SYNTHESIS OF TRANS-4-CYCLOHEXYL-L-PROLINE BY HYDROGENATION OF TRANS-4-PHENYL-L-PROLINE USING RUTHENIUM

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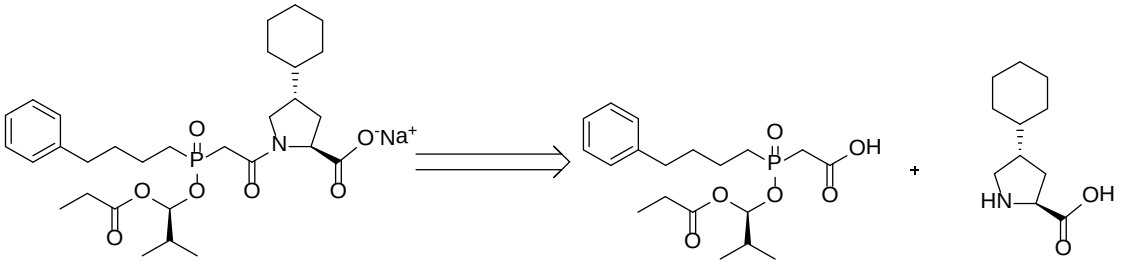
Abstract- Hydrogenation of phenyl moiety of *(trans*)-4-phenyl-L-proline **(13)** in the presence of catalyst 5%w/w ruthenium on carbon gave (*trans*)-4-cyclohexyl-L-proline **(7)** in good yield and high purity. Ruthenium on carbon is safe and suitable for hydrogenation of phenyl moiety of compound **13**, in larger scale synthesis of (*trans*)-4-cyclohexyl-L-proline **(7)**. Catalyst effect on hydrogenation of phenyl moiety of (*trans*)-4-phenyl-L-proline **(13)** is described.

Keywords-*(trans*)-4-Phenyl-L-proline;hydrogenation; (*trans*)-4-cyclohexyl-L-proline; fosinopril sodium; ruthenium.

1 INTRODUCTION

Fosinopril sodium [1-3**] (1)** is the first orally active phosphorus containing angiotensin converting enzyme (ACE) [4-8] inhibitor and is the ester prodrug of fosinoprilate. Fosinopril sodium is chemically know as [1(±) 4S-]-4-cyclohexyl-[[[2-methyl-1-(oxopropoxy) propoxy]-(4-phenyl-butyl) phosphinyl] acetyl]-L-proline monosodium salt. Fosinopril sodium is marketed under the brand name monoprile®. Fosinopril sodium is an optically active compound having total four asymmetric centers of which two asymmetric centers in (*trans*)-4-cyclohexyl-L-proline **(7)**. (*trans*)-4-Cyclohexyl-L-proline **(7) [**9-13] is a key intermediate to prepare fosinopril sodium **(1)**.



