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SYNTHESIS OF OPTICALLY ACTIVE *TRANS* 4-CYCLOHEXYL-L-PROLINE AS AN INTERMEDIATE PRODUCT IN THE PREPARATION OF FOSINOPRIL

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Abstract: A nine-step synthesis of *trans* 4-cyclohexyl-L-proline has been developed on a laboratory scale. The product is an intermediate in the preparation of fosinopril – an effective hypotensive drug. The total yield of the synthesis was 25%. The final product was 99.7% pure. Analytical methods were developed for each step of the synthesis (HPLC, TLC, IR, ^{1}H-NMR, ^{13}C-NMR, GC-MS, $[\alpha]_D$).

Keywords: trans 4-cyclohexyl-L-proline; ACE inhibitors; fosinopril; hypertension; congestive heart failure

Fosinopril (**I**) is an effective and long acting ACE (Angiotensin Converting Enzyme) inhibitor (1) used in the treatment of hypertension and acute or chronic congestive heart failure (2). Fosinopril inhibits the enzyme which converts angiotensin I into angiotensin II. As the ACE inhibitor, it has hypotensive properties because it decreases the arterial blood-pressure. It also has organoprotective and organoregenerative properties because it helps to reduce hypertrophic changes in blood vessels. Other hypotensive drugs such as β-blockers and diuretics are not able to protect and repair blood vessels in internal organs (2).

Fosinopril belongs to phosphinic acid derivatives (1). Its active substance is (4S)-4-cyclohexyl-1-{[(R)-[(1S)-2-methyl-1-(1-oxopropoxy) propoxy](4-phenylbutyl)phosphinyl]acetyl}-L-proline (3c,4). Due to the presence of a cyclohexyl substituent in 4th position of the proline ring, it is 10 times as potent as the unsubstituted compound (**III**) (1).

Fosinopril is a prodrug. It is metabolized by esterases in liver and bowels to its active form – fosinoprilan (**II**), which is strongly bound to plasma albumins (3c). Therefore, it has a long biological half-life period which is equal to 12 h. In consequence of that, fosinopril can be dosed once a day. Such a dosage is more convenient and it diminishes the risk of side effects of the therapy in comparison with the dosage of, for example, captopril (**IV**), the first orally active ACE inhibitor (5), which is dosed 2–3 times a day because of the biological half-life period which is equal to 2–3 h (3a). Fosinopril belongs to the 3rd generation of ACE inhibitors (6a). It is less toxic than captopril which belongs to the 1st generation of described drugs (6b). Fosinopril causes less side effects than, for example, enalapril (**V**) (3b) which is the precursor of the 2nd generation of ACE inhibitors (6c).

The semiproduct for preparation of fosinopril (7) is trans 4-cyclohexyl-L-proline (8).

EXPERIMENTAL

Analytical methods

HPLC was used for qualitative and quantitative determination of the starting materials, products and impurities. HPLC was performed on a Merck Hitachi Lachrom instrument equipped with a UV-VIS detector. A refractometric detector was used for the detection of compounds **7** and **10** (Scheme 1).

Progress in the reaction was controlled by TLC performed on Merck's silica gel $60F_{254}$ plates. Chromatograms were developed in (12:1 or 10:1 v/v) chloroform-methanol system or (2:1, 1:1, 1:2 v/v) ethyl acetate-hexane system. Compounds on the chromatograms were detected by a treatment with iodine vapors or by using a 0.2% ninhydrin solution in ethanol and they were observed by using a UV lamp (365/254 nm) supplied by the Cole-Parmer Instrument Co.

The melting points of solids were measured on a Mel-Temp II capillary instrument (Laboratory Devices, USA) and were uncorrected.

