The present invention provides an improved process for the preparation of Linezolid of formula (I). The present invention relates to preparation of intermediate (R)-N-[3-[3-fluoro-4-morpholinyl] phenyl]-2-oxo-5-oxazolidinyl] methanol of formula (II), Linezolid amine of formula (Ia) and their use in the preparation of Linezolid. The present invention further provides process for the preparation of Form I of Linezolid of formula (I).
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(b))
— of inventorship (Rule 4.17(iv))

Published:
— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
Description

Title of Invention: PROCESS FOR THE PREPARATION OF LINEZOLID

Field of the invention

The present invention provides an improved process for the preparation of Linezolid of formula (I).

Formula (I)

The present invention relates to preparation of intermediate (R)-N-[[3-[3-fluoro-4-morpholinyl] phenyl]-2-oxo-5-oxazolidinyl] methanol of formula (II), Linezolid amine of formula (la) and their use in the preparation of Linezolid.

Formula (II)

Formula (la)

The present invention further provides process for the preparation of Form I of Linezolid of formula (I).

Background of the invention

Linezolid is chemically known as \( \text{N} \cdot \text{[(5S)} \cdot -3-[3-\text{Fluoro}-4-(4-\text{morpholinyl})\text{phenyl}]-2-\text{oxo}-5-\text{oxazolidinyl}]\text{methyl} \) acetamide and marketed by Pfizer in US under brand name Zyvox. Linezolid is a synthetic antibacterial agent of the oxazolidinone class. It is used for the treatment of infections...
caused by multi-resistant bacteria including *streptococci* and methicillin-resistant *Staphylococcus aureus*.

[8] Linezolid was first disclosed in U.S. Pat. No. 5,688,792. The process for synthesis is as disclosed in Scheme-I

![Scheme-I](image)

[10] In the process disclosed above the key intermediate (II) is obtained by reacting N-carbobenzyloxy-3-fluoro-4-morpholinyl aniline of formula (IVa) with (R)-glycidyl butyrate of formula (III) in the presence of n-butyl lithium to obtain compound of formula (II). Compound of formula (II) is converted to (lib) by tosylation and reaction with sodium azide. Reduction of Linezolid azide of formula (lib) in the presence of palladium/carbon in ethyl acetate solvent to obtain Linezolid amine (la), which is further treated with acetic anhydride in presence of pyridine to obtain Linezolid of formula (I). The purification process involves chromatography and separating the desired fraction, followed by evaporation and triturating the product to obtain pure Linezolid.

[11] The polymorphic form obtained by following process disclosed in U.S. Pat. No. 5,688,792 is designated as Form I. Figure-1 depicts the PXRD graph of Form I obtained by following prior art process.
Disadvantage of the process disclosed in U.S. Pat. No. 5,688,792 is that it involves use of n-butyl lithium. Due to its explosive nature it is difficult to handle at plant scale. Also, the said reaction is carried out at temperature of -78°C, which is difficult to attain during commercial production. Further the intermediate obtained requires purification by column chromatography. Column chromatography is a cumbersome technique and difficult to practice during commercial scale production. The above described process to obtain pure Linezolid results in very low yields. Further, such a process is difficult to follow at commercial level. Also, practice of chromatographic techniques requires large quantities of solvent and its subsequent recovery which increases the overall cost of production.

The process for the preparation of Linezolid is also disclosed in Journal of Medicinal Chemistry (1996), 39(3), 673-9, U.S. Pat. Nos. 6,492,555, 5,837,870, 6,887,995, 7,307,163, 7,429,661, etc.

None of the above mentioned prior arts offer simple and cost effective method for the production of compound of formula (I) from compound of formula (Ia). Nor any of the prior art process describes a process for preparation of Form I of Linezolid. Therefore, there is need to develop an efficient method, which is simple, cost-effective and commercially scalable for synthesis of Linezolid of formula (I) from Linezolid amine of formula (Ia). Further, it would be desirable to develop a process for preparation of Form I of Linezolid which is reproducible.

Object of the invention

It is an object of the present invention to provide a process for the preparation of Linezolid formula (I).

Another object of the present invention is to provide process for the preparation of compound of formula (II).

Another object of the present invention is provided a process for preparing Form I of Linezolid of formula (I).

