



A Novel Synthesis of (4a*S*,7a*S*)-Octahydro-1*H*-pyrrolo[3,4-*b*]pyridine: An Intermediate of Moxifloxacin Hydrochloride

G. PRASHANTH REDDY^{1,2} and RAKESHWAR BANDICHHOR^{1,*}

¹API R&D, Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd, Bachupally, Qutubullapur, Hyderabad-500 072, India

²Center for Environment, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad-500 072, India

*Corresponding author: Fax: +91 40 446285; Tel: +91 40 44346117; E-mail: rakeshwarb@drreddys.com

(Received: 31 January 2013;

Accepted: 26 August 2013)

AJC-14030

A novel synthesis of (4a*S*, 7a*S*)-octahydro-1*H*-pyrrolo[3,4-*b*]pyridine (**1**) is demonstrated alongwith recovery and reuse of chiral auxiliary naproxen. Further to this alternative stereoselective reduction procedures on 6-benzyl-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione **3** enabling the desired chirality in the nonane **1** is demonstrated.

Key Words: Nonane, Racemization, Naproxen, Naproxamide, L-Proline.

INTRODUCTION

(4a*S*,7a*S*)-Octahydro-1*H*-pyrrolo[3,4-*b*]pyridine **1**, is an important intermediate in the manufacture of moxifloxacin and commonly known as “nonane”. For the past few decades, enormous amount of research has been carried out and several processes are reported¹⁻⁸.

Literature¹⁻⁸ illustrated that the majority of manufacturers follow the resolution process (**Scheme-I**), which involves coupling of 2,3-pyridine dicarboxylic acid **2** with benzylamine to obtain **3** followed by pyridine ring reduction to afford intermediate **4** which upon reduction of carbonyl groups afforded N-benzyl nonane intermediate **5**. There after intermediate **5** was subjected to resolution with D(-) tartaric acid in ethanol followed by deprotection to afford nonane **1**.

Herein, we report alternative stereoselective reduction procedures on dione **3** as a source of chirality in the nonane **1**.

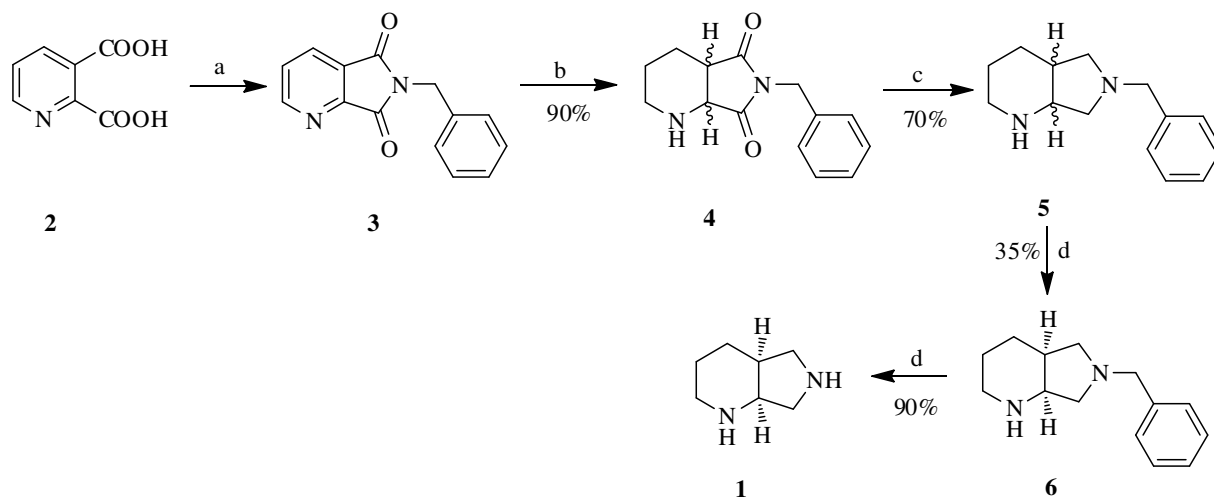
EXPERIMENTAL

General: Solvents and reagents were used for all the reactions as received. The ¹H and ¹³C NMR spectra were recorded in CDCl₃/DMSO-*d*₆ on Varian Gemini 400 MHz or 500 MHz FT NMR spectrometer; the chemical shifts were reported in δ ppm relative to tetramethylsilane TMS (0 ppm). The FT-IR spectra were recorded in the solid state KBr/neat dispersion using Shimadzu IR Prestige-21 spectrophotometer. The mass spectra were recorded on SSMS PESCIEX, API-3000 machine in electron spray mode. The melting points were determined by using Polmon (Model No.: MP96) melting point apparatus. The specific optical rotation was recorded on Jasco P-2000

polarimeter and at 589 nm. The chiral HPLC was recorded on Agilent Model 1260 by using Chiral AGP, 150 × 4.0 mm, 5 μ.