The resulting products were identified by IR spectra recorded on a Spectrum 2000 FT-IR instrument, ^{1}H-NMR and ^{13}C-NMR spectra recorded on a Brucker instrument, 500 MHz; TMS as an internal

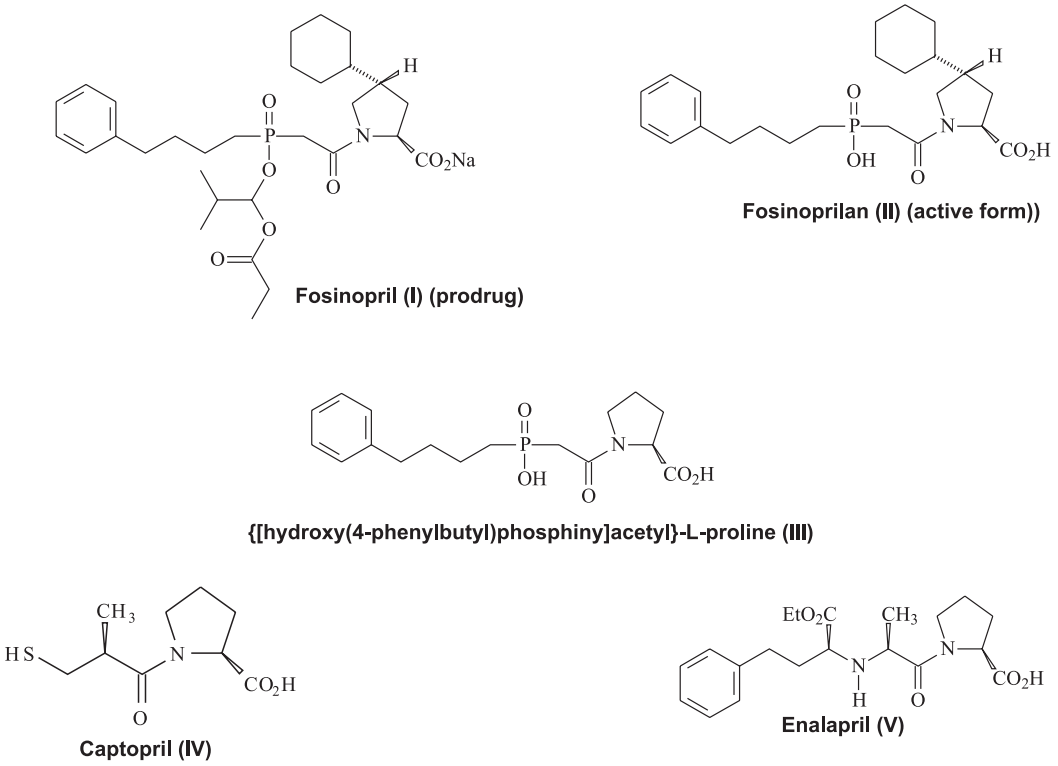
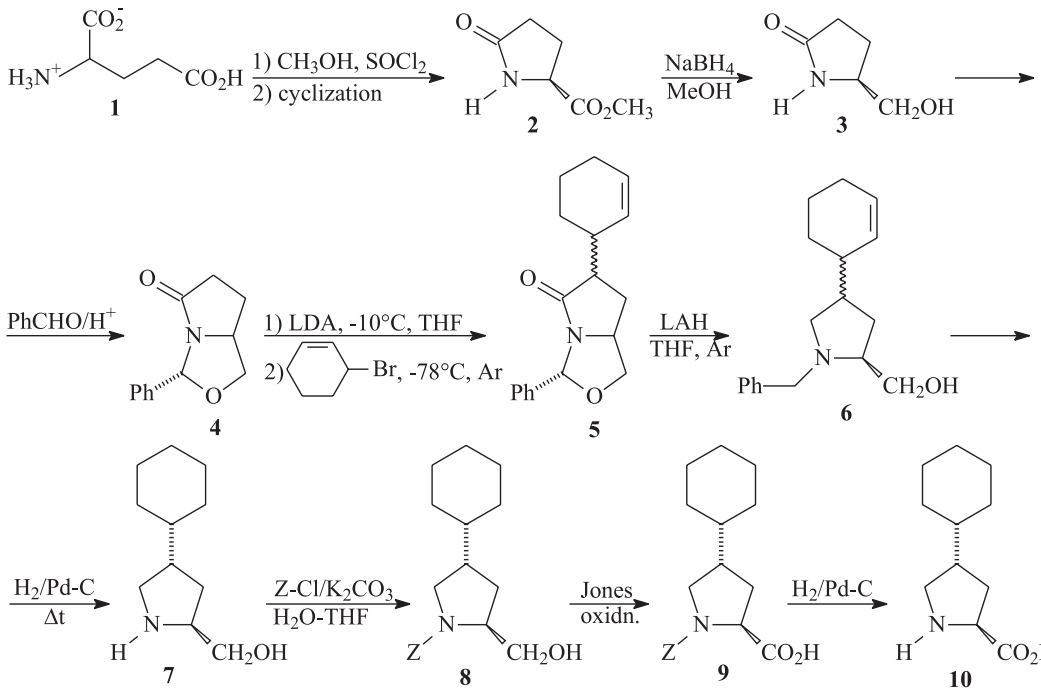


