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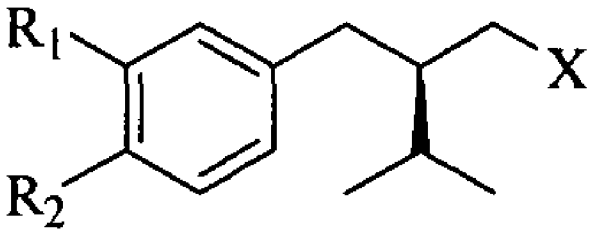
(54) Title: NOVEL PROCESS FOR THE PREPARATION OF RENIN INHIBITORS



Formula-II

(57) Abstract: The present invention relates to an improved process for the preparation of compound of Formula-II, which is an intermediate in the preparation of Aliskiren and further conversion of compound of Formula-II into Aliskiren or its pharmaceutically acceptable salts. Formula-II wherein Ri and R2 are independently of one another H, Ci-C6 alkyl, C\- C6 halogenalkyl, C]-C6 alkoxy, Ci-C6 alkoxy-Ci-C6 alkyl, or Ci-C6 alkoxy-Ci- C6 alkyloxy and X is halogen selected from fluoro, chloro, bromo and iodo

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

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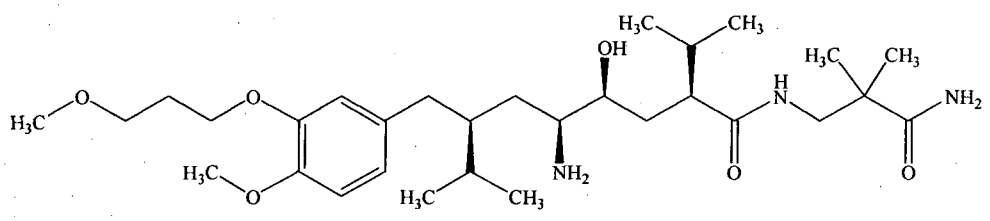
This application claims priority to Indian patent application number 4342/CHE/201 1 filed on Dec 13, 201 1.

FIELD OF THE INVENTION

The present invention relates to novel process for the preparation of Aliskiren intermediates and further conversion into Aliskiren and its pharmaceutically acceptable salts.

BACKGROUND OF THE INVENTION

Aliskiren, (2S, 4S, 5S, 7S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl] octanamide having the Formula-I, a new antihypertensive has been developed which interferes with the renin-angiotensin system at the beginning of angiotensin II biosynthesis.

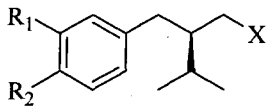


Formula-I

Aliskiren is marketed by Novartis as TEKTURNA® in the form of its hemifumarate salt in a once-daily formulation.

U.S. pat. No. 5,559,1 11 discloses Aliskiren and related compounds along with the synthesis of Aliskiren.

Further US 7132569, US 7009078, US 6730798 and US 6800769 claims novel intermediates used in the preparation of Aliskiren and process for the preparation of Aliskiren, which are incorporated here for reference. US 5,559,1 11 discloses compound of Formula-II, which is used as an intermediate in the preparation of Aliskiren.



Formula-II

wherein Ri and R_2 are independently of one another H, Ci-C_6 alkyl, C_1- Qhalogenalkyl, C_1-C_6 alkoxy, Ci-C_6 alkoxy-Ci-C_6 alkyl, or Ci-C_6 alkoxy-Ci- C_6 alkyloxy, and X is CI, Br and I.

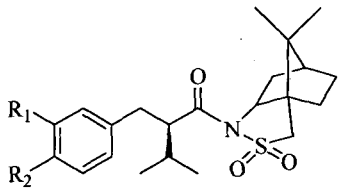
As the Aiiskiren comprises, 4 chiral carbon atoms, the synthesis of the enantiomerically pure compound is quite demanding. Therefore, novel routes of synthesis needed for the preparation of Aiiskiren. The intermediate of Formula-II is having commercially important in the synthesis of Aiiskiren. Therefore novel route of synthesis is needed for that intermediate.

The present invention provides novel compounds used in the preparation of Aiiskiren intermediate and further process for the preparation of Aiiskiren.

OBJECT AND SUMMARY OF THE INVENTION

Principle object of the present invention is to provide a novel process for the preparation of intermediate of Formula-II of Aiiskiren.

Another object of the present invention is to provide novel intermediate (Formula-V) used in the preparation of Aiiskiren.