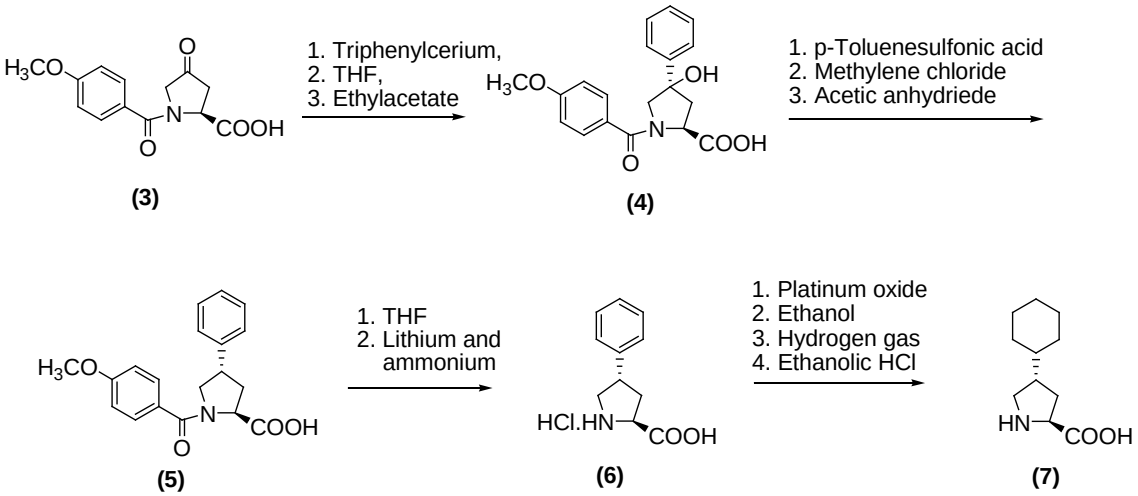
(1) **(2)** **(7)**

Fosinopril sodium Intermediate-I Intermediate-II

Thottathil et. al. [14-16] reported the process for preparation of (*trans)*-4-cyclohexyl-L-proline **(7)** starting from L-pyroglutamic acid. This process has some draw backs (a) use of highly pyrophoric reagent like LDA and LAH (b) required highly safety measurement in industrial scale.

The same author reported [17] another process (Scheme 1) for compound **7**, which involves conversion of compound **4** from compound **3** with triphenylcerium. O-sulfation of compound **4** with p-toluenesulfonic acid followed by hydrolysis with acetic anhydride gave compound **5**. Amide hydrolysis of compound **5** with ammonia in the presence of lithium gave compound **6**. Further, compound **6** on reduction in the presence of platinum oxide catalyst gave compound **7**. The disadvantage of above process is use of platinum oxide which is pyrophoric and costly reagent.

Herein we explored the synthesis of (*trans)*-4-cyclohexyl-L-proline by reduction of (*trans)*-4-phenyl-L-proline using ruthenium on carbon as a catalyst which is safe than platinum oxide in industrial scale.



Scheme 1. Literature route for (*trans)*-4-cyclohexyl-L-proline (**7**)

2 RESULTS AND DISCUSSION

Stage 1. Preparation of (*trans*)-1-benzoyl-4-hydroxy-L-proline (9): Condensation of **(***trans*)-4-hydroxy-L-proline **(8)** with benzoyl chloride in the presence of aqueous sodium hydroxide gave compound **9** (Scheme 2). Mole equivalent of benzoyl chloride and addition temperature of benzoyl chloride were studied and the results are produced in table 1. From table 1, it was clear that the addition of benzoyl chloride to compound **8** in the presence of aqueous sodium hydroxide at lower temperature results higher yield whereas the addition of benzoyl chloride at higher temperature resulted lower yield of compound **9**. The reason for lower yield is due to exothermicity of reaction which leads formation of number of process impurities.

Table-1. Optimization of m.eq of benzoyl chloride and addition temperature of benzoyl chloride

Entry	m.eq of benzoyl chloride	addition temperature (°C)	yield (%)
1	1.03	20	73.60
2	1.03	5	79
3	1.12	5	96

Moreover, certain quantity of benzoyl chloride may be degraded into benzoic acid in the presence of strong base at higher temperature which results insufficient of benzoyl chloride in the reaction mixture to prepare compound **9.** Once the temperature of benzoyl chloride addition was fixed, then we were increased the molar equivalent of benzoyl chloride from 1.03 to 1.12. The isolated product yield was drastically increased to 95%.

Further, the reaction mass pH was also critical to effect yield of compound **9**. When the reaction was carried out at pH 8.0, there was no crystallization of solid product during acidifying the reaction mass. At pH 8.0, number of process impurities is formed that not allowing to precipitate the product. When the reaction mass pH was maintained at 9.2 to 9.5, the product was precipitated from aqueous layer during acidification. Conclusion was drawn from the above studies that the reaction of (*trans*)-4-hydroxy-L-proline **(8)** with 1.12 molar equivalent of benzoyl chloride in the presence of aqueous sodium hydroxide at pH 9.2 to 9.5 resulted compound **9** with higher yield (95%).

