step 2).

The benzyl amide formation can be performed by adding to a compound of formula II an amount of benzylamine in the presence of

(a) a base such as triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium bicarbonate or a morpholine derivative, preferably 4-methylmorpholine and
(b) an activator of the carboxyl group such as a carbodiimide or an alkyl chloroformate, preferably isobutyl chloroformate.

This step 2 has been basically described in US 6,048,899.

Suitable protecting groups in the method according to the present invention are e.g. t-butoxycarbonyl (Boc) or carbobenzoxy (Cbz), with the Boc group being particularly preferred.

In the compound of formula III the protecting group Rx can be cleaved off to obtain (R)-2-amino-N-benzyl-3-methoxypropionamide by appropriate measures known from the art. For example, if the protecting group Rx is a carbobenzoxy group it may be cleaved off with H2, Pd/C as described in US 6,048,899. If the protecting group is a Boc group this group may be conveniently removed with an acid, such as hydrochloric acid, e.g. at room temperature (step 3).

(R)-2-amino-N-benzyl-3-methoxypropionamide can then be transformed to lacosamide by N-acetylation using acetic anhydride (step 4).
This step has been also described in US 6,048,899. However, US 6,048,899 suggests the use of acetic anhydride in the presence of pyridine. It has now been found unexpectedly that the pure (R)-enantiomer can be also obtained effectively if the toxic pyridine is removed from the reaction mixture.

One embodiment of the present invention is thus the production of lacosamide comprising a step of N-acetylation of (R)-2-amino-N-benzyl-3-methoxypropionamide with acetic anhydride in the absence of pyridine.

Finally, lacosamide can be isolated from the reaction mixture of step 4 with improved purity by crystallisation in appropriate solvents, such as ethyl acetate.

The invention also relates to important intermediates of the current process.

The most important intermediate (R)-2-N-Boc-amino-3-methoxypropanoic acid (C-936) results from the improved O-methylation step according to the present invention (see figure 1). The compound can be easily isolated from the reaction mixture as the free acid or by forming a salt, such as e.g. a cyclohexylammonium salt. Suitable C-936 salts are also regarded to be part of the invention.

Also, (R)-N-benzyl-2-N-Boc-amino-3-methoxypropionamide (C-937) which results from the benzyl amide formation (step 2 of figure 1) constitutes a part of the invention.

Another aspect of the invention pertains to a method of producing a pharmaceutical formulation by the subsequent steps of

(a) producing lacosamide by the method according to the present invention and
(b) mixing lacosamide with pharmaceutically acceptable excipients.

The invention is further illustrated by Figure 1 (comprising alternative steps 1a or 1b) and the following Examples:

Example 1: Production of (R)-2-N-Boc-amino-3-methoxypropanoic acid (C-936) using butyllithium (step 1a)

A solution of N-Boc-D-serine (22g, 0.107 mol) in dry tetrahydrofuran (352ml) was cooled to <-10°C under a nitrogen atmosphere. To this was added via a dry addition funnel 15% w/w n-butyllithium in hexanes (134ml, 0.216mol) keeping the temperature <10°C. The resultant slurry was aged for 1 hour at 0-5°C. Dimethyl sulphate (12.1 ml, 0.128mol) was added keeping the temperature at 0-5°C and the reaction mixture aged at 0-5°C for 9 hours. The reaction was quenched by the addition of water (110ml), basified to pH 10-13 with 30% sodium hydroxide (3ml) and the tetrahydrofuran/hexane evaporated in vacuo. The residue was washed with toluene (44ml) and then acidified to a pH of <3.5 with 50% citric acid. The acidified aqueous phase was extracted with methylene chloride (2x91 ml, 1x66ml) and the combined C936 extracts dried by azeotropic distillation. Yield on evaporation 23.7g, 100%. HPLC purity 90.0%, Chiral purity 100%.