Figure 1. Some examples of ACE inhibitors.



LDA = $(iPr)_2NLi$, Z-Cl = $PhCH_2OCOCl$

Scheme 1. Synthesis of *trans* 4-cyclohexyl-L-proline.

reference, and GC-MS spectra recorded on an HP 5890 II$^+$ series instrument equipped with an FFAP capillary column (30 m long, 0.25 mm I.D.) and an HP 5972 mass spectrometry detector (GC-MS analysis of compound **6**, Scheme 1). Compound **10** was silylated with BSTFA (NO-bis (trimethylsilyl) trifluoroacetamide) before GC-MS analysis in order to get a volatile derivative. GC-MS spectra of **10** were recorded on a Shimadzu GCMS-QP5000 instrument equipped with an OV-101 capillary column (25 m long, 0.25 mm I.D.)

Specific rotations were determined with a Perkin-Elmer 241 polarimeter.

Column chromatography was carried out on a Merck Silica gel 60 adsorbent (particle size 0.040-0.063 mm, 230–400 mesh).

Cation exchange was performed on a Serva ion exchange resin Dowex® 50 WX12 (H$^+$) (50–100 mesh size).

Preparation

ESTERIFICATION OF L-GLUTAMIC ACID WITH METHANOL AND THIONYL CHLORIDE. (S)-(+)-5-CARBOMETHOXY-2-PYRROLIDINONE (**2**) (9, 10)

Freshly distilled thionyl chloride, (60 mL (0.82 mole)), was added to a suspension of L-glutamic acid (**1**,(2S)-amino-pentanedioic acid) (50.0 g (0.34 mole)), in 300 mL of anhydrous methanol cooled in a dry ice-acetone bath (–10 ÷ –5^{o}C). The suspension changed into a solution after having been stirred at room temperature for 0.5 h. Then methanol and thionyl chloride were distilled off under reduced pressure. A thick oily product was obtained. It was dissolved in 100 mL of methanol and alkalized with 160 mL of 10% KOH in methanol to pH = 8.5–9.0. The potassium chloride precipitate was filtered off and methanol was evaporated. When the product was alkalized, it was spontaneously cyclized to yield (S)-(+)-5-carbomethoxy-2-pyrrolidinone (**2**) which on distillation (146–148^{o}C/3 mmHg) yielded 34.0 g (0.24 mole, 70% yield) of oily distillate; purity 99.1% (by HPLC); $[\alpha]_D^{20}$ +6.95^o (c10, EtOH).

IR (film), ν: 3244 (ν N-H), 2957 (ν C-H, CH_3), 1743 (ν C=O, ester), 1699 (ν C=O, ketone), 1218 (ν C-N) cm^{-1}.

^{1}**H-NMR** ($CDCl_3$, TMS), δ: 7.68 (s, 1H, NH), 4.31–4.28 (dd, 1H, CH), 3.77 (s, 1H, CH_3), 2.50–2.17 (m, 4H, CH_2-CH_2) ppm.

