Synthesis of Potent Calcimimetics (+)-NPS R-568 by Palladium-Catalyzed Oxidative Kinetic Resolution

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A practical and efficient procedure for the synthesis of potent calcimimetics (+)-NPS R-568 was developed. This procedure includes palladium-catalyzed oxidative kinetic resolution of benzylic alcohol with molecular oxygen and (-)-sparteine, as a source of chirality. The synthesis was achieved in six steps from commercially available 3-methoxyacetophenone at 18.58% overall yield and the final compound, calcimimetics (+)-NPS R-568 1 had 87% enantioselectivity.

Key words: Oxidative kinetic resolution; enantioselective synthesis; Steglich reaction; Mitsunobu reaction; kinetic resolution

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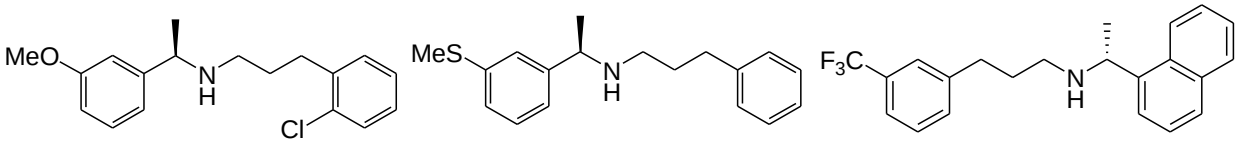
Hyperparathyroidism occurs when the parathyroid glands fail to regulate the amount of calcium in the blood stream, resulting in elevated calcium levels [1]. The current treatment for this disease involves the surgical removal of abnormal parathyroid glands. Chemotherapeutically, it is controlled by calcimimetics drugs, which activate the calcium receptors in the parathyroid glands [2]. NPS R-568 **1** has a great potential as a novel type of calcimimetics for the treatment of primary and secondary hyperparathyroidism. Clinical studies have shown that the (R) enantiomer of **1** is 10-100 times more potent than the (S) enantiomer [3]. Hence, considering the medicinal importance of (+)-NPS R-568, we developed an asymmetric strategy for the synthesis of (+)-NPS R-568. Cinacalcet hydrochloride (CNC·HCl, **3**, **Fig. 1**), under the trade name Sensipar, is the active pharmaceutical drug used for the treatment of secondary hyperparathyroidism by inhibiting the parathyroid glands from releasing thyroid stimulating hormone (TSH) [4]. Compound SF_5-calcimimetics **2** is an analogue of calcimimetics Sensipar and is used for the treatment of hypercalcemia and hyperparathyroidism [5].

A few literature reports are available for the enantioselective synthesis of **1**, in which the chiral center was developed by chiral poll approach [6,7,8], asymmetric hydrosilylation of imine [9,10,11], asymmetric reductive acylation of a ketoxime[12], diastereoselective addition of Grignard reagent [13], organolithium and dimethylzinc to imines bearing a chiral auxiliary[14,15,16], reductive amination of aromatic ketone [17,18,19], diastereoselective N-alkylation of amines with racemic alcohol [20,21], chiral ligand-promoted cobalt-catalysed radical hydroamination of alkene [22] or enantioselective arylation of aliphatic imines [23]. However, most of these methods have several drawbacks, such as tedious and time consuming experiments, unavailability or expensive chiral starting materials, low yield and lower enantiomeric purity, etc. Herein, we report a new method for the enantioselective synthesis of **1** by using palladium-catalyzed oxidative kinetic resolution of secondary benzylic alcohol in the presence of molecular oxygen and (-)-sparteine, a chiral base as a source of chirality. The other salient features of this method include high levels of selectivity, easy availability of the racemic mixture of benzyl alcohol, and the low loadings and easy recyclability of the commercially available catalyst, which make it an extremely simple work.