6-Benzyltetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*,7a*H*)-dione (4**):** 50 g, (0.21 mol, 1.0 eq) of 6-benzyl-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione **3** was added to 250 mL of toluene in hydrogen vessel, 29 g, (0.252, 1.2 eq) of L-proline was added and continued the stirring for 10 min, 3.5 g, (7 %) of palladium charcoal on carbon was added. Stirring was continued for 15-30 min and warmed to 70 °C with 7-8 kg/cm² hydrogen pressure for 5-6 h and further warmed the reaction mass to 80-85 °C with 8 kg/cm² hydrogen pressure for 9-10 h, after completion of the reaction cooled to room temperature and catalyst was separated and washed with 100 mL of toluene. The clear filtrate was concentrated under reduced pressure at below 70 °C to furnish 49.5 g, (0.20 mol, 97.05 %) of 6-benzyltetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*, 7a*H*)-dione **4** with 15 % ee. IR (KBr, ν_{max}, cm⁻¹): 3382.49 (NH), 3034.40 (aromatic CH), 2957.04 (aliphatic CH), 1718.93 (C=O); ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 7.25-7.34 (m, 5H), 4.56 (s, 2H), 4.00 (d, 1H, *J* = 6.8 Hz), 2.99 (q, 1H, *J* = 6.4 Hz), 2.57-2.70 (m, 2H), 1.77-1.84 (m, 1H), 1.63-1.69 (m, 1H), 1.42-1.48 (m, 1H), 1.30-1.36 (m, 1H); ¹³C NMR (400 MHz, DMSO-*d*₆): δ (ppm) 178.20, 177.09, 136.25, 128.52, 127.39, 127.30, 72.16, 54.47, 41.73, 41.15, 40.12, 21.67; MS (ESI): *m/z* calculated for C₁₄H₁₆N₂O₂ (M + H): 244.2; found: (M + H⁺) 245.5.

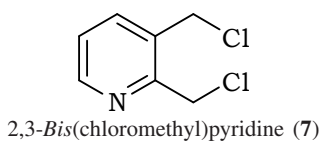
2,3-Bis(chloromethyl)pyridine (7**):** 25 g, (0.142 mol, 1 eq) of pyridine-2,3-diyl dimethanol hydrochloride was dissolved in 51.3 g, (0.431 mol, 2.4 eq) of thionyl chloride



a) Ac_2O , toluene, benzylamine, water; b) H_2 , Ru-C; b) LiAlH_4 , THF, 0 - 5°C, 10h; c) DMF, IPA, ethanol, D(-)-tartaric acid; d) Pd/C, methanol.

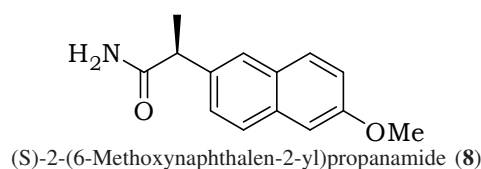
Scheme-I: Precedented approach for **1**^{1,2}

with stirring at 0-10 °C and temperature increased to 15-20 °C for 1 h, 60 mL of MTBE was added and continued stirring for 30-60 min. Reaction mass was cooled to 0-5 °C for 1 h, filtered the precipitated material and washed with 20 mL of MTBE to furnish 27 g of dichloro compound in the form of hydrochloride salt as a white solid. This material was added to 150 mL of DCM with stirring, 100 mL of water also added and pH of the reaction mass was adjusted to 7.5-8.0 with 5 % sodium carbonate solution. Organic layer was separated and extracted aqueous layer with 50 mL of DCM. Combined extracts were concentrated under reduced pressure at below 40 °C to furnish 20 g, (0.113 mol, 88 %) of 3-bis(chloromethyl)pyridine **7** as a light brown coloured oil. IR (KBr, ν_{max} , cm^{-1}): 3033.52 (aromatic CH), 2928.21 (aliphatic CH), 1612.04 (aromatic C=C); ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 8.68 (q, 1H, $J = 2\text{Hz}$), 8.23 (q, 1H, 1.6Hz), 7.68 (q, 1H, $J = 5.2\text{Hz}$), 5.05 (s, 2H), 5.01 (s, 2H); ^{13}C NMR (400 MHz, CDMSO- d_6): δ (ppm) 153.12, 147.63, 140.97, 133.25, 125.08, 42.69, 41.54; MS (ESI): m/z calculated for $\text{C}_7\text{H}_7\text{Cl}_2\text{N}$ (M + H): 175.0; found: (M + H⁺) 176.0.



(S)-2-(6-Methoxynaphthalen-2-yl)propanamide (8): 100 g, (0.43 mol, 1.0 eq) of (S)-naproxen **13** was dissolved in 500 mL of DCM and 1 mL of DMF with stirring and cooled to 0-5 °C. 103.47 g, (0.86 mol, 2.0 eq) of thionyl chloride was added through addition dropper at 0-5 °C, reaction mass was heated to reflux for 6-8 h, after completion of the reaction, concentrated under reduced pressure at below 50 °C and diluted with 500 mL of dichloromethane. Anhydrous ammonia was continuously added up to pH of the reaction mass was 10 and stirring was continued for 1 h. Filtered precipitated material and washed with 200 mL of dichloromethane, this wet material was added to 200 mL of 2 % sodium carbonate solution and

continued stirring for 30-60 min stirring. Filtered the material and washed with 100 mL of water. Wet material dried at 60 °C to furnish 95 g (0.414 mol, 95.4 %) of 2-(6-methoxynaphthalen-2-yl)propanamide **8** as a off-white powder. IR (KBr, ν_{max} , cm^{-1}): 3350.04 (NH), 3195.34 (aromatic CH), 2983.51 (aliphatic CH), 1606.38 (aromatic C=C); ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 7.70-7.78 (m, 3H), 7.43 (q, 1H, $J = 2\text{Hz}$), 7.40 (s, 1H), 7.26 (s, 1H), 7.12 (d, 1H, $J = 2.4\text{Hz}$), 6.83 (s, 1H), 3.85 (s, 1H), 3.70 (q, 1H, $J = 6.8\text{Hz}$), 1.37 (d, 3H, $J = 6.8\text{Hz}$); ^{13}C NMR (400 MHz, DMSO- d_6): δ (ppm) 176.47, 157.42, 137.76, 133.58, 129.27, 128.79, 127.12, 126.86, 125.75, 119.03, 106.12, 55.59, 45.21, 18.67; MS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{15}\text{NO}_2$ (M + H): 229.27; found: (M + H⁺) 230.4.