REDUCTION OF (S)-(+)-5-CARBOMETHOXY-2-PYRROLIDINONE WITH SODIUM BOROHYDRIDE. (S)-(+)-5-HYDROXYMETHYL-2-PYRROLIDINONE (**3**) (11)

Small portions of $NaBH_4$, 7.0 g, (0.19 mole), were added to a stirred solution of 26.0 g (0.18 mole) of compound **2** in 150 mL of anhydrous methanol in an ice bath (–1÷ 4^{o}C). Progress in the reaction was controlled by TLC [developing system: (10:1 v/v) chloroform-methanol]. After having been stirred for 1.5 h, the reaction mixture was acidified to pH = 6 with 50 mL of 20% acetic acid. Then methanol and water were evaporated under reduced pressure to yield a thick oily crude product. It was applied to a Dowex 50 WX12 (H$^+$) column. The resin was washed with 1.5 L of water and the eluate was evaporated to dryness under reduced pressure. An oily compound **3** was obtained, 17.5 g (0.15 mole, 85% yield), which solidified on standing; purity 99.7% (by HPLC); m.p. 64–65^{o}C, lit. (13) m.p. 65–67^{o}C; $[\alpha]_D^{18}$ +32.6^o (c3, MeOH), lit. (10) $[\alpha]_D^{20}$ +29^o (c5, EtOH).

IR (film), ν: 3283 (ν OH, ν NH), 2921 (ν C-H, CH_2), 1670 (ν C=O), 1262 (ν C-N), 1057 (ν C-OH) cm^{-1}.

^{1}**H-NMR** (DMSO-d^6, TMS), δ: 7.51 (s, 1H, NH), 4.76–4.74 (m, 1H, OH), 3.51–3.48 (m, 1H, OH), 3.31–3.29 (m, 2H, CH_2 near OH), 2.15–1.96 (m, 2H, CH_2 near C=O; m, 1H, CH_2), 1.72–1.66 (m, 1H, CH_2) ppm.

CONDENSATION OF (S)-(+)-5-HYDROXYMETHYL-2-PYRROLIDINONE WITH BENZALDEHYDE. O,N-ACETAL (**4**) (12)

A mixture of 10.5 g (0.09 mole) of compound **3**, 10 mL (0.10 mole) of benzaldehyde and 0.19 g (0.001 mole) of *p*-toluenesulfonic acid in 65 mL of toluene was refluxed under a Dean-Stark water separator with vigorous stirring in an oil bath. The reaction was conducted for 6 h and was followed by TLC [developing system: (12:1 v/v) chloroform--methanol]. Then the reaction mixture was cooled and washed with 5% sodium bicarbonate solution (2 × 10 mL), saturated sodium bisulfite solution (4 × 10 mL), brine (2 × 10 mL), and distilled water (2 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated to obtain 17.2 g (0.071 mole, 78% yield) of a crude oily compound **4**, (3R)-tetrahydro-3-phenyl-3H, 5H-pyrrol[1,2-*c*]oxazol-5-one. Silica gel column chromatography was used to purify the crude product [developing system: (1:1÷2.5:1 v/v) ethyl acetate-hexane]. As a result, 14.6 g (0.07 mole, 80% yield) of pure O,N--acetal (**4**) was obtained; purity 99.8% (by HPLC); $[\alpha]_D^{18}$ +268.8^o (c1, $CHCl_3$), lit. (12) $[\alpha]_D^{20}$ +269.6^o (c1, $CHCl_3$).

IR (film), ν: 3033 (ν C-H, Ar), 2946 (ν C-H, -CH_2), 1704 (ν C=O), 1600, 1494, 1452 (skeletal C=C, Ar), 1222 (ν C-N), 1026 (ν C-O-C), 745, 700 (δ C-H, Ar) cm^{-1}.

^{1}H-NMR ($CDCl_3$, TMS), δ: 7.45–7.31 (m, 5H, Ar), 6.32 (s, 1H, CH), 4.28–4.20 (dd, 1H, CH_2), 4.14–4.11 (m, 1H, CH), 3.48–3.45 (dd, 1H, CH_2), 2.83–2.75 (m, 1H, CH_2), 2.56–2.50 (m, 1H, CH_2), 1.96–1.88 (m, 1H, CH_2) ppm.

