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WO 2009/115902 A1

(54) **Title**: PROCESS FOR THE PREPARATION OF CARVEDILOL VIA SILYL PROTECTION OF SUBSTITUTED AMINE

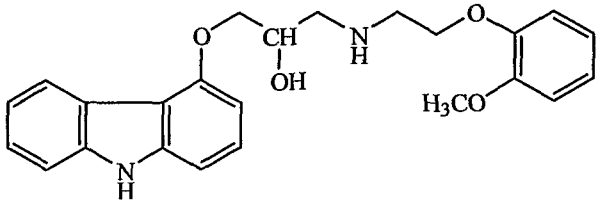
(57) **Abstract**: The invention provides new process for preparing Carvedilol by reaction of 4-(oxiran-2- yl-methoxy)-9H-carbazole and substituted silyl protected 2-(2-methoxy phenoxy)-ethylamine compound to give silyl protected Carvedilol intermediate. The silyl protected Carvedilol intermediate on desilylation gives Carvedilol. The invention also provides a novel substituted silyl protected 2-(2-methoxy phenoxy)-ethylamine as key intermediate for the preparation of Carvedilol.

FIELD OF INVENTION

The invention relates to an improved process for preparation of Carvedilol.

BACKGROUND OF INVENTION

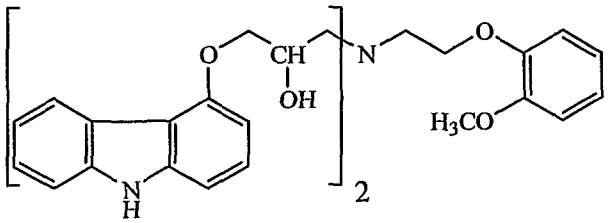
The present invention relates to process for making Carvedilol, chemically known as (±)-1-(carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]-amino]-2-propanol having structural formula -I



Formula-I

It is nonselective β-adrenergic blocker with α_1-blocking activity, indicated for the treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin.It is marketed in USA as COREG®.

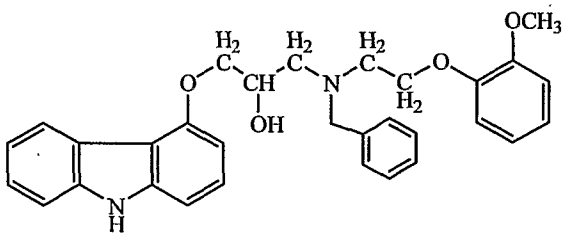
The US patent 4,503,067 discloses process for preparation of Carvedilol comprising reaction of 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)-ethylamine using ethylene glycol dimethyl ether as solvent The reported yield of carvedilol is 39% . The draw back of this process is formation of "bis- impurity" having structural Formula-II.



Formula-II

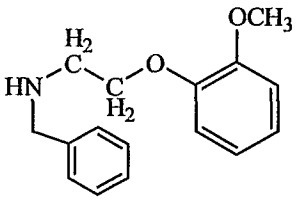
Once formed it is very difficult to remove this impurity and obtain pure carvedilol suitable for pharmaceutical use. Carvedilol contains one chiral center. The racemic mixture containing equal amounts of R(+) and S(-) enantiomers is commercial product.

European patent no. 918055 discloses two processes for preparation of Carvedilol. The process (A) comprises reaction of 4-(oxiranylmethoxy)-9H-carbazole with N-[2-{2'-(methoxy)-phenoxy}-ethyl]-benzylamine in a protic organic solvent to give benzyl protected Carvedilol [Formula-III], which on debenzylation using catalytic hydrogenation gives carvedilol.

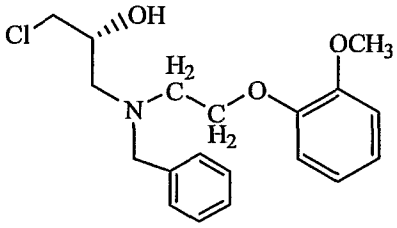


Formula-III

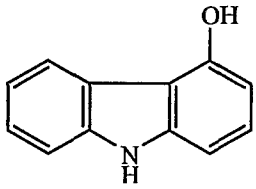
The process (B) comprisies reaction of protected N-[2-{2'-(methoxy)-phenoxy}-ethyl]-benzyl amine (Formula-IV) with epichlorohydrin to form chloro compound, 1-[N-{benzyl}-2'-({2"-(methoxy)-phenoxy)-ethyl}-amino]-3-chloro-propan-2-ol (Formula-V). The intermediate chloro compound (Formula-V) reacts with 4-(hydroxyl)-9H-carbazole (Formula-VI) in the presence of base to give benzyl protected carvedilol (Formula-III) which is converted to carvedilol using catalytic hydrogenation.



