



Studies on Diastereofacial Selectivity of a Chiral *tert*-Butanesulfinimines for the Preparation of (S)-3-Methyl-1-(2-piperidin-1-yl-phenyl)butylamine for the Synthesis of Repaglinide

PERIYANDI NAGARAJAN^{1,2,*}, CHINNAPILLAI RAJENDIRAN¹, A. NAIDU² and P.K. DUBEY²

¹Suven Life Sciences Ltd., R & D Center, Plot No.18, Phase-III, IDA, Jeedimetla, Hyderabad-500 055, India

²Department of Chemistry, J.N.T. University, Hyderabad-500 085, India

*Corresponding author: Fax: +91 40 23193541; Tel: +91 40 32921690; E-mail: nagarajan@suven.com

(Received: 25 March 2013;

Accepted: 25 September 2013)

AJC-14175

A new method for the asymmetric synthesis of a series of chiral amines including (S)-3-methyl-1-(2-piperidin-1-yl-phenyl)butylamine (**2a**) a key intermediate to prepare antidiabetic drug repaglinide by using Ellman's reagent *tert*-butanesulfinamide. Diastereoselective addition of organometallic reagents to *t*-butanesulfinimines and followed by acidic and basic treatment. The obtained chiral amines were characterized by NMR, MS and other analytical data.

Key Words: R(+)-*tert*-butanesulfinamide, S(-)-*tert*-butanesulfinamide, 2-Piperidin-1-yl-benzaldehyde, Titanium tetraethoxide.

INTRODUCTION

Repaglinide¹, S(+)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}aminocarbonylmethyl]benzoic acid (**1**) (Fig. 1) is a pharmacologically active enantiomer which is marketed by Boehringer Ingelheim. Repaglinide is a known non-sulfonyl urea hypoglycemic agent, which has an insulinotropic effect by blocking the K_{ATP} channels of pancreatic β -cells. It is particularly lowering the blood glucose levels in patients suffering from type II diabetes mellitus (NIDDM)²⁻⁵.

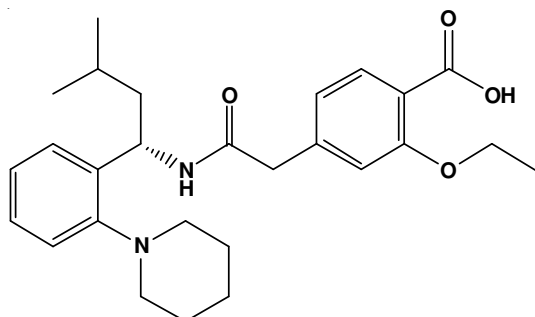


Fig. 1. Structure of S(+)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}aminocarbonylmethyl]benzoic acid

The (S)-3-methyl-1-(2-piperidin-1-yl-phenyl)butylamine (**2a**) a subunit of repaglinide is a chiral molecule having chiral centre alpha to the nitrogen atom has not been documented its preparation by simple and economical methods though there

are several methods known in the literature⁶⁻¹⁰ (Fig. 2). In order to find a simple and viable method, an extensive efforts have been focused on synthesis of (S)-chiral amine (**2a**) using Ellman's reagent *tert*-butanesulfinamide¹¹ by nucleophilic addition of organometallic reagents followed by amine liberation. To our surprise it was found that from the same single source of sulfinimine (**5a**) by changing the anion source one could get both isomers of the amine (**2a** and **8a**).

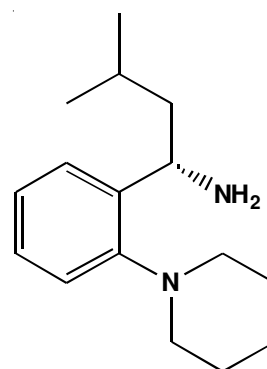


Fig. 2. Structure of (S)-3-methyl-1-(2-piperidin-1-yl-phenyl)butylamine

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectrum were recorded as Neat or KBr using Perkin-Elmer 2000 FT-TR

spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker 400 MHz and ARX-200, respectively with Tetramethylsilane as internal standard (Chemical shifts in δ ppm). Solvents and reagents were used directly from the manufacturer, or purified when required by standard procedures.