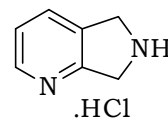
(S)-2-(6-methoxynaphthalen-2-yl)-1-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)propan-1-one (9): A mixture of 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine hydrochloride **12** (20 g, 0.12 mol) and dichloromethane was stirred for 10-15 min. To this mixture diisopropylethylamine (82.42 g, 0.63 mol, 5.25 eq), was added slowly through addition dropper at 10-20 °C, followed by (S)-2-(6-methoxynaphthalen-2-yl)propanoyl chloride (40 g, 0.16 mol, 1.34 eq), in dichloromethane (500 mL) was added at below 25 °C and maintained for 2 h at 25-35 °C. After completion of the reaction water (400 mL) was added and stirred for 15 min. Organic layer was separated and extracted aq. layer with dichloromethane (2 × 200 mL), combined organic layer was washed with 10 % sodium carbonate solution. Final organic layer was dried with sodium sulphate and solvent was evaporated under reduced pressure at below 40 °C to afford 22 g, (0.094 mol, 74 %) of (S)-2-(6-methoxynaphthalen-2-yl)-1-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)propan-1-one **9** as a light brown coloured liquid. IR (KBr,

ν_{\max} , cm^{-1}): 3035.30 (aromatic CH), 2965.07 (aliphatic CH), 1606.37 (C=C), 1163.61 (C-O); $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 8.39-8.43 (m, 1H), 7.68 – 7.81 (m, 4H), 7.46 (d, 1H, $J = 4$ Hz), 7.23-7.27 (m, 2H), 7.13 (dd, 1H, $J = 2.8$ Hz, $J = 2.8$ Hz), 5.10 (t, 1H, $J = 16.8$ Hz), 4.41-4.77 (m, 3H), 4.15-4.20 (m, 1H), 3.84 (s, 3H), 1.42 (d, 3H, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 172.12, 157.17, 152.72, 148.86, 136.40, 133.17, 131.39, 130.30, 129.09, 128.47, 127.18, 126.35, 125.70, 122.48, 118.68, 105.69, 55.12, 52.21, 50.31, 42.68, 20.07; HRMS (ES) calcd. (%) for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_2$ (MH^+) 333.1603 and found 333.1587; SOR: $[\alpha]_{\text{D}25} = 67.5^\circ$ ($c = 0.04$ % in ethanol).

(*S*)-1-[(4a*S*,7a*S*)-Hexahydro-1*H*-pyrrolo[3,4-*b*]pyridin-6(2*H*)-yl]-2-(6-methoxynaphthalen-2-yl)propan-1-one (10): 10 g, (0.03 mol, 1.0 eq) of (*S*)-2-(6-methoxynaphthalen-2-yl)-1-(5*H*-pyrrolo[3,4-*b*]pyridin-6(7*H*)-yl)propan-1-one **9** was added to 100 mL of toluene, 3 g, of 5 % palladium carbon was added in hydrogen pressure vessel. Reaction mass was warmed to 80 °C under 8 kg/cm² hydrogen pressure for 20-24 h, after completion of the reaction was cooled to room temperature, catalyst was separated by filtration on hyflow and washed with 100 mL of methanol. The combined filtrates were concentrated under reduced pressure to obtain crude in the form of residue. This residue was dissolved in IPA and dry HCl gas was passed up to reaction mass pH attained to below 2 and continued stirring for additional 5 h. Precipitated material was filtered and washed with 5 mL of chilled IPA. This wet material was extracted into DCM by adjusting the pH to 10 with 5 % Na_2CO_3 solution. Volatiles were removed under reduced pressure at below 45 °C under reduced pressure to afford 4.5 g, (0.013 mol, 45 %) of (*S*)-1-((4a*S*,7a*S*)-hexahydro-1*H*-pyrrolo[3,4-*b*]pyridin-6(2*H*)-yl)-2-(6-methoxynaphthalen-2-yl)propan-1-one **10** as a light yellow coloured liquid. IR (KBr, ν_{\max} , cm^{-1}): 3127.82 (aromatic CH), 2933.73 (aliphatic CH), 1635.64 (C=O), 1504.48 (aromatic C=C), 1172.72 (C-O); $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 7.77 (d, 2H, $J = 8.5$ Hz), 7.70 (s, 1H), 7.42 (t, 1H, $J = 7$ Hz), 7.27 (s, 1H), 7.14 (dd, 1H, $J = 2.5$ Hz, 2 Hz), 3.89-4.00 (m, 1H), 3.86 (s, 3H), 3.60-3.66 (m, 1H), 3.03-3.45 (m, 7H), 2.32-2.44 (m, 1H), 1.96-2.06 (m, 1H), 1.50-1.55 (m, 2H), 1.35 (d, 3H, $J = 6.5$ Hz); $^{13}\text{C NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 191.92, 160.18, 138.19, 134.15, 132.27, 131.03, 127.86, 127.67, 123.54, 119.87, 106.04, 55.39; HRMS (ES) calcd. (%) for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_2$ (MH^+) 339.2073 and found 339.2056; SOR: $[\alpha]_{\text{D}25} = 122.8^\circ$ ($c = 0.01$ % in ethanol).

