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(54) **Title:** A PROCESS FOR THE PREPARATION OF EZETIMIBE VIA A NOVEL INTERMEDIATE

(57) **Abstract:** The present invention relates to a process for the preparation of Ezetimibe via a novel intermediate. Trans-3(R)-(3-[2-oxo-4(S)-(4-benzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanoic acid is converted to trans-N-methoxy-N-methyl-3(R)-3-[2-oxo-4(S)-(4-benzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanamide and the resultant intermediate is subjected to Grignard reaction to obtain trans-1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-benzyloxyphenyl)-2-azetidinone. Reduction of trans-1-(4-JGiuorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl) propyl]-4(S)-(4-benzyloxyphenyl)-2-azetidinone, followed by debenzylation provides Ezetimibe. The invention also relates to the preparation of the intermediate occurring in the above process.

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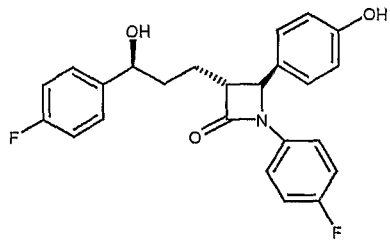
# TITLE - A PROCESS FOR THE PREPARATION OF EZETIMIBE VIA A NOVEL INTERMEDIATE

## FIELD OF THE INVENTION

The present invention is related to a process for the preparation of Ezetimibe through a novel intermediate.

## BACKGROUND OF THE INVENTION

US 5767115 disclose the hypocholesterolemic activity of hydroxy-substituted azetidinones [(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxy propyl]-4-(4-hydroxyphenyl)-2-azetidinone] compound of formula (I) and processes for its preparation.




Formula I

WO 97/16424 discloses the process for the preparation of Ezetimibe [formula (I)] by alkylating a chiral 3-unsubstitute azetidone with 4-fluorocinnamyl bromide, oxidizing the intermediate so formed, followed by chiral reduction and debenzylation.

WO 97/45406, US 5886171 and *J. Org. Chem.* 1999, *64(10)*, 3714-18 discloses a process which comprises reaction of a 4(S)-hydroxytetrahydrofuran-2-one with an imine to form a chiral diol, which was oxidized to an aldehyde. The resultant aldehyde was condensed with an enolate and hydrogenation of the product followed by chiral reduction gave the compound of formula (I).

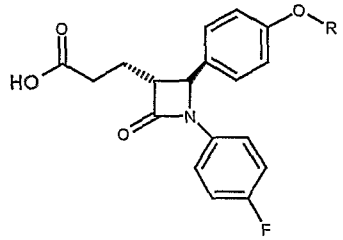
WO 2000/34240 discloses the process which comprises: (a) reacting p-fluorobenzoylbutyric acid with pivaloyl chloride and acylating the product with a chiral auxiliary to obtain a ketone; (b) reducing the ketone in the presence of a chiral catalyst to obtain a chiral alcohol; (c) reacting the chiral alcohol with an imine in presence of silyl protecting agent, then condensing the protected compound to form a

β-(substituted-amino)amide; (d) cyclisation of the β-(substituted-amino)amide with silylating agent and fluoride ion to give protected lactam followed by deprotection.

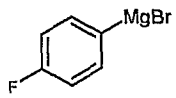
US6627757 and *Tet. Lett.* 2003, *44*, 801-804 discloses the chiral catalytic reduction of ketone using (R)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo(1,2-c)(1,2,3)-oxazoborolidine [(R)-MeCBS] or R-diphenylprolinol as a catalyst and borane tetrahydrofuran complex as reducing agent.

WO2005/066120 and WO2005/049592 disclose the stereoselective reduction of ketone using (-)-B-chlorodiisopinocampheylborane.

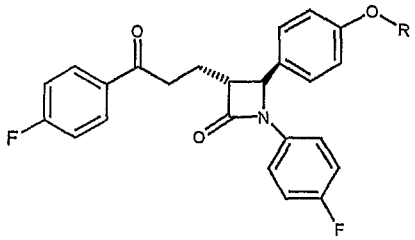
US 5767115, discloses the process for the preparation of Ezetimibe. This process involves the use of moisture sensitive, acid chloride derivative of trans- 3(R)-(3-[2-oxo-4(S)-(4-benzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl] propanoic acid of formula (II) and 4-fluorophenylmagnesium bromide of formula (III), anhydrous $ZnCl_2$ and the expensive reagent tetrakis(triphenylphosphine)palladium to obtain trans-1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-benzyloxyphenyl)-2-azetidinone of formula (IV) in low yield. This intermediate is finally converted to Ezetimibe (formula (I)).




