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Alternative Route towards the Convergent Synthesis of an Orally Active Renin Inhibitor Aliskiren

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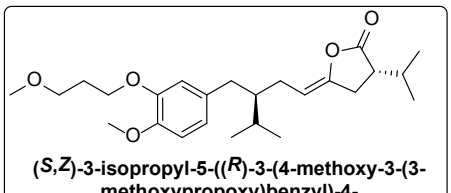
Abstract: Alternative route towards the convergent synthesis of an orally active renin inhibitor Aliskiren is described.

Keywords: An alternative approach, alkene impurity, Bromolactoneaminolysis

Introduction

The synthesis of Aliskiren **1** hemifumarate involves number of challenging steps in which, azidation step is poor yielding (~42%) due deplorable degree of elimination side product **7** was observed (**Figure-1**).Such a side reaction plausibly leads to the poor yielding substitution step imposing great challenge to avoid the side product **7**. Myriad of reactions conditions on intermediate **3** have been tried to effect substitution to obtain azide intermediate **4** in high yield.



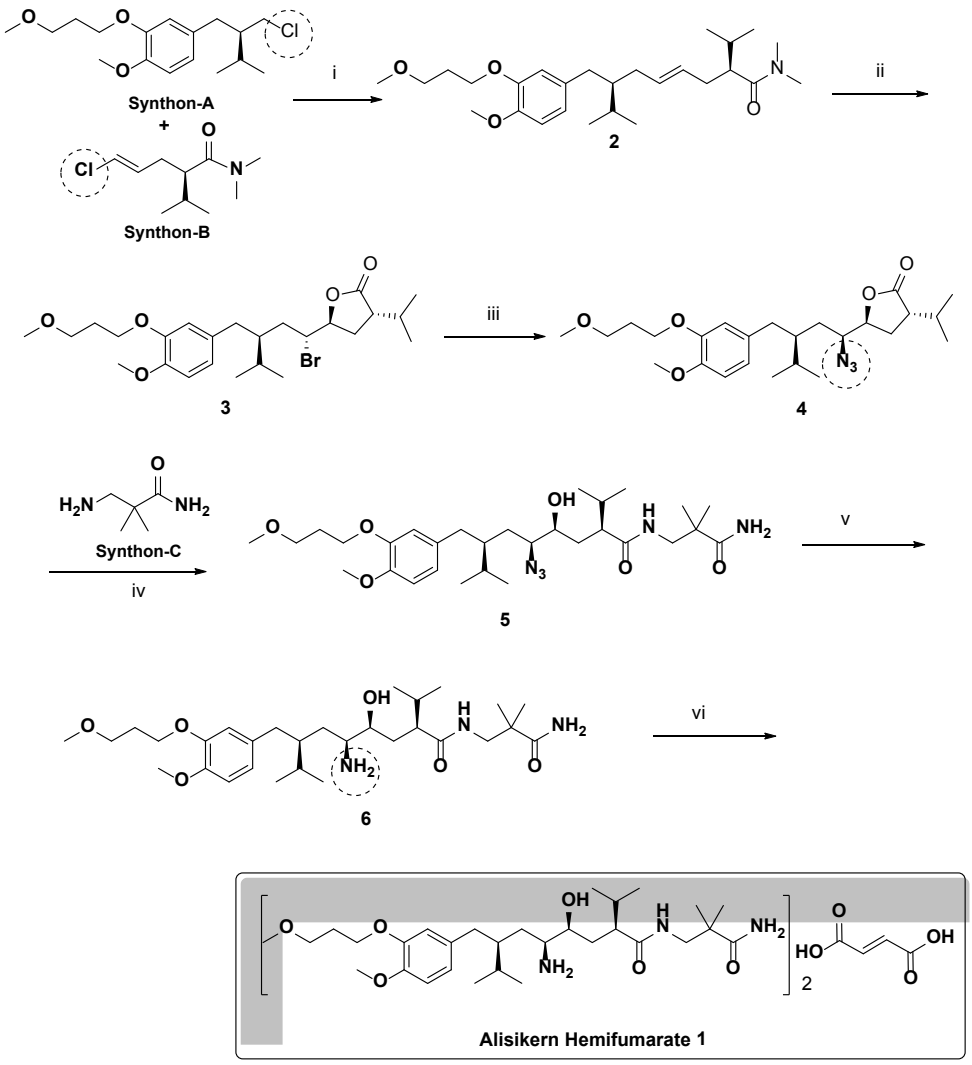
(*S*,*Z*)-3-isopropyl-5-((*R*)-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-4-methylpentylidene)dihydrofuran-2(3*H*)-one

7

Figure-1. Structures of alkene intermediate **7**.