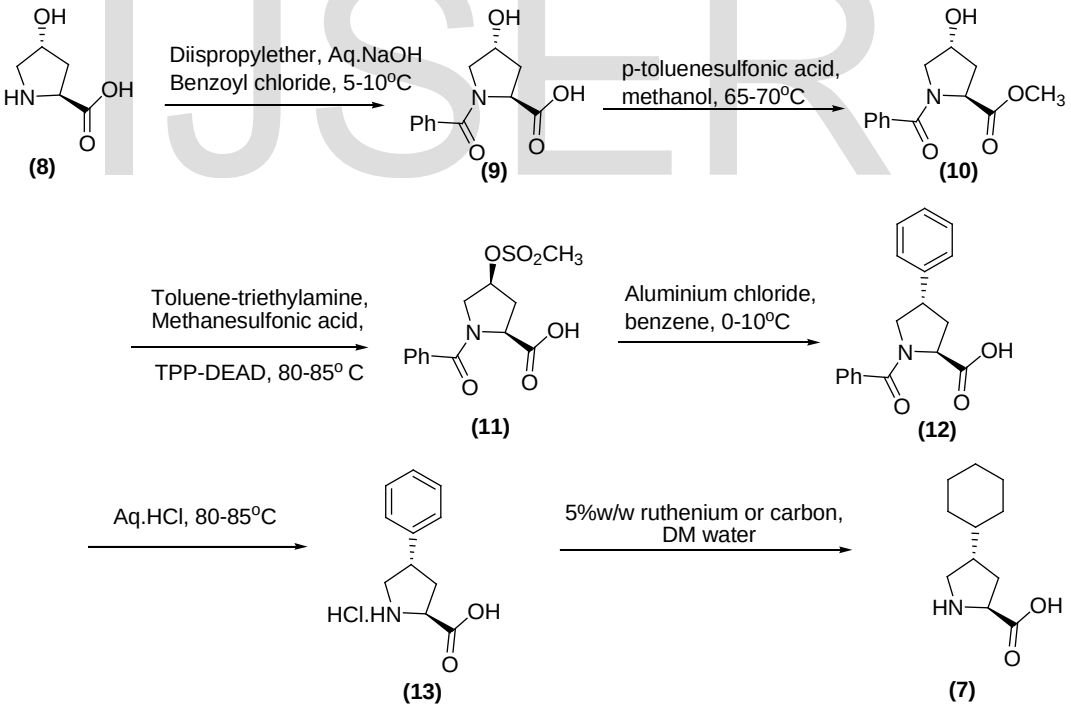
Table-2. Optimization of quantity of PTSA, and reaction time

Entry	methanol (Vol)	PTSA (%, w/w)	temperature (°C)	time (h)	yield (%)
1	3	2.4	65-70	5	60
2	5	2.9	65-70	5	65
3	5	5	65-70	12	87
4	5	5	65-70	6	86

Stage 2. Preparation of (*trans*)-methyl-1-benzoyl-4-hydroxy-L-proline ester (10): Esterification of (*trans*)-1-benzoyl-4-hydroxy-L-proline **(9)** with methanol in the presence of p-toluenesulfonic acid catalyst at higher temperature resulted (*trans)*-methyl-1-benzoyl-4-hydroxy-L-proline ester **(10)**. In this reaction, the quantity of p-toluenesulfonic acid (PTSA) catalyst and

reaction time were studied and the results are produced in table 2. It was clear that at least 5% w/w quantity of PTSA catalyst was required to get maximum conversion of (*trans*)-methyl-1-benzoyl-4-hydroxy-L-proline ester **(10)** from compound **9** at 65-70°C.

