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A dimethylzinc/diphenylphosphinoylimine approach to the asymmetric synthesis of the calcimimetic agent NPS R-568

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An asymmetric synthesis of the calcimimetic agent NPS R-568 using a (1*R*,2*S*)-*N*-benzylephedrine-promoted addition of dimethylzinc to a diphenylphosphinoylimine derived from 3-methoxybenzaldehyde is described. The enantiomeric ratio of the key amine fragment was determined to be 93 : 7 (86% ee), favoring the (*R*)-enantiomer by derivatization and chiral stationary phase HPLC analysis.

Supporting information may be found in the online version of this article.

Keywords: asymmetric addition; dimethylzinc; diphenylphosphinoylimine; NPS R-568; calcimimetic

Introduction

NPS R-568 (**1**), also known by the generic name of tecalcet and the tradename norcalcin, is an active calcimimetic agent of medicinal utility that was initially developed by NPS Pharmaceutics, Inc. in the early 1990s for the treatment of primary and secondary hyperparathyroidism (HPT) (Figure 1).[1] Primary hyperparathyroidism originates in the parathyroid gland and is often manifested through a parathyroid adenoma. In contrast, secondary hyperparathyroidism originates externally from this gland and is commonly associated with chronic renal failure. These two diseases are characterized by both elevated levels of plasma parathyroid hormone (PTH), a polypeptide containing 84 α-amino acid residues, and serum Ca^{2+}. PTH is a key endocrine regulator secreted from parathyroid cells. PTH acts on bone, kidney and the intestinal tract via the kidneys to release Ca^{2+} into the blood stream. Elevated levels of Ca^{2+} are detected by cell-surface Ca^{2+} receptors (i.e. seven transmembrane G-coupled receptors) on the cells of parathyroid glands. Activation of the Ca^{2+} receptor by these elevated levels of Ca^{2+} initiates a complex cellular response (involving the increase of intracellular Ca^{2+}) which ultimately results in the inhibition of PTH secretion from these cells. Thus, there is an inverse relationship between the concentration of extracellular Ca^{2+} and PTH which serves as the foundation for the regulation of bodily Ca^{2+} homeostasis.[2]

Calcimimetics, such as NPS R-568, are agonists and activate the Ca^{2+} receptor in a non-competitive fashion. They do not compete directly with Ca^{2+} that activates the receptor through binding in the extracellular domain of these receptors, but rather, calcimimetics such as NPS R-568, bind allosterically in the seven transmembrane to 'sensitize' the receptor to extracellular Ca^{2+}. Compounds of this type do not activate Ca^{2+} receptors in the absence of Ca^{2+}. In this context, enantiomerically enriched phenylalkyl amines, such as NPS R-568, have been found to activate the Ca^{2+} receptor in the presence of Ca^{2+} in bovine parathyroid cells, evidenced by increasing intracellular calcium and inhibiting the secretion of PTH. As such, calcimimetics have clinical utility in treating diseases such as primary and secondary HPT and therefore the subject of synthetic preparation. In this context, NPS R-568 is a phenylalkylamine that has been shown to be clinically effective[2] and the subject of synthetic preparation.[3–6] In particular, the asymmetric synthesis of this medicinal agent is of interest as it has been demonstrated that the (*R*)-enantiomer is considerably more active than the corresponding (*S*)-enantiomer.[2] The reported methods for the preparation of NPS R-568 vary in terms of synthetic design and asymmetric induction. The first literature report on the synthesis of NPS R-568 by Van Wagenen and coworkers was focused primarily on a coupling process that required the use of two equivalents of the chiral, non-racemic amine component for the synthesis of the calcimimetic agent from a diisobutylaluminum-imine complex.[3] Hansen and Buchwald developed a very efficient synthesis of NPS R-568 by using a chiral, non-racemic *ansa*-titanocene, ethylene bis(tetrahydroindenyl)titanium difluoride as a catalyst precursor in the hydrosilylation of an imine precursor to afford **1** (Scheme 1).[4]