6,7-Dihydro-5*H*-pyrrolo[3,4-*b*]pyridine (12): 17 g, (0.062 mol, 1.0 eq) of 6-(2,4-dimethoxybenzyl)-6,7-dihydro-5*H*-pyrrolo [3,4-*b*] pyridine was added to 15 mL of trifluoroacetic acid and 5 mL of triethyl silane with stirring at room temperature. This mixture was heated to 60-65 °C for 4 h, after completion of the reaction, 50 mL of ethyl acetate was added with stirring and cooled to room temperature, 50 mL of 5 % HCl in ethyl acetate was added slowly drop by drop at room temperature in 30-45 min and stirring was continued till material precipitation, filtered the precipitated material and washed with 25 mL of ethyl acetate to furnish 11 g, (0.056 mol, 90 %) of 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine hydrochloride **12** as a brown solid. IR (KBr, ν_{\max} , cm^{-1}): 3431.58 (NH), 3031.97 (aromatic CH), 2971.44 (aliphatic CH), 1622.84

(aromatic C=C); $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 10.07 (s, 1H), 8.52(d, 1H, $J = 4.4$ Hz), 7.85 (d, 1H, $J = 7.2$ Hz), 7.38 (q, 1H, $J = 4.8$ Hz), 4.65 (s, 2H), 4.54 (s, 2H); $^{13}\text{C NMR}$ (400 MHz, CDCl_3): δ (ppm) 191.92, 160.18, 138.19, 134.15, 132.27, 131.03, 127.86, 127.67, 123.54, 119.87, 106.04, 55.39; MS (ESI): m/z calcd. (%) for $\text{C}_7\text{H}_8\text{N}_2$ ($\text{M} + \text{H}$): 120.15; found: ($\text{M} + \text{H}^+$) 121.1.



6,7-Dihydro-5*H*-pyrrolo[3,4-*b*]pyridine (**12**)

(4a*S*,7a*S*)-Octahydro-1*H*-pyrrolo[3,4-*b*]pyridine (1): 5 g (0.014 mol, 1 eq) of (*S*)-1-((4a*S*,7a*S*)-hexahydro-1*H*-pyrrolo[3,4-*b*]pyridin-6(2*H*)-yl)-2-(6-methoxy naphthalen-2-yl)propan-1-one **10** was added into round bottom flask. To this 30 mL of 20 % aq. methanol and 8.2 g, (0.14 mol, 10 eq) of KOH was added with stirring at room temperature. Warmed the reaction mass to reflux for 72 h, after completion of the reaction, methanol was evaporated under reduced pressure at below 60 °C. 25 mL of water was added, extracted aqueous layer with 3 × 25 mL of CHCl_3 ; combined organic layer was dried over Na_2SO_4 , clear filtrate was concentrated under reduced pressure at below 50 °C to furnish 1.8 g, (0.014 mol, 96 %) of (4a*S*, 7a*S*)-octahydro-1*H*-pyrrolo[3,4-*b*]pyridine **1** as a light brown coloured liquid.

Aqueous layer was taken and adjusted the pH to 2 with aqueous HCl and extracted into toluene; isolated *racemic* naproxen **14** from toluene at 0-5 °C after charcoal treatment as half white coloured powder (3.23 g, 95 % yield with 97 % purity).

(4a*S*,7a*S*)-Octahydro-1*H*-pyrrolo[3,4-*b*]pyridine (1): Purity by HPLC: 96.7 %; chiral purity by HPLC: 98.93 %; $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 2.95-2.98 (m, 1H), 2.63-2.82 (m, 4H), 2.54 (dd, 1H, $J = 1.6$ Hz, $J = 1.2$ Hz), 2.39-2.45 (m, 1H), 2.16-2.45 (br, s, 2H), 1.81-1.89 (m, 1H), 1.59-1.66 (m, 2H), 1.35-1.46 (m, 1H), 1.24-1.31 (m, 1H); $^{13}\text{C NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ (ppm) 57.43, 53.37, 47.78, 44.49, 37.85, 23.51, 21.90; MS (ESI): m/z calcd. (%) for $\text{C}_7\text{H}_{14}\text{N}_2$ ($\text{M} + \text{H}$): 126.20; found (%): ($\text{M} + \text{H}^+$) 126.7; SOR: $[\alpha]_{\text{D}25} = -3.769^\circ$ ($c = 2$ % in ethanol).

Racemic naproxen (14): m.p. 155-158 °C; $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 7.66-7.68 (d, 3H, $J = 8.8$ Hz), 7.39 (dd, 1H, $J = 1.5$ Hz, $J = 8.3$ Hz), 7.08-7.13 (m, 2H), 3.8 (s, 3H), 3.82-3.86 (m, 1H), 1.56 (d, 3H, $J = 6.8$); $^{13}\text{C NMR}$ (400 MHz, CDCl_3): δ 180.91, 157.65, 134.83, 133.77, 129.27, 128.84, 127.20, 126.16, 126.11, 119.01, 105.52, 55.27, 45.21, 18.10; MS: calcd. (%) for $\text{C}_{14}\text{H}_{14}\text{O}_3$ 230 (M^+), found 23 (MH^+); IR (KBr, ν_{\max} , cm^{-1}): 3201.02 (OH), 1728 (C=O), 3002.9 (aromatic CH), 855.66 (C=C), 1264.69 (CO); SOR: $[\alpha]_{\text{D}25} = 0.02^\circ$ ($c = 1$ % in chloroform).