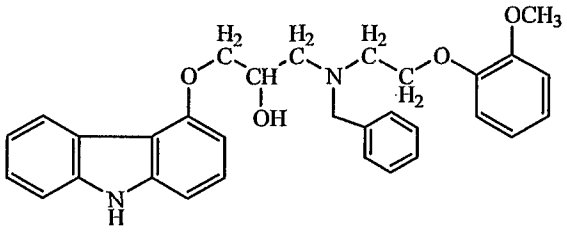
Formula-IV



Formula-V



Formula-VI



Formula-III

The processes disclosed in this patent make use of expensive catalyst in the debenzylation stage.

The US patent 7,126,008 discloses process for preparing Carvedilol comprising reaction of 4-(oxiran-2-yl-methoxy)-9H-carbazole with 2-(2-methoxyphenoxy)-ethylamine, wherein the ethyl amine compound is taken in large excess to minimize the formation of bis impurity (Formula-II) making the process commercially less attractive.

Other processes for making Carvedilol are also known, international application No. WO2004/041783 discloses the process for preparation of Carvedilol comprising reacting 4-

(oxiranylmethoxy)-9H-carbazole with a salt of 2-(2-methoxyphenoxy)-ethylamine in presence of alkaline earth metal carbonate in C_2-C_5 alcohols as solvents. The product on crystallization in ethyl acetate yields 41% Carvedilol. The international application No. WO/2006/061364 discloses reaction of 4-(oxiran-2-ylmethoxy)-9H-carbazole with 2-(2-methoxyphenoxy)-ethylamine using ethyl acetate as solvent.

All the processes reported so far, produce Carvedilol in low yields or make use of expensive catalyst.

Thus, there is a need to provide a commercially viable process which does not make use of expensive catalyst and at the same time produces carvedilol of high purity by limiting formation of bis-impurity [Formula-II].

SUMMARY OF THE INVENTION

An object of the invention is to provide a novel process for preparing Carvedilol by reaction of 4-(oxiran-2-yl-methoxy)-9H-carbazole [Formula-VII] and substituted silyl protected 2-(2-methoxy phenoxy)-ethylamine compound [Formula-VIII] to give substituted silyl protected Carvedilol [Formula-IX] intermediate . The substituted silyl protected Carvedilol on desilylation gives Carvedilol.

Yet another object of the invention is to provide novel substituted silylated carvedilol intermediate [Formula-IX]

The preferred substituents (R_1,R_2,& R_3) in silyl protecting group P are R_1=R_2=R_3= -CH_3 ; R_1=R_2=R_3= -CH_2CH_3; R_1=R_2= -CH_3, R_3= -$C(CH_3)_3$. The most preferred being one with R_1=R_2=R_3= -CH_3.

Still, yet another object of the invention is to provide a novel substituted silyl protected 2-(2-methoxy phenoxy)-ethylamine as an intermediate for the preparation of Carvedilol and process for the preparation thereof.

DETAILED DESCRIPTION OF THE INVENTION

The novel process of this invention is illustrated in scheme-1.

The process comprises of following steps.