Example 2: Production of (R)-2-N-Boc-amino-3-methoxypropanoic acid (C-936) using PTC (step 1b)

A suspension of N-Boc-D-serine (22g, 0.107 mol) and tetrabutylammonium bromide (1.3g, 0.004mol) in toluene (110ml) was cooled to <-10°C. To this was added 20% sodium hydroxide (17.6ml, 0.107mol) keeping the temperature <10°C and the resultant mixture was aged for 30 minutes at <10°C. Dimethyl sulphate (40.6ml, 0.429mol) and 50% sodium hydroxide (25.4ml, 0.485mol) were added keeping the temperature <10°C and the reaction mixture aged at 10°C for 1 hour. Water (66ml) was added to the mixture and the phases separated. The aqueous layer was acidified to a pH of <3.5 with 50% citric acid, extracted with methylene chloride (2x91 ml, 1x66ml) and the combined C936 extracts dried by azeotropic distillation. (Yield on evaporation 27.5g, 100%, HPLC purity 96.3%, Chiral purity 98.1%)
Example 3: Steps 2 to 4

**(R)-N-benzyl-2-N-Boc-amino-3-methoxypropionamide (C-937) solution (step 2)**

[0043] The C936 solution prepared as above in example 2 was cooled to <10°C and isobutyl chloroformate (14.2ml, 0.107mol) at <5°C. N-methylmorpholine (11.8ml, 0.17mol) was added at <5°C and the mixture aged for 30 minutes at <5°C. A solution of benzylamine (12.2ml, 0.11mol) in methylene chloride was added at <5°C and the mixture warmed to room temperature. After aging for 1 hour the mixture was washed with water (44ml), 1 N HCl (44ml), 8% sodium bicarbonate (44ml) and water (44ml) to yield a C937 solution in methylene chloride.

**(R)-2-amino-N-benzyl-3-methoxypropionamide solution (step 3)**

[0044] To the C937 solution prepared above was added 36% HCl (46.5ml, 0.541 mol) and the mixture aged for 1 hour. Water (66ml) was added and the phases separated. The organic phase was extracted with water (22ml) and the aqueous layers combined. The aqueous was basified to pH 10-12 with 30% sodium hydroxide at <35°C and sodium chloride (8.8g) added. The aqueous layer was extracted with methylene chloride (2x110ml) and the combined organic layers washed with water (44ml) yielding a methylene chloride solution of (R)-2-amino-N-benzyl-3-methoxypropionamide.

**Lacosamide (step 4)**

[0045] The (R)-2-amino-N-benzyl-3-methoxypropionamide solution prepared above was cooled to <5°C and acetic anhydride (10ml, 0.106mol) added at <15°C. The reaction mixture is warmed to room temperature over 30 minutes and aged for a further 30 minutes. The mixture is then washed with water (44ml), 8% sodium bicarbonate (44ml) and water (44ml). The methylene chloride was exchanged for ethyl acetate by distillation and the solution distilled to a volume of 115ml. The product was crystallised by cooling the solution to 0-5°C and the pure Lacosamide isolated by filtration (18.7g, 69.8%) HPLC purity 99.98%, Chiral purity 99.8% ee.

Example 4: Isolation of (R)-2-N-Boc-amino-3-methoxypropanoic acid (C-936)

[0046] The (R)-2-N-Boc-amino-3-methoxypropanoic acid (C-936) solution prepared in example 1 was evaporated in vacuo yielding (R)-2-N-Boc-amino-3-methoxypropanoic acid (C-936) as a waxy solid (23.7g, 100%). HPLC purity 90.0%. Elemental analysis Calculated for C_{9}H_{17}NO_{4} 49.31% C; 7.82% H; 6.39% N. Found 49.12% C; 7.72% H; 8.97% N.

Example 5: Isolation of (R)-N-benzyl-2-N-Boc-amino-3-methoxypropionamide (C-937)

[0047] The (R)-N-benzyl-2-N-Boc-amino-3-methoxypropionamide (C-937) solution prepared in example 3 above was evaporated in vacuo yielding crude C937 as an oily solid. The crude solid (2g) was dissolved in 10% chloroform in hexane (30ml) at 60°C, cooled to room temperature and left stand for 1 hour at this temperature. The resulting solids were isolated by filtration yielding crude C937 (1.1 g). This crude solid was further recrystallised twice in 10 volumes of 10% chloroform in hexane to yield (R)-N-benzyl-2-N-Boc-amino-3-methoxypropionamide (C-937) as a white crystalline solid (0.28g, 14%). HPLC purity 97.3%. Elemental analysis Calculated for C_{16}H_{24}N_{2}O_{5} 62.32% C; 7.84% H; 9.08% N. Found 62.19% C; 7.79% H; 9.04% N.