Kibayashi and coworkers used an approach involving the use of a chiral oxime ether with methyllithium for the asymmetric induction process to form the amine component of the calcimimetic.[5] Khiar and coworkers pursued a similar pathway but employed a chiral *N*-isopropylsulfinylimine as the template forming the chiral amine.[6] Based on our ongoing interest in the use of *Ephedra* alkaloids in asymmetric synthesis, we became focused on developing an *N*-benzylephedrine promoted dimethylzinc addition to a diphenylphosphinoylimine. Herein, we report our efforts on the first diorganozinc approach to the synthesis of NPS R-568.

Results and Discussion

We initiated our work with the synthesis of the *N*-benzylephedrine (**7**) as the chiral agent for the promotion of the asymmet-

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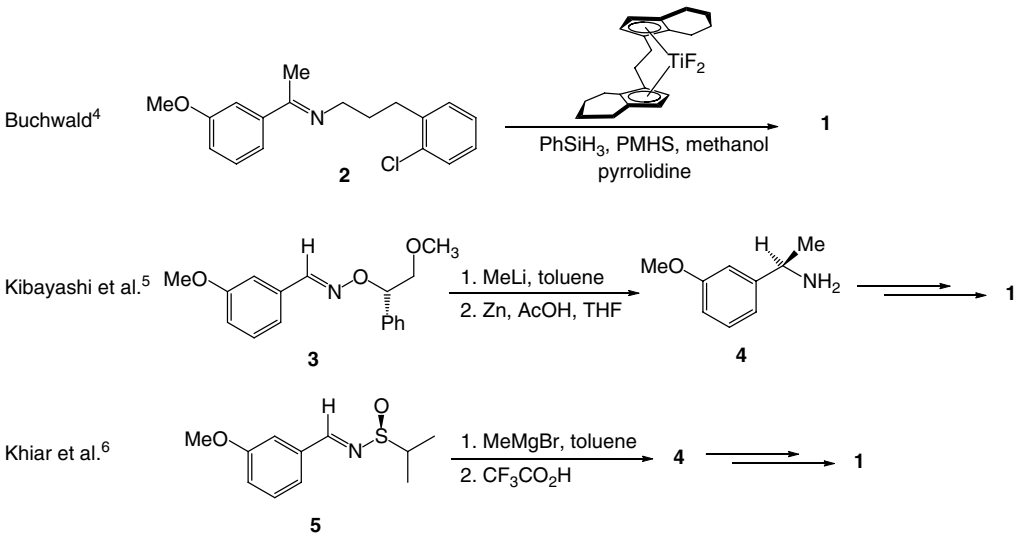


Scheme 1. Asymmetric syntheses of NPS R-568.

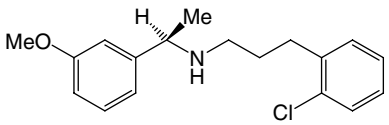


Figure 1. Calcimimetic agent NPS R-568 (**1**).[1,2]

ric addition reaction with dimethylzinc. *N*-Benzylephedrine was selected for its ease of preparation and successful application in diorganozinc reactions with aldehydes[7a] and with diphenylphosphinoylimines.[7b] Thus, (1*R*,2*S*)-ephedrine (**6**) was alkylated at nitrogen with benzyl bromide to afford **7** in 82% yield after chromatographic purification (Scheme 2). The requisite diphenyl phosphinoylimine **9** was prepared from 1-(3′-methoxyphenyl)-1-ethylamine using the method of Lovely and coworkers.[8] At this stage, the asymmetric addition of dimethylzinc to **9** was conducted with **7** to afford the addition product **10** in 81% yield with a enantiomeric ratio of 95.4 : 4.6 (*R* : *S*, ~90% ee) via proposed transition state **TS-9**. The addition product was then hydrolyzed with concentrated HCl in methanol to afford the key amine component of the calcimimetic agent in 84% yield. The specific rotation of the amine was determined to be $[\alpha]_D^{20} = +12.4$ (*c* 0.72, MeOH), lit. $[\alpha]_D^{20} = +23.6$ (*c* 0.8, MeOH);[5b] $[\alpha]_D^{20} = +17.6$ (*c* 2, MeOH).[9]