General procedure for making sulfinimines: To a stirred solution of aldehydes (**3a-g**) and R(+)-*tert*-butanesulfinamide (**4**) (1.1 eq.) in THF at room temperature, was added titanium tetraethoxide (2.0 eq.). The mixture was heated to 60-65 °C for 5-10 h. Cooled the reaction mass and added saturated sodium chloride solution. Filtered the reaction mass through celite and the aqueous layer was extracted with ethyl acetate. The organic layer was concentrated and purified through column chromatography.

2-Methyl-propane-2-sulfinic acid [1-(2-piperidin-1-yl-phenyl)methylidene]amide (5a): Yield: 79 %; ^1H NMR (CDCl_3): δ 8.97 (s,1H), 7.92-7.94 (dd, 1H, $J = 1.2$, 7.0Hz), 7.41-7.45 (m,1H), 7.05-7.09 (t, 2H, $J = 8.2$ Hz), 2.94-2.96 (t,4H, $J = 5.27$ Hz), 1.74-1.80 (m,4H), 1.57-1.61 (m,2H), 1.27(s, 9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): δ 161.37, 155.43, 132.75, 128.54, 127.25, 122.10, 118.96, 57.49, 55.03(2C), 26.01(2C), 23.98, 22.48 (3C); IR (KBr, ν_{max} , cm^{-1}): 2936, 1603, 1588, 1455, 1356, 1346, 1286, 1228, 1080, 776; MS (m/z) = 293.3 $[\text{M} + 1]^+$; MR: 81.5-82.0 °C.

2-Methyl-propane-2-sulfinic acid [(1-phenyl)methylidene]amide (5b): Yield : 61.5 %; ^1H NMR (CDCl_3): δ 8.55 (s,1H), 7.80-7.82 (d, 2H, $J = 7.3$ Hz), 7.41-7.47 (m, 3H), 1.23 (s,9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): δ 162.53, 133.89, 132.26, 129.18(2C), 128.77(2C), 57.50, 22.42(3C); IR (Neat, ν_{max} , cm^{-1}): 2978, 2961, 1606, 1574, 1450, 1363, 1216, 1086, 759, 731, 691; MS (m/z) = 210.2 $[\text{M} + 1]^+$.

2-Methyl-propane-2-sulfinic acid [1-(2-chloro-1-yl-phenyl)methylidene]amide (5c): Yield: 64.6 %; ^1H NMR (CDCl_3): δ 9.00 (s,1H), 8.00-8.02 (d, 1H, $J = 7.5$ Hz), 7.35-7.38 (m,2H), 7.28-7.31(m,1H), 1.22(s, 9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): δ 159.55, 136.31, 133.06, 131.16, 130.15, 129.05, 127.00, 57.81, 22.51(3C); IR (Neat, ν_{max} , cm^{-1}): 2960, 2926, 1590, 1568, 1457, 1363, 1223, 1085, 760, 716; MS (m/z) = 244.2 $[\text{M} + 1]^+$.

2-Methyl-propane-2-sulfinic acid [1-(2-methyl-1-yl-phenyl)methylidene]amide (5d): Yield: 55.95 %; ^1H NMR (CDCl_3): δ 8.85 (s,1H), 7.89-7.91 (d, 1H, $J = 7.64$ Hz), 7.37-7.40(t,1H, $J = 7.3$ Hz), 7.29-7.31 (d, 1H, $J = 7.5$ Hz), 7.24-7.26 (d, 1H, $J = 7.6$ Hz), 2.60 (s,3H), 1.27 (s, 9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): δ 161.62, 139.38, 132.04, 131.92, 131.27, 129.40, 126.24, 57.44, 22.47(3C), 19.85; IR (Neat, ν_{max} , cm^{-1}): 2961, 2927, 2868, 1591, 1568, 1457, 1363, 1288, 1224, 1182, 1160, 1085, 758, 717; MS (m/z) = 224.2 $[\text{M} + 1]^+$.