Formula II



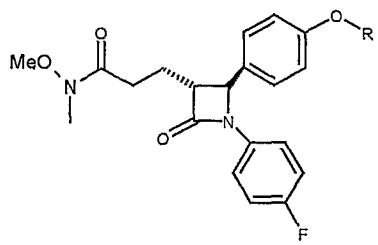

Formula III



Formula IV

where R is alkyl or alkylaryl group from $C_1$ to $C_4$.

It is therefore our objective of the present invention to make available an economical, practicable and commercially viable process for the preparation of Ezetimibe. The present invention involves use of less expensive reagent for converting acid of formula (II) to a novel intermediate, trans-N-methoxy-N-methyl-3(R)-3-[2-oxo-4(S)-(4-benzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanamide of formula (V) and subsequently treated with Grignard reagent of formula (III) to obtain trans-1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-benzyloxyphenyl)-2-azetidinone of formula (IV) in high yield. The ketone of formula (IV) is then reduced using CBS-catalyst and subsequently debenzylated to give Ezetimibe (formula (I)).



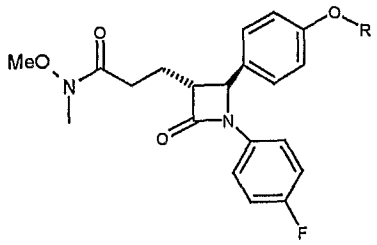
Formula (V)

where R is as defined above.

**SUMMARY OF THE INVENTION**

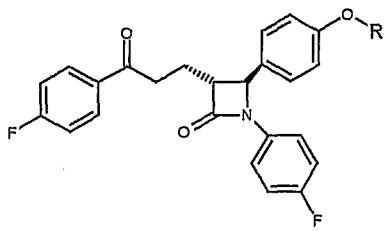
The objective is achieved by a process for preparing the Ezetimibe of formula (I), which comprises;

a) reacting a compound of formula (II) with an acid activator in a suitable inert solvent and subsequent reaction with N,O-dimethylhydroxylamine salt, optionally in presence of a suitable base to give compound of formula (V)



Formula (V)

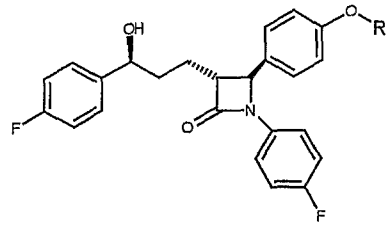
b) reacting compound of formula (V) with p-fluorophenylmagnesium bromide of formula (III) to obtain ketone of formula (IV)



Formula (IV)

wherein R is as defined above.

c) reducing the ketone of formula (IV) with CBS catalyst to corresponding hydroxyl compound of formula (VI) under the conditions well known in the art.



Formula (VI)

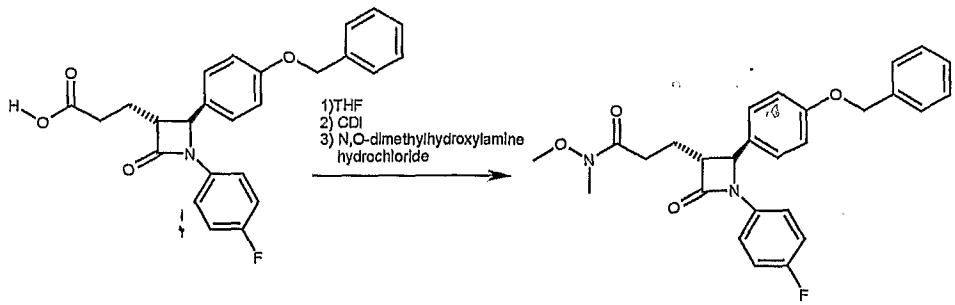
d) debenzylating the compound of formula (VI) by hydrogenation to obtain the compound of formula (I).