ALKYLATION OF O,N-ACETAL WITH 3-BROMOCYCLOHEXENE IN THE PRESENCE OF LDA. ALKYLATED O,N-ACETAL (**5**) (12)

The reaction was conducted under argon in anhydrous conditions. A solution of 11.8 mL (0.09 mole) of diisopropylamine in 250 mL of THF was cooled to –10°C in a dry ice-acetone bath. Then 66 mL (0.11 mL) of 1.6 M n-butyllithium solution in hexanes was added to the stirred mixture in order to yield lithium diisopropylamide (LDA) as a deprotonating agent. After 15 min of vigorous stirring of the reaction mixture at –10°C, the reaction temperature was lowered to –78°C and 14.6 g (0.07 mole) of O, N--acetal (**4**) in 50 mL of THF was slowly added dropwise. After 0.5 h of stirring, 10.5 mL (0.09 mole) of freshly distilled 3-bromocyclohexene was added dropwise to the reaction mixture. The temperature of the reaction mixture was raised to –20°C after 0.5 h of stirring. The progress of the reaction was monitored by TLC [developing system: (1:1 v/v) ethyl acetate-hexane] and HPLC. After 12 h, there was no increase in the product concentration and the reaction mixture was poured into 1 l of crushed ice and water, and sodium chloride was added to saturate the aqueous phase. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 × 200 mL). The combined organic extracts were washed with brine (2 × 200 mL) and distilled water (2 × 200 mL), then dried over $MgSO_4$, and concentrated to collect 20.5 g (0.06 mole, 89% yield) of a crude semisolid **5**, (3R)-6-(2-cyclohexenyl)tetrahydro-3-phenyl-3H, 5H-pyrrolo[1,2-*c*]oxazol-5-one as a mixture of diastereoisomers; purity 88% (by HPLC).

IR (film), ν: 3062 (ν =C-H, alkene), 3019 (ν C-H, Ar), 2929 (ν_{as} C-H, -CH_2-), 2860 (ν_s C-H, -CH_2-), 1703 (ν C=O), 1494, 1450 (skeletal C=C, Ar), 1222 (ν C-N), 1027 (ν C-O, ester), 742, 699 (δ C-H, Ar), 723 (skeletal C-H, -CH_2-) cm^{-1}.

^{1}H-NMR ($CDCl_3$, TMS), δ: 7.45-7.31 (m, 5H, Ar), 6.33 (s, 1H, CH), 5.85-5.82 and 5.55-5.48 (m, 1H, 1H, -HC=CH-), 4.24-4.20 (m, 1H, CH_2 near O), 4.04-4.01 (m, 1H, CH), 3.42-3.37 (dd, 1H, CH_2, near O), 2.83-2.79 (m, 1H, CH), 2.17-2.11 (m, 1H, CH_2 near C=O), 2.00-1.32 (m, 1H, CH_2 near C=O; m, 1H, CH; m, 4H, 2H, -CH_2-) ppm.

REDUCTION OF ALKYLATED O,N-ACETAL (**5**) WITH $LiAlH_4$. N-BENZYL-4-CYCLOHEXENYL-L-PROLINOL (**6**) (12)

The reaction was carried out under argon in anhydrous conditions. A solution of 20.5 g (0.06 mole) of the alkylated O,N-acetal (**5**) in 100 mL of THF was added dropwise to a gently refluxed suspension of 180 mL (0.18 mole) of 1.0 M $LiAlH_4$ solution in THF. Then the reaction mixture was refluxed for 5 h and progress in the reaction was followed by TLC [developing system: (1:3 v/v) ethyl acetate-hexane]. After the reduction has been completed, the reaction mixture was cooled in an ice bath and a saturated aqueous solution of Na_2SO_4 was added dropwise very slowly to decompose the $LiAlH_4$ excess. Evolution of hydrogen was observed to occur and a white, greasy precipitate was formed. The mixture was diluted with 200 mL of diethyl ether and the organic layer was separated from the suspension over the precipitate. The greasy precipitate was filtered through a Celite pad on a Schott funnel. The residue was washed with diethyl ether (3 × 100 mL). The combined organic extracts were washed with water (3 × 100 mL), dried over $MgSO_4$ and concentrated to collect 15.5 g (0.05 mole, 95% yield) of a crude semisolid **6**, (2S)-1-(benzyl)-4-(2-cyclohexenyl)-2-pyrrolidinemethanol as a mixture of diastereoisomers. Product purity 90.7% (by HPLC).