Formula-V

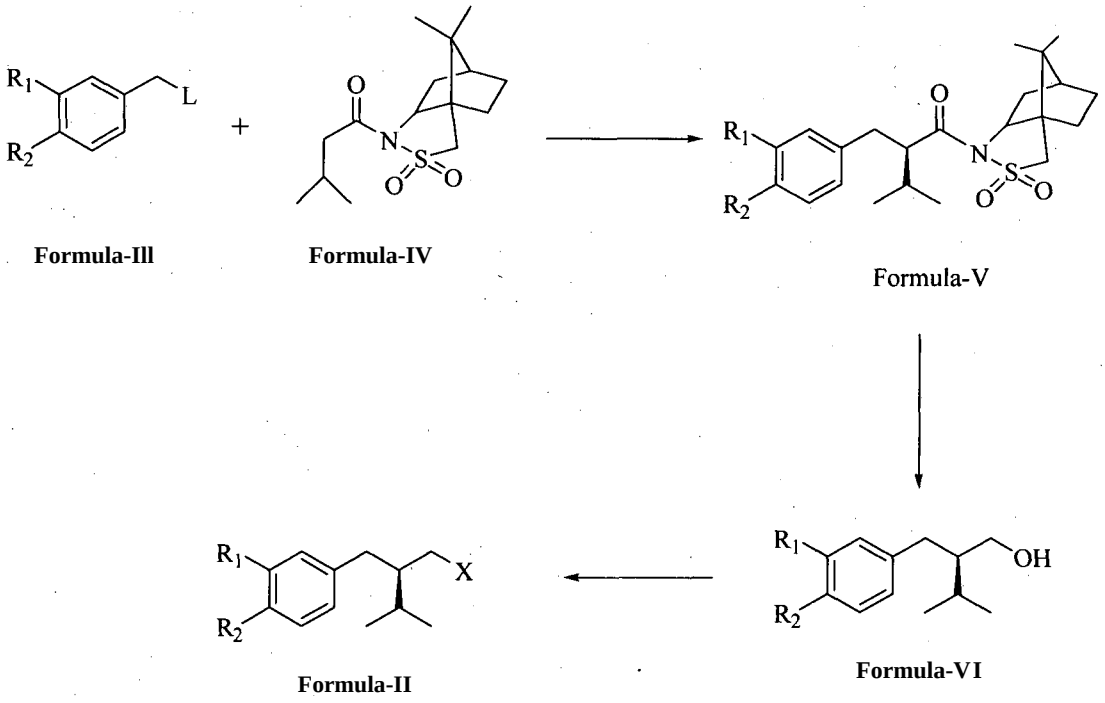
wherein Ri and R_2 are independently of one another H, Ci-C_6 alkyl, Ci- C_6 halogenalkyl, Ci-C_6 alkoxy, Ci-C_6 alkoxy-Ci-C_6 alkyl, or Ci-C_6 alkoxy-Ci- C_6 alkyloxy.

One more object of the present invention is to provide further conversion of intermediate of Formula-II into Aliskiren or its pharmaceutically acceptable salts.

One aspect of the present invention provides, novel process for the preparation of compound of Formula-II comprising the steps of:

a) condensing the compound of Formula-Ill with compound of Formula-IV in presence of a base to give compound of Formula-V;
b) converting compound of formula V to compound of formula VI.
c) converting compound of formula VI to compound of formula II

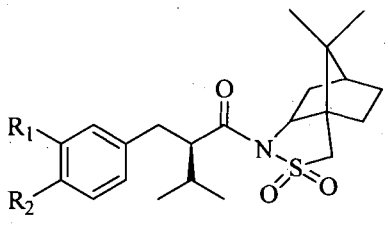
Preparation of compound of Formula-II is depicted in scheme-I.



SCHEME-I

wherein Ri and R_2 are independently of one another H, Ci-C_6 alkyl, C_1- C_6 halogenalkyl, C_1-C_6 alkoxy, Ci-C_6 alkoxy-Ci-C_6 alkyl, or Ci-C_6 alkoxy-Ci- C_6 alkyloxy, and L is a leaving group, selected from CI, Br, I, arylsulfonyloxy such as tolylsulfonyloxy and alkylsulfonyloxy such as methylsulfonyloxy; X is halogen selected from fluoro, chloro, bromo and iodo.

Another aspect of the present invention provides, novel intermediate compound of Formula-V.



Formula-V

wherein R_1 and R_2 are as defined above.

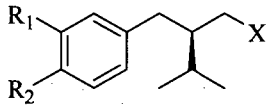
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel process for the preparation of intermediate of Formula-II of Aliskiren.

The present invention further relates to novel intermediate (Formula-V) used in the preparation of Aliskiren.

The present invention also relates to further conversion of compound of Formula-II into Aliskiren or its pharmaceutically acceptable salts.

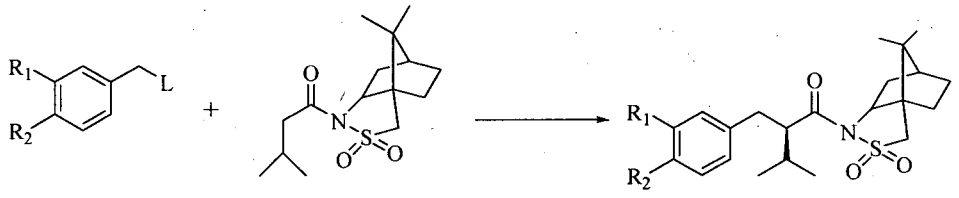
The main aspect of the present invention provides novel process for preparation of compound of Formula-II comprising the steps of:



Formula-II

wherein Ri and R_2 are independently of one another H, Ci-C_6 alkyl, *C*\- C_6 halogenalkyl, C]-C_6 alkoxy, C]-C_6 alkoxy-Ci-C_6 alkyl, or C_1-Cealkoxy-Ci- C_6 alkyloxy and X is halogen selected from fluoro, chloro, bromo and iodo

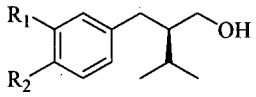
a) condensing the compound of Formula-Ill with compound of Formula-IV in presence of a base to give compound of Formula-V,



Formula-Ill Formula-IV Formula-V

wherein Ri and R_2 are defined above; and L is a leaving group,

b) converting compound of formula V to compound of formula VI, and



Formula-VI

wherein R_1 and R_2 are defined above

c) converting compound of formula VI to compound of formula II.