Summary of the invention
[29] An aspect of the present invention provides a process for the preparation of Linezolid of formula (I) comprising a step of

reacting compound of formula (IV), wherein R is Hydrogen or Nitrogen protecting group, with compound of formula (III) in presence of n-butyl lithium and n-butanol in a suitable solvent to obtain compound of formula (II)

[32] Another aspect of the present invention provides an improved process for the preparation of compound of formula (II) comprising of

reacting compound of formula (IV), wherein R is Hydrogen or Nitrogen protecting group, with compound of formula (III) in presence of n-butyl lithium and n-butanol in a suitable solvent to obtain compound of formula (II)
Yet another aspect of present invention provides a process for preparation of Linezolid and its key intermediate which is simple, safe, cost-effective and easy to follow at commercial scale.

In one embodiment of the present invention is provided a process for the preparation of Linezolid of formula (I) comprising,

acylating Linezolid amine of formula (la) using acylating agent in the presence of ketonic solvent.

In another embodiment of the present invention is provided a process for preparing Form I of Linezolid of formula (I) comprising steps of:

(a) acylating Linezolid amine of formula (la) using acylating agent in the presence of ketonic solvent.
(b) crystallizing Linezolid obtained in step (a) from suitable solvent.

Linezolid obtained by the process of present invention has content of (R)-enantiomer less than about 0.1% and bis-Linezolid content less than 0.15%. Further the purity of Linezolid is more than 99% and the yield of the reaction is high.

Therefore, the process of present invention can be employed advantageously by avoiding the cumbersome and lengthy procedure of chromatography.

Brief description of the invention

Figure-1: PXRD graph of Form I obtained by following prior art process.

Figure-2: FTIR (Nujol) Form I obtained by following prior art process.

Figure-3: PXRD graph of Form I obtained by following Example 9.

Figure-4: FTIR (Nujol) Form I obtained by following Example 9.

Detailed description of the invention

The present invention provides a process for the preparation of Linezolid of formula (I) comprising a step of

reacting compound of formula (IV), wherein R is Hydrogen or Nitrogen protecting group, with compound of formula (III) in presence of n-butyl lithium and n-butanol in a suitable solvent to obtain compound of formula (II)
Another preferred embodiment of the present invention provides an improved process for the preparation of compound of formula (II) comprising of reacting compound of formula (IV) wherein R is Hydrogen or Nitrogen protecting group, with compound of formula (III) in presence of n-butyl lithium and n-butanol in a suitable solvent to obtain compound of formula (II)

The compound of formula (IV) can be prepared by any process disclosed in the prior art or methods known perse.

In one of the preferred embodiment compound of formula (IV) wherein R is
Nitrogen protecting group preferably carbobenzoxy group is prepared by the process disclosed in Scheme-II. The compound of formula (IV) is converted to compound of formula (II) by reacting compound of formula (IV), with compound of formula (III) i.e. (R)-(-)-Glycidyl butyrate in the presence of n-butyl lithium and n-butanol in a suitable solvent.

The example of suitable solvent includes but is not limited to tetrahydrofuran. The reaction is carried out in the temperature range of -30°C to 30°C. The reaction proceeds via formation of lithium salt of n-butanol.

After the completion of reaction the reaction mass is worked-up and the product obtained is used as such without further purification for the next step.

Compound of formula (II) is converted to Linezolid via formation of mesylate which is converted to azide by the methods known per se. The azide is reduced and acylated to obtain Linezolid.

In another embodiment of the present invention, Linezolid of formula (I) is prepared by process comprising acylating Linezolid amine of formula (la) using acylating agent in the presence of ketonic solvent.

As used herein, acylating agent refers to acetic anhydride, acetyl chloride, acetic acid or any such reagent which is capable of introducing acetyl group.

As used herein, ketonic solvents refers to acetone, methyl iso-butyl ketone, methyl
ethyl ketone, and the like or mixtures thereof.

The step of acylation is carried out at about 0°C to about room temperature, preferably at about 0°C-5°C.

Linezolid amine of formula (la) can be used directly or without isolation after the step of reduction from Linezolid azide of formula (lib). The step of reduction of Linezolid azide of formula (lib) is preferably carried out using palladium on carbon in presence of ethyl acetate as solvent.

In a preferred embodiment of the present invention, a one pot process is provided wherein Linezolid amine of formula (la) is not isolated from the reduction mixture, but the residue obtained after removal of catalyst and solvent used for reduction step, is converted to Linezolid of formula (I) by acylation using acylating agent in the presence of ketonic solvent.