**DETAILED DESCRIPTION OF THE INVENTION**

The compound of formula (II) was prepared according to the process described in *Bioorganic and Medicinal Chemistry*, 1998, *6*, 1429-1437 and converted to a novel intermediate of formula (V), which is a useful intermediate for the preparation of Ezetimibe.

Preferred stepwise reaction conditions are shown in the following scheme.

Step (a): reacting a compound of formula (II) with an acid activator in a suitable inert solvent and subsequent reaction with N,O-dimethylhydroxylamine salt, optionally in presence of a suitable base to give compound of formula (V)




Step (a) is carried out in a suitable inert solvent such as tetrahydrofuran, diglyme, acetonitrile, dioxane, N,N-dimethylformamide, dimethylsulfoxide, dichloromethane, chloroform, tert-butyl methyl ether, diisopropyl ether, however more preferably in dichloromethane and tetrahydrofuran and most preferably in tetrahydrofuran.

The preferred reaction temperature to activate the acid of formula (II) is below the boiling temperature of the solvent used, more preferably between –20°C to boiling temperature of the solvent, still more preferably between about –10°C to 35°C and most preferably between 25°C to 30°C.

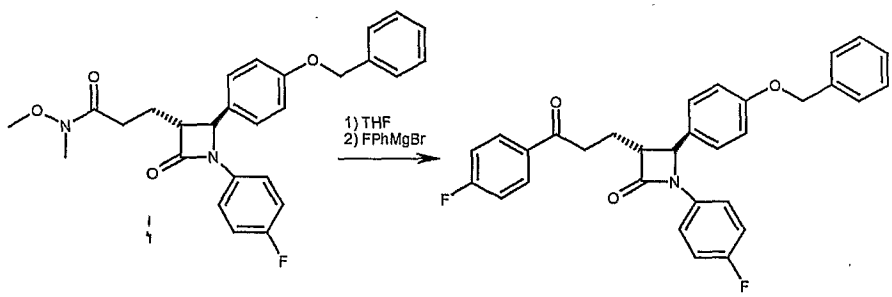
The activators for acid of formula (II) are oxalyl chloride, ethyl chloroformate, methyl chloroformate, pivaloyl chloride, N,N-carbonyldiimidazole (CDI), more preferably ethyl chloroformate, pivaloyl chloride and N,N-carbonyldiimidazole, most preferably N,N-carbonyldiimidazole. These acid activators are usually used in excess of 1 to 1.5 moles, more preferably 1.1 to 1.3 moles per mole of the compound of formula (II).

Bases used for the reaction are tertiary amines e.g. triethylamine, diethylpropylamine, diisopropylethylamine, N-methylpyrrolidine and N-methylmorpholine, more preferably N-methylmorpholine, N-methylpiperidine, most preferably N-methylmorpholine. It has particularly been proven to use these bases in about 3 to 5 moles excess; more preferably in 2.2 to 2.5 moles excess. If N,N-carbonyldiimidazole is used as an acid activator, then no external base is required for the reaction.

N,O-dimethylhydroxylamine salt is used in excess of 1 to 2 moles, more preferably 1 to 1.5 moles, most preferably 1.1 to 1.3 moles per mole of compound of formula (II).

The reaction between N,O-dimethylhydroxylamine salt and the resultant compound after the activation of acid of formula (II) is carried out at 0°C to 35°C. The addition of N,O-dimethylhydroxylamine salt is done at 0°C. After the addition, the reaction mixture temperature is maintained at 20°C to 35°C, most preferably 25° to 30°C, for about 1 to 4 hours, preferably 2 hours.

Step (b): reacting compound of formula (V) with p-fluorophenylmagnesium bromide of formula (III) to obtain ketone of formula (IV).