There was a concern that the measured specific rotation of **11** was not an accurate reflection of its enantiomeric purity. Thus, commercially available *rac*-1-phenyl-1-ethylamine and (*R*)-1-phenyl-1-ethylamine [*rac*-**12**/(*R*)-**12**] were each coupled with 2-chlorophenylpropanoic acid using EDC and DMAP (Scheme 3). The resultant amides [*rac*-**13**/(*R*)-**13**] were analyzed by chiral stationary phase (CSP) HPLC and it was determined that the (*R*)-enantiomer elutes first based on the comparison between the racemic mixture and the amide derived from the commercial (*R*)-amine.

With a reliable method for the analysis, the enantiomerically enriched 3′-methoxyphenyl-1-ethylamine (**11**) and its racemic variant (*rac*-**11**) were coupled with 2-chlorophenylpropanoic acid using EDC and DMAP (Scheme 4). The analysis of the resultant amides [*rac*-**13** and (*R*)-**13**] by CSP HPLC revealed that, by analogy with the analysis of **12**, the (*R*)-enantiomer eluted first and the ratio of enantiomers was 93 : 7 (86% ee).

The amide (*R*)-**14** was reduced using diisobutylaluminum hydride (Dibal-H) in dichloromethane as described in the experimental procedure established by Kibayashi and coworkers (Scheme 5).[5a] It was determined that the use of 4 equivalents of the reducing agent was optimal and in the case of (*R*)-**13** afforded the corresponding amine (*R*)-**15** in 60% yield after purification. Using these conditions on amide (*R*)-**14**, we were able to isolate the calcimimetic NPS R-568 (**1**) in 68% yield after chromatographic purification in ~86% ee based on the prior analysis of the amide precursor (*R*)-**14**. The specific rotation was determined to be $[\alpha]_D^{24} = +39.3$ (*c* 1.20, $CHCl_3$) [lit.[5b] $[\alpha]_D^{20} = +41.9$ (*c* 1.10, $CHCl_3$); lit.[4] $[\alpha]_D = +38.6$ (*c* 1.10, $CHCl_3$)].