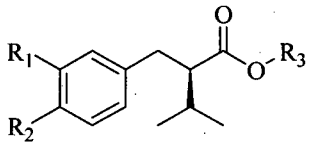
In one embodiment, the compound of Formula-V is prepared by condensing compound of Formula-Ill with the compound of Formula-IV in presence of a base. The base is selected from LiHMDS (Lithium bis(trimethylsilyl)amide), NaHMDS (sodium hexamethyldisilazide), KHMDS (potassium hexamethyldisilazide), LDA (Lithium diisopropylamide), n-BuLi (n-Butyllithium). The reaction is carried out in inert solvents such as ether, hydrocarbons, selected from tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentyl methyl ether, diethyl ether , dioxane, diglyme, tetrahydropyran, diisopropyl ether, methyl tertiary butyl ether and their mixtures, aliphatic and aromatic hydrocarbons such as cyclohexane, toluene, heptanes, hexanes, methyl cyclohexane etc. and their mixtures, preferably tetrahydrofuran or mixture of tetrahydrofuran with hexanes, heptanes to give the compound of Formula-V.

In one embodiment of the present invention, compound of Formula-V is converted into compound of Formula-VI by reducing the compound of Formula-V. The reduction of the compound of Formula-V is carried out with suitable reducing agents such as transition metal catalysts and hydride reagents, preferably using hydride reagents. The reducing reagent is selected from sodium borohydride, sodium cyano borohydride, lithium

aluminium hydride, lithium tri-tert-butoxy aluminium hydride, diborane and vitride, preferably sodium borohydride.

Alternatively the compound of Formula- VI is prepared from compound of Formula-V comprising the steps of:

a) converting the compound of Formula-V into compound of Formula-VII, and



Formula-VII

wherein **Ri** and **R_2** are independently of one another H, **Ci-C_6** alkyl, **Cj- C_6** halogenalkyl, **Ci-C_6** alkoxy, **C_1-C_6 alkoxy-Ct-Ce** alkyl, or **C_1-C6 alkoxy-Ci-C_6** alkyloxy, and **R_3** is **C]-C_6** alkyl or aryl.

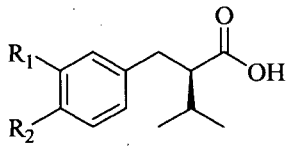
b) reducing the obtained compound of Formula-VII to get compound of Formula- VI.

In one more embodiment, the compound of Formula-V is reacted with a base such as alkalimetal alkoxide in a solvent such as aromatic/aliphatic hydrocarbon solvents, preferably toluene, cyclohexane, tetrahydrofuran, methanol or mixture there of, to obtain alkyl or aryl ester of compound of Formula-VII. Alkalimetal alkoxide used in this reaction is selected from sodium, alkoxide, potassium alkoxide, preferably sodium methoxide. This reaction is carried out in presence of alkyl carbonate such as dimethylcarbonate and diethyl carbonate etc.

In another embodiment of the present invention, reduction of compound of Formula-VII to compound of Formula-VI is carried out in the presence of hydride reagents selected from sodium borohydride and lithium aluminium hydride, lithium tri-tert-buotoxy aluminium hydride, diborane and vitride.

Alternatively the compound of Formula-VI is prepared from compound of Formula-V comprising the steps of:

a) hydrolyzing the compound of Formula-V to get compound of Formula-VIII; and



Formula-VIII

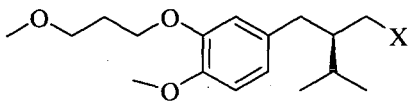
wherein Ri and R_2 are independently of one another H, Ci-C_6alkyl, C_1-C_6halogenalkyl, CrQalkoxy, Ci-Qalkoxy-CrQalkyl, or Ci-C_6alkoxy-Ci-C_6alkyloxy.

b) reducing the compound of Formula-VIII into compound of Formula-VI.

In one more embodiment, hydrolysis of compound of Formula-V is carried out with a base in presence of hydrogen peroxide in suitable polar aprotic solvents. The base used in this reaction is selected from alkali metal hydroxides such as sodium hydroxide, potassium hydroxide or lithium hydroxide, preferably lithium hydroxide. The polar aprotic solvents used in the reaction are tetrahydrofuran, methyl tetrahydrofuran, cyclopentyl methyl ether, methanol, ethanol etc. Mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid etc., or bases such as potassium hydroxide, sodium hydroxide, lithium hydroxide etc., can be used for hydrolysis to get compound of Formula-VIII.