Stage 3. Preparation of *(cis)*-1-benzoyl-4-[(methylsulfonyl) oxy]-L-proline (11): Mitsunobu reaction of (*trans*)-Methyl-1-benzoyl-4-hydroxy-L-proline ester **(10)** with methanesulfonic acid (MSA) in presence of triphenylphosphine (TPP), diethylazodicarboxylate (DEAD) and triethyl amine at higher temperature afforded (*cis*)-1-benzoyl-4-[(methylsulfonyl)oxy]-L-proline methyl ester. Further, hydrolysis of (*cis*)-1-benzoyl-4-[(methylsulfonyl) oxy]-L-proline methyl ester with aqueous sodium hydroxide at ambient temperature yielded (*cis*)-1-benzoyl-4-[(methylsulfonyl) oxy]-L-proline methyl ester (**11)** in 75% theory yield.



Scheme 2. Manufacturing route of (*trans*)-4-cyclohexyl-L-proline (7) **[**18]

Stage 4. Preparation of (*trans*)-1-benzoyl-4-phenyl-L-proline (12): Friedel-Crafts alkylation of (*cis*)-1-benzoyl-4-[(methylsulfonyl) oxy]-L-proline **(11)** with benzene in the presence of anhydrous aluminum chloride at lower temperature gave compound **12**. The un-reacted (*cis*)-1-benzoyl-4-[(methylsulfonyl) oxy]-L-proline **(11)** was achieved less than 0.5% by HPLC in 4 hrs. Thereafter, the reaction mixture was treated with concentrated hydrochloric acid to precipitate the product **12**. The initial lot of hydrochloric acid addition to the reaction mass results sticky mass, which in-turns as free flow slurry at end of hydrochloric acid addition. Further, about 10% w/w aqueous sodium chloride solution was added to the above slurry in order to complete the precipitation of product **12**. The precipitated product was filtered and slurred in DM water to remove all inorganic impurities and obtained (*trans*)-1-benzoyl-4-phenyl-L-proline **(12)** as a white solid in good yield (90.18%).

Stage 5. Preparation of (*trans*)-4-phenyl-L-proline hydrochloride (13): Acid hydrolysis of amide moiety of (*trans*)-1-benzoyl-4-phenyl-L-proline **(12)** in DM water at higher temperature gave (*trans*)-4-phenyl-L-proline hydrochloride **(13)**. The reaction mass was maintained at 80-85°C for 24 h to achieve less than 0.5% of (*trans*)-1-benzoyl-4-phenyl-L-proline **(12)** as an un-hydrolyzed by HPLC. Initially the product was isolated from aqueous, in low yield. It may due to partial solubility of product in water. To achieve better yield, the reaction mass was washed with toluene at above 85°C (*product starts precipitated at below 75°C*) to remove unreacted and other process impurities. Further, the aqueous layer containing product was concentrated completely at 70°C under reduced pressure followed by toluene azeotropically distillation to remove moisture. Thereafter, fresh toluene was added to the above slurry and isolated the compound **13** in good yield (75.5%) and high purity.

Stage 6. Preparation of (*trans*)-4-cyclohexyl-L-proline (7): [18] Hydrogenation of (*trans*)-4-phenyl-L-proline hydrochloride **(13)** in the presence of metal catalyst at higher temperature afforded (*trans*)-4-cyclohexyl-L-proline **(7)**. Several metal catalysts were screened to perform hydrogenation of phenyl moiety of compound **13**. In our hand, we have found that hydrogenation of compound **13** with ruthenium on carbon produced better result. [18] Ruthenium on carbon is safe than platinum oxide in industrial scale. Thereafter, we started to optimize the process with 5%w/w ruthenium on carbon and the results are tabulated below.

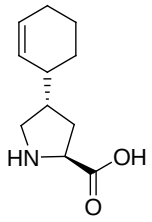
From the above studies, it was clear that no hydrogenation was observed in case of 10% load of catalyst whereas 20% and 25% load of catalyst were produced almost same yield.