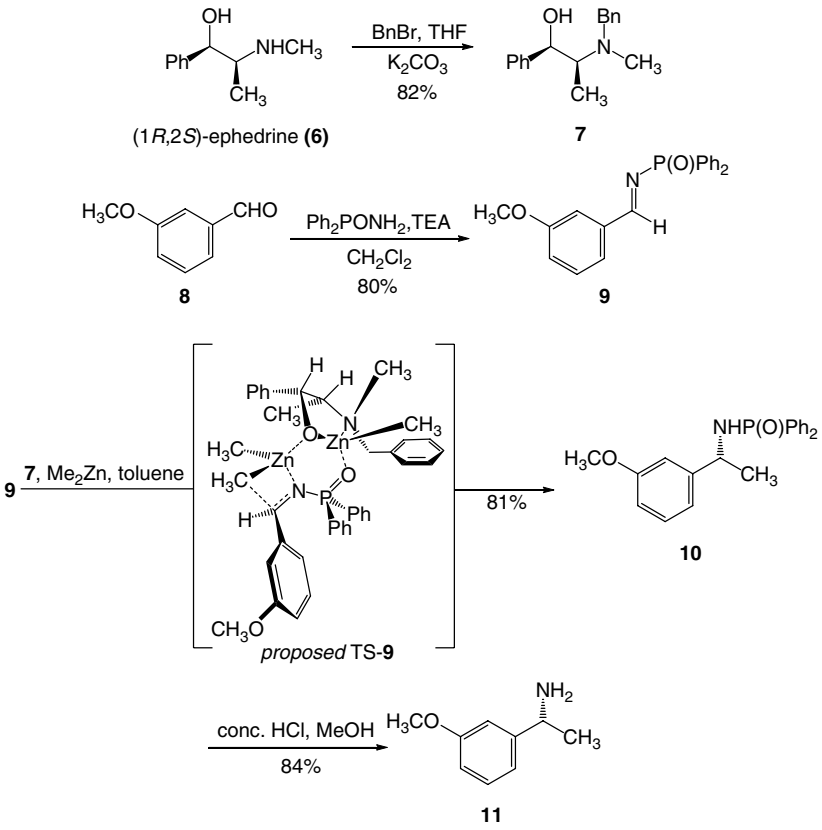
Conclusions

We have developed an asymmetric pathway to the synthesis of the clinically effective calcimimetic agent NPS R-568 through the use of an *N*-benzylephedrine promoted dimethylzinc addition to a phosphinoylimine. The hydrolysis of the diphenylphosphinoylamine yielded the key amine fragment in 86% ee, favoring the (*R*)-enantiomer as determined by analysis of the derivatized amine by CSP HPLC. This synthesis represents the first application of diorganozinc reagent to the preparation of NPS R-568.

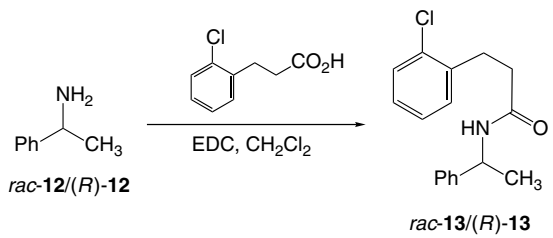
Experimental

General Remarks

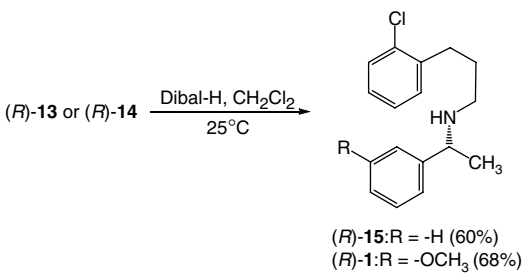
All reactions were run under a nitrogen atmosphere. Anhydrous toluene was purchased and stored under a nitrogen atmosphere. Dimethylzinc was purchased in 1.2 M solution in hexanes. Dichloromethane was purchased as an anhydrous reagent. All ^1H and ^{13}C NMR spectra were recorded on Varian spectrometer at 25 °C in $CDCl_3$ operating in 500 MHz and 125 MHz respectively. Chemical shifts are recorded in parts per million (δ scale), and the coupling constant (*J* values) are listed in hertz. Optical activities are measured using 589 nm using Jasco digital polarimeter. Infrared spectra were reported in reciprocal centimeters (cm^{-1}). Flash chromatography was conducted with an Analogix chromatograph. Mass spectral analyses



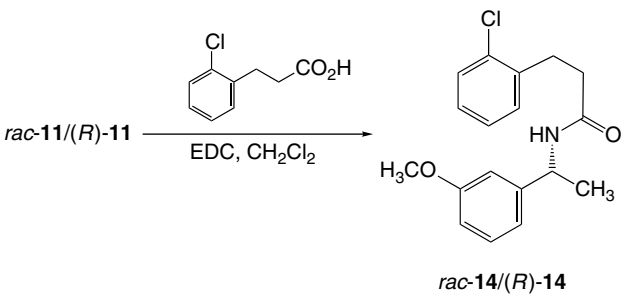
Scheme 2. Synthesis of the amine fragment of NPS R-568.



Scheme 3. Formation of racemic **13** and (*R*)-**13**.



Scheme 5. Synthesis of NPS R-568.