RESULTS AND DISCUSSION

In our endeavor, we attempted to improve the enantioselectivity during the reduction of 6-benzyl-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (**3**) involving the reduction of pyridine ring using L-proline as a chelating agent and 5 % palladium

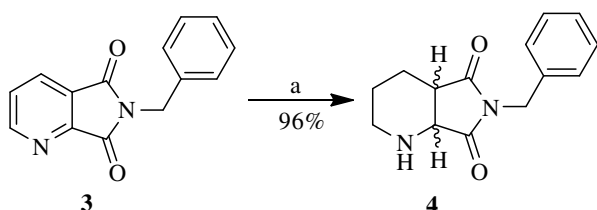
TABLE-1
 REDUCTION OF COMPOUND **3** IN PRESENCE OF L-PROLINE

Entry	Solvent	Reducing agent	L-Proline qty (eq)	Yield (%)	*Chiral HPLC (%)	
					Desired	Undesired
1	Toluene	Pd/C	0.00	94	50.5	49.4
2	Toluene	Pd/C	0.10	96	50.2	49.8
3	Toluene	Pd/C	1.2	96	57.4	42.6
4	Methanol	Pd/C	1.2	96	53.6	46.4
5	AcOH	Pd/C	1.2	90	54.1	45.9
6	Ethanol	Pd/C	1.2	92	53.5	46.5
7	Toluene	Pd-Cu/C	00	90	51.5	48.5
8	Toluene	Pd-Cu/C	1.2	91	57.5	42.5

*Intermediate 4 was further converted to 1 and analyzed for chiral HPLC.

on carbon as reducing agent. The required amide **3** for employed in the reduction was synthesized using known procedure³. Present studies involve varying the mole ratio of L-proline by using Pd/C and Pd-Cu/C as a reducing agents were conducted and the results are summarized in Table-1. When the reaction was performed with the catalytic quantity of L-proline there was no enhancement in the *ee* and it was similar to racemic mixture (entry 2 in Table-1). Increasing the quantity of additive (L-proline) to stoichiometric amount brought about a marginal increase in *ee* in favour of the desired isomer (entry 3 in Table-1).

In the next step, various solvents were screened to find out the impact on selectivity. It can be observed that there was no big impact on enantioselectivity with various solvents screened except toluene as shown in Table-1 (entry 3).



a) Pd/C, L-proline, toluene, 80°C, 24h.

Scheme-II: Reduction of **3**

While the possible hydrogen bonding effect of L-proline was demonstrated to achieve the selectivity up to 15 % *ee* further study focused on the reducing agent. Copper-palladium couple on carbon catalyst was used as a reducing agent. However selectivity could not be improved (Table-1; entry 7).

It was observed that there was no remarkable effect of solvent and additive L-proline on the selective hydrogenation of the pyridine ring. In continuation with the studies, we shifted our focus to find an alternative route that could furnish the enantiomerically pure nonane.

At first *bis*-(chloromethyl)pyridine **7** was synthesized following the known procedure⁹. Our attempts to cyclize the chloro intermediate **7** by using benzamide was not successful. In addition to this, various other bases screened to couple the benzamide and chloro intermediate and attempts were unsuccessful.

In order to increase the reactivity of amide component, (S)-2-(6-methoxynaphthalen-2-yl)propanamide **8** was selected for condensation assuming that it is more reactive than the

benzamide and being chiral it might help in getting selectivity during the reduction.

Substantial improvement was observed in reaction time and yield. Unprecedented reaction conditions employed for condensation involved reaction temperature of 80-90 °C using 5 mol equivalents of sodium hydride in 10 volume toluene. The results are summarized in Table-2.

 TABLE-2
 OPTIMIZATION OF NaH QUANTITY

Entry	Base	Solvent	Base Qty (Eq)	Temp. (°C)	9 (%)
1	NaH	Toluene	3	80-90	60
2	NaH	Toluene	4	80-90	75
3	NaH	Toluene	5	80-90	90

*Confirmed by TLC.

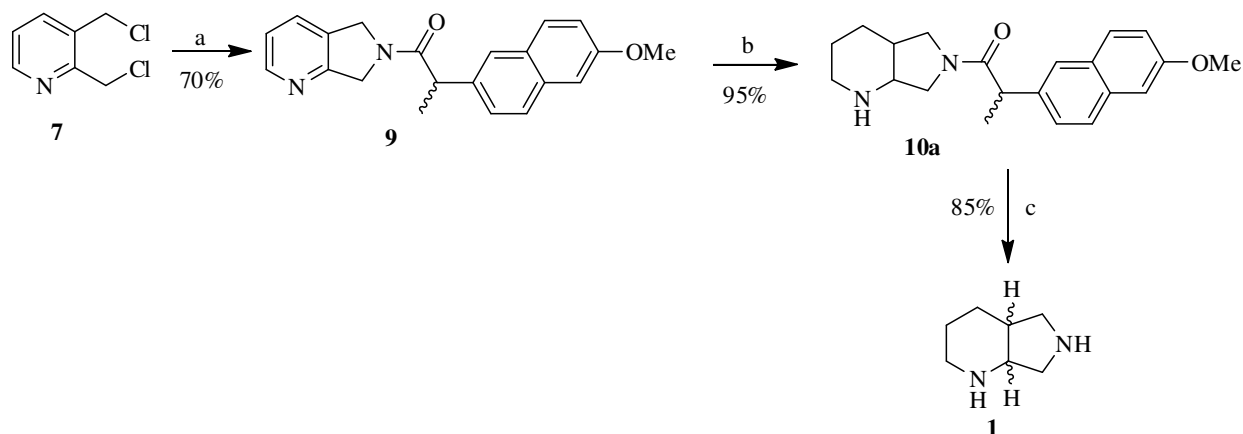
Thereafter (S)-2-(6-methoxynaphthalen-2-yl)-1-(5H-pyrrolo [3,4-b]pyridin-6(7H)-yl)propan-1-one **9** was subjected to hydrogenation with 5 % palladium catalyst followed by deprotection with HBr in acetic acid to afford the target nonane **1** (Scheme-III). The resulted nonane was analyzed for chiral purity and it was found to be a racemic. However, the reaction time was reduced along with the improvement in the yield.