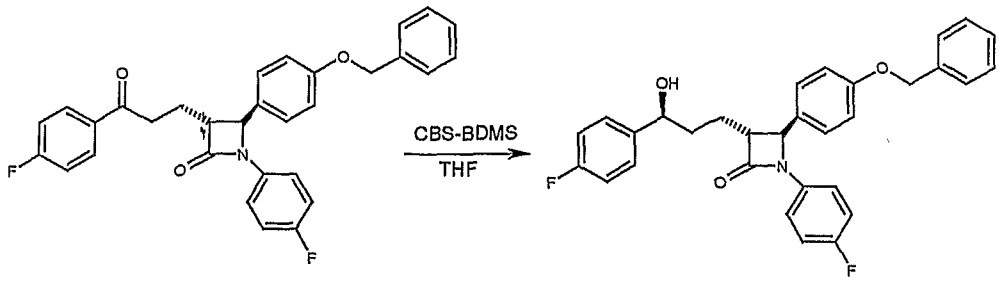



Step (b) is carried out in a suitable inert solvent like tetrahydrofuran, diglyme, dioxane, diethyl ether, diisopropyl ether and tert-butyl methyl ether, more preferably tetrahydrofuran and diethyl ether, most preferably tetrahydrofuran.

Grignard reagent of formula (III) is used in excess of 1 to 5 moles, more preferably 2 to 4 moles, most preferably 2.5 to 3 moles per mole of compound of formula (V).

The preferred reaction temperature is below the boiling temperature of the solvent used, more preferably between –20°C to boiling temperature of the solvent, still more preferably between –10°C to 35°C and most preferably between –5°C to 5°C, for about 0.5 to 2 hours, preferably 1 hour. After completion of the reaction, the reaction mixture is acidified and extracted with suitable solvent.

Step (c): reducing the ketone of formula (IV) with CBS catalyst to corresponding hydroxyl compound of formula (VI).

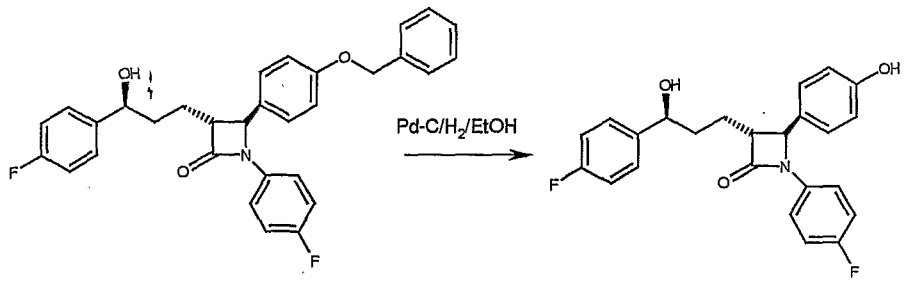



Step (c) is carried out in a suitable inert solvents like tetrahydrofuran, dichloromethane, 1,2-dichloroethane, dioxane, diethyl ether, diisopropyl ether, tert-butyl methyl ether and toluene, more preferably tetrahydrofuran and dichloromethane, most preferably tetrahydrofuran.

The preferred reducing reagent is borane dimethyl sulfide complex with (R)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo(1,2-c)(1,2,3)-oxazoborolidine (R-MeCBS) or R-diphenylprolinol as a catalyst.

The preferable reaction temperature is below the boiling temperature of the solvent used, more preferable between –30°C to boiling temperature of the solvent, still more preferably between –10°C to 35°C and most preferably –5°C to 0°C for about 0.5 to 2 hours, preferably 1 hour.

Step (d): debenzylating the compound of formula (VI) by hydrogenation to obtain the compound of formula (I).




Step (d) is carried out in suitable inert solvents like ethanol, methanol, propanol, isopropanol and ethyl acetate more preferably ethanol and methanol, most preferably ethanol.

The preferred reaction temperature is below the boiling temperature of the solvent used, more preferably between 10°C to boiling temperature of the solvent, more preferably 20°C to 35°C and most preferably 28°C to 30°C, for about 0.5 to 8 hours, preferably 3 hours.

The invention can be illustrated by the following example, which is for illustration purpose only and is not intended to limit the scope of the invention in any way.

Example 1:

Preparation of trans-N-methoxy-N-methyl-3(R)-(3-[2-oxo-4(S)-(4-benzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanamide.