Scheme 4. Synthesis of racemic **14** and (*R*)-**14**.

were conducted by the mass spectrometry analytical laboratories of the University of Illinois at Urbana–Champaign using quadruple time of flight mass spectrometer hybrid with MS/MS capability. Enantiomeric ratios were determined using a Shimadzu HPLC with chiral stationary phase chiralcel AD column.

(1*R*,2*S*)-2-(Benzyl(methyl)amino)-1-phenyl-1-propanol (7)

The title compound was obtained from the alkylation of (1*R*,2*S*)-ephedrine with benzyl bromide (1.1 equiv.) dissolved in refluxing anhydrous THF and potassium carbonate (3 equiv.) in 82% yield as a colorless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.98 (3H, d, J = 6.9 Hz), 2.18 (3H, s), 2.91 (1H, dq, J = 6.9, 4.9 Hz), 3.57 (1H, d, J = 13.4 Hz), 3.63 (1H, d, J = 13.4 Hz), 4.85 (1H, d, J = 4.9 Hz), 7.21–7.32 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 38.5, 59.0, 63.3, 73.6, 126.1, 126.8, 127.9, 128.6, 139.4, 142.6. FT-IR (neat) 3081, 1599, 1061, 1006, 733, 700 cm^{-1}. $[\alpha]_D^{23}$ − 22.2 (*c* 1.03, CH_2Cl_2). HRMS $(M + H)^+$ calcd for $C_{17}H_{22}NO$: 256.3627; found: 256.3625. Anal. calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.30; found: C, 79.31; H, 8.46; N, 5.30. This material was identical to that of known literature examples.[8]

N-(3-Methoxybenzylidene)-P,P-diphenylphosphinic amide (9)

In a 250 ml round bottom flask were placed diphenylphosphinamide (3.00 g, 13.8 mmol) and dichloromethane (55 ml) and then cooled to 0 °C. At this point, triethylamine (5.80 ml, 41.3 mmol), titanium tetrachloride (0.90 ml, 8.3 mmol) and *m*-anisaldehyde (1.70 ml, 13.8 mmol) were added. The reaction mixture was allowed to warm to 25 °C and was stirred for 1.5 h and then gravity filtered to remove titanium dioxide. The filtrate was collected and the solvent was removed by rotary evaporation. The residue was treated with diethyl ether (40 ml) and filtered to remove triethylammonium chloride. The filtrate from this process was collected and the solvent was removed by rotary evaporation. The resultant yellow residue was purified by flash chromatography (hexanes : EtOAc, 4 : 6); yellow oil (80%). IR (nujol): 3100, 2998, 1600, 1200 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.85 (s, 3H), 7.09–7.12 (m, 1H), 7.43–7.58 (m, 9H) 7.92–7.96 (m, 4H), 9.29 (d, J_{PH} = 30.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ^{13}C–^{31}P coupling observed) 55.3, 113.5, 119.9, 123.5, 128.3, 128.4, 129.8, 131.4, 131.5, 131.6, 131.7, 132.2, 133.2, 136.9, 137.1, 159.9, 173.5, 173.6. ESI- HRMS calcd for $C_{20}H_{19}NO_2P$ ($M + H^+$): 336.1153. Found: 336.1148. Anal. calcd for $C_{18}H_{20}NOP \cdot 0.2\ CHCl_3$ (multiple analyses from different samples yielded results consistent with the presence of 0.2 equiv. of $CHCl_3$ for every 1 equiv. of the phosphinoylimine substrate): C, 67.54; H, 5.11; N, 3.90; found: C, 67.05; H, 5.17; N, 3.87.