Following comparison table indicates the content of (R)-enantiomer, bis-Linezolid impurity and purity of Linezolid when acylation is carried out in ethyl acetate and acetone:

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<th>Sr. No.</th>
<th>Batch No.</th>
<th>UPLC Purity</th>
<th>Bis-Linezolid impurity</th>
<th>(R)-enantiomer</th>
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<td>Ethyl acetate</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>Batch-1</td>
<td>99.57</td>
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<td>0.08</td>
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<td>0.43</td>
</tr>
<tr>
<td>Acetone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>Batch-1</td>
<td>99.62</td>
<td>0.12</td>
<td>0.03</td>
</tr>
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<td>0.05</td>
</tr>
</tbody>
</table>

The data clearly indicates significant reduction in bis-Linezolid impurity and (R)-enantiomer when acylation reaction is carried out in the presence of acetone as solvent.
Therefore, Linezolid prepared by the process of the present invention has content of (R)-enantiomer less than about 0.1%, preferably less than 0.5%. Further, Linezolid prepared by the process of the present invention has content of bis-Linezolid less than about 0.15%. Also, the purity of Linezolid prepared by the process of the present invention is greater than 99%, preferably greater than 99.5%.

Further, embodiment of the present invention provides a process for preparing Form I of Linezolid of formula (I) comprising steps of:

(a) acylating Linezolid amine of formula (la) using acylating agent in the presence of ketonic solvent.

(b) crystallizing Linezolid obtained in step (a) from suitable solvent.

In a preferred embodiment, crystallization of linezolid is preferably carried out in the presence of n-propanol or methyl isobutyl ketone.

In another preferred embodiment of the present invention, Linezolid azide of formula (lib) is reduced using palladium on carbon in presence of ethyl acetate as solvent. After completion of the reaction the reaction mass is filtered and ethyl acetate is removed from the filtrate. In the same pot i.e. without isolating or further purifying the Linezolid amine of formula (la), acetone is added followed by acetic anhydride and triethyl amine at about 0-5°C. Then, the reaction mass is heated to reflux at about 65-75°C followed by cooling at about 0-5°C to obtain a solid which is isolated by conventional methods like filtration, centrifugation and the like and dried. The solid thus obtained in dissolved in n-propanol and treated with activated charcoal and filtered.
The filtrate is concentrated and cooled to about 0-5°C to obtain Linezolid Form I.

The synthetic reaction scheme of the present invention is as shown below.

Scheme-II

The advantages of process of present invention are:

1. It does not require temperature as low as -78°C, which is practically difficult to maintain during scale up process.

2. The product obtained does not require further purification by cumbersome process such as column chromatography which is difficult to perform at commercial scale.

The following examples illustrate the invention further. It should be understood however, that the invention is not confined to the specific limitations set forth in the individual example but rather to the scope of the appended claims.

Examples

Example 1: Preparation of 3-Fluoro-4-morpholinyl nitrobenzene.

To a solution of Methanol (90ml) and 3, 4-Difluoronitrobenzene (100g) at 25-30°C add Morpholine (115g) drop wise at 25-30°C in more than 1 hour under stirring. Stir
the reaction mass at 25-30°C for 1-2 hours. Then add slowly Water (400ml) with stirring the reaction mass at 25-30°C for 1 hour. Filter the solid & wash it with water. The solid is dried at 55-60°C. Yield: 1.408.; Percentage 99.0 %w/w.

**Example 2: Preparation of N-Carbobenzyloxy-3-fluoro-4-morpholinylaniline**

Take 3-Fluoro-4-morpholinyl nitrobenzene (100g), Methanol (1000ml) and 10% palladium on carbon catalyst (2.0g 50% wet) in the autoclave at 20-30°C for 3-4 hrs at 1-2kg hydrogen pressure. Filter it and dry the mixture under nitrogen atmosphere.

Apply vacuum to remove traces of methanol & add Acetone (100ml) to distill out completely below 70°C. Cool it & further add Acetone (400ml) and sodium carbonate (46.9g) to the residue. After cooling the mix at 0-5°C, 166g of Benzyl chloroformate (50% solution in Toluene) was added slowly at 0-5°C under stirring. Water (800ml) & n-Hexane (100ml) are added at 0-5°C for 1 hour at constant stirring. The mixture was filtered & solid was washed with water (200mlx2) and n-Hexane (100ml). The solid is dried at 55-60°C. Yield: 1.43.; Percentage 97.9 %w/w.

**Example 3: Preparation of**

(R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methanol.

Take n-Butanol (51.5g) and THF (100ml) at 20-30°C under Nitrogen atmosphere.

