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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF S(+)-2-ETHOXY-4-[N-{1-(2-PIPERIDINOPHELYL)-3-METHYL-1-BUTYL} AMINOCARBONYLMETHYL]BENZOIC ACID DERIVATIVES

(57) Abstract: The present invention relates to a novel process for the preparation of S(+)-2-ethoxy-4-[N-{1-(2-piperidinophelyl)-3-methyl-1-butyl} aminocarbonylmethyl]-benzoic acid derivatives.

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Process for the preparation of S(+)-2-ethoxy -4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}aminocarbonylmethyl]benzoic acid derivatives

FIELD OF THE INVENTION

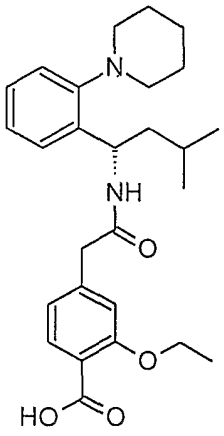
The present invention relates to a novel process for the preparation of S(+) 2-ethoxy-4-[N-{1-(2-piperidinophelyl)-3- methyl-1-butyl aminocarbonylmethyl]-benzoic acid derivatives.

BACKGROUND OF THE INVENTION

EP 0 147850 claims racemate (forms A, B and C) of 2-ethoxy-4-[N-{1-(2-piperidinophelyl)-3- methyl-1-butyl aminocarbonylmethyl]-benzoic acid having the Formula IV and process for preparation thereof.

EP 0 207 331 claims two polymorphous forms B and C of 2-ethoxy-4-[N-{1-(2-piperidinophelyl)-3- methyl-1-butyl aminocarbonylmethyl]-benzoic acid having the Formula IV and process for preparation thereof.

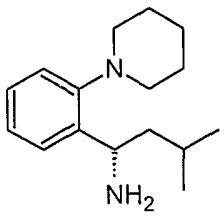
EP 0 589 874 claims S(+) 2-ethoxy-4-[N-{1-(2-piperidinophelyl)-3- methyl-1-butyl aminocarbonylmethyl]-benzoic acid having the Formula IV and process for preparation thereof.



FORMULA IV

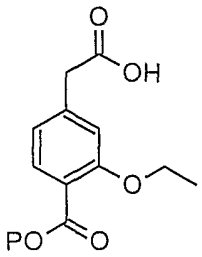
The compound of formula (IV) is from a new class of hypoglycemic benzoic acid derivatives for the treatment of non-insulin dependent diabetes mellitus (NIDDM).

The patents mentioned above also claim processes for the preparation of 2-ethoxy-4-[N-{1-(2-piperidinophelyl)-3- methyl-1-butyl aminocarbonylmethyl]-benzoic acid which involves the reaction of an amine or S (+) amine of Formula II,



FORMULA II

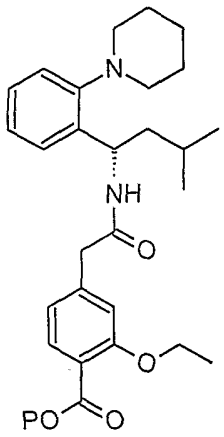
with a carboxylic acid of Formula III,



FORMULA III

where P is a protecting group

or a reactive derivative thereof to obtain compound of Formula I.



FORMULA I

where P is a protecting group

The reaction of the amine of Formula II with a carboxylic acid of Formula III is carried out in the presence of N,N'-carbonyldimidazole, N,N'dicyclohexylcarbodiimide or triphenylphosphine/carbon tetrachloride and triethylamine.

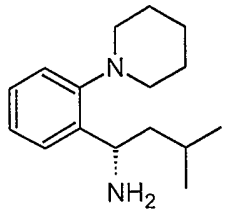
WO 2003/027072 claims process for preparation of compound of formula I by reacting an S(+) amine compound of formula II with a carboxylic acid of formula III in the presence of pivaloyl chloride and a base.