In order to understand whether the zero enantioselectivity was due to non-selective hydrogenation or early on racemization of chiral centre present in naproxen amide **8** under basic conditions or not, we performed control experiment by employing similar reaction condition *i.e.*, NaH/toluene. Chiral HPLC analysis of the product showed the complete racemization (Scheme-IV). Results are summarized in Table-3.

 TABLE-3
 CHIRAL HPLC RESULTS OF **8**

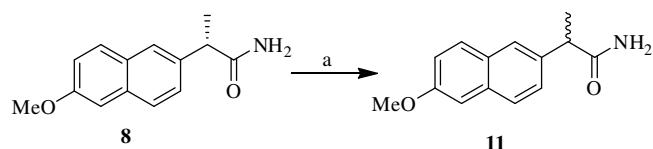
Entry	(S)-2-(6-Methoxynaphthalen-2-yl)propanamide (8)	S-Isomer (%)	R-Isomer (%)
1	Initial	98	2
2	After 0.5 h maintenance at 80-90 °C	55	45

Since the reaction conditions employed for di-alkylation was leading to racemization of the (S)-2-(6-methoxynaphthalen-2-yl)propanamide **8**, we adopted another approach featuring the preparation of 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine **12** following the known procedure¹⁰. Alkylation of the 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine **12** with (S)-naproxen **13** was carried out in presence of phenyl boronic acid as catalyst in *o*-xylene at 145 °C. The intermediate obtained after 2-(6-methoxynaphthalen-2-yl)-1-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)propan-



a) (*S*)-Naproxamide (**8**), toluene, NaH, 80 - 90°C, 5h, AcOH, EA, H₂O, n-heptane; b) 5% Pd/C, toluene, 80°C, 8 kg/cm², 24h; c) 48% HBr, propionic acid, phenol, reflux, 6 - 7h, MTBE, EA, NaOH, H₂O, NaCl, CHCl₃.

Scheme-III: Novel approach for **1**



a) NaH, toluene, 85 - 90°C, 30 minutes.

Scheme-IV: Racemization of **8**

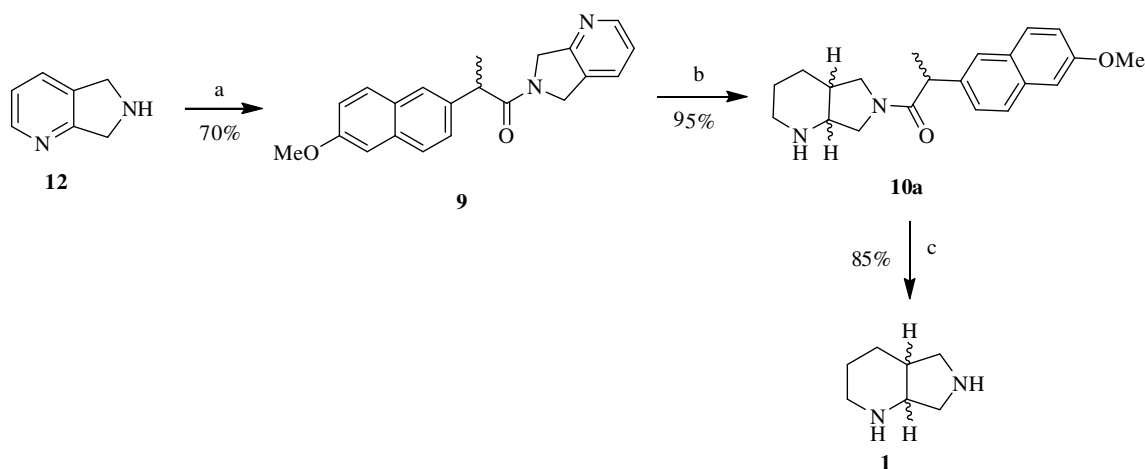
1-one **9** was subjected to reduction of pyridine ring using 5% palladium on carbon catalyst in toluene to afford the 1-(hexahydro-1*H*-pyrrolo[3,4-*b*]pyridin-6(2*H*)-yl)-2-(6-methoxynaphthalen-2-yl) propan-1-one **10**, which was subjected to de-coupling to yield the target intermediate nonane **1** (Scheme-V).

To our surprise, we once again encountered with racemization. The reason for ending up with racemic compound was found to be due to racemization of the (*S*)-naproxen **13** during the coupling with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine **12**. This was confirmed by chiral HPLC analysis of (*S*)-naproxen **13** before and after reflux in *o*-xylene in presence of phenyl boronic acid as a catalyst and in absence of intermediate **12**, respectively. Chiral HPLC results are summarized in Table-4 (Scheme-VI).