Table-3. Optimization of catalyst for hydrogenation of compound 13

Entry	5% ruthenium on carbon (w/w)	temperature (°C)	yield (%)
1	10%	85-90°C	-
2	15%	85-90°C	71
3	20%	85-90°C	85
4	25%	85-90°C	86

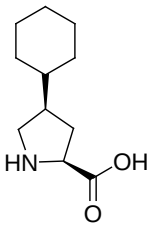
After completion of hydrogenation, the catalyst was removed by filtration and washed with DM water. The filtrate pH was adjusted carefully to 5.4 to 5.6 with 15%w/w aqueous sodium hydroxide solution. As the isoelectric point of (*trans*)-4-cyclohexyl-L-proline **(7)** is 5.4 to 5.6, the product was precipitate at pH 5.4. Below and above the range of pH, the product may dissolve in water which results lower yield. The precipitated product was filtered from aqueous layer and washed with ethyl acetate to remove moisture and other process impurities. The resulting wet product was dried at 60-65°C under reduced pressure to yield compound **7.**

Producing of compound **7** by this method was suffered from three major impurities. Impurity I was observed in level of 0.3 % in the HPLC of compound **7**. The LC-MS analysis of the compound **7** revealed m/z of 195 atomic mass unit which was 2 atomic mass unit less than that of compound **7** (m/z: 197). Based on the synthetic sequence and LC-MS mass data, the structure of impurity I was proposed as below

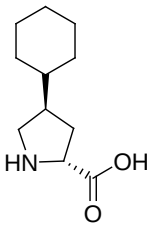


(**14**)

Further, the other two impurities such as (*cis*)-4-cyclohexyl-L-proline **(15),** (*trans*)- 4-cyclohexyl-D-proline **(16)** are isomeric impurities which were formed in level of 0.3 to 0.5 % in HPLC. However, these impurities were not separated in reversed phase column in HPLC. But these two impurities were separated in normal phase method at 1.16 and 1.39 RRT in HPLC respectively. (*cis*)-4-Cyclohexyl-L-proline **(15)** and (*trans*)-4-cyclohexyl-D-proline **(16)** impurities was prepared by this method starting from cis-4-hydroxy-L-proline, trans-4-hydroxy-D-proline respectively and confirmed by spiking the experiment with HPLC. These impurities can be converted into corresponding impurities in fosinopril API which required multiples purification to achieve ICH quality.



(**15**)



(**16**)

However, these critical impurities get eliminated into mother liquor during purification of compound **7** in a mixture of methanol-water-ethyl acetate (1.6:3.3:5). This total process was performed on a commercial scale of 100 Kg of **8** to **7** successfully. The obtained compound **7** by novel hydrogenation of compound **13** with 5% ruthenium on carbon was converted into fosinopril sodium and achieved ICH quality.

3 EXPERIMENTAL

General. HPLC analysis were performed using an Shimadzu VP series system with a Chiralpak-AD 250% 4.6 mm Column, pump mode is isocratic, flow rate is 1.0 ml /min, detection is UV, 210 nm, column oven temp at 40°C, injection volume is 20µl, data acquisition time for 35 min. ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker 300 spectrometer at 300 MHz and 75 MHz, respectively, and the chemical shifts were reported as δ values in parts per million relative to TMS as an internal standard. Infrared spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer spectrophotometer. Mass spectra were recorded on API 2000 Perkin-Elmer PE-SCIEX mass spectrometer. The melting points were recorded on open capillaries and are uncorrected.