Calcimimetics(+)NPS R-568 **1** **2** Cinacalcet **3**

Figure 1. General calcimimetics drugs

EXPERIMENTAL

Materials and Methods

All reagents were purchased from commercial sources and were used without further purification unless otherwise stated. Reactions were carried out with distilled and dried solvents using oven-dried glassware. TLC was performed on Merck Kiesel gel 60, F254 plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane or chloroform and methanol as the mobile phase. IR spectra were recorded on Perkin–Elmer RX-1 FT-IR machine. ^{1}H and ^{13}C-NMR spectroscopic data were collected at 300 and 75 MHz, respectively. ^{1}H-NMR spectroscopic data are given as chemical shifts in ppm, followed by multiplicity (s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet), number of protons, and coupling constants. ^{13}C-NMR chemical shifts are expressed in ppm. Optical rotations were measured with a JASCO digital polarimeter. GCMS spectroscopic data were collected using a mass spectrometer. HRMS were obtained from Bruker Impact HD ESI source at Shimadzu Analytical Centre, University of Pune.

1-(3-Methoxy-phenyl)-ethanol (5)

To a solution of **4** (2.5 g, 16.44 mmol) in methanol (50 mL), sodium borohydride (943 mg, 24.97 mmol) was added at 0^0C. The reaction mixture was stirred at 0^0C for 10 min and at room temperature for 1 h. Progress of the reaction was monitored by TLC using 20% ethyl acetate and hexane as the mobile phase. After completion of reaction, the reaction mixture was quenched by the addition of H_2O (2 mL), and methanol was evaporated. The mixture was basified with NaOH 3N (15 ml) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (20% EtOAc/hexane) affording racemic alcohol **4** as a colorless oil, yield 98%, 2.48 g. IR ($CHCl_3$, cm^{-1}): ν_{max} = 3381(-OH), 2970(C-H), 1600(C=C), 1589(C-O), 1487(C-H), 1360, 1257(C-O-C), 1045, 700; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 8.1 Hz, 1H), 6.94 (m, 2H), 6.81 (dd, *J* = 8.1 Hz, *J* = 2.6 Hz, 1H), 4.87 (q, *J* = 6.4 Hz, 1H), 3.81(s, 3H), 1.87 (br s, 1H), 1.48 (d, 3H, *J* = 6.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.47, 147.55, 129.26, 117.56, 111.58, 110.72, 69.93, 54.97, 24.98 ppm; GCMS: m/z = 153.09(M+1).

(-)-1-(3-Methoxyphenyl) ethanol (6)

To a 100 mL side arm flask, 128 mg (0.73 mmol, 0.05 equiv.) of $PdCl_2$ was added followed by 40 mL of dichloroethane and 672 µl (2.93 mmol, 0.2 equiv.) of (-)-sparteine. A condenser and a balloon filled with O_2 were then attached to the top of the flask and the system was purged of air and refilled with O_2 from the balloon. The flask was placed in an oil bath at 70^0C. After stirring the reaction mixture for 30 min, 2.2 g (7.25 mmol, 1.0 equiv.) of 1-(3-Methoxyphenyl)-ethanol in 5 mL of dichloroethane was added slowly and the reaction was continued. Progress of the reaction was monitored by thin layer chromatography using 20% ethyl acetate and hexane mixture. After stirring the reaction for 40 h at the same temperature, it was then cooled to room temperature and 25 mL of 2% TFA/methanol was added to quench the reaction. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (10% Ethyl acetate/ hexanes) to give (R)-1-(3-methoxyphenyl)ethanol **6** (876 mg, 41.7 %) as a colorless liquid in 87% enantiomeric excess and oxidized product ketone **4** (1.03 g, 49%). The IR and ^{1}H and ^{13}C-NMR data of compound (-) **6** were found to be the same as to compound **5**. The optical rotation value of alcohol (-) **6** was $[\alpha]^{28}_{D}$ = -39.8 (c 1.0, $CHCl_3$).