Aliskiren Hemifumarate is the first in a new class of orally effective, nonpeptide direct renin inhibitors developed for the treatment of hypertension. It is approved by the U.S. Food and Drug Administration in 2007 for the treatment of hypertension and related cardiovascular diseases.[1-2]

Aliskiren Hemifumarate **1** has been synthesized as per **scheme 1** with slight modification of reported synthesis.[3] Coupling of **Synthon-A** Grignard reagent with **Synthon–B** using catalytic amount of $Fe(acac)_3$, NMP to afford **2** in 72% yield. Streo selective bromo lactonization of **2** was carried outusing NBS, H_3PO_4 in THF solvent to gives **3** in 72% yield. Nucleophilic substitution of bromowith azide of **3** in S_N2 manner using sodium azidein presence of TPG to afford **4** in 52% yield. Condensation of **Synthon-C** and **4** in presence of 2-hydroxy pyridine and TEA gives open azido Aliskiren **5** in 90% yield. Reduction of **5** using 5% Pd/C in presence of $MeOH.NH_3$ and MeOH gives Aliskiren Free base **6** in 90% yield. Final step is saltformation of **6** with fumaric acid in presence of $MeOH:CH_3CN$ to afford Aliskiren



Scheme-1. Synthesis of Aliskiren hemifumarate **1.***Reagents and conditions:*(i) (a) for RMgX preparation: Mg, THF, 1,2-Dibromomethane, 60-65 °C, (b) for coupling: $Fe(acac)_3$, NMP, 0-5 °C, 10% HCl solution, Toluene, 72 %; (ii) NBS, H_3PO_4, THF, 0-5 °C, 5% $NaHSO_3$, Ethyl acetate, 5% $NaHCO_3$, DM water, sat. NaCl solution, 72 %; (iii) NaN_3, TPG, DM water, DMAP, 80-85 °C, DMAP, Toluene, 52 %; (iv) **Synthon-C**, TEA, 85-90 °C, Ethyl acetate, Dm water, sat NaCl solution, 90%; (v) 10 % Pd-C, Methanol, Methanolic NH_3, 5-6 Kg/cm^2 H_2 Gas pressure, 25-35 °C, 90 %; (vi) Fumaric acid, Methanol, Acetonitrile, 25-35 °C, 90 %.

hemifumarate **1** in 90% yield.

Result and Discussion

In order to improve the yield in the azidation step, it becomes imperative to understand the effect of solvent(s) on substrate **3** and product **4**. In addition to this, use of additives that can mortgage the bromo moiety in intermediate **3** to preferentially offer substitution product **4** over elimination species **7** may be considered as one of the strategies to improve yield. Strategically, choice of azidation reagent may also be crucial to obtain higher yield.

The process parameters were studies using Design of Experiment (DoE) tool and the outcome conditions for reaction also ended with formation of side product **7**. The process for synthesis of azide derivative was; bromo derivative **3**(65-68% purity), and NaN_3 (5.2 eq.) were dissolved in TPG and H_2O [15.6 vol. (9:1.1 ratio)] and stirred for 12 h at 88-92°C. Thereafter, an additional lot of NaN_3 (1.0 eq.) was added to the reaction mixture. After additional stirring for 12 h, the temperature of the reaction mixture was brought down to the 25-35 °C. To a resulting reaction mass was added DMAP to wash out the alkene impurity **7** and subjected to aq. acid base work up followed by extraction and evaporation to yield crude azide product **4** as a thick residue.

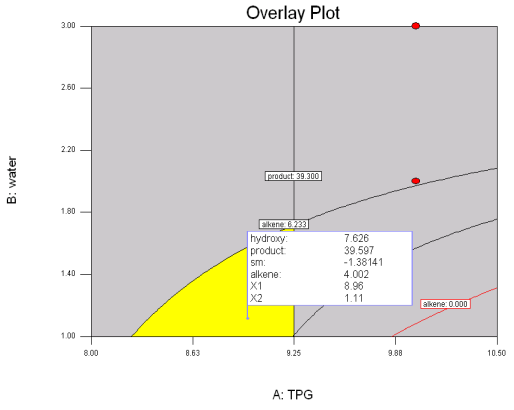


Figure-2. Overlay plot of DoE.

HPLC monitoring of reaction mixture revealed that the alkene impurity **7** was in the order of 16-19% and the desired product **4** was found to be ~40% in the reaction mixture. After work up, impurity **7** was detected only with <1% and the product was enriched from 52 to 56%. Subsequently, product **4** was isolated with 94-97% purity (impurity **7** was up to un-detectable level) by crystallization employing a mixture of diisopropyl ether and methyl cyclohexane solvent in a 0.2:1 ratio at 10-15°C under stirring for 10-12 h.

Table-1. Experimental details pertaining to azidation step.

Before isolation (crude)		After isolation	
Yield (%)	Purity by HPLC	Yield (%)	Purity by HPLC
67	56.74	44	94.91
64.2	50.7	42	97.46

Kinetic study for azidation reaction

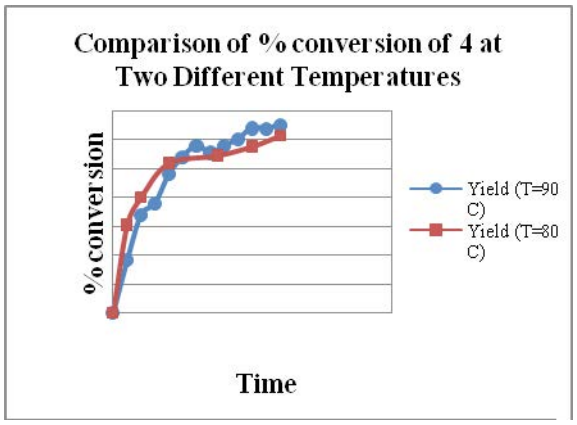


Figure-3. Comparison of % conversion of **4**at two different temperatures.

From the graph above, after addition of 1st lot of NaN_3 the yield is better at lower temperature (80 °C) andafter addition of 2nd lot of NaN_3it is evident that conversion is better at higher temperature (90 °C). A possible implication of that would be impurity **7** formation is more pronounced in the first lot which decreases the conversion.

