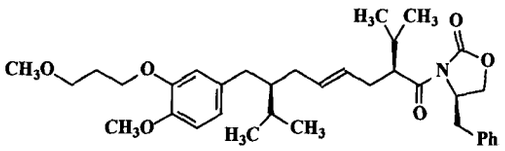
ABSTRACT

PROCESS FOR PREPARING ALISKIREN INTERMEDIATE

The present invention relates to a novel process for preparing a compound of Formula I,

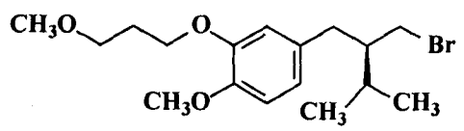


I

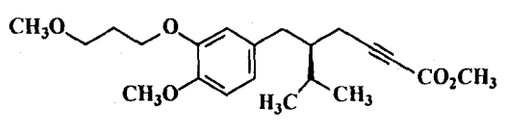
which is useful intermediate in the preparation Aliskiren.

presence of LiOH, H_2O_2 followed by treating with HCl to give compound of Formula X.

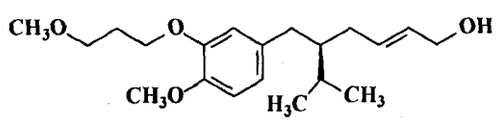
9. Use of compound of formula III, compound of formula V, compound of formula VI, compound of formula VII and compound of formula IX in the preparation of Aliskiren



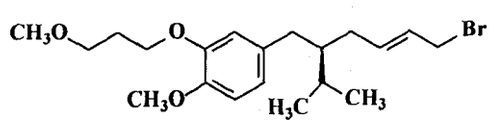
III



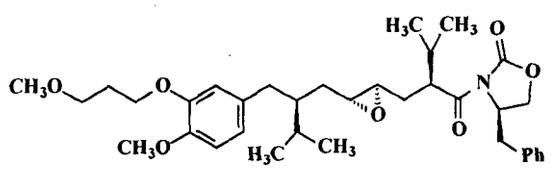
V



VI



VII



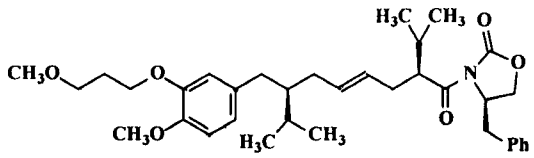
IX

Dated this the 28th day of September 2012.

Dr. M. SIVAKUMARAN
(DIRECTOR)

FIELD OF THE INVENTION

The present invention relates to a novel process for preparing a compound of Formula I,

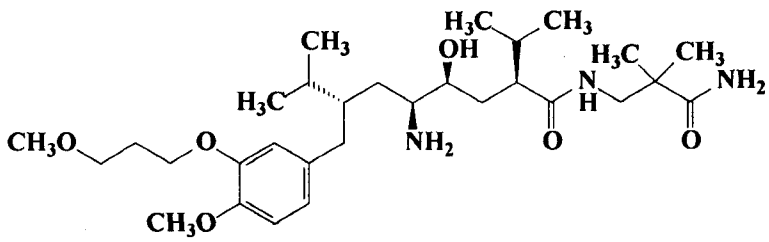


I

which is useful intermediate in the preparation Aliskiren.

BACKGROUND OF THE INVENTION

Aliskiren is the first orally active non-peptidic rennin inhibitor, which is chemically known as (2S,4S,5S,7S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide, represented as Formula I.