The reagents used here suffer from disadvantages like probable racemisation, expensiveness, additional reagents e.g. a base, low yields of the product, extra purification steps to obtain final product, repeated crystallization, hazardous and industrially impossible.

Thus, there is a need to solve the problems associated with the prior art and to provide an efficient process for the preparation of compounds of formula I.

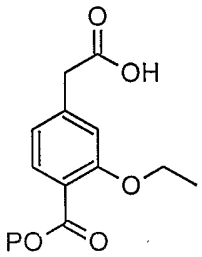
SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of compound of formula I comprising, reacting the (S) amine of Formula II



FORMULA II

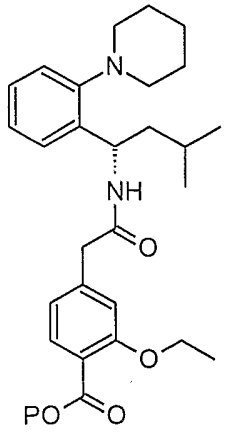
with a carboxylic acid of Formula III,



FORMULA III

where P is a protecting group

in the presence of propane phosphonic acid anhydride to obtain compound of formula I.



FORMULA I

where P is a protecting group

The novel process employed in the instant invention has following definite advantages:

a) Remarkably low risk of allergization compared to other reagents like DCC.

b) Low toxicity of Propane phosphonic anhydride and its reaction products.

c) Low racemization of products during reaction.

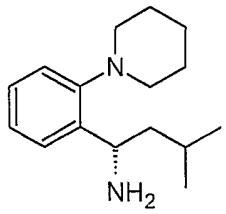
d) By products are water soluble leading to simple work up and easy isolation of product.

e) Reaction proceeds under ambient conditions.

f) High yields.

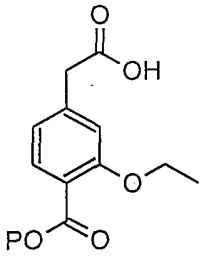
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of compound of formula I comprising, reacting the (S) amine of Formula II



FORMULA II

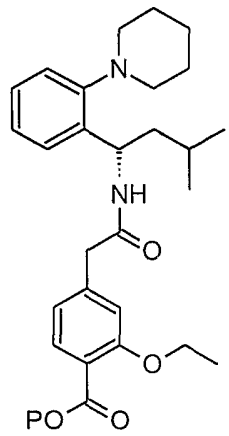
with a carboxylic acid of Formula III,



FORMULA III

where P is a protecting group

in the presence of Propane phosphonic acid anhydride to obtain compound of formula I.



FORMULA I

where P is a protecting group

The protecting group P in the compound of Formula III is any carboxylic acid protecting group which can be easily removed, like ester groups. The reaction may be carried out in any suitable solvent such as ethyl acetate, dichloromethane etc.

The reaction is carried out at temperatures of between –25°C and 40°C, but preferably at ambient temperatures.

The removal of a carboxylic acid protecting group is achieved by suitable methods known in the art like acidic or basic hydrolysis or hydrogenolysis.

The following examples and scheme are used to illustrate the invention which are not to be considered as limiting.

EXAMPLES

EXAMPLE 1

2-ethoxy-4-{[3-methyl-1-(2-piperidin-1-yl-phenyl)-butylcarbamoyl]-methyl}-benzoic acid ethyl ester: To a mixture of (1*S*)-3-methyl-1-(2-piperidin-1-ylphenyl)butan-1-amine (49g, 0.2 mol), [3-ethoxy-4-(ethoxycarbonyl)phenyl]acetic acid (50 g, 0.2 mol) and triethylamine (100 g, 0.99 mol) in ethyl acetate (1.0 L), a solution (50% w/w) of propane phosphonic acid anhydride (278 g, 0.44 mol) in ethyl acetate was added dropwise over a period of 30 minutes, maintaining the temperature at 0-5° C and stirred for 18 hours at ambient temperature. The reaction mixture was washed with 1.5 N HCl, 5% sodium bicarbonate solution and brine. The organic layer was concentrated to give title compound.