IR (film), ν: 3401 (ν O-H), 3062 (ν =C-H, alkene), 3023 (ν -C-H, Ar), 2928, 2835 (ν C-H, -CH_2-), 1649 (ν C=C, alkene), 1604, 1495, 1453 (skeletal C=C, Ar), 1206 (ν C-N), 1029 (ν C-O), 700 (δ C-H, Ar) cm^{-1}.

GC-MS, *m*/*z*: 271 (M^+, 1%), 240 (M^+-CH_2OH, 98%), 91 ($C_6H_5CH_2^+$, 100%).

HYDROGENATION OF N-BENZYL-4-(2-CYCLOHEXENYL)-L-PROLINOL (**6**). *TRANS* 4-CYCLOHEXYL-L-PROLINOL (**7**) (12)

Compound **6,** 15.5 g (0.05 mole), was dissolved in 75 mL of (1:2 v/v) ethyl acetate-glacial acetic acid and 2.1 g (0.002 mole) 10% Pd-C was added. The mixture was heated to 50°C and hydrogenated at atmospheric pressure. Progress in the reaction was followed by TLC [developing system: (10:1 v/v) chloroform-methanol]. After 7 h the substrate **6** was no longer present. Then the catalyst was filtered off and the solvents were evaporated. The resulting thick oil was dissolved in 70 mL of water and alkalized with aqueous 30% NaOH with vigorous stirring. The precipitate was filtered, washed with 70 mL of water and air-dried to give 10.7 g of crude **7**, (2S-*trans*)-4-cyclohexyl-2-pyrrolidinemethanol. It was contaminated with diastereoisomer *cis*- and, therefore, it was purified by crystallization from toluene-hexane to give 7.2 g (0.04 mole, 78% yield) of **7**; purity 99.5% (by HPLC);

m.p. 97–99°C, lit. (12) m.p. 98–100°C; $[\alpha]_D^{20}$ +12.5° (c1, $CHCl_3$), lit. (12) $[\alpha]_D^{20}$ +12.9° (c1, $CHCl_3$).
IR (KBr), ν: 3339 (ν O-H, ν N-H), 2924, 2851 (ν C-H), 1623 (δ N-H), 1448 (δ C-H), 1261 (δ O-H), 1049 (ν C-O), 805 (skeletal C-H, -CH_2-) cm^{-1}.
^{1}H-NMR ($CDCl_3$), δ: 3.60–3.49 (m, 1H, OH), 3.40–3.29 (m, 2H, -CH_2-), 3.18–3.10 (dd, 1H, -CH_2-), 2.60 (t, J = 9.9 Hz, 1H, -CH_2-), 2.52–2.43 (br, 1H, NH; m, 1H, CH), 1.91–1.62 (m, 2H, -CH_2-; m, 1H, CH; m, 4H, -CH_2-), 1.57–1.45 (m, 1H, CH), 1.31–1.07 (m, 4H, -CH_2-), 1.05–0.90 (m, 2H, -CH_2-) ppm.

N-PROTECTION OF TRANS 4-CYCLOHEXYL--L-PROLINOL (**7**) WITH BENZYLOXYCARBONYL CHLORIDE. N-BENZYLOXYCARBONYL – *TRANS*-4-CYCLOHEXYL-L-PROLINOL (**8**) (12)