(R)-2-(1-(3-methoxyphenyl)ethyl)isoindoline-1,3-dione (7)

To a solution of **6** (800 mg, 5.25 mmol) in dry THF (25 mL), PPh_3 (1.37 g, 5.25 mmol) and phthalimide (771 mg, 5.25 mmol) were successively added under a nitrogen atmosphere. The resulting solution was cooled to 0^0C and DEAD (1.02 mL, 5.25 mmol) was added slowly. The mixture was allowed to warm to room temperature and stirred for 3 h until no starting material was detected on TLC. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 97:3) to yield (+)-**7** as a colourless solid (1.29g, 88% yield). $[\alpha]^{28}_{D}$= + 14.8 (c 1.0, $CHCl_3$); mp 83 ^{0}C; IR ($CHCl_3$, cm^{-1}): ν_{max} = 2995(C-H), 2843, 1766(OC-N),1597(C=C), 1348(C-H), 1259(C-N), 1045, 873, 723 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.8 (dd, *J* = 8.1, 2.6 Hz, 2H), 7.68 (dd, *J* = 8.1, 2.6 Hz, 2H), 7.25 (t, *J* = 8.1 Hz, 1H), 7.1(m, 2H), 6.8 (ddd, *J* = 8.1, 2.6, 1.1 Hz, 1H), 5.5(q, *J* = 6.4 Hz, 1H), 3.79(s, 3H), 1.92 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.05, 159.54, 141.83, 133.83, 131.86, 129.40, 123.09, 119.63, 113.24, 112.8, 55.12, 49.50,17.5 ppm; GCMS: m/z = 281.

(+)1-(3-Methoxyphenyl)ethanamine (8)

To a stirred solution of (+)-**7** (1.2 g, 4.26 mmol) in ethanol (20 mL), hydrazine hydrate (99%) solution (1.65 mL, 34.12 mmol) was added and the resulting mixture was refluxed for 3 h. The precipitated solid was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in ether and extracted with 2N HCl. The aqueous phase was treated with 2N NaOH until pH >12. The aqueous phase was extracted with ether (3 × 20mL) and the combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica

gel, CH_2Cl_2/MeOH, 97:3) to afford amine (+)-**8** (503 mg, 78% yield) as a clear oil. $[\alpha]^{28}_D$ = +20.02 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} = 3362(N-H), 3296(N-H), 2962(C-H), 1600(C=C), 1585(N-H), 1487(C-C), 1317(C-N), 1259, 1155, 1042, 850, 785 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) D_2O exchange: δ = 7.2 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.8 (m, 2H), 6.7 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1H), 4.04 (q, *J* = 6.8, 1H), 3.81 (s, 3H), 1.37 (d, *J* = 6.8, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): *δ* = 159.63, 149.41, 129.36, 117.90, 111.92, 111.5, 55.1, 51.19, 25.6 ppm; GCMS: m/z = 151.

(+)-3-(2-Chlorophenyl)-N-[(R)-1-(3-methoxyphenyl) ethyl]-propanamide (9)

To a stirred solution of 3-(2-chlorophenyl)-propionic acid (584 mg, 3.17 mmol) in CH_2Cl_2 (10 mL), dicyclohexylcarbodiimide (655mg, 3.17mmol) and *N*,*N*-(dimethylamino)pyridine (32 mg, 0.264 mmol) were added. Stirring was continued for 30 min at room temperature until a white precipitate deposited on the side of the flask, then (R)-(3-Methoxyphenyl) ethanamine (400 mg, 2.64 mmol) was added in 5 mL of CH_2Cl_2, the mixture was stirred for an additional 1 h at room temperature. The white precipitate was removed by filtration through a celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography ($CHCl_3$-MeOH 98:2) to give (772 mg, 91%) as colorless needles. $[\alpha]^{28}_D$ = +30.8 (c 1.1, $CHCl_3$), mp = 92-94^{0}C, IR ($CHCl_3$, cm^{-1}): ν_{max} = 3286(N-H),1766(OC-N),1607(C=C),1310(C-H), 1260(C-N), cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): *δ* = 7.34 (dd, *J* = 6.8, 2.3, 1H), 7.24-7.2 (m, 2H), 7.17-7.1 (m, 2H), 6.78-6.81 (m, 3H), 5.56 (br d, *J* = 7.1, 1H), 5.07 (quint, *J* = 7.1, 1H), 3.79 (s, 3H), 3.08 (t, *J* = 7.6, 2H), 2.49 (td, *J* = 7.4, 0.9 Hz, 2H), 1.40 (d, *J* = 6.9, 3H); ^{13}CNMR (75 MHz, $CDCl_3$): δ = 170.8, 159.9, 144.8, 140.4, 133.9, 130.9, 129.8, 129.6, 127.9, 127.0, 118.5, 112.6, 112.3, 53.3, 48.8, 36.5, 29.7, 21.7 ppm; GCMS: m/z = 317.