2-Methyl-propane-2-sulfinic acid [1-(2-tolyl)phenyl-methylidene]amide (5e): Yield: 92.5%; ^1H NMR (CDCl_3): δ 8.67 (s,1H), 8.15-8.14(d,1H, $J = 7.5$ Hz), 7.51-7.55 (m, 1H), 7.41-7.46 (m, 2H), 7.20-7.28 (m, 4H), 2.40 (s, 3H), 1.27 (s, 9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): δ 162.36, 144.58, 137.72, 135.55, 131.68, 131.61, 130.58, 129.93(2C), 129.16 (2C), 127.85, 127.33, 57.72, 22.55 (3C), 21.09; IR (KBr, ν_{max} , cm^{-1}): 2974, 2922, 1692, 1589, 1474, 1086, 820, 776, 757; MS (m/z) = 300.2 $[\text{M} + 1]^+$.

2-Methyl-propane-2-sulfinic acid [1-(2-methoxy-phenyl)methylidene]amide (5f): Yield: 60 %; ^1H NMR

(CDCl_3): δ 9.06 (s,1H), 7.97-7.99((dd, 1H, $J = 1.2$, 8.0Hz), 7.44-7.48 (m, 1H), 6.94-7.02 (m,2H), 3.86 (s, 3H), 1.25(s, 9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): δ 159.52, 158.63, 133.86, 128.08, 122.62, 120.54, 111.30, 57.50, 55.40, 22.51 (3C); IR (Neat, ν_{max} , cm^{-1}): 2960, 2841, 1595, 1571, 1487, 1465, 1362, 1352, 1287, 1251, 1161, 1082, 757, 721; MS (m/z) = 240.4 $[\text{M} + 1]^+$.

2-Methyl-propane-2-sulfinic acid [1-(4-piperidin-1-yl-phenyl)methylidene]amide (5g): Yield: 84.4 %; ^1H NMR (CDCl_3): δ 8.40(s,1H), 7.66-7.68 (d, 2H, $J = 8.2$ Hz), 6.84-6.86 (d, 2H, $J = 8.2$ Hz), 3.30 (br, 4H), 1.61 (br, 6H), 1.21(s,9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): 161.42, 153.98, 131.04(2C), 123.60, 113.93(2C), 57.24, 48.59(2C), 25.24(2C), 24.22, 22.42(3C); IR (KBr, ν_{max} , cm^{-1}): 2931, 1606, 1583, 1552, 1516, 1354, 1235, 1186, 1125, 1081, 822, 747; MS (m/z) = 293.2 $[\text{M} + 1]^+$; MR: 146.4-147.9 °C.

2-Methyl-propane-2-sulfinic acid [1-(2-piperidin-1-yl-phenyl)methylidene]amide (10): Followed the above general procedure by using 2-piperidin-1-yl benzaldehyde (**3a**) and S(-)-*tert*-butanesulfinamide (**9**). Yield: 75.0 %; ^1H NMR (CDCl_3): δ 8.97 (s,1H), 7.92-7.94 (dd, 1H, $J = 1.0$, 7.6Hz), 7.41-7.43 (m, 1H), 7.05-7.09 (t, 2H, $J = 8.0$ Hz), 2.94-2.96 (t,4H, $J = 5.26$ Hz), 1.74-1.80 (m,4H), 1.57-1.61 (m, 2H), 1.27 (s, 9H, $-\text{CH}_3$); ^{13}C NMR (CDCl_3): δ 161.37, 155.43, 132.75, 128.54, 127.25, 122.11, 118.96, 57.48, 55.03(2C), 26.01(2C), 23.98, 22.48 (3C); IR (KBr, ν_{max} , cm^{-1}): 2936, 1603, 1588, 1455, 1356, 1346, 1286, 1228, 1080, 776; MS (m/z) = 293.4 $[\text{M} + 1]^+$; MR: 80.5-81.8 °C.

General procedure for the reaction of Grignard reagent with sulfinimines: Prepared the Grignard reagents from 1-bromo-2-methylpropane (3.0 eq.) using magnesium (3.1 eq.) in THF. To a stirred solution of sulfinimines (**5a-g**) (1.0 eq.) in MDC at -40 to -50 °C, was added the above prepared Grignard reagent. The mixture was stirred for 1 h and warmed to room temperature.

The above reaction mass was quenched in to 15 % HCl solution and stirred at room temperature. Separated the organic layer and the aqueous layer was basified and extracted in MDC. The organic extracts were washed with water and concentrated to get the product and purified through column chromatography.