Benzyloxycarbonyl chloride (Z-Cl), 6.1 mL (0.04 mole), was added dropwise to a mixture of 7.2 g (0.04 mole) of compound **7** in 70 mL of THF and 2.8 g (0.02 mole) of K_2CO_3 in 18 mL of H_2O. The reaction mixture was stirred vigorously and cooled to –2÷0°C in an ice-salt bath. Progress in the reaction was followed by TLC [developing system: (12:1 v/v) chloroform-methanol]. After 1.5 h, the reaction was complete. The reaction mixture was poured into 80 mL of water and crushed ice, and sodium chloride was added to saturate the aqueous phase. The aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with aqueous 5% HCl (3 × 20 mL), water (2 × 20 mL) and brine (2 × 20 mL). The organic phase was dried over $MgSO_4$ and concentrated to collect 12.6 g (0.039 mole, 98% yield) of oily **8**, (2S-*trans*)-1-[(benzyloxy)carbonyl]-4-cyclohexyl-2-pyrrolidinemethanol; purity 98.5% (by HPLC); $[\alpha]_D^{20}$ –20.0° (c1, $CHCl_3$), lit. (12) $[\alpha]_D^{20}$ –21.0° (c1, $CHCl_3$).
IR (film), ν: 3419 (ν O-H), 3033 (ν C-H, Ar), 2925, 2852 (ν C-H), 1681 (ν C=O), 1497, 1450 (skeletal C=C, Ar), 1048 (ν C-O), 698 (δ C-H, Ar) cm^{-1}.
^{1}H-NMR ($CDCl_3$), δ: 7.37–7.32 (m, 5H, Ar), 5.91–5.53 (m, 2H, CH_2 near phenyl), 4.70 (s, 1H, OH), 4.10 (br, 1H, CH near N), 3.65–3.59 (m, 2H, CH_2 near OH; m, 1H, CH_2 near N), 3.07–3.03 (t, 1H, CH_2 near N), 2.00–1.92 (m, 2H, CH_2), 1.72–1.64 (m, 1H, CH; m, 1H, CH; m, 4H, -CH_2-), 1.22–1.10 (m, 4H, -CH_2-), 0.96–0.93 (m, 2H, -CH_2-) ppm.

JONES OXIDATION OF N-BENZYLOXYCARBONYL-*TRANS*-4-CYCLOHEXYL-L-PROLINOL (**8**) WITH CrO_3 and H_2SO_4. N-BENZYLOXYCARBONYL-*TRANS*-4-CYCLOHEXYL-L-PROLINE (**9**) (12)

Compound **8**, 12.6 g (0.039 mole), in 65 mL of acetone, was slowly added to 30 mL (0.078 mole of CrO_3) of Jones reagent in 80 mL of acetone. Jones reagent was prepared by dissolving 13.38 g of CrO_3 in 11.5 mL of concentrated H_2SO_4 and diluting to 50 mL with water. The reaction was conducted at a temperature of –5°C (dry ice-acetone bath) and followed by TLC [developing system: (12:1 v/v) chloroform-methanol]. After 3 h, there was no substrate in the reaction mixture and 5 mL (0.066 mole) of 2-propanol was added to reduce the Cr (VI) excess and to collect the $Cr_2(SO_4)_3$ precipitate that was filtered off. The residue was diluted with 250 mL of water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (2 × 20 mL), then dried over $MgSO_4$, and concentrated to collect 12.1 g (0.037 mole, 96% yield) of glassy **9**, (2S-*trans*)-1-[(benzyloxy) carbonyl]-4-cyclohexyl-2-pyrrolidinecarboxylic acid; purity 97.8% (by HPLC); $[\alpha]_D$ –48.7° (c1, $CHCl_3$), lit. (12) $[\alpha]_D^{20}$ –49.1° (c1, $CHCl_3$).
IR (film), ν: 3400 (ν O-H), 3034 (ν C-H, Ar), 2926, 2852 (ν C-H, -CH_2-), 1708 (ν C=O), 1498, 1450 (skeletal C=C, Ar), 1049 (ν C-O), 698 (δ C-H, Ar) cm^{-1}.
^{1}H-NMR ($CDCl_3$), δ: 12.16 (s, 1H, COOH), 7.41-7.35 (m, 5H, Ar), 5.85-5.48 (m, 2H, CH_2 near phenyl), 4.17-4.14 (dd, 1H, CH near N), 3.63-3.60 (dd, 1H, CH_2 near N), 3.08-3.04 (t, J=10.1 Hz, 1H, CH_2 near N), 2.31-2.29 (m, 1H, CH_2), 2.02-1.86 (m, 1H, CH_2; m, 1H, CH), 1.73-1.65, 1.24-1.15, 0.98-0.93 (m, 10H, -CH_2-; m, 1H, CH) ppm.