Yield: 86 g, 89.5%

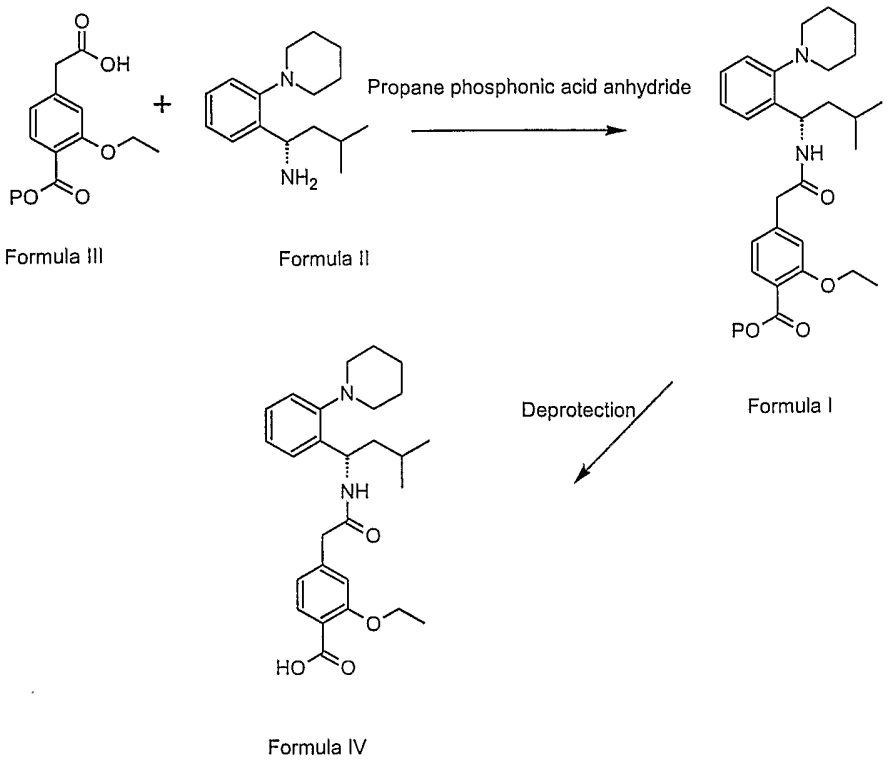
EXAMPLE 2

S(+) ethoxy [N-{I-(2-piperidinophelyl) methyl 1-butylaminocarbonyl methyl] benzoic acid:

To a solution of 2-ethoxy-4-{[3-methyl-1-(2-piperidin-1-yl-phenyl)-butylcarbamoyl]-methyl}-benzoic acid ethyl ester (86 g, 0.18 mol) in ethanol (860 mL), a solution of sodium hydroxide (10.3 g, 0.26 mol) in water (260 mL) was added and stirred at 60-65° C for 2 h. Activated chrcoal (9 g) was added to the reaction mixture and filtered over celite bed. After adjusting the pH of the clear filtrate to 4.0 – 4.2, the mixture was stirred at 40-45° C for 30 minutes. The mixture further cooled to 0-5° C and stirred for 1 h. The product was filtered and dried.

Yield: 66 g, 81%

SCHEME



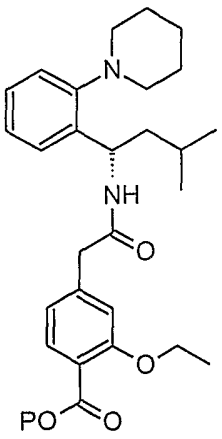
Formula III Formula II Formula I

Formula IV

where P is a protecting group

We claim:

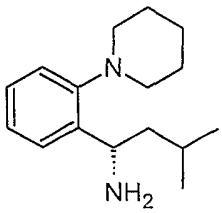
1. A process for the preparation of S(+) 2-ethoxy-4-[N-{1-(2-piperidinophelyl)-3- methyl-1-butyl aminocarbonylmethyl]-benzoic acid derivatives of FORMULA I,