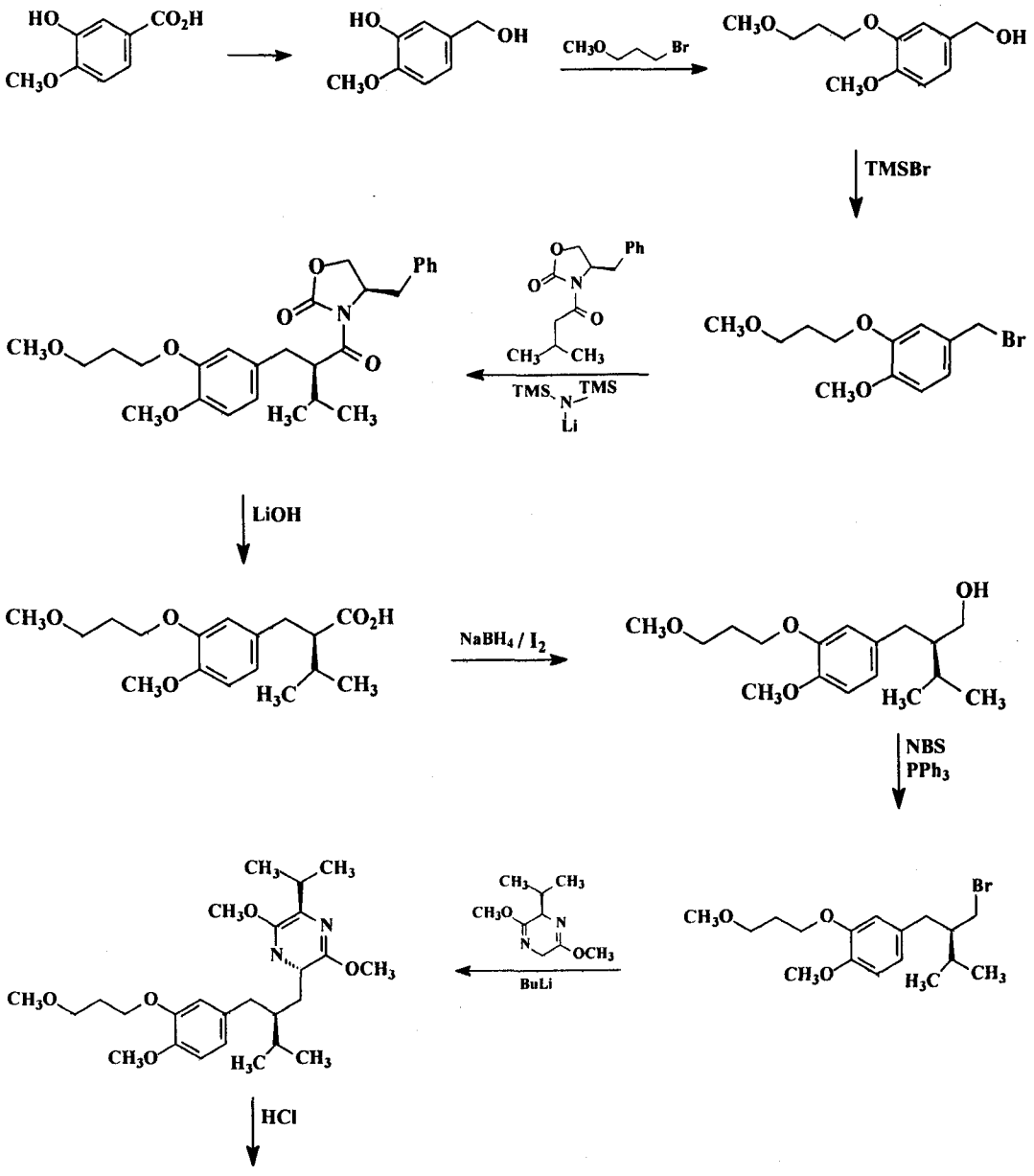


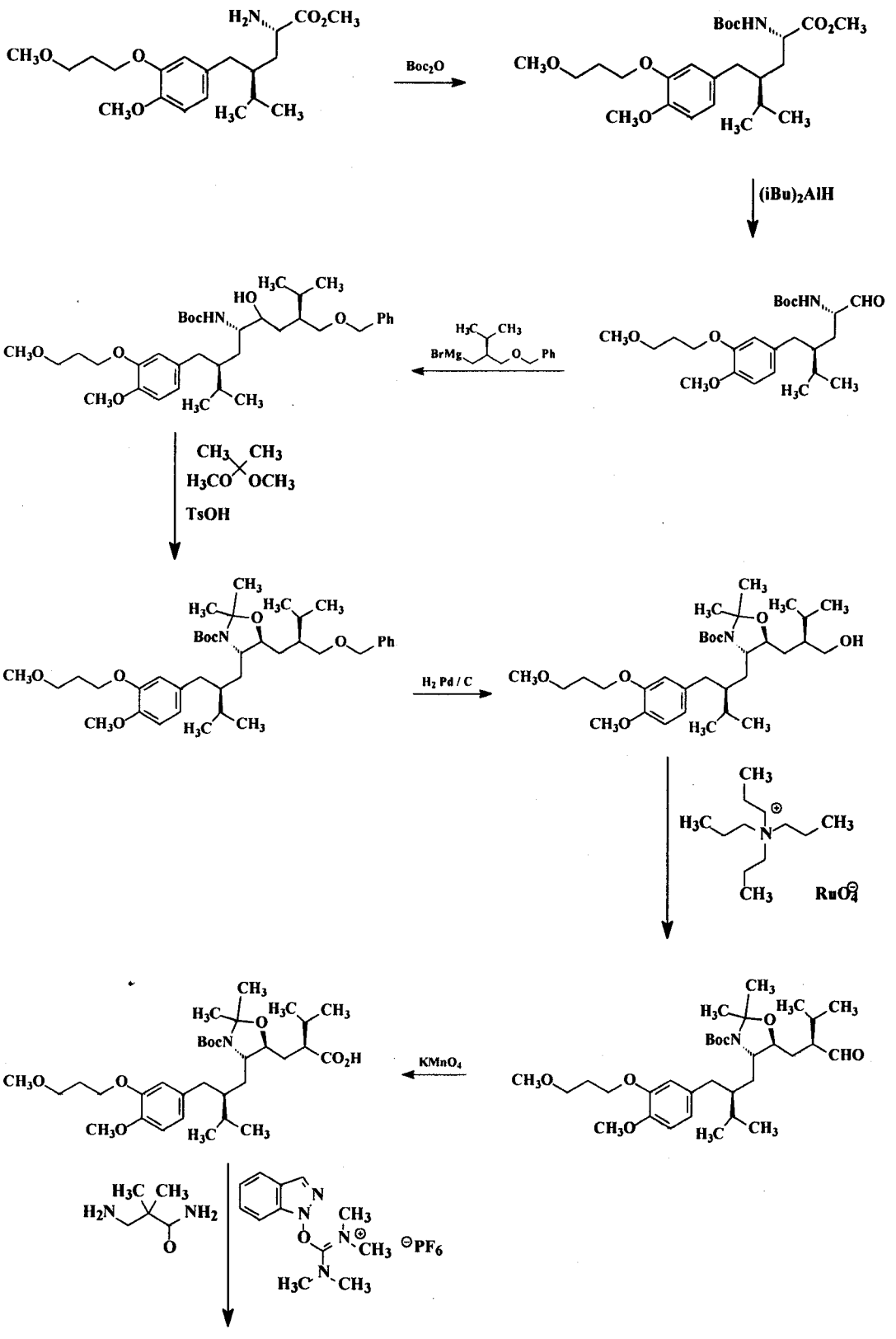
II

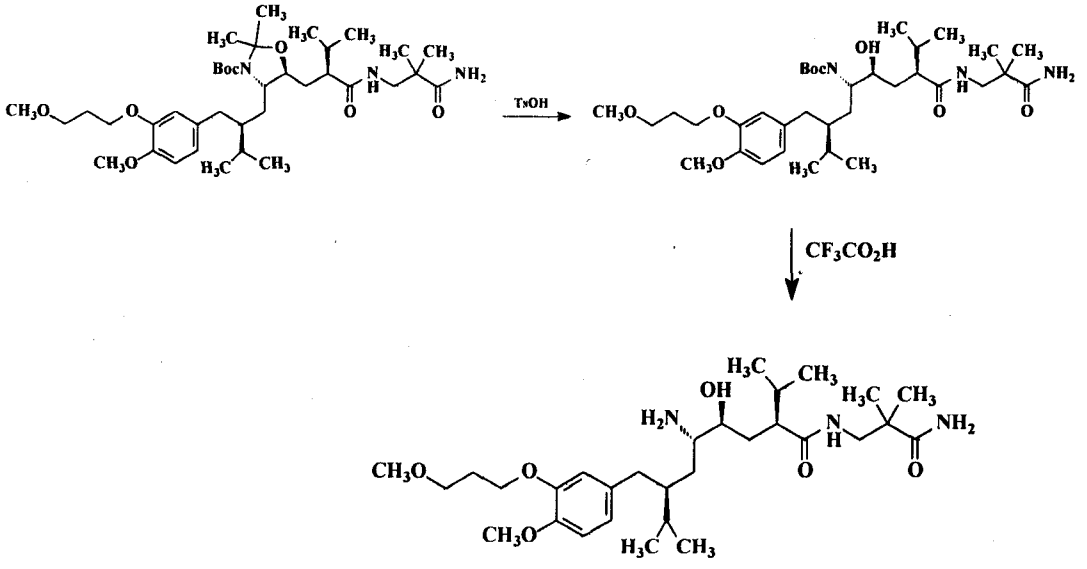
Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to Ang I. Aliskiren is being marketed under the brand name Tekturna® in its hemifumarate salt, as an oral tablet with different dosage forms.