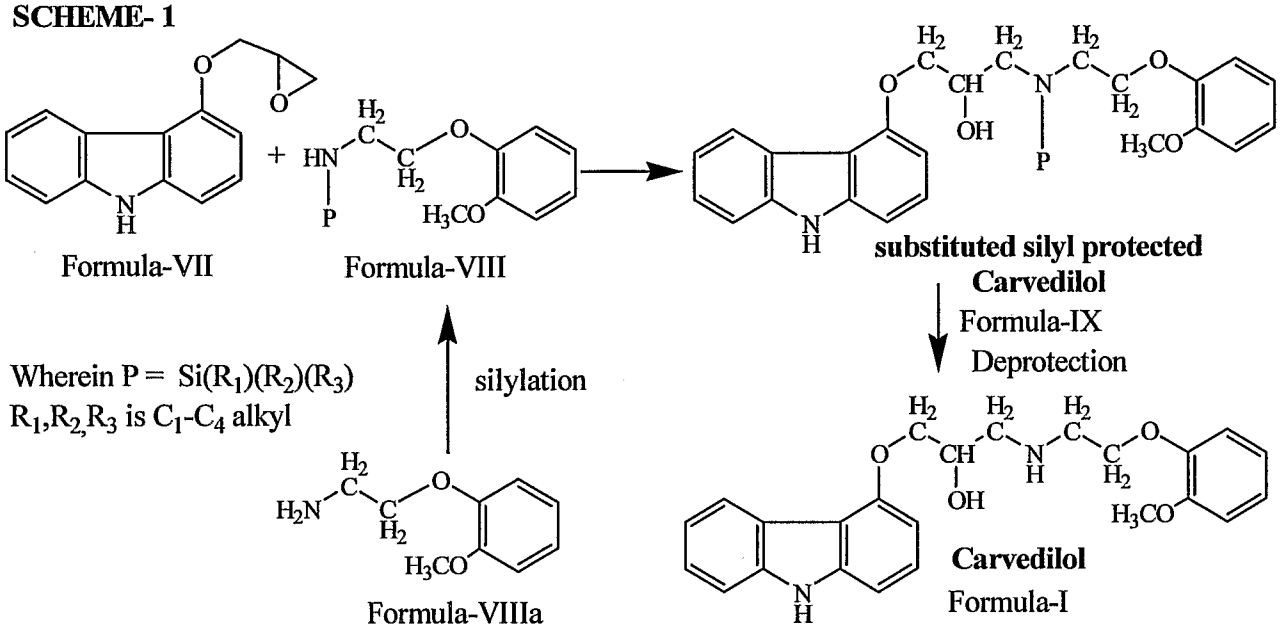
a) reacting 2-(2-methoxyphenoxy)ethylamine [Formula-VIIIa] with silylating agent in an organic solvent to give N-substituted silylated compound of Formula-(VIII),

wherein silyl substituent P is - $Si(R_1)(R_2)(R_3)$ wherein R_1,R_2,& R_3 is C_1-C_4 alkyl ,

b) reacting compound of Formula-(VIII) with 4-(2,3-Epoxypropoxy)-carbazole [Formula-VII] to give substituted silyl protected compound [Formula-IX] , wherein P is as defined above,

c) desilylation of substituted silyl protected Carvedilol to give Carvedilol, followed by isolation and purification to give high purity carvedilol.

SCHEME- 1



Yet another aspect of the invention is to provide a novel substituted silyl protected 2-(2-methoxy phenoxy)-ethylamine (Formula-VIII) as an intermediate for the preparation of Carvedilol. The silyl protected amine compound is prepared by silylation of an amine compound using silylating agents such as hexamethyl disilazane, trimethyl chlorosilane, bistrimethyl silyl urea (BSU), bistrimethyl acetamide (BSA), tert-butyl dimethyl silyl chloride.

The reaction is carried out at 20°C to 150°C, preferably at 25°C to 100°C, more preferably at 50°C to 100°C. In a preferred embodiment the substituted silyl protected amine compound [Formula-VIII] is reacted with an epoxy intermediate [Formula-VII] to give substituted silyl protected Carvedilol [Formula-IX] .

The reaction is carried out in solvent selected from aromatic hydrocarbons such as benzene, toluene, xylene or mixtures thereof ; ethers such as Tetrahydrofuran [THF] ,dioxane,2-methyl THF, dipropyl ether,di n-butyl ether, Methyl tertiary butyl ether [MTBE], monoglyme or mixtures thereof; chlorinated solvents such as dichloro methane, chloroform, carbon tetra chloride, chlorobenzene or mixtures thereof; amides such as N,N-dimethyl formamide, N,N-

dimethyl acetamide, N-methyl pyrrolidone , N,N'dimethyl imidazolidine 2-one, N,N,N',N'-tetramethyl urea or mixtures thereof ; nitriles such as acetonitrile, propionitrile or mixtures thereof; the preferred solvent being toluene.

The substituted silyl protected Carvedilol compound gives carvedilol upon deprotection. The deprotection is preferably carried out in aqueous acid followed by isolation of Carvedilol from reaction mass and purification to provide high purity carvedilol.