In one more embodiment, reduction of the compound of Formula-VIII is carried out as such or optionally converting into corresponding acid chloride/anhydride and subjecting to reduction with suitable reducing agents such as transition metal catalysts and hydride reagents, preferably using hydride reagents selected from sodium borohydride, sodium cyano borohydride, lithium aluminium hydride, diborane and vitride, most preferably with in-situ generated diborane. Diborane can be generated using sodium borohydride in combination with iodine, sulfuric acid, hydrochloric acid, lewis acids such as boron trifluoride diethyl etharate etc.

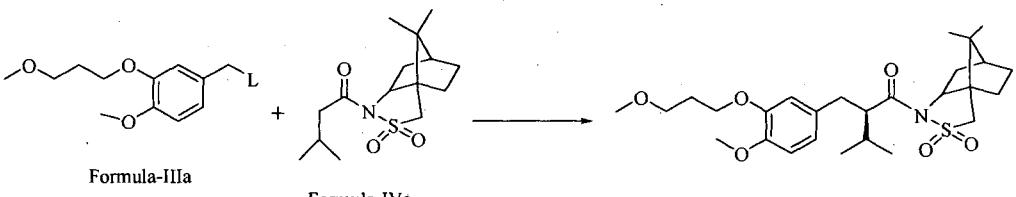
One more aspect of the present invention provides, process for the preparation of compound of Formula-IIa comprising the steps of:



Formula-IIa

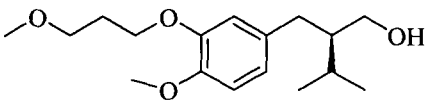
wherein X is halogen selected from fluoro, chloro, bromo and iodo

a) condensing the compound of Formula-IIIa with compound of Formula-IVa in presence of a base to give compound of Formula-Va,



Formula-IIIa Formula-IVa Formula-Va

b) compound of formula Va to compound of formula Via, and

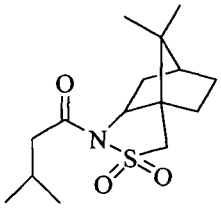


Formula-Via

c) converting compound of formula Via to compound of formula Ila.

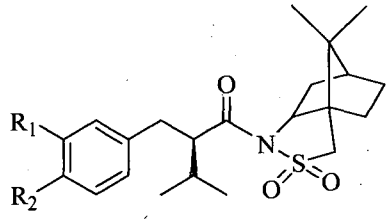
In one embodiment of the present invention, L is halogen selected from fluoro, chloro, bromo and iodo.

One more aspect of the present invention provides novel intermediate of compound of Formula-IV, i.e. (S)-N-Isovaleryl camphorsultam.



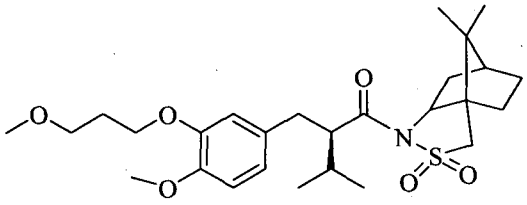
FormuIa-IV

One more aspect of the present invention provides novel intermediate of compound of Formula- V.