3.1 (*trans*)-1-Benzoyl-4-hydroxy-L-proline (9). (*trans*)-4-Hydroxy-L-proline (**8,** 100 g, 0.7627 mol) was dissolved in DM water (300 mL) at 20-30°C. The reaction mass was cooled to 5-10°C and adjusted pH to 9.2 to 9.5 with 20%w/w aqueous sodium hydroxide solution (5 mL) at 5-10°C. Benzoyl chloride solution in isopropyl ether [(120 g, 0.8536 mol) benzoyl chloride in 330 mL of isopropyl ether] was added to the reaction mass at 5-10°C in 2 h while maintaining the reaction mass pH 9.3 to 9.5 with 20%w/w aqueous sodium hydroxide solution (300 mL). The reaction mass was stirred at 5-10°C for 30 min and heated to 20-30°C. The reaction mass was

stirred for 15 h at 20-30°C to complete reaction. Thereafter, the aqueous layer was separated and washed with isopropyl ether (250 mL) at 20-30°C. The aqueous layer was cooled to 5-7°C and acidified with concentrated hydrochloric acid (200 mL) at 5-7°C. The precipitated product was filtered, washed with cold DM water (50 mL) and dried at 60-65°C under reduced pressure to yield compound **9** (170.3 g) in 95.03% yield. IR (KBr) (cm^{-1}): 1739 (-C=O str.), 1607 (-C=O str.). Mass: *m/z* =236 $[M + H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.61 (br, 1H), 7.54-7.39 (m, 5H), 5.08 (m, 1H), 4.52-4.46 (m, 1H), 4.27 (m, 1H), 3.74-3.70 (m, 1H), 3.37-3.26 (m, 1H), 2.21-2.17 (m, 1H), 1.99-1.94 (m, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ: 173.6, 173.4, 168.7, 136.0, 130.3, 129.6, 128.2, 126.7, 69.0, 58.0, 54.8, 37.3. Anal.Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; O, 27.21. Found: C, 61.17; H, 5.37; N, 5.85; O, 27.41.

3.2 (*trans*)-Methyl-1-benzoyl-4-hydroxy-L-proline ester (10). (*trans*)-1-Benzoyl-4-hydroxy-L-proline (**9,** 170 g, 0.7234 mol) was added to methanol (850 mL) at 20-30°C. p-Toluenesulfonic acid (8.5 g, 0.0444 mol) was added to the above slurry at 20-30°C. The reaction mass was heated to 65-70°C and stirred for 6 h. After esterification, the reaction mass was cooled to 50-53°C and treated with sodium acetate (5.1 g). The reaction mass was concentrated completely at 50°C under reduced pressure. DM water (460 mL) was added to the above concentrated mass and heated to 65-70°C for 1 h. Further, the reaction mass was cooled to 20-30°C and stirred for 1 h. The precipitated product was filtered, wash with cold DM water(170 mL) and dried at 60-65°C under reduced pressure to afford **10** (154.91 g) in 86% yield. IR (KBr) (cm^{-1}): 1739 (-C=O str.), 1607 (-C=O str.). Mass: *m/z* = 250 $[M + H]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.5-7.25 (m, 5H), 4.85-4.78 (m, 1H), 4.43 (m, 1H), 3.75 (s, 3.5H), 3.55-3.39 (m, 1.3H), 2.39-2.30 (m, 1H), 2.15-2.03 (m, 1H). ^{13}CNMR (75 MHz, $CDCl_3$) δ: 173.3, 170.7, 135.9, 130.9, 130.5, 127.8, 70.5, 68.8,

58.3, 55.6, 52.8, 40.2, 38.1. Anal.Calcd for $C_{13}H_{15}NO_4$; C, 62.64; H, 6.07; N, 5.62; O, 25.67. Found: C, 62.54; H, 6.27; N, 5.42; O, 25.37.