(+)-NPS R-568 (1)

To a stirred solution of 9 (600 mg, 1.88 mmol) in dry CH_2Cl_2 (10 mL), 1 M solution of DIBAL-H in toluene (2 mL, 2.07 mmol) was added at 0^{0}C. After being stirred for 3 h at room temperature, the reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). Then the mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo*. Purification of the residue by chromatography ($CHCl_3$-MeOH, 96:4) gave calcimimetics (+)-NPS R-568 1 (403 mg, 70%) as pale yellow oil. $[\alpha]_{28}^D$ = +30.8 (c 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} = 3344(N-H), 2929(C-H),1597(C=C),1444(C-H),1265(C-N),1045(, 740, 705 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 7.11- 7.33 (m, 5H), 6.89-6.90 (m, 2H), 6.79 (ddd, *J* = 8.3, 2.4, 0.9, 1H), 3.82 (s, 3H), 3.74 (q, *J* = 6.5 Hz, 1H), 2.70-2.77 (m, 2H), 2.50-2.59 (m, 2H), 1.76-1.81 (m, 2H), 1.5 (s broad, 1H), 1.35 (d, *J* = 6.6, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.9, 147.7, 139.9, 134.0, 130.4, 129.5, 129.4, 127.3, 126.8, 119.1, 112.3, 112.2, 58.4, 55.3, 47.0 ppm.; HRMS (ESI) $C_{18}H_{23}ClNO$ $[M+H]^+$ 304.1468, found 318.1472.

RESULTS AND DISCUSSION

The synthesis of calcimimetics (+)-NPS R-568 **1** was started from ketone **4**, which was quantitatively converted to alcohol **5** by reduction with sodium borohydride [24]. This racemic benzylic alcohol was then subjected to oxidative kinetic resolution by using $PdCl_2$ (5 mol%) and (-)-sparteine (20 mol%) with molecular oxygen and dichloroethane solvent at 60^{0}C this method is a powerful tool for the generation of enantio-enriched and optically pure alcohol (*S*)-**6** and ketone **4** [25,26]. The recyclability of catalyst $PdCl_2$ and sparteine is well explored with 1, 2-dichloroethane or tert-butyl alcohol as the solvent and has provided for an improved catalyst system [27]. The optical purity of alcohol **6** was determined by optical rotation value and also by chiral HPLC using Lux 5u Cellulose-1 column. The optical purity of compound **6** was found to be more than 87%. The appearance of a signal at δ 1.48 corresponded to methyl group of the side chain, and the peak at 3.81 corresponded to protons of the –OMe methyl. The required stereochemistry and amine functionality at the chiral center were achieved by treatment of alcohol **6** with phthalimide in the presence of triphenylphosphine and di-isopropyl azodicarboxylate (DIAD) in dry THF under standard Mitsunobu reaction conditions. After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give corresponding phthalimide-protected amine **7** [28]. The presence of eight protons in the aromatic region in ^{1}H-NMR and two phthalimide carbons in the amide region of ^{13}C-NMR indicated the formation of compound **7** and at δ 5.5 showed quartet for benzylic CH. A facile hadrazinolysis of phthalimide **7** with hydrazine hydrate in ethanol at 65^{o}C afforded optically pure substituted benzyl amine **8** at 72% yield [29]. The formation of chiral amine **8** was confirmed by ^{1}H, ^{13}C, and mass spectroscopy. It showed four protons in the aromatic region and the mass of amine **8** was 151 that matched the calculated mass of the compound. Coupling of amine **8** with 2-chlorobenzenepropionic acid was carried out by using DCC-DMAP in dry dichloromethane at room temperature under Steglich reaction conditions to get **9** at 91% yield [30]. Intermediate compound **9** quantitatively converted to final compound (+)-NPS R-568 **1** by reduction of amide with DIBAL-H in dry DCM at room temperature at 70% yield. Targeted compound (+)-NPS R-568 **1** was characterized by IR,