To a solution of trans-3(R)-(3-[2-oxo-4(S)-(4-benzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanoic acid (12g, 0.0286mol) in tetrahydrofuran (60ml), N,N-carbonyldiimidazole (5.56g, 0.0343mol) was added over a period of 10 to 15 minutes at 27°C to 30°C and stirred for another 1 hour. To this, N,O-dimethylhydroxylamine salt (3.35g, 0.0343mol) was added at 27°C to 30°C and stirred for 2 another hours. After completion of reaction (TLC solvent system, ethyl acetate:hexane; 30:70), 60ml of ethyl acetate and 50ml of water was added and stirred for 15 minutes. Organic layer was separated, washed with 0.5N aqueous HCl (2×30ml) followed by 5% aqueous sodium bicarbonate (2×30ml) and saturated aqueous sodium chloride (40ml). Organic layer was dried over sodium sulphate, filtered and concentrated under vacuum to product.

$^1$H-NMR (400MHz) δ in ppm ($CDCl_3$): 2.15 (m, 2H), 2.6 (t, 2H), 3.06 (m, 4H), 3.56 (s, 3H), 4.6 (d, 1H), 4.98 (s, 2H), 7.05 (m, 13H)

Example 2

Preparation of trans-1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-benzyloxyphen yl)-2-azetidinone.

To a suspension of magnesium turning (1.82g, 0.0746mol) in tetrahydrofuran (50ml) was added p-bromofluorobenzene (8.2ml, 0.0746mol) while the maintaining temperature between 40°C and 45°C and stir for another 30 minutes. The reaction

mixture was refluxed for 30 minutes and cooled to 5°C to10°C. The reaction mass thus formed was added to a solution of trans-N-methoxy-N-methyl-3(R)-(3-[2-oxo-4(S)-(4-benzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanamide (11.5g, 0.0249mol) in THF (60ml) over a period of 15-20 minutes under nitrogen atmosphere at 0°C to 5°C and stirred for another 30 minutes. After completion of reaction, (TLC solvent system, ethyl acetate:hexane; 70:30) reaction mixture was cooled to 10°C and 0.5N aqueous HCl (10ml) was added at 10°C to 15°C. Reaction mixture was concentrated under vacuum at 40°C. Dichloromethane (100ml) was added to the concentrated solution and washed with 5% aqueous sodium bicarbonate (2×30ml) followed by saturated aqueous sodium chloride (40ml). Organic layer was dried over sodium sulphate, filtered and concentrated under vacuum to get the product (12.68g). $^1$H-NMR (400MHz) δ in ppm ($CDCl_3$): 2.18 (m, 1H), 2.31 (m, 1H), 3.05 (m, 2H), 3.21 (m, 1H), 4.6 (d, 1H), 4.96 (s, 2H), 6.82-7.34 (m, 15H), 7.9 (dd, 2H).

Example 3

Preparation of (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxy propyl]-4-(4-hydroxyphenyl)-2-azetidinone

To a solution of tetrahydrofuran (15ml), α,α-diphenylprolinol (0.17g, 0.689mmol), trimethyl borate (0.093ml, 0.827mmol) was added with stirring at 27 °C to 29°C. After stirred for 20 minutes a solution of trans-1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-benzyloxyphenyl)-2-azetidinone (6.85g, 0.0138mol) in tetrahydrofuran (20ml) was added and stirred for 15 minutes. Reaction mixture was cooled to –5°C to 0°C. To this solution borane dimethyl sulfide complex (1.05ml, 0.011mol) was added at –5°C to 0°C. Stirred for 4 hours between –5°C and 0°C. After completion of the reaction (TLC solvent system, ethyl acetate:hexane, 70:30), methanol (5ml) was added between –5°C and 0°C in 5 minutes duration, followed by dichloromethane (70ml) with stirring. Reaction mixture was washed with mixture of 5% $H_2O_2$ (15ml) and 4N aqueous $H_2SO_4$ (1.5ml), followed by 2N aqueous $H_2SO_4$ (15ml), followed by 10% aqueous $Na_2SO_3$ (35ml) finally with saturated aqueous NaCl (40ml). Organic layer was dried over sodium sulphate, filtered and concentrated at 40°C to obtain product.

$^1$H-NMR (400MHz) δ in ppm($CDCl_3$): 1.85 (4H, m), 2.15 (m,1H), 3.00 (1H, m), 4.5 (1H, d), 4.65 (1H, t) 5 (2H, s), 6.8-7.4 (17H, m).