(S)-3-Methyl-1-(2-piperidin-1-yl-phenyl)butylamine (2a): Yield: 33.7 %; ^1H NMR (CDCl_3): δ 7.32-7.34 (m, 1H), 7.09-7.22 (m, 3H), 4.46-4.50 (t, 1H, $J = 6.8$ Hz), 2.80-2.86 (m, 4H), 1.71-1.77 (m, 4H), 1.50-1.60 (m, 7H), 0.94-0.97 (t, 6H, $J = 6.5$ Hz); ^{13}C NMR (CDCl_3): δ 152.18, 142.74, 127.04, 126.28, 124.35, 120.89, 54.86, 48.54(2C), 47.58, 26.59(2C), 25.27, 24.21, 23.11, 22.36; IR (Neat, ν_{max} , cm^{-1}): 2933, 2866, 2795, 1596, 1487, 1466, 1449, 1381, 1220, 921, 752; MS (m/z) = 247.5 $[\text{M} + 1]^+$; SOR (C = 1 % in methanol at 20 °C): + 6.9°.

3-Methyl-1-phenylbutylamine (2b): Yield: 38.6%; ^1H NMR (CDCl_3): δ 7.22-7.33 (m,5H), 3.94-3.97 (t, 1H, $J = 6.5$ Hz), 1.97 (br, s, 2H), 1.51-1.59 (m, 3H), 0.89-0.93 (m, 6H); ^{13}C NMR (CDCl_3): δ 146.68, 128.53, 126.75, 126.18, 54.00, 48.76, 24.97, 22.72, 22.42; IR (Neat, ν_{max} , cm^{-1}): 2955, 2926, 2869, 1655, 1602, 1492, 1466, 1453, 1384, 1366, 757, 700; MS (m/z) = 164.2 $[\text{M} + 1]^+$.

3-Methyl 1-(2-chlorophenyl)butylamine (2c): Yield: 44.4 %; $^1\text{H NMR}$ (CDCl_3): δ 7.46-7.48 (d, 1H, $J = 7.7\text{Hz}$), 7.32-7.34 (d, 1H, $J = 7.9\text{Hz}$), 7.25-7.28 (t, 1H, $J = 7.3\text{Hz}$), 7.14-7.18 (m, 1H), 4.45-4.48 (q, 1H, $J = 5.8, 8.1\text{Hz}$), 2.04 (br, s, 2H), 1.52-1.83 (m, 3H), 0.93-0.97 (dd, 6H, $J = 6.5, 11.4, \text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): δ 143.51, 132.66, 129.46, 127.72, 127.06, 126.99, 49.84, 46.96, 25.10, 23.16, 21.90; IR (Neat, ν_{max} , cm^{-1}): 2955, 2928, 2869, 1593, 1572, 1468, 1439, 1385, 1367, 1048, 1035, 754, 694; MS (m/z) = 198.3 $[\text{M} + 1]^+$.

3-Methyl-1-*o*-tolyl-butylamine (2d): Yield: 37.8 %; $^1\text{H NMR}$ (CDCl_3): δ 7.45-7.47 (d, 1H, $J = 7.57\text{Hz}$), 7.14-7.22 (m, 3H), 4.30-4.33 (t, 1H, $J = 6.4\text{Hz}$), 3.95 (br, s, 2H), 2.36 (s, 3H), 1.58-1.71 (m, 3H), 0.90-0.94 (dd, 6H, $J = 5.5, 10.9\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): δ 141.50, 134.92, 130.45, 127.03, 126.48, 125.27, 49.08, 46.40, 24.93, 22.96, 22.16, 19.24; IR (Neat, ν_{max} , cm^{-1}): 2955, 2927, 2868, 1600, 1464, 1384, 1367, 1049, 754, 726; MS (m/z) = 178.3 $[\text{M} + 1]^+$.