(*R*)-*N*-(1-(3-Methoxyphenyl)ethyl)-P,P-diphenylphosphinic amide (10)

In a 100 ml round bottom flask were placed anhydrous toluene (7.5 ml), (1*R*,2*S*)-*N*-benzylephedrine (0.380 g, 1.49 mmol), *N*-(3-methoxybenzylidene)-P,P-diphenylphosphinic amide (9) (0.50 g, 1.5 mmol) and dimethylzinc (6.30 ml, 7.5 mmol). The reaction mixture stirred for 48 h and was quenched by the addition of an saturated aqueous solution of ammonium chloride (50 ml). The organic layer was diluted with ethyl acetate (50 ml), washed with brine (50 ml), and dried ($MgSO_4$). The solvents were removed via rotary evaporation and the product was purified by flash chromatography (hexanes : EtOAc, 4 : 6). Colorless oil (81%). $[\alpha]_D^{25}$ = +26.3 (*c* 1.03, $CHCl_3$). HPLC [Chiralcel AD coloumn, 80 : 20 (hexanes : isopropanol), 1.0 ml min^{-1}]: t_R = 7.0 min. and t_S = 10.3 min. IR (nujol): 3200, 3010, 2990, 1580, 1200 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.54 (d, J = 6.8 Hz, 3H), 3.45 (s, 1H), 3.75 (s, 3H), 4.31–4.38 (m, 1H), 6.75–6.88 (m, 1H), 7.19–7.47 (m, 9H), 7.79–7.91 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ^3C–^{31}P coupling observed): 25.9, 51.1, 55.2, 55.5, 111.8, 112.1, 118.1, 128.1, 128.2, 128.3, 129.4, 131.4, 131.5, 131.6, 1321.8, 132.3, 146.6, 146.7, 159.5. ESI-HRMS calcd for $C_{21}H_{23}NO_2P$ ($M + H^+$): 352.1466; found: 352.1463. Anal. calcd for $C_{21}H_{22}NO_2P$: C, 71.78; H, 6.31; N, 3.99; found: C, 71.79; H, 6.36; N, 4.17.

(*R*)-1-(3′-Methoxyphenyl)-1-ethylamine (11)

In a 100 ml round bottom flask were placed (*R*)-*N*-[1-(3-methoxyphenyl)ethyl]-P,P-diphenylphosphinic amide (**10**) (2.0 g, 5.7 mmol), methanol (40 ml) and concentrated HCl (10 ml) at room temperature. The reaction mixture stirred overnight at room temperature and was quenched by the addition of 1 M NaOH solution until the reaction mixture was completely neutralized as determined by the use of pH paper. Methanol was removed from the reaction mixture via rotary evaporation and the residue was reconstituted with dichloromethane (50 ml) was added. The solution was washed with brine (50 ml) and dried ($MgSO_4$). The solvent was evaporated via rotary evaporation. Colorless oil (84%). $[\alpha]_D^{25}$ = +15.6 (*c* 0.90, $CHCl_3$). IR (nujol): 3500, 3000, 2900, 1590, 1200, 760, 695 (cm^{-1}). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.38 (d, J = 6.7 Hz, 3H), 3.82 (s, 3H), 4.06–4.12 (m, 1H) 6.77–6.79 (m, 1H), 6.91–6.93 (m, 1H) and 7.23–7.26 (m, 2H). The protons associated with the amino group (-NH_2) were not observed. ^{13}C NMR (125 MHz, $CDCl_3$): 25.6, 51.3, 55.2, 111.4, 112.0, 118.0, 129.5, 149.6, 159.8. ESI-HRMS calcd for $C_9H_{14}NO$ ($M + H^+$): 152.1075; found: 152.1070. Anal. calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; found: C, 71.35; H, 8.71; N, 8.52.