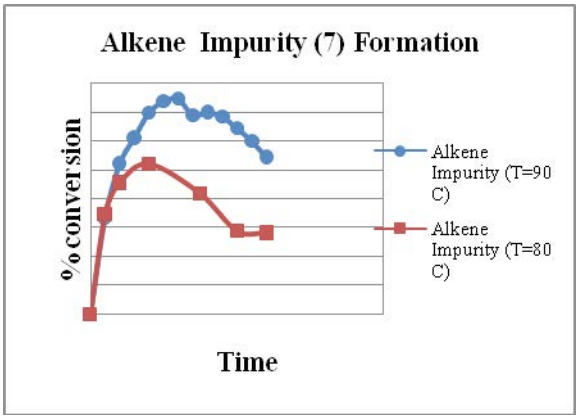


Figure-4. Alkene impurity **7**, % conversion with respect to time.

From the above figure, it is clear that formation of **7** is more pronounced at a higher temperature. Moreover **7** concentration starts decreasing at the onset of the 2nd lot of NaN_3 suggesting the formation of hydroxyl impurity**8**.

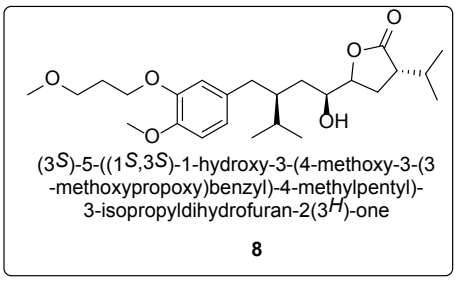


Figure-5. Structure of hydroxyl impurity**8**

Design around synthesis

Attempts were continued to overcome the formation of **7** inazidation step by using various azides and different solvents were studied. As the experimental results were not very successful, it was thought to explore other nitrogen nucleophilic sources under mild conditions to overcome the issues associated in the present azidation process. In this context, *N*, *N*–dibenzyl Grignard complex approach was felt to be one of the possible best ways that can be exploited as alternative to the azide. The synthetic route based on present *N*, *N*- dibenzyl amine Grignard complex approach was shown in below **Scheme-1**.

The Grignard complex of *N*, *N*-dibenzyl amine was generated *insitu* upon reacting with isopropyl magnesium chloride in THF solvent medium. The resulting Grignard complex was treated with bromo lactone intermediate **3** at 0-5 °C and the product obtained is shown in **Scheme-1**.

The detailed experimental procedure to a mixture of DBA (2.0 eq with respect to R-Br,) in THF (10 vol), was added the *i*PrMgCl (2eq with respect to DBA) at 0-5°C and stirred for 15-20 min. then to a solution of 3 in THF was added the 1.0eq of DBA.MgCl reagent (50%) at 0-5°C stirred for 15-20 min. After that added the 0.5eq (25%) of DBA MgCl at 0-5°C and stirred for 20-30 min. and quenched with 10% aq.HCl solution, extracted the compound in to CH_2Cl_2 to afford the compound **9** in 75% yield. After workup the obtained crude compound was subjected for EI-MS, and the data revealed that *m/z* was not matched with the expected dibenzyl product **9,** this results also supported by ^{1}H NMR, HSQC analysis. The ^{1}H NMR, HSQC analysis revealed the structure is not as expected dibenzyl product **9,** it is keto-amide intermediate **10.**

The plausible mechanism was explained in the below **Scheme-2.** The anionic species of dibenzyl amine magnesium bromide Grignard complex was attached at keto group of lactone ring to form an anionic derivative **11**, which up on polarization was eliminated the bromo group form the moiety lead to keto-amide intermediate **10**. Further, the present reaction was attempted in various temperature conditions (preferably mild conditions) upon varying mole equivalents of Grignard complex to check the desired product formation. But, all the experiments were yielded above keto-amide intermediate only (**Table-3**).

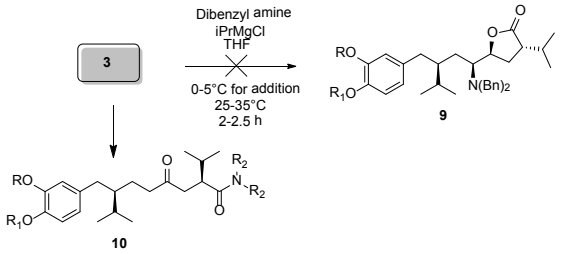
Design around synthesis of alsikiren to control the formation of 7.

After extensive work to reduce the ene impurity **7**formation and to replace the azide with other amine sources, we didn`t observed desired

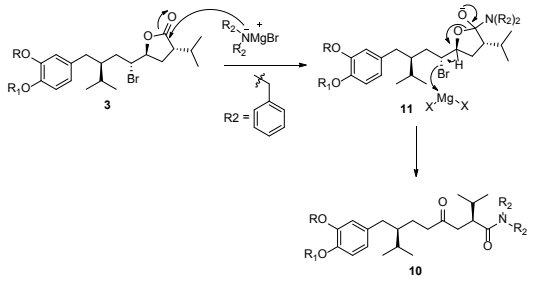
Table-2. Experimental details of nucleophilc substitution reaction using NaN_3 in combination with different solvents, reagents and additives used.