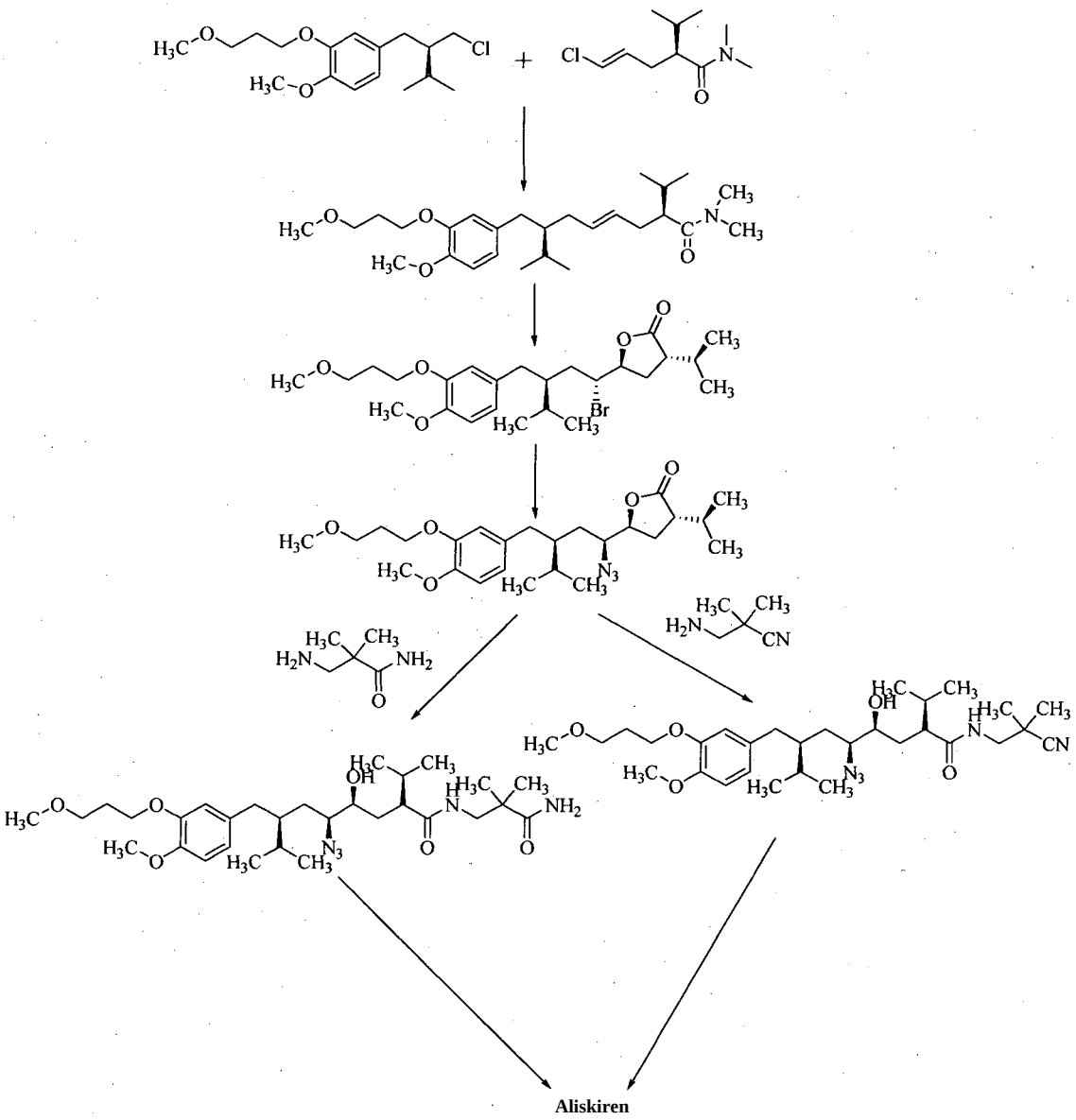
Formula-V

wherein Ri and R_2 are independently of one another H, Ci-C_6 alkyl, C_1- C_6 halogenalkyl, Ci-C_6 alkoxy, Ci-C_6 alkoxy-Ci-C_6 alkyl, or Ci-C_6 alkoxy-Ci- C_6 alkyloxy. The preferred compound of Formula-V is as shown below.



In one more aspect of the present invention provides, conversion of alcoholic compound (compound of Formula- VI) into compound of Formula-II (X=C1, Br, I etc.,) by reacting with suitable reagents such as thionyl chloride, thionyl bromide, trimethyl silyl bromide trimethyl silyl iodide etc. In some cases initially the X= CI (chloro compound) is prepared which is further converted in to bromo/iodo compound by reacting with Nal, KI, NaBr etc.

One more aspect of the present invention provides further conversion of Compound VI or compound of Formula-II into Aliskiren by conventional methods as disclosed in US 5,559,1 11, US 7009078 and WO 2012052829 for example as depicted in scheme-II.



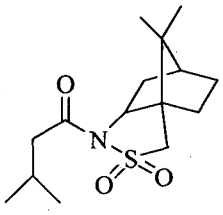
SCHEME-II

All patents, patent applications, and non-patent publications cited herein by reference should be considered in their entirety. The following examples are provided to illustrate the process of the present invention. They, are however, not intended to limiting the scope of the present invention in any way and several variants of these examples would be evident to person ordinarily skilled in the art.

Experimental procedure:

Example-1

Process for the preparation of (S)-N-Isovaleryl camphorsultam :



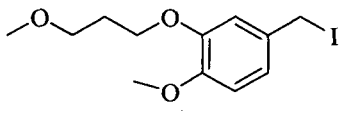
A solution of (lS)-(-)-2, 10-Camphorsultam (lOg) in toluene (50ml) was added to the mixture of triethylamine (6.15gm) and 4-Dimethylaminopyrdine (0.57gm). The resulting solution was cooled to 0°C, and a solution of isovaleryl chloride (6.15gm) in toluene (20ml) was added slowly at 0°C. The temperature was raised to 20-25°C and stirred at for 6-9 hours. The reaction mixture was quenched with aqueous hydrochloric acid. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated under vacuum to obtain l1g of N-Isovaleryl camphorsultam.

'H NMR ($CDCl_3$) δ: 0.97 (m, 9H, CH_3) , 1.15 (s , 3H , CH3) , 1.33 (m, lH) , 1.42 (m, 1H) , 1.86 - 2.10 (m, 5H) , 2.22 (m, 1H, CH) , 2.58 (2 dd, 2H) , 3.46 (dd, 2H) , 3.7 (t , 1H) , 4.15 (br s , lH , NH) .