HYDROGENATION OF N-BENZYLOXYCARBONYL-*TRANS*-4-CYCLOHEXYL-L-PROLINE (**9**). *TRANS* 4-CYCLOHEXYL-L-PROLINE (**10**) (12)

A 10% Pd-C catalyst, 1.6 g (0.002 mole), was added to compound **9,** 12.1 g (0.037 mole), dissolved in 95 mL of methanol. The mixture was hydrogenated under atmospheric pressure at room temperature. Progress in the reaction was followed by TLC [developing system: (10:1 v/v) chloroform--methanol]. After 4 h, the reaction was complete, the catalyst was filtered off and the solvent was evaporated to collect a white solid which was suspended in 30 mL of ethyl acetate and heated at 60°C for 15 min. After filtration, the solid was washed with 30 mL of ethyl acetate to give 7.0 g (0.033 mole, 90% yield) of **10**: purity 95.2% (by HPLC); m.p. 249–252°C, lit. (12) m.p. 250–253°C; $[\alpha]_D^{20}$ –29.8° (c1, acetic acid), lit. (12) $[\alpha]_D^{20}$ –30.3° (c1, acetic acid). The product was purified by crystallization from methanol-diethyl ether to obtain 6.1 g (0.031 mole, 84% yield) of **10**, (2S-*trans*)-4-cyclohexyl-2-pyrrolidinecarboxylic acid: purity 99.7% (by HPLC); m.p. 260–262°C, lit. (12) m.p. 265–267°C;

$[\alpha]_D^{20}$ –31.5° (c1, acetic acid), lit. (12) $[\alpha]_D^{20}$ –32.0° (c1, acetic acid).

IR (KBr), ν: 3392 (ν NH_2^+), 2930, 2849 (ν C-H), 1619 (ν_{as} CO_2^-, δ N-H), 1448 (δ C-H, -CH_2-), 1384 (ν_s CO_2^-), 1215 (ν C-N), 1077 (ν C-O) cm^{-1}.

^{1}H-NMR (CD_3OD, TMS), δ: 3.98-3.96 (dd, 1H, CH), 3.50-3.47 (dd, 1H, CH_2), 2.81-2.77 (t, J=10.9 Hz, 1H, CH_2), 2.29–2.27 (m, 1H, CH_2), 1.95–1.79 (m, 1H, CH_2; m, 1H, CH), 1.68–1.59, 1.23–1.14, 0.97–0.92 (m, 10H, -CH_2-; m, 1H, CH) ppm.

^{13}C-NMR (CD_3OD), δ: 174.37, 62.39, 50.47, 44.52, 42.08, 34.69, 32.99, 32.63, 27.28 and 27.04 ppm.

GC-MS, *m*/*z*: 341 (M^+, 6%), 326 ($M^+ - CH_3\cdot$, 78%), 312 (326 – $CH_2\cdot$, 18%), 298 (312 – $CH_2\cdot$, 100%), 285 (298 – $CH_2\cdot$ + H·, 8%).

CONCLUSIONS

The present method of preparation of *trans* 4-cyclohexyl-L-proline, as an intermediate in the synthesis of fosinopril, is highly selective (99.7% of *trans* 4-cyclohexyl-L-proline) and competitive with other methods.

L-Glutamic acid used as a starting material in this method is readily accessible and cheap. Other methods (1, 14–16) start from *trans* 4-hydroxy-L--proline which is more expensive than L-glutamic acid. Moreover, other reagents used in those methods are more expensive and more toxic than the compounds used in the present method.

The formation of the oxazolidine ring in O,N--acetal (**4**) is a convenient method of bidentate protection of two reactive hydrogen atoms in compound **3**.

The present method can be used to prepare other 4-substituted proline derivatives which could possibly serve as intermediates in the synthesis of new ACE inhibitors.

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