3.3 (*Cis*)-1-Benzoyl-4-[(methylsulfonyl) oxy]-L-proline (11). Methanesulfonic acid (62.6 g, 0.65 mol) was dissolved in toluene (1350 mL) at 20-30°C. Triethylamine (65.79 g, 0.650 mol), triphenylphosphine (177.7 g, 0.6775 mol), (*trans*)-methyl-1-benzoyl-4-hydroxy-L-proline ester (**10,** 135g, 0.5421 mol), and diethylazodicarboxylate (11 8 g, 0.6775 mol) was added to the above solution. The reaction mixture was heated to 80-85°C for 4 h. The reaction mass was concentrated completely at 70°C under reduced pressure. DM water (675 mL) was added to the above resulting residue and treated with 40% w/w aqueous sodium hydroxide solution (113.5 mL) and stirred for 2 h at 20-30°C. The reaction mass was cooled to 2-5°C, filtered to remove insoluble material and washed with cold DM water (270 mL). The filtrate pH was adjusted to 0.3 to 0.8 with concentrated hydrochloric acid (140 mL) at 20-30°C and cooled to 2-5°C. The precipitated product was filtered, wash with cold DM water (135 mL), followed by cold ethyl acetate (135 mL) and dried at 60-65°C under reduced pressure to afford **11** (127.3 g) in 75% yield. IR (KBr) (cm^{-1}):1747 (-C=O str.), 1610 (-C=O str.). Mass: *m/z* = 313 $[M + H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 12.90-12.80 (br, 1H), 7.51-7.43 (m, 5H), 5.36-5.23 (m, 1H), 4.67-4.53 (m, 1H), 3.88-3.66 (m, 2H), 3.21 (s, 3H), 2.73-2.68 (m, 1H), 2.26 (m, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ: 172.5,172.0, 169.6, 168.5, 136.7, 136.0, 130.3, 129.8, 128.3, 127.1, 126.8, 78.7, 59.3, 57.0, 54.3, 52.8, 37.5, 34.8. Anal.Calcd for $C_{13}H_{15}NO_6S$; C, 49.83; H, 4.83; N, 4.47; O, 30.64; S, 10.23, Found: C, 49.93; H, 4.63; N, 4.37; O, 30.84; S, 10.43.

3.4 (*trans*)-1-Benzoyl-4-phenyl-L-proline (12). Anhydrous aluminum chloride (199.37 gm, 1.4952 mol) was added to benzene (650 mL) and (*cis*)-1-benzoyl-4-[(methylsulfonyl) oxy]-L-proline (**11,** 130 g, 0.4153 mol) at 0-5°C and stirred for 4 hr at 0-10^{o}C. The reaction mass was

quenched in concentrated hydrochloric acid (1625 mL) at 20-30°C. 10%w/w aqueous Sodium chloride (325 mL) was added to reaction mass at 20-30°C and stirred for 2h at 15-20°C. The precipitated product was filtered, wash with DM water (200 mL) and dried at 60-65°C under reduced pressure to afford **12 (**110.5 g) in 90.18% yield. IR (KBr) (cm^{-1}):1741 (-C=O str.), 1604 (-C=O str.). Mass: *m/z* = 296 $[M + H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 12.70 (br, 1H), 7.55-7.22 (m, 10H), 4.59-4.56 (m, 1H), 3.85 (m, 1H), 3.60-3.49 (m, 2H), 2.43-2.29 (m, 2H). ^{13}CNMR (75 MHz, DMSO-d_6) δ: 173.4, 173.0, 169.4, 168.1, 140.7, 140.2, 137.0, 136.2, 130.1, 129.5, 128.5, 128.3, 127.1, 127.0, 126.8, 126.5, 61.1, 59.1, 55.5, 52.7, 42.4, 37.8, 35.4. Anal.Calcd for $C_{18}H_{17}NO_3$; C, 73.20; H, 5.80; N, 4.74; O, 16.25, Found: C, 73.40; H, 5.60; N, 4.64; O, 16.35.