Aliskiren Hemifumarate is also marketed with Amlodipine Besylate and Hydrochlorothiazide as combination products under the brand names Tekamlo®, Amturnide®, as an oral tablet with different dosage forms.

US Patent US 5,559,111 and European patent EP 0 678 503 for the first time discloses Aliskiren. Since Aliskiren contains 4 chiral centers, synthesis of enantiomerically pure compound is very complex. The process disclosed in this patent is as shown below:




Boc2O
(iBu)2AlH
TsOH
H2 Pd / C
KMnO4
RuO4



Alternative routes for preparing Aliskiren have been disclosed in PCT patent applications WO 01/09079, WO 02/02508, WO 02/02500, WO 02/02487, WO 02/092828, WO 02/02500, WO 03/103653, WO 2005/054177, WO 2005/090305, WO 2005/051895, WO2006/095020, WO2007/054254, WO2007/048620, WO2007/118681, WO2010/010165, WO 2007/006532, WO2007/045420, WO2008/155338, WO2008/119804, WO2009/049837; US 6,800,769, US 7,009,078, US 7,767,831, US 7,772,405, US 7,910,774, US 7,973,175, US 8,203,005, US2009/0076062, US 2011/0092706, US 2011/008852, US 2010/0130749, European patent EP 1 215 201, EP 2 062 874, EP 1958 666, EP 2 189 442; UK patents GB 2 431 640, GB 2 431 641, GB 2 431 642, GB 2 431 643, GB 2 431 644, GB 2 431 645, GB 2 431 646, GB 2 431 647, GB 2 431 48, GB 2 431 649, GB 2 431 650, GB 2 431 651, GB 2 431 652, GB 2 431 653, GB 2 431 654, Tetrahedron Letters 2000, 41, 10085, ibid. 2000, 41, 10091, ibid. 2001, 42, 4819, Drugs Fut. 2001, 1139, J. Org. Chem. 2002, 67, 4261, Helv. Chim Acta 2003, 86, 2848, Tetrahedron Letters 2005, 46, 6337, J. Org. Chem. 2006, 71, 4766, Organic Process & Develop 2007, 11, 584, Tetrahedron Letters 2008, 49, 5980 and Org. Lett. 2010, 12, 1816. Nevertheless, none of them fulfill requirements for a cost effective manufacturing process.

Although the existing processes may lead to the desired renin inhibitors, in particular the (2S,4S,5S,7S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amide derivatives, there is a need to provide an alternative synthetic route to ensure its manufacture in a simple and efficient manner.

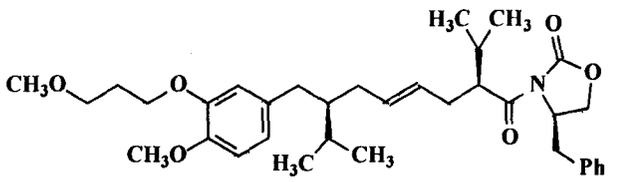
OBJECTIVE OF THE INVENTION

The objective of the present invention is to provide a novel process for preparing a compound of Formula I, which is an useful intermediate in the preparation of Aliskiren and its pharmaceutically acceptable salts.

In yet another objective of the present invention is to provide novel intermediates, which are useful in the preparation of Aliskiren and its pharmaceutically acceptable salts.