Solvent (volumes)	Reagent (eq)	additative	Purity by HPLC (%)						Conditions/ time
			3	4	7	Imp1	8	Imp2	
-[a]	-	-	70.52	-	-	-	-	-	45-50 °C, neat /24 h
DMF (7.2 vol)[a]	-	-	66.85	-	-	-	-	-	45-50 °C /4 h
Toluene (7.2 vol)[a]	-	-	66.38	-	-	-	-	-	45-50 °C /4 h
DMAc (7.2 vol)[a]	-	-	69.99	-	-	-	-	-	45-50 °C /4 h
TPG (7.2 vol)[a]	-	-	70.20	-	-	-	-	-	45-50 °C /4 h
TPG (7.2 vol)[b]	NaN_3(4.7 eq)	5 % 18 Crown-6	18.7	40.2	33.3				80-85 °C/8 h
DMPU (7.0 vol)[b]	NaN_3(4.7 eq)	5 % 18 Crown-6	0.03	41.0	53.3				80-85 °C/8 h
DMAc (10.0 vol)[c]	NaN_3(1.2 eq)	-	57.39	2.51	3.48	10.73	2.10	4.10	25-30 °C/8 h
DMF (10.0 vol)[b]	NaN_3(4.7 eq)	-	14.28	26.89	39.12	3.51	0.23	1.72	55-60 °C/8 h
Toluene (5.0 vol)[b]	NaN_3(4.7 eq)	DMPU	34.0	17.54	27.18	4.59	0.58	1.46	55-60 °C/8 h
Toluene(2.5 vol)/TPG (5.0 vol) /H_2O(2.5 vol)[c]	NaN(3.0 eq)	-	73.43	6.0	5.33	0.39	1.0	1.89	55-60 °C/8 h
TPG (7.1vol):H_2O (2.4 vol)[c]	NaN_3(8.0 eq)	-	1.82	58.79	21.41	2.34	3.18	0.68	80-85 °C/48 h
TPG (10 vol):H_2O (1 vol)[c]	NaN_3(1.0 eq)	-	24.89	37.99	30.38	3.22	0.33	0.10	80-85 °C/22 h
TPG (8 vol):H_2O (2.5 vol)[c]	NaN_3(4.0 eq)	-	8.0	26.43	26.43	2.6	3.37	0.10	80-85 °C/30 h
TPG (8 vol):H_2O (2.5 vol)[c]	NaN_3(4.0 eq)	-	42.39	33.75	21.13	1.39	0.14	0.44	80-85 °C/24 h
TPG (7 vol):H_2O (2.4 vol)[c]	NaN_3(5.0 eq)	-	25.53	43.70	26.15	1.95	0.98	0.51	80-85 °C/20 h

*[a]input purity 72.1% by HPLC, [b]input purity 96.0% by HPLC, [c]nput purity 86.0% by HPLC.imp1 & 2-other than **4** and **8.***



Scheme-1. Synthetic route of Aliskiren via N, N-dibenzyl amine approach



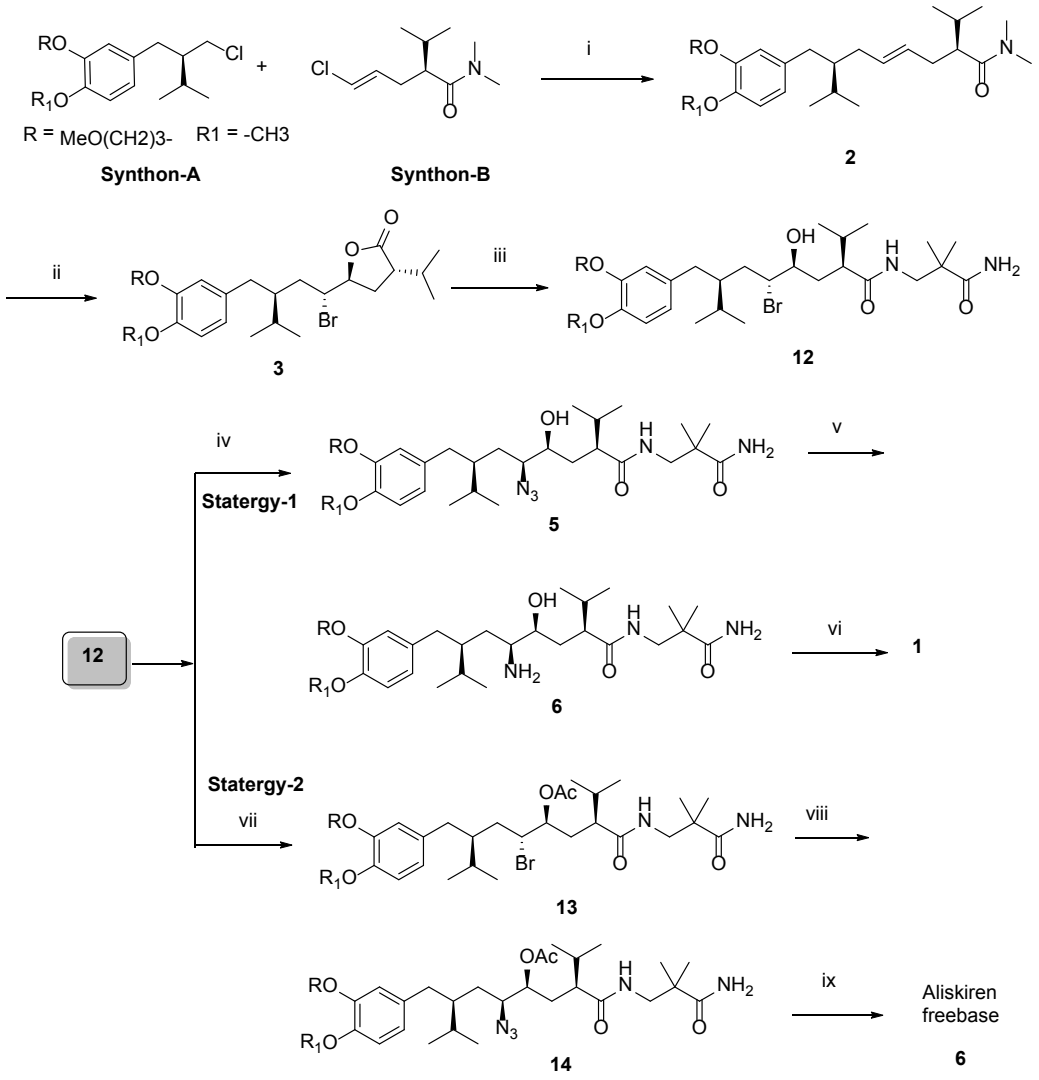
Scheme-2. Formation of Keto-amide intermediate