MS (EI) m/z: 299

Example-2

Process for the preparation of compound of Formula-III (where R_1= $OCH_2OCH_2CH_3$, R_2=OCH_3, X=I):

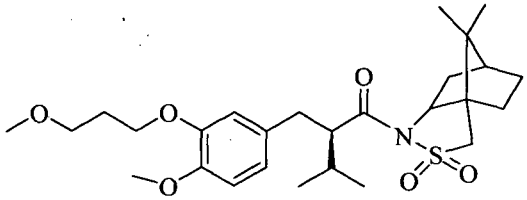


A solution Thionyl chloride (57.74 gm) in Dichloromethane (500ml) was added to a mixture of [4-Methoxy-3-(3-methoxy-propoxy)-phenyl] methanol (100 gm) in dichloromethane (200 ml) at 0°C over a period of 60 minutes. The resulting mixture was stirred for 60 minutes. The reaction mixture was concentrated in vacuum and the residue was crystallized in ethyl acetate (225ml) and hexane (1275 ml) to give 80g 4-Chloromethyl-l-methoxy-2-(3-methoxy-propoxy)-benzene. Sodium iodide (3.3g) was added to a small portion of 4-Chloromethyl-l-methoxy-2-(3-methoxy-propoxy)-benzene

(4.6 g) in tetrahydrofuran and reaction mixture was stirred at 25-30°C for 16h and reaction mass was filtered. The filtrate was used in the next step with out any purification.

ExampIe-3

Process for the preparation of compound of Formula- V



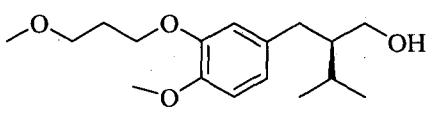
A solution of Hexamethyldisilazane (3.5gm) in anhydrous tetrahydrofuran (30ml) was cooled in an ice-water bath. To this butyl lithium in hexane (13.5ml) was added drop wise over 5-10 minutes under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for one hour, cooled to -30°C to -25°C and 5.0 g of N-Isovaleryl camphorsultam in anhydrous tetrahydrofuran (10ml) was added drop wise over 30 minutes. After stirring for 1h at the same temperature, a solution of 4-Iodomethyl-l-methoxy-2-(3-methoxy-propoxy)-benzene obtained from example-2 in tetrahydrofuran (Formula-Ill) was added and the temperature raised slowly to -5°C for 16h. The reaction mixture was quenched with 10% hydrochloric acid. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated under vacuum. The product was stirred in diisopropyl ether and filtered to give compound of Formula- V.

Ή NMR (CDC1 $_3$) δ : 0.44 (s , 3H , CH_3) , 0.82 (s, 3H , CH_3) , 1.05 -1.07 (2 s , 6 H, CH_3) , 1.2 -1.3 (m , 2H , CH) , 1.7 (m, 3H) , 1.7 -1.9 (m , 3 H) , 2.0 - 2.13 (m, 3 H) 2.7 (m, 1H) , 2.9 (dd , 1H) , 3.2 (m , 1H) , 3.3 (s, 2H , CH_2), 3.35(s, 3H , CH_3), 3.56 (t , 2H , CH_2) , 3.8 (s, 3H , CH_3) , 4.1 (t , 2H , CH_2) , 6.7 (s, 2H) , 6.77 (s , 1H)

MS (EI) m/z: 505

Example-4

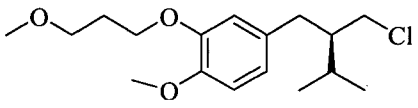
Process for the preparation of compound of Formula- VI



A solution of sodium borohydride (0.3 gm) in water (2ml) was added to a cooled solution of Formula-V (l.Og) obtained from example-3 in THF (10.0ml). The mixture was stirred at room temperature and the completion of the reaction was monitored by TLC. The mixture was cooled to 0°C and quenched with aq. HC1. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated and purified by Si02 chromatography to get the compound of Formula-VT (150mg), using 15% ethyl acetate/hexanes as an eluent.

Example-5

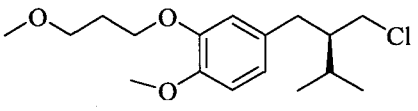
Process for the preparation of compound of FormuIa-II



To a solution of compound of Formula- VI (lOOg) in toluene (750 ml) was added to N,N-dimethyl acetamide and reaction mixture was heated to 89-95°C. Thionyl chloride (61g) was added slowly drop wise over period of 1h at 89-95°C and stirred the reaction mixture at the same temperature for 90 minutes. ~200ml of toluene was distilled at 40-50°C under reduced pressure to remove excess thionyl chloride. The reaction mass was cooled to 5-10°C and quenched in to pre cooled aq. Sodium hydroxide solution. Toluene layer was separated and washed with aq. Sodium hydroxide solution followed by DM water. Carbon was added to the toluene layer and stirred for 30 minutes at 40-45°C, filtered through hyflo and concentrated under reduced pressure to give a residue. The compound was re-crystallized in hexanes at -20°C to give of Formula-II as off white solid.

