Abstract:
The invention relates to a process for producing an optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one (Cis-lactam). More particularly, this invention relates to a process for making (2R,3S)-3-(4-methoxyphenyl)glycic acid methyl ester employing enzymes, which is simple, industrially applicable and economically viable.
## INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

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

**B. FIELDS SEARCHED**

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

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

- EPO-Internal
- WPI Data
- COMPENDEX
- FSTA
- BIOSIS
- EMBASE
- CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WANG, Y. ET AL.: &quot;Significantly Improved Expression and Biocatalytic Properties of Recombinant Serratia marcescens Lipase as Robust Biocatalyst for Kinetically Resolved Chi Rat Ester&quot;. APPLIED BIOCHEMISTRY AND BIOTECHNOLOGY, vol. 162, no. 8, December 2010 (2010-12), pages 2387-2399, XP002720358, page 2390, line 23 - line 31; page 2396, line 1 - page 2397, line 6; figure 7; table 4; page 2397, line 19 - line 22</td>
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- See patent family annex.

**Date of the actual completion of the international search**

14 February 2014

**Date of mailing of the international search report**

19/05/2014

**Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016**

**Authorized officer**

Fuchs, Ulrike
### Observations where certain claims were found unsearchable
(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Observations where unity of invention is lacking
(Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   I-5(partial ly)

#### Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.
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<td>ZHAO, L. L. ET AL.: &quot;Bioc hemi cal properties and potenti al applications of an organi c sol vent-toler ant lipase isolated from Serrati a marcescens ECUIOIO&quot;, PROCESS BIOCHEMISTRY, vol. 43, no. 6, June 2008 (2008-06), pages 626-633, XP022637311, page 626 - page 627, paragraph 1 page 628, colon umn 1, line 28 - line 33 page 630, colon umn 1, line 33 - colon umn 2, line 2 page 631; table 5; compound 3a</td>
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<td>Wo 90/04643 AI (SEPRACOR, INC.) 3 May 1990 (1990-05-03) page 1, line 15 - line 28 page 1, line 32 - page 2, line 3 page 3, line 5 - line 11 page 8, line 24 - page 10, line 2 page 12, paragraph 5 - page 25, paragraph 5.2.3; examples 1, 2 page 28 - page 29; tables 1, 2 page 32, line 1 - page 33, line 7 page 34, paragraph 5.2.9 page 36; table 8 page 38 - page 39, paragraph 5.2.12; example 12 page 45, line 12 - line 34 page 61 - page 62, paragraph 5.4.8; example 24 page 64; table 12 page 66, paragraph 5.4.12 - page 70, paragraph 5.4.13; examples 28, 29; table 14 page 74 - page 76, paragraph 5.5.1; tables 16, 17 page 84 - page 89; claims 1, 2, 5, 8, 13, 15, 16, 33-36, 39-42, 44 figures 3-9</td>
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This International Search has multiple (groups of) inventions in this International application, as follows:

1. Claims: 1-5 (partially)

   process for producing an optically active (2R,3S)-3-(4-methoxyphenyl)glycine diacid methyl ester, comprising enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl)oxirane-2-carboxylate with an enzyme, where n the enzyme is obtained from Serratia marcescens

2. Claims: 1-5 (partially)

   process for producing an optically active (2R,3S)-3-(4-methoxyphenyl)glycine diacid methyl ester, comprising enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl)oxirane-2-carboxylate with an enzyme, where n the enzyme is obtained from Candida cylindracea

3. Claims: 6-8 (partially)

   process for producing an optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-l,5-benzotriazepine 4-(5H)-one of formula (I) comprising:
   (a) enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl)oxirane-2-carboxylate of formula (2R,3S)·MMPG of step (a)
   (b) optically isolated non-hydrolyzed (2R,3S)-3-(4-methoxyphenyl)glycine diacid methyl ester of formula (2R,3S)·MMPG of step (a)
   (c) treatment of (2R,3S)-3-(4-methoxyphenyl)glycine diacid methyl ester with 2-amino-3-phenol to obtain n an optically active

4. Claims: 6-8 (partially)

   process for producing an optically active (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-l,5-benzotriazepine 4-(5H)-one of formula (I) comprising:
   (a) enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl)oxirane-2-carboxylate of formula (2R,3S)·MMPG of step (a)
   (b) optically isolated non-hydrolyzed (2R,3S)-3-(4-methoxyphenyl)glycine diacid methyl ester of formula (2R,3S)·MMPG of step (a)
   (c) treatment of (2R,3S)-3-(4-methoxyphenyl)glycine diacid methyl ester with 2-amino-3-phenol to obtain n an optically active
(2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one of formula (I)

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5. Claims: 9-13 (partially)

process for producing 4-methoxy phenyl acetic acid comprising the steps:
(a) enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate with an enzyme, where the enzyme is obtained from Serratia marcescens,
(b) interconversion of the hydrolyzed (3R,2S)-3-(4-methoxyphenyl)glycidic acid of step (a) to 4-methoxy phenyl acetaldehyde,
(c) optionally isolating 4-methoxy phenyl acetaldehyde of step (b), and
(d) treating the 4-methoxy phenyl acetaldehyde with oxidizing reagent to obtain 4-methoxy phenyl acetic acid

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6. Claims: 9-13 (partially)

process for producing 4-methoxy phenyl acetic acid comprising the steps:
(a) enantioselective hydrolysis of racemic methyl 3-(4-methoxyphenyl) oxirane-2-carboxylate with an enzyme, where the enzyme is obtained from Candida cylindracea,
(b) interconversion of the hydrolyzed (3R,2S)-3-(4-methoxyphenyl)glycidic acid of step (a) to 4-methoxy phenyl acetaldehyde,
(c) optionally isolating 4-methoxy phenyl acetaldehyde of step (b), and
(d) treating the 4-methoxy phenyl acetaldehyde with oxidizing reagent to obtain 4-methoxy phenyl acetic acid

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