Table-3. Experimental details of nucleophilc substitution reaction using other than NaN_3.

S.No	Reagent/ PTC	Solvent	Reaction conditions	Observations /Results
1	$MeOH.NH_3$/-	MeOH	**3**, 2 volume of MeOH and 5 eq of $MeOH.NH_3$was stirred at 25-35 °C for 12 hr, then 0.01 eq of Captryl ammonium chloride (CACl) was added and reaction maintained at 40°C for 8 hrs.	No product formation
2	$TMSN_3$/CACl	THF	**3**, 5 volume of THF and 4.0 eq of $TMSN_3$ was stirred at 25-35 °C for 12 hr, and then 0.01 eq of CACl was added and reaction maintained at 40°C for 8 hrs.	No product formation
3	$TMSN_3$/CACl	CH_2Cl_2	**3**, 5 volume of CH_2Cl_2 and 4.0 eq of $TMSN_3$ stirred at 25-35 °C for 12 hr, and then 0.01 eq of CACl was added and reaction maintained at 40°C for 8 hrs.	No product formation
4	Benyl amine/-	neat	**3** and benzyl amine (3vol) was stirred at 25-35 °C for 12 hr, and then 0.01 eq of CACl was added and reaction maintained at 40°C for 8 hrs.	No product formation
5	$MeOH.NH_3$/ TBAB	MeOH	**3**, 2 volume of MeOH and 5 eq of MeOH.NH3 were stirred at 25-35 °C for 12 hr, then 0.01 eq of TBAB was added and reaction maintained at 40°C for 8 hrs.	No product formation
6	$TMSN_3$/ TBAB	CH_2Cl_2	3 volume of CH_2Cl_2, 0.01 eq of TBAB and 4.0 eq of $TMSN_3$was stirred at 25-35 °C for 12 hr.	No product formation
7	$TMSN_3$/-	DMF	3 volume of DMF and 4.0 eq of $TMSN_3$was stirred at 25-35 °C for 12 hr	No product formation
8	Dibenzyl amine/ *i*PrMgCl	THF	To the mixture of 2.0 eq of DBA in THF (5.0 vol) and **3** was added 1.3 eq of Isopropyl MgCl at 0-5°C stirred for 12 hr.	~10-15% alkene impurity (based on TLC)
9	$TMSN_3$/CACl	DMF	**3**, 2 volume of DMF and 4.0 eq of $TMSN_3$ were stirred at 25-35 °C for 12 hr, then 0.01 eq of CACl was added and reaction maintained at 40°C for 8 hrs.	No product formation
10	$TMSN_3$/CACl	NMP	**3**, 2 volume of NMP and 4.0 eq of $TMSN_3$ were stirred at 25-35 °C for 12 hr, then 0.01 eq of CACl was added and reaction maintained at 40°C for 8 hrs.	No product formation
11	DBA/-	DMF	**3**, 2 volume of DMF and 4.0 eq of DBA were stirred at 25-35 °C for 12 hr.	No product formation

results. Hence, designed a new synthetic process to mitigate the formation of ene impurity. The below depicted synthetic scheme is followed for the synthesis of Aliskirenhemifumarate to reduce the formation of **7**.

In which compound **3** is subjected for lactone aminolysis with **Synthon-C** in presence of 2-ethyl hexanoic acid in THF solvent to afford compound **12** in 60 % yield. The product was



Scheme-3: Design around synthesis to control the formation of 7**.** *Reagents and conditions:*(i) (a) for RMgX preparation: Mg, THF, 1,2-Dibromomethane, 60-65 °C, (b) for coupling: $Fe(acac)_3$, NMP, 0-5 °C, 10% HCl solution, Toluene, 72 %; (ii) NBS, H_3PO_4, THF, 0-5 °C, 5% $NaHSO_3$, Ethyl acetate, 5% $NaHCO_3$, DM water, sat. NaCl solution, 72 %; (iii) Synthon-C, 2-ethyl hexanoic acid, THF, 50-60 °C, Ethyl acetate, Dm water, sat NaCl solution, 60%. **Strategy 1:** (iv) NaN_3, DMPU, 80-85 °C, 51 %; (v)10 % Pd-C, Methanol, Methanolic NH_3, 5-6 Kg/cm^2 H_2 Gas pressure, 25-35 °C, 75 %; (vi) Fumaric acid, Methanol, Acetonitrile, 25-35 °C, 90 %.**Strategy 2:** (vii) Pyridine, DMAP, Acetic anhydride, CH_2Cl_2, 0-5 °C to 25-35 °C, 2-3 hr, 75 %;(viii) aqueous LiN_3, DMPU, 60-65 °C, 50 %; (ix)10 % Pd-C, Methanol, Methanolic NH_3, 5-6 Kg/cm^2 H_2 Gas pressure, 25-35 °C, 75%.

confirmed by ^{1}H NMR, in which the protons corresponding to the **Synthon-C** dimethyl groups were found in the spectrum as siglet at δ 1.22. Additional conformation by mass, a single peat at *m/z* 639 $[M + Na]^+$ in the EI-MS spectrum appeared.