FORMULA I

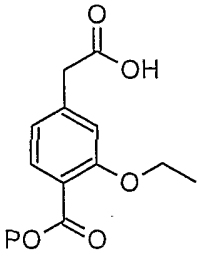
where P is a protecting group comprising,

reacting the (S) amine of FORMULA II,



FORMULA II

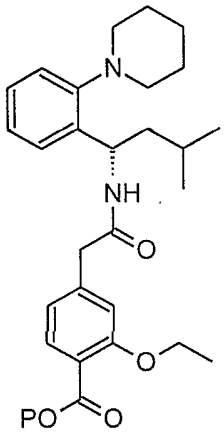
with a protected carboxylic acid of Formula III,



FORMULA III

where P is a protecting group

in the presence of propane phosphonic acid anhydride to get a compound of formula I.



FORMULA I

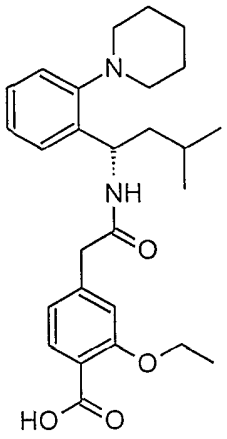
2. The process according to claim 1 wherein the protecting group P is selected from the group consisting of methyl, ethyl, t-butyl, benzyl or any suitable group protecting carboxylic acid.

3. The process according to claim 1 wherein the reaction is carried out in a water immiscible solvent.

4. The process according to claim 3, wherein the water immiscible solvent is selected from the group consisting of dichloromethane or ethyl acetate.

5. The process according to claim 1, wherein the reaction is carried out temperature of between –25°C and 40°C.

6. A process as in claim 1 - 5, wherein the compound of formula I is deprotected to get Formula IV.



FORMULA IV

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN03/00197

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 295/135

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)

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)
Database: STN, File: CA, WPIDS. Keywords: propane phosphonic acid anhydride

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/027072 A1 (RANBAXY LABORATORIES LIMITED) 3 April 2003. See entire document.	1-6
Y	AU 37210/84 B (K. Thomae) 1 August 1985. See entire document, especially example 11 page 54.	1-6
Y	AU 59139/86 B (K. Thomae) 8 January 1987. See entire document, especially example 1 page 11 and claim 9	1-6

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"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
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Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2003	15 AUG 2003
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **FRANCES RODEN** Telephone No : (02) 6283 2239

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN03/00197

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AU 80781/91 B (K. Thomae) 25 Janaury 1993. See entire document.	1-6
Y	Pharmaceutial Biotechnology International, 1996, pages 31-34, W. Bernhagen, "PPA: a new reagent for peptide synthesis." See entire document, especially page 32.	1-6
Y	Synthetic Communications, 2000, vol. 30(20), pages 3737-3744, K. S. Crichfield et al, "Propane phosphonic acid anhydride: A mild reagent for beta-lactam synthesis." See entire document.	1-6
Y	EP 1031575 A1 (Pfizer Products Inc.) 30 August 2000. See entire document, especially claims 1 and 4.	1-6
Y	US 5945543 (E. Buschmann et al) 31 August 1999. See entire document.	1-6
Y	DE 19503325 A1 (Hoechst AG) 8 August 1996. See entire document.	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN03/00197

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2003027072	NONE					
AU	37310/84	AU	37310/85	BR	8500039	CA	1238166
		DK	71/85	EP	152994	ES	539358
		ES	8606072	FI	850046	GR	850027
		JP	60158229	NO	850044	PT	79805
		US	4690860	ZA	8500073		
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		EP	207331	ES	556495	ES	8802145
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		SU	1831481	CA	2111851		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN03/00197

EP	1031575	AU	200019471	BG	104175	BR	200000967
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		DE	19527574	EP	842142	HU	9802403
		WO	9705096				
DE	19503325	NONE					

END OF ANNEX