Entry	(<i>S</i>)-Naproxen (13)	S-Isomer (%)	R-Isomer (%)
1	Initial	99.8	0.2
2	After 10 h, maintenance at 145 °C	51.5	48.5

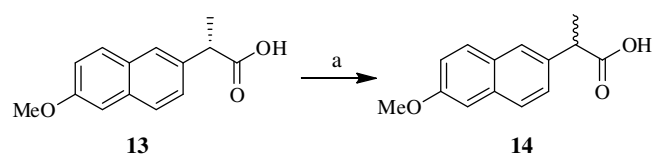
Hence, we concluded that the racemization of the coupling agent was not only due to presence of strong base, but also due to the reaction temperature in the presence of acidic catalyst.

Keeping in view of the extreme reaction conditions leading to racemization of the coupling agent, the coupling agent was primarily activated by making its acid chloride and then coupled with the 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine **12** using DIPEA as a HCl scavenger at 0-5 °C. The coupled intermediate **9** was further reduced with 5% palladium on carbon to get the reduced intermediate **10** followed by de-coupling with HBr to afford the target intermediate nonane **1**. The obtained nonane was analyzed for chiral purity and the enantioselectivity was found to be much improved (20% *ee*) but still it is extremely poor proposition from synthesis standpoint (Scheme-VII).



a) (*S*)-Naproxene (**13**), *o*-xylene, phenylboronic acid, Na₂CO₃, H₂O, reflux, 24h; b) 5% Pd/C, toluene, 80°C, 8 kg/cm², 24h; c) HBr in AcOH, phenol, propionic acid, reflux, 6 - 7h, NaCl, NaOH, CHCl₃.

Scheme-V: Modified novel approach for **1**



a) *o*-xylene, phenyl boronic acid, reflux, 10h.

Scheme-VI: Racemization of **13**

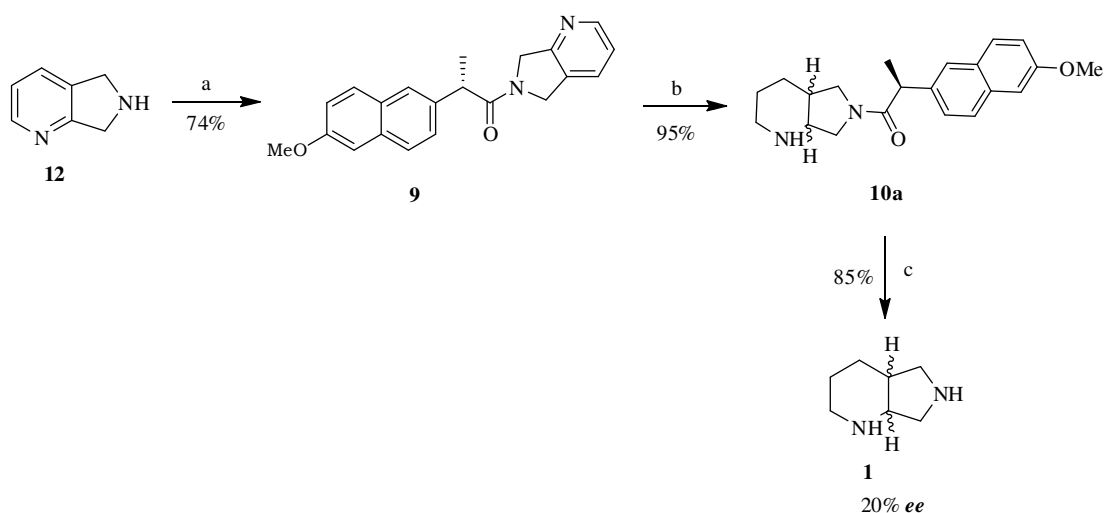
Having gained intellectual control over reaction sequence, we decided to develop a simple method for purification and hydrolysis of **10** to obtain the nonane **1** and naproxen **13**. At first the required isomer was isolated by making the HCl salt in IPA thereafter various bases were screened to hydrolyze **10**. Among all the bases KOH and K⁺OBU were afforded the best results (Table-5, entry-1 and 2).

Based on the results and observations from the experiments conducted to attain enantioselectivity of nonane, the following process was finalized. The cyclic amine intermediate¹⁰ **12** was coupled with the acid chloride of (*S*)-naproxen **13** in presence of DIPEA at 0-5 °C. The crude material obtained after

Entry	Base	Temp. (°C)	% of 1	% of 32
1	KOH	80	92	96
2	K ⁺ OBU	80	90	97
3	LiOH	80	Reaction incomplete	
4	NaOMe	80	Reaction incomplete	
5	NaOC ₂ H ₅	80	Reaction incomplete	