Example-6

Alternative Process for the preparation of compound of Formula-II

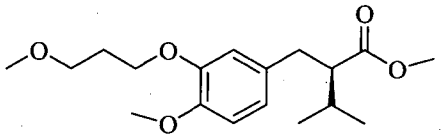


To a solution of compound of Formula-VI (lOOg) in toluene (750 ml) was added to N,N-dimethyl formamide and reaction mixture was heated to 89-95°C. Thionyl chloride (61g) was added slowly drop wise over period of 1h at 89-95°C and stirred the reaction mixture at the same temperature for 90 minutes. ~200mi of toluene was distilled at 40-50°C under reduced pressure to remove excess thionyl chloride. The reaction mass was cooled

to 5-10°C and quenched in to pre cooled aq. Sodium hydroxide solution. Toluene layer was separated and washed with aq. Sodium hydroxide solution followed by DM water. Carbon was added to the toluene layer and stirred for 30 minutes at 40-45°C, filtered through hyflo and concentrated under reduced pressure to give a residue. The compound was re-crystallized in hexanes at -20°C to give of Formula-II as off white solid.

Example-7

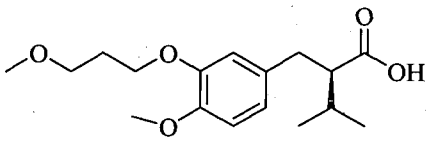
Process for the preparation of compound of Formula-VII



A mixture of compound of Formula-V obtained from example-3 (lOgm), sodium methoxide (5.32gm), dimethyl carbonate (4.43gm) and methanol (0.5ml) in Toluene (25ml) was stirred at room temperature for 8-10 h. After completion of the reaction water (5ml) was added and the organic layer was separated. The aqueous layer was acidified with hydrochloric acid pH was adjusted to 7 and layers were separated. The combined organic layer was dried over MgS04, filtered, and concentrated in vacuum. The mixture was chromatographed on silica gel by ethylacetate-hexane (3:7) to give 4g of compound of Formula-VII as a gummy residue.

Example-8

Process for the preparation of compound of Formula-VIII

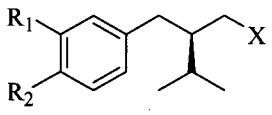


The compound of Formula-V obtained from example-3 (lOgm, 19.7mol) was dissolved in THF (60ml) and water (20ml). The reaction mixture was cooled to 0°C. To this 30% hydrogen peroxide (13.5ml, 30%solution) was added followed by lithium hydroxide (2.07gm,50 mol), while the temperature was maintained at 0 °C. Temperature was slowly raised to 20-25° and the reaction mixture was stirred at this temperature for 10-12h. The reaction was quenched by the addition of a cold aqueous solution of sodium sulfite. The temperature of the reaction mixture was raised to 20 °C and stirred at this temperature for 30 min. The solution was concentrated under reduced pressure. The concentrate was

extracted with dichloromethane and then acidified with 3 N HCl to a final pH of 3-4. The product was extracted into ethyl acetate, and the extracts were combined and washed with water. The combined dichloromethane layers were concentrated under vacuum to give 5g of compound of Formula-VIII.

We claim:

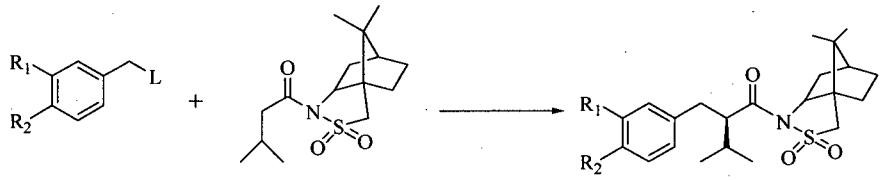
1. A process for the preparation of compound of Formula-II comprising the steps of:



Formula-II

wherein R_1 and R_2 are independently of one another H, Ci-C_6 alkyl, Ci-C_6 halogenalkyl, Ci-C_6 alkoxy, Ci-C_6 alkoxy-Ci-C_6 alkyl, or Ci-C_6 alkoxy-Q-C_6 alkyloxy and X is halogen selected from fluoro, chloro, bromo and iodo

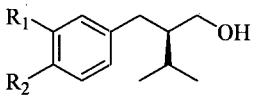
a) condensing the compound of Formula-Ill with compound of Formula-IV in presence of a base to give compound of Formula-V,



Formula-Ill **Formula-IV** **Formula-V**

wherein R_1 and R_2 are defined above; and L is a leaving group,

b) converting compound of formula V to compound of formula VI, and



Formula-VI

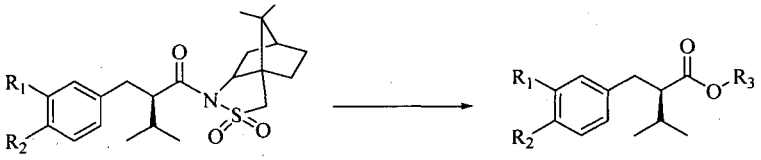
wherein Ri and R_2 are defined above

c) converting compound of formula VI to compound of formula II.

2. The process according to claim 1, wherein the base is selected from LiHMDS, NaHMDS, KHMDS, LDA or n-BuLi.
3. The process according to claim 1, wherein the compound of Formula VI is obtained by reducing the compound of Formula V.
4. The process according to claim 3, wherein the reducing agents are selected from transition metal catalysts or hydride reagents.
5. The process according to claim 4, wherein the reducing agents are selected from sodium borohydride, sodium cyano borohydride, lithium aluminium hydride, lithium tri-tert-butoxy aluminium hydride, diborane or vitride.