In one of the preferred embodiments of this invention, 2-(2-methoxyphenoxy)ethyl amine in toluene is reacted with with trimethylsilylchloride in presence of acid scavenger like trialkyl amine, preferably triethyl amine to give trimethyl silyl protected2-(2-methoxyphenoxy)ethyl amine which is then reacted with 4-(2,3-epoxypropoxy)carbazole at about reflux temperature for about 4-5 hrs. The reaction mass is then cooled and acid preferably , phosphoric acid solution is added slowly, followed by addition of water (50ml). The layer is allowed to separate and liq. ammonia is added to give pH ~9-9.5. Ethyl acetate is added and organic layer is separated, washed with water and dried over anhydrous sodium sulphate. The 50% of organic layer was distilled under reduced pressure. The mass was allowed to cool at 0^0C -5°C temperature. Carvedilol is isolated by filtration and dried.

The present invention is further illustrated by following non-limiting examples.

Example -1 Preparation of Carvedilol

Bis-trimethylsilylurea (21.35gm) was added to 2-(2-methoxyphenoxy)ethyl amine (17.47gm) in toluene (75 ml) at RT. The reaction mass was heated at reflux temperature for 3 hrs and allowed to cool at 80 to 85°C temperature. 4-(2,3-epoxypropoxy)carbazole (25gm) was added and refluxed for 5-6 hrs. The reaction mass was further allowed to cool at temperature of 55 to 60°C. Water (25 ml) was added and stirred for 15 minutes. The solvent is removed by distillation under reduced pressure at 55 to 60°C. Ethyl acetate (2x 500ml) was added and stirred. The solvent was distilled under reduced pressure to give an oily mass. Ethyl acetate (100ml) and water (50 ml) was added to oily mass and the layer was separated. The organic layer was washed with water and dried over anhydrous sodium sulphate (10gm). The 50 % of ethyl acetate was distilled under reduced pressure. 4.81 ml of 85% H_3P0_4 was added at 20-25°C and stirred for 30 minutes. Water (25 ml) and liq ammonia (25%) was slowly added to get pH ~9.5. The reaction mass was cooled to 0-5°C and filtered to give 15.5gm Carvedilol

Example 2: Preparation of Carvedilol

Trimethylsilyl chloride (31.68 ml) was added to a solution of 2-(2-methoxyphenoxy) ethylamine (20 gm) in toluene at RT over 30-45 minutes and stirred for two hours. Triethyl amine (42 ml)

was added drop wise in 15-30 min. The reaction mass was heated up at 50°C and a solution of 4-(2,3-Epoxypropoxy)carbazole (28.60gm) in 1,4-dioxane (100 ml) was added over 10 minutes. The reaction was heated at reflux temperature and stirred for 4 - 5 hour. On completion of reaction, the solvent was distilled under reduced pressure at 70 - 75^{0}C to yield an oily mass. The oily mass was cooled to 25 – 30°C. Water (50 ml) and ethyl acetate (50 ml) was added and stirred for 30 minutes. Ethyl acetate layer was separated and washed with water (2x50 ml). Ethyl acetate layer was dried with anhydrous sodium sulfate and distilled under reduced pressure at 50 - 55°C to give result the silylated Carvedilol as oily mass. [m/z = 478.5]

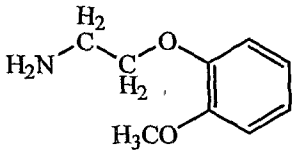
Wt. of oil= 18 gms

The oily mass (5 gm) was taken in 25 ml of DM water and stirred with H_2SO_4 (2.56 gm) for 15 minutes and then heated at 65-70^{0}C. The reaction mass was allowed to cool at 15 - 20°C. The pH was adjusted to ~ 9.5-10 using 10 %NaOH solution. Ethyl acetate (50 ml) was added and the layer was allowed to separate which was washed with water (2x 50 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give residue which were crystallized using ethyl acetate to give pure Carvedilol (3.0gm)

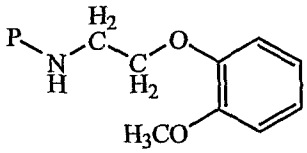
We claim,

1. A process of preparing carvedilol comprising following steps:

a) reacting 2-(2-methoxyphenoxy)ethylamine [Formula-VIIIa] with silylating agent in an organic solvent to give the compound of Formula-(VIII),