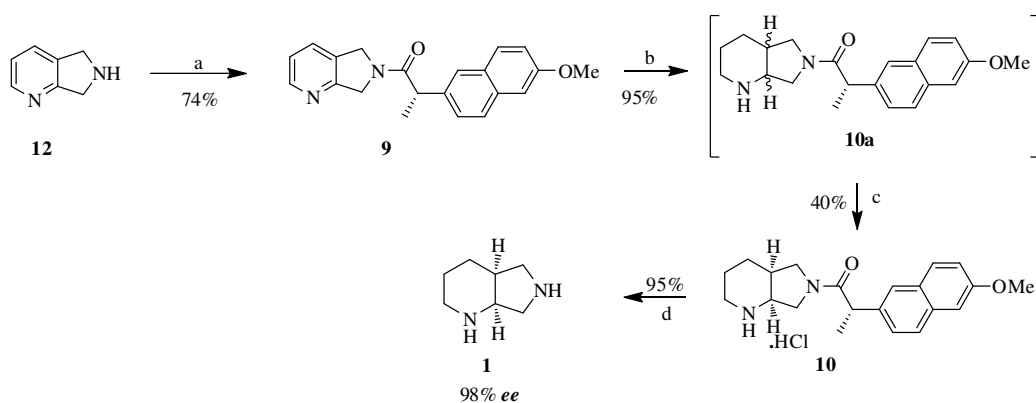
*Reactions carried out in aq. methanol.

workup was purified through column chromatography to afford the coupled intermediate **9**. The pyridine ring of the intermediate **9** was reduced using palladium on carbon as catalyst in toluene solvent. The catalyst was filtered off and the target diastereomeric intermediate was obtained as a crude. Diastereomers were separated by making the hydrochloride salt in isopropyl alcohol. After separation, intermediate **10** converted to nonane by hydrolyzing with KOH in aqueous methanol to afford nonane **1** and racemic naproxen **14** with an excellent yield (95 and 90 %) was recovered (**Scheme-VIII**).



a) (*S*)-Naproxenacidchloride, toluene, DIEPA, Na₂CO₃, H₂O, 0 - 5°C, 2h; b) 5% Pd/C, toluene, 80°C, 8 kg/cm², 24h; c) HBr in AcOH, phenol, propionic acid, reflux, 6 - 7h, NaCl, NaOH, CHCl₃.

Scheme-VII: Modified novel approach for **1**



a) (*S*)-Naproxenacidchloride, DIEPA, MDC, Na₂CO₃, H₂O, 0 - 5°C, 1h; b) 5% Pd/C, toluene, 80°C, 8 kg/cm², 24h; c) IPA, dry HCl; d) KOH, Aq.methanol, reflux, 72h, NaCl, CHCl₃, Aq.HCl, toluene.

Scheme-VIII: Optimized Final novel scheme for **1**

Conclusion

An efficient process for pyridine ring reduction with 15-20 % *ee* has been developed by using L-proline or naproxene as a chiral auxiliary. Enantiomerically enriched novel process has been developed for (4a*S*,7a*S*)-octahydro-1*H*-pyrrolo[3,4-*b*]pyridine by investigating three different approaches. We demonstrated coupling between 2,3-*bis*(chloromethyl)pyridine **7** and (S)-2-(6-methoxynaphthalen-2-yl)propanamide **8** for the first time in presence of sodium hydride in toluene with 70 % of yield and recovery process for racemic naproxen **14** by hydrolyzing of **10** with KOH in aq. methanol was also established.

ACKNOWLEDGEMENTS

The authors thank the Management of R&D-CTO and IPDO, Dr. Reddy's Laboratories Ltd., for supporting this work. Cooperation from the colleagues from Analytical Development is highly appreciated.

REFERENCES

1. U. Petersen, T. Schenke, A. Krebs, K. Grohe, M. Schriewer, I. Haller, K. Metzger, R. Endermann and H. Zeiler, EP 0,350,733 (1990).
2. U. Petersen, A. Krebs, T. Schenke, T. Philipps, K. Grohe, K.D. Bremm, R. Endermann, K.G. Metzger and I. Haller, EP0, 550, 903 (1992).
3. A. Ramakrishnan and S.B. Narayan, V. WO 125,425 (2009).
4. J.W. Kim, H.T. Park, H.M. Kim, J.B. Kim and D.N. Pearson, US Patent 5,770,597 (1998).
5. (a) W. Zheqing, F. Shushan and C. Yongzhi, WO085480 (2008); (b) Z. Wang, S. Feng and Y. Cheng, US Patent 0,221,329 (2008).
6. W. Tianjun, *Faming Zhuanli Shenqing*, 7 (2010).
7. O. Masatoshi and N. Akira, WO 122,774 (2010).
8. (a) F. Peter, WO58, 532, 1999; (b) D. Claus, Ger.Offen. WO 09, 200, 1999; (c) F. Peter, US Patent 6, 235, 908 (2001); (d) D. Herbert, K. Andreas, L. Walter, P. Hanns-Ingolf, S. Dietrich, G. Rolf and R. Tobias, US Patent 0,044,205 (2004); (e) L. Mingliang, W. Yonggang, S. Lanying and G. Huiyuan, *Zhongguo Yiyao Gongye Zazhi*, **35**, 129 (2004); (f) P. Xianhua, T. He, O. Wenhua, R. Libo and Y. Wenqiu, *Faming Zhuanli Shenqing*, 13 (2009); (g) M. Riccardo, A. Glancarlo, B. Elisabetta, C. Andrea, F. Stefano and G. Marco, WO100,215 (2010).
9. J.S. Grimm, C.A. Maryanoff, M. Patel, D.C. Palmer, K.L. Sorgi, S. Stefanick, R.R.H. Webster and X. Zhang, *Org. Process Res. Dev.*, **6**, 938 (2002).
10. M.S. Sakya, D.V.M. Berg, K. Pouwer, M.J. Humphrey, J.C. Helal and J.C. O'Donnel, *Tetrahedron Lett.*, **51**, 5859 (2010).