(*R*)-3-(2-Chlorophenyl)-*N*-(1-phenylethyl)propanamide (13)

In a 250 ml round bottom flask were placed dichloromethane (17 ml), EDC (1.2 g, 5.5 mmol), 4-dimethylaminopyridine (0.12 g, 1.1 mmol) and 3-(2-chlorophenyl)propanoic acid (1.0 g, 5.5 mmol). The reaction mixture was stirred for 30 min. Commercially available (*R*)-1-(phenyl)-1-ethylamine (0.70 ml, 5.5 mmol) was then added to the reaction mixture. The reaction mixture was stirred overnight at room temperature and quenched with an aqueous 1 M HCl solution (50 ml). The reaction mixture was diluted with dichloromethane (50 ml), washed with brine (50 ml), and dried ($MgSO_4$). The solvent was removed via rotary evaporation and the product was purified by flash chromatography (hexanes : EtOAc, 8 : 2). White solid (74%). M.p.: 102–104 °C. $[\alpha]_D^{25}$ = +39.8 (*c* 0.90, $CHCl_3$). HPLC (Chiralcel AD column, 95 : 5 (hexanes : isopropanol), 1.0 ml min^{-1}): t_R = 12.9 min. and t_S = 19.9 min. IR (nujol): 3300, 2990, 1600, 790, 650 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.40 (d, J = 7.0 Hz, 3H), 2.43–2.53 (m, 2H), 3.06 (t, J = 7.5 Hz, 2H), 5.08 (p, J = 7.0 Hz, 1H), 5.78 (s, 1H), 7.12–7.32 (m, 9H). ^{13}C NMR (125 MHz $CDCl_3$): 21.6, 29.6, 36.3, 48.6, 126.0, 126.9, 127.2, 127.7, 128.5, 129.4, 130.8, 133.7, 138.2, 143.0, 170.8. ESI- HRMS calcd for $C_{17}H_{19}NOCl$ ($M + H^+$): 288.1155; found: 288.1159. Anal. calcd for $C_{17}H_{19}NOCl$: C, 70.95; H, 6.30; N, 4.87; found: C, 69.75; H, 6.13; N, 4.91. The racemic mixture of **13** was prepared in the same fashion had the same physical properties as (*R*)-**13** with the exception of polarimetry.

(*R*)-3-(2-Chlorophenyl)-*N*-(1-(3′-methoxyphenyl) ethyl)propanamide (14)

In a 100 ml round bottom flask were placed dichloromethane (9.3 ml), EDC (0.590 g, 3.08 mmol), 4-dimethylaminopyridine (0.068 g, 0.56 mmol) and 3-(2-chlorophenyl)propanoic acid (0.517 g, 2.80 mmol). The reaction mixture was stirred for 30 min. and (*R*)-1-(3′-methoxy phenyl)ethylamine (**11**) (0.423 g, 2.80 mmol) was added to the reaction mixture. The reaction mixture was stirred overnight at room temperature and quenched with an aqueous solution 1 M HCl solution (50 ml). The reaction mixture was diluted with dichloromethane (50 ml), washed with brine (50 ml) and dried ($MgSO_4$). The solvent was removed via rotary evaporation and the product was purified by flash chromatography (hexanes: EtOAc, 8 : 2). White solid (66%). M.p.: 86–88 °C. $[\alpha]_D^{24}$ = +34.9 (*c* 1.20, $CHCl_3$). HPLC (Chiralcel AD column, 95 : 5 (hexanes: IPA), 1.0 ml min^{-1}): t_R = 17.4 min and t_S = 24.7 min. IR (nujol): 3200, 2990, 1650, 1200 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.39 (d, J = 7.0 Hz, 3H), 2.48 (td, J = 7.6 Hz, 2.2 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 3.77 (s, 3H), 5.05 (p, J = 7.0 Hz, 1H), 5.76 (s, 1H), 6.76–6.80 (m, 3H), 7.11–7.15 (m, 2H), 7.19–7.22 (m, 1H), 7.29–7.33 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 21.6, 29.5, 36.2, 48.6, 55.1, 112.1, 112.3, 118.3, 126.8, 127.7, 129.3, 129.5, 130.7, 133.6,

138.2, 144.8, 159.7, 170.8. ESI- HRMS calcd for $C_{18}H_{21}NO_2Cl$ (M + H^+): 318.1261; found: 318.1266. Anal. calcd for $C_{18}H_{20}NO_2Cl$: C, 68.03; H, 6.34; N, 4.41; found: C, 67.62; H, 6.46; N, 4.51. The racemic mixture of **14** was prepared in the same fashion had the same physical properties as (*R*)-**14** with the exception of polarimetry.