3-Methyl-1-(4-piperidin-1-yl-phenyl)butylamine (2g): Yield: 35.5 %; $^1\text{H NMR}$ (CDCl_3): δ 7.17-7.19 (d, 2H, $J = 8.2\text{Hz}$), 6.89-6.91 (d, 2H, $J = 8.2\text{Hz}$), 3.90-3.93 (t, 1H, $J = 7.2\text{Hz}$), 3.13 (br, 4H), 2.78 (br, s, 2H), 2.00 (s, 2H), 1.40-1.51 (m, 9H), 0.87-0.90 (t, 6H, $J = 7.5\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): 151.62, 131.68, 127.51(2C), 116.26(2C), 53.17, 50.31(2C), 45.53, 25.70(2C), 24.63, 24.16, 22.84, 21.88; IR (KBr, ν_{max} , cm^{-1}): 2632, 1614, 1577, 1521, 1401, 1238, 1130; MS (m/z) = 247.4 $[\text{M} + 1]^+$.

(R)-3-Methyl-1-(2-piperidin-1-yl-phenyl)butylamine (8a) (from 10): Yield: 35.6 %; $^1\text{H NMR}$ (CDCl_3): δ 7.33-7.35 (m, 1H), 7.08-7.20 (m, 3H), 4.46-4.49 (t, 1H, $J = 6.8\text{Hz}$), 2.80-2.86 (m, 4H), 1.71-1.73 (m, 4H), 1.50-1.70 (m, 7H), 0.93-0.96 (t, 6H, $J = 6.3\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): δ 152.19, 142.78, 127.03, 126.27, 124.34, 120.90, 54.86, 48.53(2C), 47.58, 26.58(2C), 25.27, 24.20, 23.10, 22.34; IR (Neat, ν_{max} , cm^{-1}): 2934, 2866, 2798, 1597, 1487, 1466, 1449, 1381, 1220, 921, 752; MS (m/z) = 247.5 $[\text{M} + 1]^+$; SOR (C = 1 % in methanol at 20°C): - 8.0°.

General procedure for the reaction of organolithium reagents with sulfinimines: Added slowly of 1-bromo-2-methylpropane (6 eq.) in diethyl ether to lithium metal (9.0 eq.) in diethyl ether at -10 to -15 °C over the period of 1 h. Stirred for 1 h to get clear solution. Cooled the mass further to -45 to -60 °C and added slowly sulfinimines (**5a-g**) (1.0 eq) in THF at -45 to -60 °C. The mixture was stirred for 1 h.

The above reaction mass was quenched in to 15 % HCl solution and stirred for 1 h at room temperature. Separated the organic layer and washed with toluene. The aqueous layer was basified and extracted in toluene. The organic extracts were washed with water, concentrated and purified through column chromatography.

(R)-3-Methyl-1-(2-piperidin-1-yl-phenyl)butylamine (8a): Yield: 55.6 %; $^1\text{H NMR}$ (CDCl_3): δ 7.33-7.35 (m, 2H), 7.09-7.21 (m, 3H), 4.46-4.50 (t, 6H, $J = 6.9\text{Hz}$), 2.80-2.86 (m, 4H), 1.71-1.73 (m, 4H), 1.50-1.61 (m, 5H), 0.93-0.96 (t, 6H, $J = 6.3\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): δ 152.18, 142.86, 127.01, 126.25, 124.32, 120.87, 54.86, 48.58(2C), 47.55, 26.57(2C), 25.27, 24.20, 23.11, 22.34; IR (Neat, ν_{max} , cm^{-1}): 2933, 2866, 2796, 1597, 1487, 1466, 1449, 1381, 1220, 922, 753; MS (m/z) = 247.5 $[\text{M} + \text{H}]^+$; SOR (1 % in methanol at 20 °C): - 4.2°.

3-Methyl-1-phenylbutylamine (8b): Yield: 51 %; $^1\text{H NMR}$ (CDCl_3): δ 7.23-7.34 (m, 5H), 3.93-3.97 (t, 1H, $J = 6.1\text{Hz}$), 1.96 (br, s, 2H), 1.54-1.59 (m, 3H), 0.91-0.93 (m, 6H); $^{13}\text{C NMR}$ (CDCl_3): δ 146.68, 128.50, 126.77, 126.21, 53.98, 48.71, 24.97, 22.54, 22.42; IR (Neat, ν_{max} , cm^{-1}): 2955, 2927, 1655, 1602, 1492, 1466, 1453, 1384, 1366, 757, 700; MS (m/z) = 164.2 $[\text{M} + 1]^+$.