Approach A: Synthesis of Aliskiren without protection of OH group

Afterwards **12** subjected for azidation step using NaN_3 in DMPU solvent and the conversion is monitored by HPLC, in which derivative **5** was formed in 53 %. Afterwards crude compound **5** was purified by column chromatography and the compound **5** was analyzed and the confirmed the product by ^{1}H NMR. Additional conformation by mass, a single peat at *m/z* 600 $[M + Na]^+$ in the EI-MS spectrum appeared. Intermediate **5** on reduction followed by salt preparation using fumaric acid in presence of CH_3CN and MeOH as solvents afforded Aliskiren 1 as shown in **Scheme-5**.

Approach B: Synthesis of Aliskiren with protection of OH group

In another approach the compound **12** subjected for aceylation using Ac_2O, pyridine and DMAP in CH_2Cl_2 solvent to afford **13** in 75% yield. After purification of crude **13** by column chromatography the compound was analyzed and the product was confirmed by ^{1}H NMR. The product was confirmed by ^{1}H NMR, in which the protons corresponding to the acetyl groups were found in the spectrum as multiplet peaks at δ 2.08 as siglet. Additional conformation by mass, a single peat at *m/z* 659 $[M + H]^+$ in the EI-MS spectrum appeared.

The compound **13** was subjected for azidation step using aqueous LiN_3 in DMPU solvent to afford compound **14** and the conversion is monitored by HPLC, in which derivative **14** is formed in 52%. After purification of crude **14** by column chromatography the compound was analyzed and the product was confirmed by ^{1}H NMR. Additional conformation by mass, a single peat at *m/z* 642 $[M + Na]^+$ in the EI-MS spectrum appeared.The compound **14** is subjected for reduction in using MeOH.NH_3 in MeOH to afford the compound **6** in 75 % yield.

Conclusion

We demonstrated here an un-optimized design around synthesis of Aliskiren**1** by avoiding the formation elimination product **1**, through lactone aminolysis of intermediate **3** with **Synthon-C** instead of azidation reaction.

Experimental Section

(2*S*,4*S*,5*R*,7*S*)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-5-bromo-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-8-methylnonanamide (12)

To a mixture of **3** (0.5 gm, 0.001 mol) and **Synthon-C** (0.58 gm, 0.005 mol) in THF solvent (2.5 mL) was added 2-ethylhexanoicacid (0.44 gm, 0.001 mol) at 20-25 °C and the mixture stirred for another 6 hours at 25-35 °C. The reaction mixture is extracted with tertiary butyl methyl ether (2×250 ml), and the resulting organic phases are consecutively washed with water (500 ml) and concentrated aqueous saline solution (brine, 200 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated by evaporation. By means of flash chromatography (SiO_2 60F/ethyl acetate/hexane 1:1), title compound **12** is obtained from the residue as a slightly yellowish oil (0.36 gm, yield 60%, purity 96.9%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.79-6.77 (1H, d, *J* = 8.4 Hz), 6.73 (1H, s), 6.72-6.68 (1H, dd, *J* = 7.6, 8.0 Hz), 6.45-6.42 (1H, t, *J* = 6.0 Hz), 6.05 (1H, s, br), 5.52 (1H, s, br), 4.16-4.09 (3H, m), 3.83 (3H, s), 3.59-3.56 (3H, t, *J* = 6.4 Hz), 3.45-3.40 (1H, dd, *J* = 6.4, 7.2 Hz), 3.35 (3H,

s), 3.30-3.31 (1H, d, *J* = 6.0 Hz), 3.18 (1H, s, br), 2.71-2.66 (1H, dd, *J* = 4.8, 9.2 Hz), 2.26-2.20 (1H, m), 2.17-2.04 (3H, m), 1.88-1.60 (7H, m), 1.22 (6H, s), 1.00-0.98 (3H, d, *J* = 6.8 Hz), 0.93-0.90 (6H, t, *J* = 6.8 Hz), 0.85-0.83 (3H, d, *J* = 6.8 Hz) ppm.**^{13}CNMR (400 MHz, $CDCl_3$):** δ 179.7, 175.6, 148.1,147.5, 133.6, 121.3, 114.3, 111.7, 72.2, 69.4, 66.0, 63.1, 58.6, 56.0, 53.4, 50.8, 47.1, 42.9, 35.2, 34.2, 33.1, 30.3, 29.5, 27.7, 24.1, 21.0, 20.3, 20.0, 17.0 ppm.**MS (ESI) (*m/z*):** calculated for $C_{30}H_{51}BrN_2O_6$: 615.65, found: 617 $[M + H]^+$, 639 $[M + Na]^+$.