(*R*)-3-(2-Chlorophenyl)-*N*-(1-phenylethyl)propylamine (15)

In a 100 ml round bottom flask were placed (*R*)-3-(2-chlorophenyl)-*N*-(1-phenylethyl) propanamide (**13**) (0.308 g, 1.07 mmol) and dichloromethane (4.0 ml). To this mixture was added dibal-H (4.30 ml, 1.0 M in toluene, 4.30 mmol). The reaction mixture stirred for 18 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 × 25 ml), extracted with dichloromethane (2 × 25 ml) washed with brine (25 ml) and dried ($MgSO_4$). The solvent was removed via rotary evaporation and the product was purified by flash chromatography (hexanes: EtOAc, 9 : 1). Yellow oil (60%). $[\alpha]_D^{24} = +38.8$ (*c* 0.70, $CHCl_3$). IR (nujol): 3200, 3100, 2990, 1498, 790, 650 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.34 (d, $J = 6.6$ Hz, 3H), 1.70–1.83 (m, 2H), 2.46–2.58 (m, 2H), 2.65–2.78 (m, 2H), 3.75 (q, $J = 6.6$ Hz, 1H), 7.06–7.31(m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 24.3, 30.1. 31.2, 47.2, 58.2, 126.5, 126.6, 126.7, 127.1, 128.3, 129.3, 130.2, 133.8, 139.7, 145.8. ESI-HRMS calcd for $C_{17}H_{21}NCl$ (M + H^+): 274.1363; found: 274.1361. Anal. calcd for $C_{17}H_{20}NCl$: C, 74.57; H, 7.36; N, 5.12; found: C, 74.10; H, 7.34; N, 5.00.

(*R*)-3-(2-Chlorophenyl)-*N*-(1-(3′-methoxyphenyl) ethyl)propylamine (1)

In a 100 ml round bottom flask were placed (*R*)-3-(2-chlorophenyl)-*N*-[1-(3-methoxy phenyl)ethyl]propanamide (**14**) (0.120 g, 0.378 mmol) and dichloromethane (1.3 ml). To the reaction mixture was added dibal-H (1.51 ml, 1.51 mmol) and the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 × 25 ml), extracted with dichloromethane (2 × 25 ml), washed with brine (25 ml), and dried ($MgSO_4$). The solvent was removed via rotary evaporation and the product was purified by flash chromatography (hexanes : EtOAc, 9 : 1). Clear oil (68%). $[\alpha]_D^{24} = +39.3$ (*c* 1.20, $CHCl_3$). IR (nujol): 3300, 3010, 2990, 1610, 1200, 720, 690 (cm^{-1}). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.33 (d, $J = 6.6$ Hz, 3H), 1.70–1.83 (m, 2H), 2.47–2.58 (m, 2H), 2.65–2.79 (m, 2H), 3.73 (q, $J = 6.6$ Hz, 1H), 3.78 (s, 3H), 6.75–6.77 (m, 1H), 6.8–6.89 (m, 2H), 7.05–7.29 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 24.4, 30.3, 31.4, 47.3, 55.2, 58.3, 11.9, 112.0, 118.9, 126.6, 127.1, 129.2, 129.3, 130.2, 133.7, 139.6, 147.6 and 159.7. ESI-HRMS calcd for $C_{18}H_{23}NOCl$ (M + H^+): 304.1468; found: 304.1472. Anal. calcd for $C_{18}H_{22}NClO$: C, 71.16; H, 7.30; N, 4.61; found: C, 70.29; H, 7.42; N, 4.55.

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Supporting information

Supporting information may be found in the online version of this article.

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