3-Methyl 1-(2-chlorophenyl)butylamine (8c): Yield: 61.6 %; $^1\text{H NMR}$ (CDCl_3): δ 7.45-7.47 (d, 1H, $J = 7.0\text{Hz}$), 7.29-7.31 (d, 1H, $J = 7.9\text{Hz}$), 7.21-7.25 (t, 1H, $J = 7.3\text{Hz}$), 7.08-7.19 (m, 1H), 4.43-4.47 (q, 1H, $J = 5.9, 8.0\text{Hz}$), 2.23 (br, s, 2H), 1.51-1.81 (m, 3H), 0.91-0.95 (dd, 6H, $J = 6.45, 10.75\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): δ 143.51, 132.67, 129.47, 127.73, 127.06, 126.97, 49.85, 46.96, 25.17, 23.16, 21.90; IR (Neat, ν_{max} , cm^{-1}): 2956, 2929, 1594, 1468, 1438, 1385, 1367, 1035, 754; MS (m/z) = 198.3 $[\text{M} + 1]^+$.

3-Methyl-1-*o*-tolyl-butylamine (8d): Yield: 40.3 %; $^1\text{H NMR}$ (CDCl_3): δ 7.46-7.48 (d, 1H, $J = 7.1\text{Hz}$), 7.14-7.20 (m, 3H), 4.80 (br, s, 2H), 4.34 (br, 1H), 2.37 (s, 3H), 1.58-1.71 (m, 3H), 0.90-0.93 (7, 6H, $J = 6.3\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): δ 140.53, 135.03, 130.50, 127.23, 126.52, 125.37, 49.15, 45.91, 24.86, 22.84, 22.19, 19.26; IR (Neat, ν_{max} , cm^{-1}): 2957, 2930, 1465, 1385, 1368, 1216, 756; MS (m/z) = 178.3 $[\text{M} + 1]^+$.

3-Methyl-1-(4-piperidin-1-yl-phenyl)butylamine (8g): Yield: 41.5 %; $^1\text{H NMR}$ (CDCl_3): δ 7.19-7.21 (d, 2H, $J = 8.4\text{Hz}$), 6.88-6.90 (d, 2H, $J = 8.5\text{Hz}$), 5.37 (br, 2H), 3.91-3.95 (t, 1H, $J = 7.45\text{Hz}$), 3.12-3.15 (t, 4H, $J = 5.3\text{Hz}$), 1.86 (s, 2H), 1.43-1.86 (m, 9H), 0.85-0.89 (dd, 6H, $J = 6.7, 9.1\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): 151.69, 130.70, 127.67(2C), 116.21(2C), 53.10, 50.26(2C), 44.97, 25.68(2C), 24.53, 24.16, 22.93, 21.71; IR (KBr, ν_{max} , cm^{-1}): 2931, 1614, 1577, 1521, 1401, 1238, 1130; MS (m/z) = 247.4 $[\text{M} + 1]^+$; MR: 148.6-152.1 °C.

(S)-3-Methyl-1-(2-piperidin-1-yl-phenyl)butylamine (2a) (from 10): Yield: 58.3 %; $^1\text{H NMR}$ (CDCl_3): δ 7.33-7.35 (m, 1H), 7.09-7.22 (m, 3H), 4.47-4.50 (t, 1H, $J = 6.8\text{Hz}$), 2.80-2.86 (m, 4H), 1.71-1.75 (m, 4H), 1.50-1.64 (m, 7H), 0.94-0.97 (t, 6H, $J = 6.4\text{Hz}$); $^{13}\text{C NMR}$ (CDCl_3): δ 152.17, 142.82, 127.02, 126.26, 124.33, 120.87, 54.86, 48.58(2C), 47.55, 26.59 (2C), 25.27, 24.21, 23.12, 22.35; IR (Neat, ν_{max} , cm^{-1}): 2933, 2866, 2796, 1597, 1487, 1466, 1449, 1381, 1220, 921, 752; MS (m/z) = 247.5 $[\text{M} + 1]^+$; SOR (C = 1 % in methanol at 20 °C): +4.5°.