After cooling the mix add slowly n-Butyl lithium (1.6M in hexane) (391.7g) at 10 to 20°C & maintain it for 45-60 minutes. Take THF (500ml) and N-Carbobenzyloxy-3-fluoro-4-morpholinylaniline (100g) at 20-30°C under Nitrogen atmosphere. Cool the mix at -15 to -5°C under stirring. To this solution add slowly n-Butyl lithium solution & maintain for 45-60 minutes at -15 to -5°C, to this solution add slowly (R)-(-) Glycidyl butyrate (48.0g) & maintain for 1 hour at -10 to -5°C. After completing addition raise the temperature to 8-13°C and maintain for 1 hour & then take it to 13-15°C and maintain for 4-5 hours. Organic layer was separated by water (800ml) and Ethyl acetate (300ml). Filter & wash the solid with mix of Ethyl acetate-n-Hexane & dried in air tray dryer at 55-60°C. Yield: 0.765.; Percentage 85%w/w.

**Example 4: Preparation of**

(R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methyl methane sulfonate

Triethyl amine (68.2g), Methane sulfonyl chloride (48.3g) are added to a flask containing Dichloromethane (1900ml) and (R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methanol (100g) at 20-30°C with constant stirring for 2-3 hours. After cooling & filtration wash the solid with Dichloromethane followed by water wash & dried in air tray dryer. Yield: 1.20.;
Percentage 95% w/w.

Example 5: Synthesis of
(R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methyl azide

Reflux the mix of Dimethyl formamide (250ml), (R)-[N-3-(3-Fluoro-4-morpholinyl phenyl)-2-oxo-5-oxazolidinyl] methyl methane sulfuronate (100g) and Sodium azide (24.3g) at 60-65°C & maintain it for 6-7 hours. Cool the mix & add water (450ml) with constant stirring for one hour at 20-30°C. Filter it; wash the solid with mix of Dimethyl formamide - water (1:1) and with water & dried at 55-60°C. Yield: 0.82.: Percentage 95% w/w.

Example 6: Synthesis of Linezolid Crude.

Ethyl acetate (3500ml) and 10% palladium on carbon catalyst (6.0g) are added in autoclave having (R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methyl azide (100g) at 20-30°C. Cool the reaction mass & maintain 2-3kg hydrogen pressure at 15-20°C for 6-7 hrs. Filter it & wash the hyflo bed by Ethyl acetate (100mlx2). Then add the Triethyl amine (35.1g) & Acetic anhydride (29.9g) slowly at 25-30°C under stirring. Cool the mix, filter it and wash the solid with chilled (0-5°C) Ethyl acetate (100 ml) followed by water (100mlx2). Finally product is dried at 55-60°C. Yield: 0.85.: Percentage 81% w/w.

Example 7: Synthesis of Linezolid Pure

Reflux the Acetone (1020ml) and Linezolid crude (100g) at 55-60°C for the 30 minutes. Filter the hot turbid solution & wash it with hot (55-60°C) acetone (50ml). Cool the reaction mixture at -5 to 0°C for 1 hour, wash the solid with chilled (-5 to 0°C) acetone (50ml). After drying the Linezolid semi pure (77g) add n-Propanol (308ml) reflux it at 95-100°C for 30 min & filter it by hot solution through hyflo bed. Cool the mix to 0-5°C for 1 hour and wash the solid with chilled (0-5°C) n-Propanol (77ml). Dry the material at 55-60°C. Yield: 0.73.: Percentage 73% w/w.

Example 8: Synthesis of Linezolid

Ethyl acetate (3500ml) and 10% palladium on carbon catalyst (6.0g) are added in autoclave having (R)-[N-3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methyl azide (100g) at 20-30°C. Cool the reaction mass & maintain 2-3kg hydrogen pressure at 15-20°C for 6-7 hrs. Filter it & wash the hyflo bed by Ethyl acetate. Distill out ethyl acetate at 75-90°C and then cool the reaction mass to 0-5°C. Add acetone (1000ml) & acetic anhydride (29.9g) at 0-5°C. Further, add Triethyl amine (37.8g) slowly at 0-5°C under stirring. Maintain the reaction mass at 0-5°C for 1-2 hrs. Heat
the reaction mass to reflux at 65-75°C for 1 hr. Again cool the reaction mass to 0-5°C for 1 hr. Filter the solid wash it with acetone and water and dry it at 55-60°C. Yield: 0.80.: Percentage 80%-w/w.