SUMMARY OF THE INVENTION

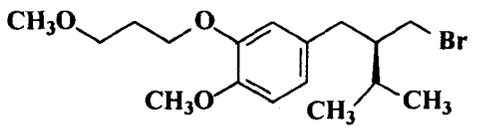
The present invention relates to a novel process for preparing a compound of Formula I,



I

which comprises,

a) reacting a compound of Formula III,



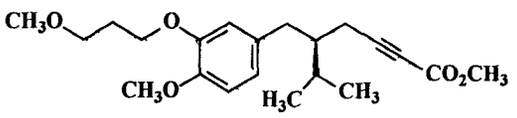
III

with a compound of Formula IV,

IV

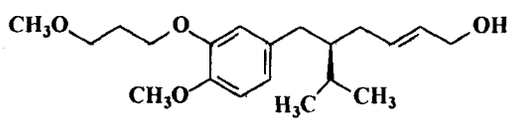
wherein R is alkyl, aryl

using Palladium catalysis to give a compound of Formula V;



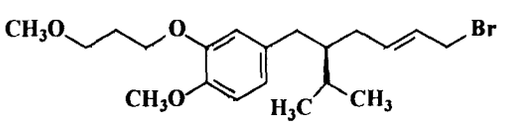
V

b) reduction of compound of Formula V using metal hydride reagents in polar aprotic solvents to give a compound of Formula VI;



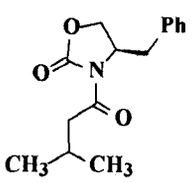
VI

c) brominating a compound of Formula VI using brominating agents in a solvent to give a compound of Formula VII;



VII

d) reacting compound of Formula VII with a compound of Formula VIII,

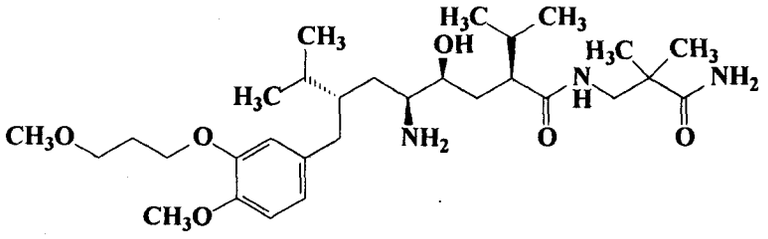


VIII

using organolithium bases in polar aprotic solvents to give a compound of Formula I; and

e) isolating the compound of Formula I.

In another embodiment of the present invention, also relates to a process for preparing Aliskiren of Formula II,

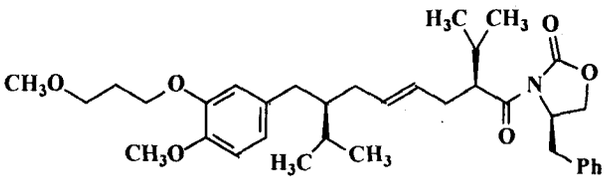


II

or its pharmaceutically acceptable salts thereof, using the compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel process for preparing a compound of Formula I,



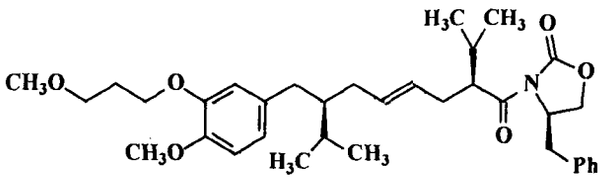
I

which comprises, reacting a compound of Formula III with a compound of Formula IV using palladium catalysis selected from CuI, Pd catalyst, tertiary amine such as triethylamine, diisopropylamine in polar aprotic solvents to give a compound of Formula V, which is reduced in the presence of metal hydride reagents selected from $NaBH_4/I_2$, $Zn(BH_4)_2/I_2$,, $Al(BH_4)_3$, $LiAlH_4$ and $NaCNBH_3/H^+$ and Vitride® in polar aprotic solvent selected from THF, diethyl ether to give a compound of Formula VI.

The compound of Formula VI is brominated using brominating agent NBS, PPh_3 (or) PPh_3, Br_2 (or) CBr_4, PPh_3 in chlorinating solvents to give a compound of Formula VII, which is reacted with compound of Formula VIII using organolithium bases selected from LiHMDS, LDA, BuLi, sec-BuLi and ^{t}BuLi (or) $TiCl_3$, $TiCl_4$ & $ZnCl_2$ in polar aprotic solvents to give compound of Formula I.