**Claims**

1. Method of producing (R)-2-acetamido-N-benzyl-3-methoxypropionamide (lacosamide) comprising the O-methylation of a compound of formula I

![formula I](image)
wherein Rx is an N-protecting group, characterised in that the O-methylation is being carried out in a one-step reaction and wherein the compound of formula II is obtained as an R-enantiomer of at least 88 % purity.

2. Method according to claim 1, characterised in that the method is performed either (a) as a phase transfer catalysis or (b) by adding a methylation agent and an organo lithium compound to the compound of formula I.

3. Method according to one of the preceding claims, wherein the method comprises the addition of a methylation agent to a phase transfer reaction system comprising the compound of formula I, an aqueous phase, an organic phase and a phase transfer catalyst.

4. Method according to claim 3, wherein a pyridinium, phosphonium, ammonium or sulfonium salt is used as a phase transfer catalyst.

5. Method according to anyone of claims 3-4, wherein the phase transfer catalyst is chosen from compounds of

(a) general formula IV

\[ R\quad Q\quad R' \quad X \]

formula IV

(b) general formula V

\[ R\quad S\quad R' \quad X \]

formula V

or

(c) general formula VI

\[ \text{Pyridinium salt} \]

formula VI

wherein R, R', R'' and R''', if present, are independently selectable alkyl, aryl or aralkyl groups;
Q, in compounds of formula IV, is a nitrogen or phosphorus; and
X is a halide, acetate, p-toluenesulfonate, trifluoromethanesulfonate, hexafluoroantimonate, hydroxide, perchlorate, hydrogensulfate, thiocyanate or tetrafluoroborate group.

6. Method according to anyone of claims 3-5, wherein the phase transfer catalyst is tetrabutylammonium bromide.

7. Method according to anyone of claims 3-6, wherein the methylating agent used in the phase transfer catalysis is chosen from dimethyl sulphate, trimethyl phosphate or methyl iodide.

8. Method according to anyone of claims 3-7, wherein the aqueous phase is aqueous sodium hydroxide, aqueous lithium hydroxide, aqueous potassium hydroxide, aqueous sodium carbonate or aqueous potassium carbonate.

9. Method according to anyone of claims 3-8, wherein the organic solvent is toluene, hexane, methylene chloride or methyl t-butyl ether.

10. Method according to anyone of claims 2-9, wherein the phase transfer catalysis is performed at 0-10 °C for at least 30 minutes.

11. Method according to anyone of claims 1 or 2, wherein the methylation agent used with the organo lithium compound is dimethylsulfate.

12. Method according to anyone of claims 2 or 11, wherein the organo lithium compound is butyl lithium.

13. Method according to claims 2 or 11 to 12, wherein the O-methylation in the presence of an organo lithium compound takes place at a temperature of 0-10°C for at least 5 hrs.

14. Method according to anyone of the preceding claims further comprising the reaction of compound II with benzylamine to give the compound of formula III,

\[
\text{formul}a \ III
\]

and then replacing the protecting group Rx with methyl carbonyl to give (R)-2-acetamido-N-benzyl-3-methoxypropionamide (lacosamide).

15. Method according to claim 14, wherein the reaction of the compound of formula II with benzylamine takes place in the presence of an activator of the carboxyl group and a base.

16. Method according to claim 15, wherein the base is 4-methylmorpholine, triethylamine, disopropylethalamine, 1.8-diazabicyclo[5.4.0]undec-7-ene or potassium bicarbonate and the activator of the carboxyl group is an alkyl chloroformate or a carbodiimide.

17. Method according to anyone of claims 14-16, wherein the N-protecting group Rx is replaced by methyl carbonyl by successively

(a) cleaving off the protecting group Rx from the compound of formula III by the addition of (i) a mineralic acid or (ii) H₂/Pd-C to yield (R)-2-amino-N-benzyl-3-methoxypropionamide and then
(b) adding the methyl carbonyl group to (R)-2-amino-N-benzyl-3-methoxypropionamide by the reaction of (R)-2-amino-N-benzyl-3-methoxypropionamide with acetic anhydride.