(3*S*,5*S*,6*R*,8*S*)-3-((3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl)-6-bromo-8-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-yl acetate (13)

A solution of 8.30 g **12** in 100 ml dichloromethane is mixed with 1.54 ml pyridine and cooled to 0° C. Then 1.73 ml acetic acid anhydride and 0.186 g 4-dimethylaminopyridine are added consecutively and the mixture is stirred for 18 hours at room temperature. The reaction mixture is poured onto 300 ml water and extracted with diethyl ether (2×300 ml). The organic phases are washed consecutively with water (300 ml), 5% aqueous sodium hydrogencarbonate solution (100 ml) and brine (100 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/hexane 1:1), title compound **13** is obtained from the residue as a colourless oil (6.65g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79-6.77 (1H, d, *J* = 8.4 Hz), 6.77 (1H, s), 6.71-6.69 (1H, d, *J* = 8.4 Hz), 6.32-6.28 (1H, t, *J* = 6.4 Hz), 6.13 (1H, s, br), 5.49 (1H, s, br), 4.74-4.71 (1H, m), 4.22-4.14 (1H, m), 4.12-4.09 (3H, m), 3.83 (3H, s), 3.59-3.56 (2H, t, *J* = 5.6 Hz), 3.37-3.35 (4H, m), 2.64-2.59 (1H, dd, *J* = 6.0, 7.6 Hz), 2.34-2.29 (1H, m), 2.12-2.08 (6H, m), 1.94-1.68 (7H, m), 1.22 (6H, s), 0.96-0.84 (12H, m) ppm. **^{13}CNMR (400 MHz, $CDCl_3$):**δ 179.7, 174.4, 171.0, 148.1, 147.5, 133.4, 121.3, 114.3, 111.6, 74.3, 69.3, 66.0, 58.5, 56.8, 55.9, 50.4, 47.1, 42.9, 42.8, 35.4, 35.1, 30.8, 30.6, 29.5, 27.7, 24.3, 23.5, 21.0, 20.2, 19.3, 17.6 ppm.**MS (ESI) (*m/z*):** calculated for $C_{32}H_{53}BrN_2O_7$: 657.69, found: 659 $[M + H]^+$, 679 $[M + Na]^+$.

(2*S*,4*S*,5*S*,7*S*)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-5-azido-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-8-methylnonanamide (5)

A mixture of 0.10 g **12**, 0.024 g sodium azide and 1 ml DMPU is stirred for 96 hours at 90° C. The reaction mixture is cooled to room temperature, 30 ml water added, and extraction carried out using diethyl ether (2×30 ml). The combined organic phases are washed with water (2×30 ml) and brine (1×10 ml), dried over sodium sulfate, filtered and concentrated by evaporation. By means of flash chromatography (SiO_2 60F/ ethyl acetate/hexane 1:1), title compound **5** is obtained from the residue as a colourless oil (46 mg, 50%).

^{1}H NMR (400 MHz, $CDC1_3$): δ 6.80 (1H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J*= 1.8 Hz), 6.73-6.70 (dd, 1H, *J*= 1.8, 6.3 Hz), 6.60 (1H, t, *J* =6.4 Hz), 6.13 (1H, bs), 5.81 (1H, bs), 4.11 (2H, t, *J* =6.4 Hz), 3.82 (3H,s) 3.62 (2H, t, *J* = 6.4 Hz), 3.46 (2H, dd, *J* = 6.8, 7.2 Hz), 3.35 (3H, s), 3.41 (1H, m), 2.91 (1H, m), 2.14 -2.06 (3H, m), 1.88-1.57 (5H, m), 1.35 (1H, m), 1.22 (6H, s), 0.93-0.86 (12H, m) ppm. **MS (ESI) (*m/z*):** calculated for $C_{30}H_{51}N_5O_6$: 577.76 found 578 $[M+H]^+$.**$[\alpha]_D^{22}$:** -12.5° (*c* 1.00, $CHCl_3$).

(3*S*,5*S*,6*S*,8*S*)-3-((3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl)-6-azido-8-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-yl acetate (14)

A mixture of 1.17 g **13,** 0.392 g lithium azide and 11.7 ml DMPU is stirred for 21 h at 60° C. The reaction mixture is cooled, and water (100 ml) added. Extraction is carried out using tertiary butyl methyl ether (3×80 ml) and the

organic phases are then washed consecutively with water (3×100 ml), 5% aqueous sodium hydrogencarbonate solution (100 ml) and brine (100 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/ hexane 3:1), title compound **14** is obtained from the residue as a colourless oil (0.55 g, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78-6.76 (1H, d, *J* = 8.4 Hz, 6.71 (1H, s), 6.67-6.65 (1H, d, *J* = 8.4 Hz), 6.49-6.46 (1H,t, *J* = 5.6 Hz), 6.18 (1H, s, br), 5.66 (1H, s, br), 4.11-4.08 (2H, t, *J* = 6.8 Hz), 3.83 (3H, s), 3.59-3.56 (2H, t, *J* = 6.8 Hz), 3.53-3.37 (2H, m), 3.35 (3H, s), 3.34-3.29 (1H, dd, *J* = 5.6, 6.0 Hz), 3.27 (1H, s, br), 2.56-2.39 (2H, m), 2.12-2.08 (5H, m), 1.49-1.25 (7H, m), 1.21 (6H, s), 0.92-0.82 (12H, m) ppm.**MS (ESI) (*m/z*):** calculated for $C_{32}H_{53}N_5O_7$: 618.80, found: 642 $[M + Na]^+$.