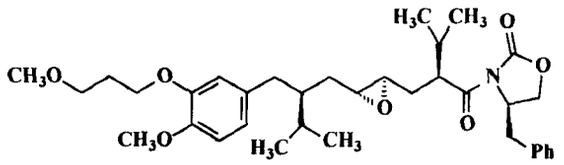
The present invention also relates to a process for preparing Aliskiren or its pharmaceutically acceptable salts thereof, which comprises:

a) epoxidation of compound of Formula I,



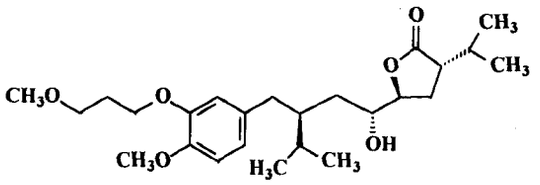
I

to give compound of Formula IX;



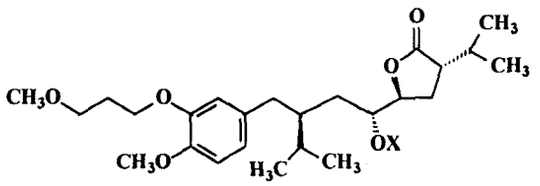
IX

b) hydrolysis of compound of Formula IX to give compound of Formula X;



X

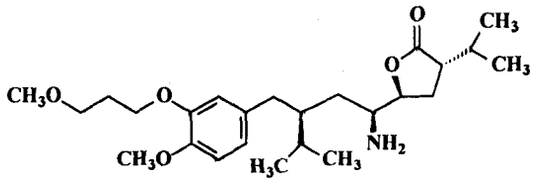
c) activating the hydroxyl group of compound of Formula X to give a compound of Formula XI;



XI

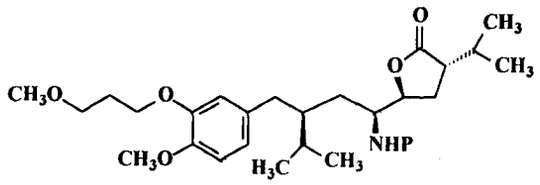
wherein X represents mesyl (or) tosyl protecting groups

d) azidation and hydrogenation of compound of Formula XI to give a compound of Formula XII;



XII

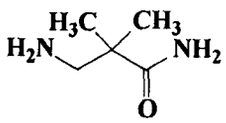
e) optionally protecting the amino group of compound of Formula XII to give a compound of formula XIII.



XIII

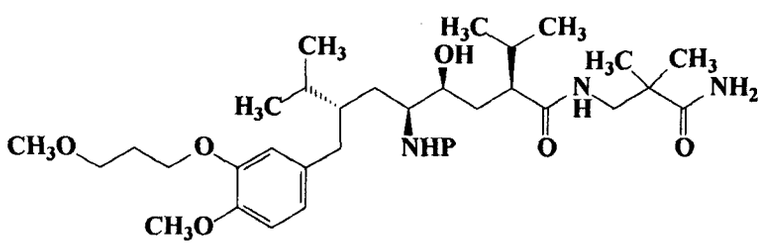
wherein P represents BOC, Cbz, Bn

f) reacting the compound of Formula XIII to with aminoamide of Formula XIV,



XIV

to give compound of Formula XV;



XV

wherein P represents BOC, Cbz, Bn

g) deprotecting compound of Formula XV to Aliskiren of Formula II; and

f) optionally converting the Aliskiren of Formula II in to its pharmaceutically acceptable salts thereof.

In another embodiment the present invention relates to a process for preparing Aliskiren and its pharmaceutically acceptable salts thereof, which comprises epoxidation of compound of Formula I to give a compound of Formula IX using Shi (or) Sharpless asymmetric epoxidation and hydrolyzing the obtained compound in the presence of LiOH, H_2O_2 followed by treating with HCl to give compound of Formula X.

Activating the hydroxyl group of compound of Formula X to give a compound of Formula XI using MsCl, triethylamine (or) TsCl, triethylamine (or) pyridine

which is azidated using NaN_3 and thereafter hydrogenated using H_2, Pd-C to give a compound of Formula XII.

Protection of the compound of Formula XII using using BOC_2O, BnBr, BnCl, CbzCl to give a compound of Formula XIII, which is reacted with amino amide of formula XIV to give a compound of Formula XV. Deprotection of compound of Formula XV using acids such as HCl, TFA, HCOOH and $HCOONH_4$, H_2, Pd-C furnishes Aliskiren of Formula II.