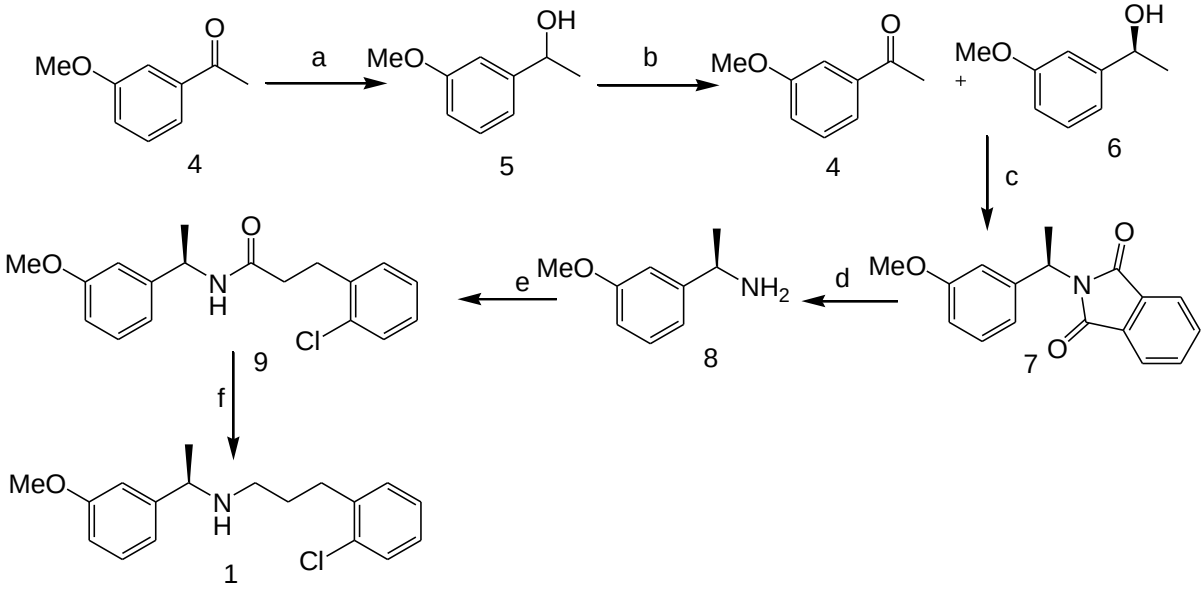


Figure 2. Scheme 1

Scheme 1: Reagents and Conditions: a) $NaBH_4$, MeOH, 2 h, 98%; b) $PdCl_2$, (-)-sparteine, DCE, O_2, 1 atm. 41.7% of (-)-**6**; c) PPh_3, DIAD, Phthalimide, THF, rt, 4 h, 93%; d) $NH_2.NH_2.H_2O$, EtOH, 60^0C, 30 min 72% for two steps; e) 3-(2-chlorophenyl) propanoic acid, DCC, DMAP, DCM, rt, 5 h, 91%; f) DIBAL-H, DCM, 0^0C to rt, 3 h, 70%.

^{1}H, ^{13}C, and mass analyses. The appearance of peaks at δ 1.35 corresponded to protons of methyl group and at δ 3.74 represented the proton of the chiral centre CH. The peaks at δ 7.11-7.33 and 6.76-6.90 were due to presence of aromatic protons. In the IR spectroscopy, the characteristic stretching frequency for secondary amine observed at 3344 cm^{-1}, and the HRMS (ESI) calculated for $C_{18}H_{23}ClNO$ $[M+H]^+$ was 304.1468 and found 318.1472. Optical purity of the final compound was confirmed by optical rotation value $[\alpha]_D^{28}$ = +30.8 (c 1.1, $CHCl_3$), which was comparable with the literature value [14].

CONCLUSIONS

In summary, a practical enantioselective synthesis of potent calcimimetics (+)-NPS R-568 **1** has been achieved using palladium-catalyzed oxidative kinetic resolution of secondary benzylic alcohol with molecular oxygen and (-)-sparteine, as a source of chirality. The main advantages of this method are good enantioselectivity and ready availability of the catalyst. Moreover, the $PdCl_2$ catalyst can be regenerated and recycled.

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