6. A process for the preparation of compound of Formula-VI comprising the steps of:

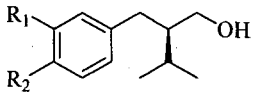
a) converting the compound of Formula-V into compound of Formula-VII, and



Formula-V Formula-VII

wherein R_1 and R_2 are independently of one another **H, Ci-C_6** alkyl, **Ci- C_6** halogenalkyl, **Ci-C_6** alkoxy, **Ci-C_6 alkoxy-Ci-C_6** alkyl, or **Ci-C_6 alkoxy-Ci-C_6** alkyloxy, and R_3 is C_1-C_6 alkyl or aryl.

b) optionally hydrolyzing and reducing the compound of Formula-VII to get compound of Formula- VI,



Formula-VI

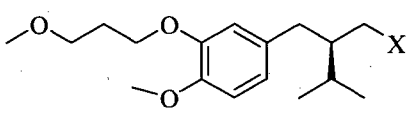
wherein R_1 and R_2 are defined above.

7. The process according to claim 6, wherein hydrolysis of compound of Formula-V is carried out in base in presence of peroxide.

8. The process according to claim 7, wherein base is selected from alkali metal hydroxides such as sodium hydroxide, potassium hydroxide or lithium hydroxide.

9. The process according to claim 6, wherein the reducing reagents selected from sodium borohydride and lithium aluminium hydride, lithium tri-tert-buotoxy aluminium hydride, diborane or vitride.

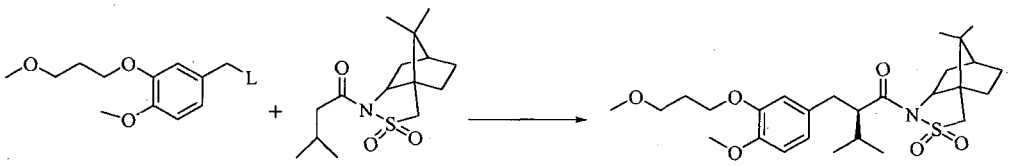
10. A process for the preparation of compound of Formula-IIa comprising the steps of:



Formula-IIa

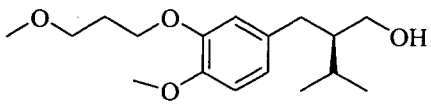
wherein X is halogen selected from fluoro, chloro, bromo and iodo

a) condensing the compound of Formula-IIIa with compound of Formula-IVa in presence of a base to give compound of Formula-Va,



Formula-IIIa Formula-IVa Formula-Va

b) converting compound of formula Va to compound of formula Via, and

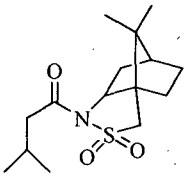


Formula-VIa

c) converting compound of formula Via to compound of formula Ila.

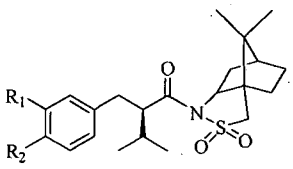
11. The process according to claim 10, wherein L is halogen selected from fluoro, chloro, bromo and iodo.

12. A compound (S)-N-Isovaleryl camphorsultam of Formula-IV.



Formula-IV

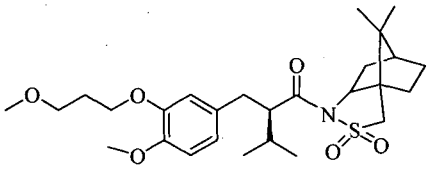
13. A compound of Formula-V.



Formula-V

wherein Ri and R_2 are independently of one another H, Ci-C_6 alkyl, C_1- C_6 halogenalkyl, Ci-C_6 alkoxy, Ci-C_6 alkoxy-Ci-C_6 alkyl, or Ci-C_6 alkoxy-Ci- C_6 alkyloxy.

14. The compound according to claim 13, wherein the compound of Formula-V is



15. Use of compound of Formula-V in the preparation of Aliskiren or its pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/0OQ815

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D275/06 C07C41/22 C07C41/26
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 C07C

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)
EPO-Internal , WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2O08/006394 Al (ITALIANA SINT SPA [IT] ; STIVANELLO MARIANO [IT] ; GRANDINI CRISTIANO [I) 17 January 2008 (2008-01-17)	12
Y	scheme 3 (page 10) ; exampl e 4	1-15

Y	MEALY N E ET AL: "ALISKI REN FUMARATE ANTIHYPERTENSIVE" , DRUGS OF THE FUTURE, PR0US SCI ENCE, ES, vol . 26, no. 12, 1 January 2001 (2001-01-01) , pages 1139-1148, XPOO9017211, ISSN : 0377-8282, D0I : 10. 1358/DOF. 2001 . 026. 12.648490 scheme 1	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2013	22/07/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Mates Valdi vi e]so, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2012/0OQ815

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008006394 A l	17-01-2008	NONE	