Example 9: Synthesis of Linezolid Form I

Reflux n-propanol (400ml) and Linezolid (100g) at 95-100°C till all solid gets dissolved. Add activated charcoal (2.0g) and heat for 30 mins. Filter through hyflo bed. Heat the filtrate and concentrate the solution by partially removing n-propanol. Cool to 0-5°C and filter the solid and dry it at 55-60°C under vacuum. Yield: 0.9.: Percentage 90%-w/w.
Claims

[Claim 1] 1. A process for the preparation of Linezolid of formula (I) comprising a step of

\[
\begin{align*}
\text{Formula (I)}
\end{align*}
\]

reacting compound of formula (IV), wherein R is Hydrogen or Nitrogen protecting group, with compound of formula (III) in presence of n-butyl lithium and n-butanol in a suitable solvent to obtain compound of formula (II)

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

\[
\begin{align*}
\text{(III)}
\end{align*}
\]

[Claim 2] 2. A process for the preparation of compound of formula (II) comprising of

\[
\begin{align*}
\text{Formula (II)}
\end{align*}
\]

reacting compound of formula (IV), wherein R is Hydrogen or Nitrogen protecting group, with compound of formula (III) in presence of n-butyl lithium and n-butanol in a suitable solvent to obtain compound of formula (II)

[Claim 3] 3. A process claimed in claim 1 and 2, wherein said suitable solvent is tetrahydrofuran.
[Claim 4] 4. A process claimed in claim 1 and 2, wherein said reaction is carried out in the temperature range of -30° to 30°C.

[Claim 5] 5. A process for the preparation of Linezolid of formula (I) comprising,

![Formula (I)](image)

acylating Linezolid amine of formula (Ia) using acylating agent in the presence of ketonic solvent.

[Claim 6] 6. A process for the preparation of Form I of Linezolid of formula (I) comprising steps of:

(a) acylating Linezolid amine of formula (Ia) using acylating agent in the presence of ketonic solvent,

![Formula (I)](image)

![Formula (Ia)](image)

crystallizing Linezolid obtained in step (a) from suitable solvent.

[Claim 7] 7. A process claimed in claim 5 and 6, wherein said acylating agent is acetic anhydride or acetyl chloride.
[Claim 8] 8. A process claimed in claim 5 and 6, wherein said ketonic solvent is acetone, methyl iso-butyl ketone, methyl ethyl ketone or mixtures thereof.

[Claim 9] 9. A process claimed in claim 6, wherein said crystallization is carried out in n-propanol or methyl iso-butyl ketone.

[Claim 10] 10. Linezolid of formula (I) obtained by process of claim 5 and 6, having content of (R)-enantiomer less than about 0.1% and content of bis-Linezolid less than about 0.15%.

[Claim 11] 11. Linezolid of formula (I) obtained by process of claim 5 and 6, having purity greater than 99%.
**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/IB2010/055678

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. C07D263/24

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

**B. FIELDS SEARCHED**
Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>1-5,7, 8</td>
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**X** Further documents are listed in the continuation of Box C. **X** See patent family annex.

* Special categories of cited documents:
  - "X" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed
  - "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  - "A" document member of the same patent family

**Date of the actual completion of the international search**
18 April 2011

**Date of mailing the international search report**
29/04/2011

**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**
Gettins, Marc

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>TOKUYAMA R ET AL: &quot;STRUCTURE-ACTIVITY RELATIONSHIPS (SAR) STUDIES ON OXAZOLIDINONE ANTIMICROBIAL AGENTS. 2. RELATIONSHIP BETWEEN LI POPHILI CITY AND ANTIMICROBIAL ACTIVITY IN 5-THIOCARBONYL OXAZOLIDINONES&quot;, CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP. vol . 49, no. 1 Apr. 1, 2001 (2001-04-01) , pages 353-360, XP001145543, ISSN: 0009-2363, DOI: D0I:16.1240/CPB . 49. 353 page 354</td>
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<td>US 2002/169312 Al (PERRAULT WILLLIAM R [US] ET AL) 14 November 2002 (2002-11-14) claim 1; example 2</td>
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Scheme 3 on page 1938, conversion of 12 to 1.
### INTERNATIONAL SEARCH REPORT

#### Box No. II  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).

#### Box No. III  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 fees, 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.:

   I-5(completely) ; 7, 8(partially)

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.:

   □ 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.

Form PCT/ISA/21 0 (continuation of first sheet (2)) (April 2005)
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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4
   Process involving the conversion of (IV) to (II)

2. claims: 5(completely); 7, 8(partially)
   Process for converting (la) to (l)

3. claims: 6, incompletely); 7, 8(partially)
   Process for converting (la) to (l) in Form I

4. claim: 10
   Product by process claim for (l) with a defined amount of an impurity

5. claim: 11
   Product by process claim for producing (l) to make (l) with a defined level of purity