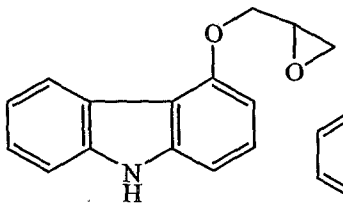
Formula-VIIIa



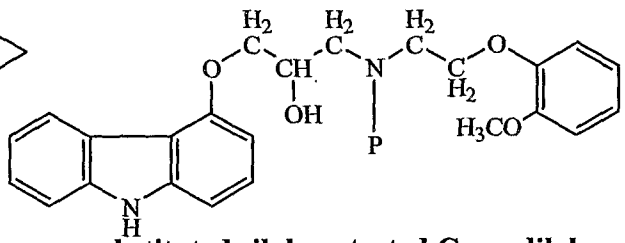
Formula-VIII

wherein, P = - $Si(R_1)(R_2)(R_3)$ wherein R_1,R_2,& R_3 is C_1-C_4 alkyl

b) reacting compound of Formula-(VIII) with 4-(2,3-Epoxypropoxy)-carbazole [Formula-VII] to give substituted silyl protected compound [Formula-IX] , wherein P is as defined above,

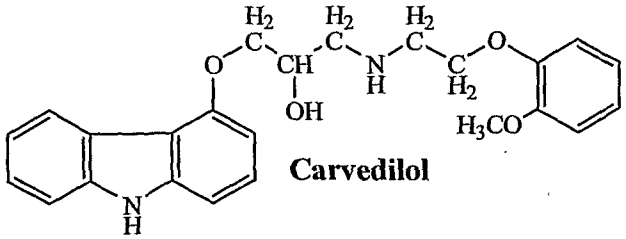


Formula-VII



substituted silyl protected Carvedilol

Formula-IX



Carvedilol

c) desilylation of substituted silyl protected Carvedilol to give Carvedilol, followed by isolation and purification to give high purity carvedilol.

2 The process as claimed in claim-1, wherein silylating agent in step-(a) is selected from trimethylchlorosilane, N,N'bistrimethylsilyl urea, N,O-bis trimethylsilyl acetamide,

hexamethyldisilazane or combination thereof , the preferred agent being N,N'bistrimethylsilyl urea or trimethylchlorosilane .

3 3. The process as claimed in claim-1, wherein the solvent used in step –(a) is selected from aromatic hydrocarbons such as benzene, toluene, xylene or mixtures thereof; ethers such as Tetrahydrofuran,dioxane,2-methyl THF, dipropyl ether,di n-butyl ether,
6 methyl tertiarybutyl ether, monoglyme, or mixtures thereof; chlorinated solvents such as dichloro methane, chloroform, carbon tetra chloride, chlorobenzene or mixtures thereof; amides such as N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone
9 , N,N'dimethyl imidazolidin-2-one, N,N,N',N'-tetramethyl urea or mixtures thereof ; nitriles such as acetonitrile, propionitrile or mixtures thereof.

4. The process as claimed in claim-3, wherein the preferred organic solvent is toluene.

12 5. The process as claimed in claim-1, wherein the compound of formula-VIII, wherein P is trimethyl silyl or triethyl silyl or tertiarybutyl dimethyl silyl.

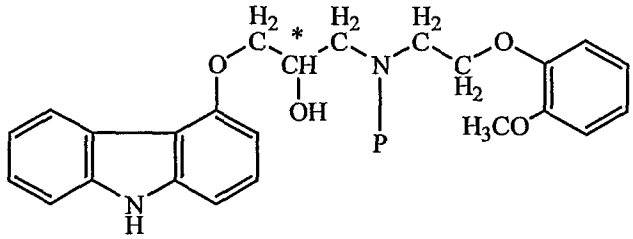
6. The process as claimed in claim-1, wherein the silylation is carried out at 20^{0}C to 150^{0}C
15 preferably at 25^{0}C to 100^{0}C.

7. The process as claimed in claim-1, wherein the desilylation in step-(c) is carried out using aqueous acid.

18 8. The process as claimed in claim-1, wherein the desilylation in step-(c) is carried out at 25^{0}C to 100^{0}C preferably at 50^{0}C to100^{0}C.

9. The process of preparing carvedilol as claimed in claim-1, wherein the purification of
21 carvedilol in step-(c) is carried out in organic solvent selected from toluene,dioxane,acetone acetonitrile, methyl ethyl ketone, methyl *i*-butyl ketone, ethyl acetate, isopropyl acetate, preferred solvent being ethyl acetate.