3.5 (*trans*)-4-Phenyl-L-proline hydrochloride (13). (*trans*)-1-Benzoyl-4-phenyl-L-proline (**12,** 110 g, 0.3729 mol) was treated with concentrated hydrochloric acid (330 mL) at 20-30°C and heated to 80-85°C. The reaction mass was stirred at 80-85°C for 24 h to complete the reaction. Toluene (250 mL) was added to reaction mass at 80-85°C and stirred for 10 min. Thereafter, the aqueous layer was separated at 80-85°C and concentrated completely at 85°C under reduced pressure. Toluene (300 mL) was added to the above concentrated mass and stirred for 30 min. Further, the reaction mass was concentrated completely at atmospheric pressure. Fresh toluene (440 mL) was added to the above concentrated mass at 20-30°C and cooled to 10-15°C. The slurry was filtered, wash with toluene (100 mL) and dried at 60-65°C under reduced pressure to afford **13** (64.04 g) in75.44% yield. IR (KBr) (cm^{-1}):1743 (-C=O str.), 1586 (-C=O str.). Mass: *m/z* = 192 $[M + H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 14.00 (br, 1H), 10.73 (br, 1H), 9.06 (br, 1H), 7.41-7.25 (m, 5H), 4.59-4.54 (m, 1H), 3.75-3.69 (m, 1H), 3.50-3.43 (m, 1H), 3.22-3.18 (m, 1H), 2.55-2.50 (m, 1H), 2.39-2.31 (m, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ: 170.3, 139.4,

128.7, 127.5, 127.2, 58.8, 50.6, 41.3, 35.7. Anal.Calcd for $C_{11}H_{13}NO_2$; C, 69.09; H, 6.85; N, 7.32; O, 16.73, Found: C, 69.19; H, 6.75; N, 7.22; O, 16.93.

3.6 (*trans*)-4-Cyclohexyl-L-proline (7). (*trans*)-4-Phenyl-L-proline hydrochloride (**13,** 100 g, 0.4395 mol) was dissolved in DM water (900 mL) and added 5%w/w ruthenium on carbon powder (20 g). The mixture was hydrogenated under hydrogen pressure of 30-35 kg/cm^2 for 10 h at 80-90°C. The reaction mass was cooled to 20-30°C. The catalyst was filtered and washed with DM water (50 mL) at 20-30°C. The filtrated pH was adjusted to 5.4 with 15 %w/w aqueous sodium hydroxide (120 mL) at 20-30°C and partially concentrated at 60°C under reduced pressure. To resulting reaction mass, methanol (300 mL) was added at 50-60°C, treated with activated carbon (3.5 g) and filtered through hyflo bed. The filtrate was partially concentrated at 50°C under reduced pressure and cooled at 20-30°C. DM water (100 mL) and ethyl acetate (120 mL) was added to the above concentrated mass at 20-30°C to crystallize the product. The resulting slurry was cooled to 2-5°C and stirred for 30 min. The product was filtered, washed with DM water (80 mL) followed by ethyl acetate (60 mL) and dried at 60-65°C under reduced pressure to afford **7** (59 g) in 68.04% yield. HPLC purity: 99.37 % and chiral purity: 100% IR (KBr) (cm^{-1}):1621 (-C=O str.). Mass: *m/z* = 198 [M + H] $^+$. ^{1}H-NMR (300 MHz, CD_3OD)[12] δ: 4.02-4.06 (m, 1H), 3.55-3.58 (m, 1H), 2.83 (t, 1H), 2.48-2.28 (m, 1H), 1.95-1.88 (m, 2H), 1.78-1.68 (m, 5H), 1.28-1.23 (m, 4H), 1.06-1.03 (m, 2H). ^{13}CNMR (75 MHz, CD_3OD) δ: 173.5, 61.4, 49.5, 43.5, 41.1, 33.7, 26.3. Anal.Calcd for $C_{11}H_{19}NO_2$; C, 66.97; H, 9.71; N, 7.10; O, 16.22, Found: C, C, 67.19; H, 9.61; N, 7.23; O, 16.16.

CONCLUSION

We have developed an improved industrially viable process for fosinopril sodium key intermediate (*trans*)-4-cyclohexyl-L-proline **(7).** Novel hydrogenation of compound **13** with 5%w/w ruthenium on carbon is safe than platinum oxide. A new process for the compound **7** by reductive method using ruthenium has been developed with high yield.

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