Preparation of repaglinide

Synthesis of (S)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}aminocarbonylmethyl]benzoic acid ethyl ester (14): To a stirred solution of 2.25 g of 3-ethoxy-4-ethoxycarbonyl phenylacetic acid (**13**) (8.92 mmol) and 2.5 g of *N*-methyl morpholine (24.33 mmol) in 20 mL of MDC at 0-5 °C, was added 1.12 g of pivaloyl chloride (9.32 mmol) slowly at below 5 °C. After 1.0 h stirring, 2.0 g amine **2a** (8.11 mmol) in 10.0 mL of MDC was added slowly at 0-5 °C. Warmed the mass to room temperature and stirred for 15.0 h. Quenched the reaction by adding water and separated the organic layer. The organic later was washed with 5 % HCl solution, 5 % NaOH solution and water. Concentrated the organic layer gave 3.5 g of **14** was obtained in 89.6 % yield as off white solid.

$^1\text{H NMR}$ (CDCl_3): δ 7.73-7.75 (d, 1H, $J = 7.76\text{Hz}$), 7.17-7.26 (m, 2H), 7.02-7.08 (m, 2H), 6.82-6.84 (d, 1H, $J = 10.0$

(Hz), 6.69-6.71(br, d, 1H, $J = 8.0$ Hz), 5.36-5.42 (q, 2H, $J = 8.4, 15.4$ Hz), 4.32-4.37(q, 2H, $J = 7.1, 14.2$ Hz), 3.96-4.03 (m, 2H), 3.53(s, 2H), 2.94(br, 2H), 2.61(br, 2H), 1.51-1.72 (m, 9H), 1.35-1.43 (m, 6H), 0.90-0.92 (d, 6H, $J = 6.5$ Hz); ^{13}C NMR (CDCl_3): δ 168.70, 166.14, 158.73, 152.41, 140.96, 138.60, 131.96, 127.80, 127.51, 124.93, 122.63, 120.69, 119.34, 113.75, 64.43, 60.64, 49.58, 46.56 (2C), 44.16, 26.65 (2C), 25.24, 24.05, 22.68, 22.43, 14.57, 14.19; IR (KBr, ν_{max} , cm^{-1}): 3236, 3063, 2932, 1731, 1630, 1557, 1244, 1180, 771; MS (m/z) = 481.5 $[\text{M} + 1]^+$; MR: 118-120.9 °C.

Synthesis of (S)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}aminocarbonylmethyl]benzoic acid (Repaglinide) (1): To a stirred solution of 1.5 gm of **14** (3.12 mmol) in 7.5 mL of ethanol at room temperature, was added 2 N NaOH solution (6.24 mmol). The reaction mixture was heated to reflux and stirred for 1 h. Concentrated the mass and cooled. Diluted the reaction mass with water and acidified pH 2 using HCl solution. Stirred for 2 h. Filtered and washed with water. Dried the product and gave 1.2 g of **1** was obtained in 84.9 % yield as off white solid.

^1H NMR (CDCl_3): δ 10.97 (br, 1H), 8.07-8.09 (d, 1H, $J = 7.95$ Hz), 7.04-7.24 (m, 5H), 6.96-7.08 (m, 2H), 5.33-5.39 (q, 2H, $J = 8.5, 15.4$ Hz), 4.13-4.27 (m, 2H), 3.56-3.57 (d, 2H, $J = 3.0$ Hz), 2.93 (br, 2H), 2.62 (br, 2H), 1.39-1.72 (m, 12H), 0.91-0.93 (dd, 6H, $J = 2.0, 6.5$ Hz); ^{13}C NMR (CDCl_3): δ 168.18, 165.22, 157.42, 152.40, 143.20, 138.46, 133.78, 127.90, 127.79, 125.07, 122.89, 122.71, 116.29, 113.16, 65.86, 50.14, 46.59 (2C), 43.89, 26.70 (2C), 25.23, 23.99, 22.65, 22.44, 14.47; IR (KBr, ν_{max} , cm^{-1}): 3308, 2935, 1687, 1636, 1567, 1216; MS (m/z) = 453.5 $[\text{M} + 1]^+$; MR: 130.8-131.8 °C.