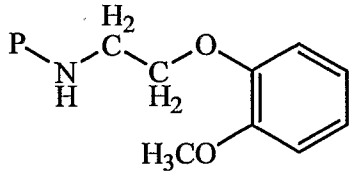
24 10. The compound of the Formula-IX useful in the preparation of carvedilol or related compounds.



Formula-IX

27 wherein, P is -Si(Me)$_3$, -Si(Et)$_3$, -Si(Me)$_2$C(Me)$_3$

11. The compound of Formula-VIII



Formula-VIII

wherein, P is -Si(Me)$_3$, -Si(Et)$_3$, -Si(Me)$_2$C(Me)$_3$

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/000551

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/88 C07F7/10

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 C07F

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, CHEM ABS Data, BIOSIS, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 503 067 A (WIEDEMANN FRITZ [DE] ET AL) 5 March 1985 (1985-03-05) cited in the application examples 2,5	1-11
Y	EP 0 918 055 A1 (EGYT GYOGYSZERVEGYESZETI GYAR [HU]) 26 May 1999 (1999-05-26) cited in the application claims	1-11
Y	US 2004/225132 A1 (HILDESHEIM JEAN [IL] ET AL) 11 November 2004 (2004-11-11) cited in the application claims	1-11

-/-

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2009	23/07/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/000551

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ATKINS R K ET AL: "ALKYLATION OF N TRIMETHYLSILYLATED PRIMARY AMINES WITH ARYLETHYLENE OXIDES AN EFFICIENT SYNTHESIS OF 1 PHENETHANOLAMINES" TETRAHEDRON LETTERS, vol. 27, no. 22, 1986, pages 2451-2454, XP002536852 ISSN: 0040-4039 the whole document	1-11
Y	SHUKER A J ET AL: "The Application of High-Throughput Synthesis And Purification To The Preparation Of Ethanolamines" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, vol. 38, no. 35, 1 September 1997 (1997-09-01), pages 6149-6152, XP004086721 ISSN: 0040-4039 the whole document	1-11
Y	KUWABE S I ET AL: "Palladium-catalyzed intramolecular C-O bond formation." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 12 DEC 2001, vol. 123, no. 49, 12 December 2001 (2001-12-12), pages 12202-12206, XP002536853 ISSN: 0002-7863 page 12206, column 1	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/000551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4503067 A	05-03-1985	AT 375639 B	27-08-1984
		AU 522975 B2	08-07-1982
		AU 4582079 A	18-10-1979
		BG 61419 B2	31-07-1997
		CA 1129416 A1	10-08-1982
		CS 227007 B2	16-04-1984
		CS 9104200 A3	15-04-1992
		DD 143607 A5	03-09-1980
		DE 2815926 A1	18-10-1979
		DK 141979 A	14-10-1979
		EP 0004920 A1	31-10-1979
		ES 479396 A1	16-04-1980
		FI 791142 A	14-10-1979
		HK 2385 A	18-01-1985
		HU 179433 B	28-10-1982
		IL 57020 A	30-07-1982
		JP 1023462 B	02-05-1989
		JP 1545837 C	28-02-1990
		JP 54157558 A	12-12-1979
		JP 63258416 A	25-10-1988
		LT 2628 R3	25-04-1994
		LU 88320 A9	04-05-1994
		MX 9203380 A1	01-09-1992
		NL 930110 I1	18-10-1993
		SG 52284 G	29-03-1985
		SU 810079 A3	28-02-1981
		ZA 7901732 A	28-05-1980
EP 0918055 A1	26-05-1999	CZ 9803561 A3	16-06-1999
		CZ 297445 B6	13-12-2006
		DE 69813729 D1	28-05-2003
		DE 69813729 T2	05-02-2004
		DE 69823394 D1	27-05-2004
		DE 69823394 T2	04-05-2005
		ES 2221875 T3	16-01-2005
		ES 2196459 T3	16-12-2003
		HR 980590 A2	31-10-1999
		HU 9802180 A1	28-12-2000
		PL 329828 A1	07-06-1999
		SK 156098 A3	11-06-1999
US 2004225132 A1	11-11-2004	US 2008194838 A1	14-08-2008
		US 2004152757 A1	05-08-2004
		US 2002143045 A1	03-10-2002