(2*R*,4*S*,5*S*,7*S*)-5-amino-N-(3-amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (6):

The **5** crude (1.5 gm, 0.0025 mol) is hydrogenated for 6 hours in the presence of 5% Pd/C (0.15 g) and 10% methanolic ammonia (0.88 gm, 0.0519 mol) in methanol (15 mL) at 25-35 °C using 5-6 kg/cm^2 hydrogen gas pressure for 5-6 h. Then reaction mixture is filtered andthe catalyst washed with methanol (5.0 mL). The mother liquors are concentrated by evaporation. The title compound **6** is obtained as slightly yellowish oil. (1.28 gm, 90 % yield).

^{1}H-NMR (400 MHz, $CDC1_3$):δ 7.43 (1H, t, *J* = 6.0 Hz), 7.13,6.82 (2H, s),6.82 (1H, d, *J* = 8.0 Hz), 6.75 (1H, s), 6.68 (1H, d, *J* = 8.0 Hz), 3.94 (2H, t, *J* =6.4 Hz), 3.48 (2H, t, *J* = 6.4 Hz), 3.33 (3H, s), 3.28 (1Ha, 3.28, m), 3.24 (3H, s), 3.16 (1Hb, m),3.12 b(1H, m), 2.95 (1H, m), 2.52 (1Ha, m), 2.32 (1Hb, m), 2.22 (1H, m),1.95 (2H, p, *J* =6.4 Hz), 1.73 (1H, m), 1.68 (1H, m), 1.69 (1Hb, m), 1.63 (1H, m), 1.30 (1Hb, m), 1.30 (1Ha, m), 1.04 (3H, s), 1.04 (3H, m), 1.10 (1Ha, m), 0.87 (3H, d, *J* = 5.6 Hz), 0.84 (3H, d, *J* = 5.6 Hz),0.79 (3H, d, *J* = 6.8 Hz), 0.77 (3H, d, *J* = 6.8 Hz) ppm

(2*S*,7*R*)-*N*,*N*-dibenzyl-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methyl-4-oxononanamide (10)

^{1}H NMR (400 MHz, $CDC1_3$): δ 7.39-7.12 (10 H, m), 6.79-6.77 (1H, d, *J* = 8.0 Hz), 6.70 (1H, s), 6.68-6.67 (1H, d, *J* = 8.0 Hz), 4.84-4.80 (1H, d, *J* =14.8 Hz), 4.67-4.63 (1H, d, *J* = 16 Hz), 4.44-4.40 (1H, d, *J* = 16 Hz), 4.23-4.19 (1H, d, *J* = 14.8 Hz), 4.11-4.08 (2H, t, *J* = 6.4 Hz), 3.82 (3H, s), 3.58-3.55 (2H, t, *J* = 6.4 Hz), 3.34 (3H, s), 3.19-3.02 (2H, m), 2.58-2.53 (1H, dd*J* = 6.0, 7.6 Hz), 2.44-2.40 (1H, t, *J* = 6.8 Hz), 2.37-2.30 (2H, m), 2.12-2.06 (2H, m), 1.95-1.87 (1H, m), 1.74- 1.39 (5H, m), 0.93-0.84 (12H, m) ppm. **^{13}CNMR (400 MHz, $CDCl_3$):**δ210.6, 174.9, 148.2, 147.5, 137.5, 136.7, 134.3, 128.7, 128.4, 128.1, 127.5, 127.4, 127.1, 21.1, 114.2, 11.7, 69.3, 66.0, 58.6, 56.0, 50.1, 47.5, 45.4, 42.2, 41.5, 40.3, 36.5, 29.6, 29.6, 28.7, 24.0, 21.1, 19.0, 18.7, 18.1 ppm. **MS (ESI) (*m/z*):** calculated for$C_{39}H_{53}NO_5$: 615.39, found: 616 $[M + H]^+$, 638 $[M + Na]^+$.

(S,Z)-3-isopropyl-5-((R)-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-4-methylpentylidene)dihydrofuran-2(3H)-one (7)

^{1}H-NMR (400 MHz, $CDC1_3$): δ 6.79-6.77 (1H, d, *J* = 8.0 Hz), 6.69 (1H, s), 6.68-6.66 (1H, d, *J* = 8. 0 Hz), 5.14-5.10 (1H, t, *J* = 8.0 Hz), 4.11-4.078 (1H, t, *J* = 6.4 Hz), 3.83 (3H, s), 3.59-3.56 (2H, t, *J* = 6.4 Hz), 3.36 (3H, s), 2.66-2.29 (5H, m), 2.22-2.13 (1H, m), 2.11-2.08 (2H, t, *J* = 6.4 Hz), 2.06-1.52 (7H, m), 1.01-0.89 (12H ,m) ppm. **^{13}CNMR (400 MHz, $CDCl_3$):**δ176.4, 148.2, 147.6, 134.1, 129.2, 128.7, 121.2, 114.3, 111.6, 103.3, 69.3, 66.1, 58.6, 56.0, 46.7, 45.4, 36.2, 29.6, 28.9, 28.5, 26.1, 25.0, 20.0, 19.1, 18.0 ppm. **MS (ESI) (*m/z*):**calculated for$C_{25}H_{38}O_5$:

418.27, found: 441 $[M + Na]^+$.

References and notes

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