Example 4

Preparation of (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxy propyl]-4-(4-hydroxyphenyl)-2-azetidinone

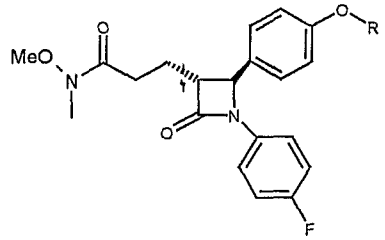
To a solution of trans-1-(4-fluorophenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl) propyl]-4(S)-(4-benzyloxyphenyl)-2-azetidinone (5g, 0.01mol) in ethanol (25ml), 10% palladium on carbon (0.5g, 10% w/w) was added in autoclave at 28°C to 30°C. The pressure of the reaction vessel was kept constant at 60 psi hydrogen pressure till completion of reaction. (TLC solvent system, ethyl acetate:hexane, 50:50). Reaction mixture was filtered through celite bed and celite bed was washed with 50ml ethanol. Combined filtrate was concentrated under vacuum at 50°C to get 3.82g yellow semisolid. Which on crystallisation followed by drying under vacuum at 60°C for 3 hours to give white product.

$^1$H-NMR (400MHz) δ in ppm(DMSO): 1.75 (4H, m), 3.1 (1H, m), 4.50 (1H, m), 4.80 (1H, d), 5.30 (1H, d), 6.70-7.30 (12H, m), 9.6 (s, 1H).

We claim:

1) A process for the preparation of Ezetimibe which comprises:
   a) reacting the compound of formula (II) with a suitable acid activating agent in a suitable inert solvent and treating the resultant compound with N,O-dimethylhydroxylamine salt, optionally in presence of a suitable base to give a compound of formula (V)
   b) reacting the compound of formula (V) with Grignard reagent of formula (III) to give the compound of formula (IV)
   c) subjecting the compound of formula (IV) for chiral reduction to obtain a compound of formula (VI) followed by deprotection.

2) Compound of formula (V)




3) A process according to claim 1a, wherein the suitable inert solvent is such as tetrahydrofuran, diglyme, acetonitrile, dioxane, N,N-dimethylformamide, dimethylsulfoxide, dichloromethane, chloroform, tert-butyl methyl ether, diisopropyl ether, diethyl ether however more preferably in dichloromethane and tetrahydrofuran and most preferably in tetrahydrofuran.

4) A process according to claim 1a, wherein the suitable acid activators are oxalyl chloride, ethyl chloroformate, methyl chloroformate, N,N-carbonyldiimidazole, more preferably oxalyl chloride, ethyl chloroformate, pivaloyl chloride and N,N-carbonyldiimidazole, most preferably N,N-carbonyldiimidazole.

5) A process according to claim 1a, wherein the acid activators are usually used in excess of 1 to 1.5 moles, more preferably 1.1 to 1.3 moles per mole of the compound of formula (II).

6) A process according to claim 1a, wherein suitable bases used for the reactions are tertiary amines e.g. triethylamine, diethylpropylamine, diisopropylethylamine, N-methylpyrrolidine and N-methylmorpholine, more preferably N-methylmorpholine, N-methylpiperidine, imidazole, most preferably N-methylmorpholine.

7) A process according to claim 1a, wherein bases used in about 3 to 5 moles excess; more preferably in 1.2 to 1.5 moles excess.

8) A process according to claim 1a, wherein N,O-dimethylhydroxylamine salt is used in excess of 1 to 2 moles, more preferably 1 to 1.5 moles, most preferably 1.1 to 1.3 moles per mole of compound of formula (II).

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2006/000364

A. CLASSIFICATION OF SUBJECT MATTER
IPC[8]: ***C07D 205/08*** (2006.01)
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)
IPC[8]: 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 practicable, search terms used)
WPI, EPODOC, Registry, CA, Internet, Pubchem

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | WO 1997/045406 A1 (SCHERING CORP) 4 December 1997 (04.12.1997)<br>**Claims** | 1-8 |
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 July 2007 (05.07.2007) | 1 August 2007 (01.08.2007) |
| Name and mailing address of the ISA/ AT<br>**Austrian Patent Office**<br>Dresdner Straße 87, A-1200 Vienna<br>Facsimile No. +43 / 1 / 534 24 / 535 | Authorized officer<br>GÖRNER W.<br>Telephone No. +43 / 1 / 534 24 / 558 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 2006/000364

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