18. Method according to claim 17, wherein step (b) is performed in the absence of pyridine.
19. Method according to anyone of the preceding claims wherein lacosamide is isolated from the final reaction mix by crystallisation.

20. Method according to anyone of the preceding claims wherein the N-protecting group is t-butoxy carbonyl (Boc).

21. Method of producing (R)-2-acetamido-N-benzyl-3-methoxypropionamide (lacosamide) comprising the step of N-acetylation of (R)-2-amino-N-benzyl-3-methoxypropionamide with acetic anhydride in the absence of pyridine.

22. (R)-2-N-Boc-amino-3-methoxypropanoic acid (C-936) and salts thereof.

23. (R)-N-benzyl-2-N-Boc-amino-3-methoxypropionamide (C-937).

24. Use of a compound according to claim 22 or 23 in a method of producing (R)-2-acetamido-N-benzyl-3-methoxypropionamide (lacosamide).

25. Method of producing a pharmaceutical formulation comprising lacosamide by the subsequent steps of

   (a) producing lacosamide by anyone of the preceding claims and
   (b) mixing lacosamide with pharmaceutically acceptable excipients

**Figure 1**

**Step 1a**

(i) Butyllithium  
(ii) (CH$_2$)$_3$SO$_4$  

\[ \text{N-Boc-D-serine} \xrightarrow{\text{THF}} \text{BocHN}{}_{\text{OH}} \quad \xrightarrow{\text{butane} + \text{CH}_3\text{LiSO}_4 + \text{(CH}_3)_2\text{SO}_4} \text{BocHN}{}_{\text{O}} \text{Me} \]

(R)-2-((t-butoxy)carbonylamino)-3-methoxypropionic acid C936

**Step 1b**

(i) Aqueous NaOH  
(ii) (CH$_3$)$_2$SO$_4$  

\[ \text{N-Boc-D-serine} \xrightarrow{\text{Toluene} \quad \text{Tertabutyl ammonium bromide}} \text{BocHN}{}_{\text{OH}} \quad \xrightarrow{\text{(R)-2-((t-butoxy)carbonylamino)-3-methoxypropionic acid C936}} \text{BocHN}{}_{\text{O}} \text{Me} \]

**Step 2**

(i) Isobutyl chloroformate
(ii) Methyl morpholine  

\[ \text{BocHN}{}_{\text{OH}} + \text{BnNH}_2 \quad \xrightarrow{\text{CH}_2\text{Cl}_2} \text{BocHN}{}_{\text{NHBN}} \quad + \text{isoctanol} \quad \text{CO}_2 \quad + \text{4-Methylmorpholine.HCl} \]

\[ 308.4 \quad \text{C}_9\text{H}_{13}\text{N}_2\text{O}_4 \]  

(R)-N-benzyl-2-((t-butoxy)carbonylamino)-3-methoxypropionamide C937

**Step 3**

\[ \text{BocHN}{}_{\text{NHBN}} \quad \xrightarrow{\text{CH}_2\text{Cl}_2} \text{BocHN}{}_{\text{ON}} \text{Me} \quad + \text{H}_2\text{N} \quad \text{NHBN} \]

\[ 208.2 \quad \text{C}_5\text{H}_8\text{N}_2\text{O}_2 \]  

(R)-2-amino-N-benzyl-3-methoxypropionamide

**Step 4**

Acetic Anhydride  

\[ \text{H}_2\text{N}{}_{\text{NHBN}} \quad \xrightarrow{\text{CH}_2\text{Cl}_2 \quad 0 - 5^\circ\text{C}} \text{AchHN}{}_{\text{NHBN}} \quad + \text{Acetic Acid} \]

\[ 250.3 \quad \text{C}_9\text{H}_{14}\text{N}_3\text{O}_3 \]  

(R)-2-acetamido-N-benzyl-3-methoxypropionamide
### DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<th>Category</th>
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The present search report has been drawn up for all claims

Place of search: The Hague

Date of completion of the search: 17 February 2005

Examiner: Fitz, W

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