From Grignard reaction: SOR (1 % in methanol at 20 °C): + 10.8°; chiral HPLC: S-Isomer-96.6 %.

RESULTS AND DISCUSSION

The reported literature methods for the synthesis of (S)-3-methyl-1-(2-piperidin-1-yl-phenyl)butylamine (**2a**), an important intermediate for the synthesis of repaglinide typically involving traditional asymmetric synthesis method of using chiral phenyl ethylamine or classical resolution of

racemic compound. As part of our research activities in our laboratories aimed at developing stereocontrolled synthesis pharmaceutically active molecule, we report herein a new protocol for the synthesis of (S)-3-methyl-1-(2-piperidin-1-yl-phenyl)butylamine (**2a**) from the source of chiral sulfinimines (**5a** and **10**) as starting material and the (R) and (S)-*tert*-butanesulfinamide as chiral auxiliaries (**4** and **9**).

In the process and to our surprise was found that when using isobutyl magnesium chloride to the chiral sulfinimine (**5a**) for alkylation, the product was a (S)-3-methyl-1-(2-piperidin-1-yl-phenyl)-butylamine (**2a**) but when we used the isobutyllithium as a reagent for alkylation it gave R-isomer (**8a**). Hence by utilizing the same versatile chiral sulfinimine building block (**5a**) we successfully synthesized both form of enantiomer by merely changing the carbanion source.

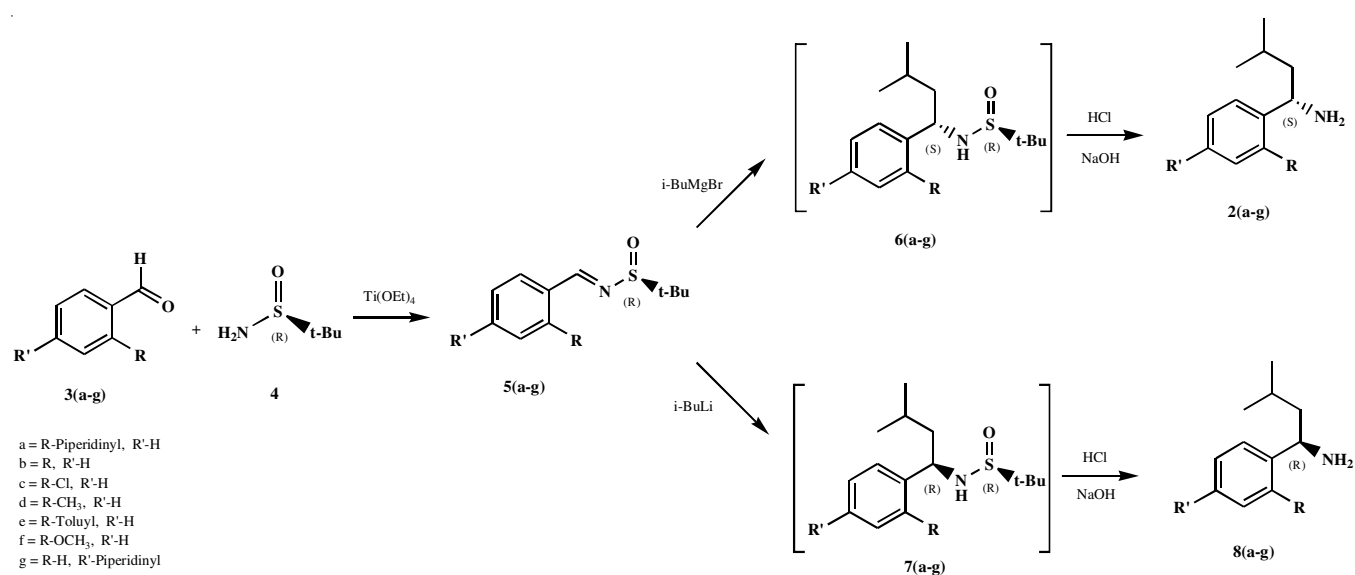
To generalize and understand further we extended our studies with other similar derivatives of chiral sulfinimines (**5b-g**) and these reaction are briefly summarized in **Scheme-I**.

Similarly attempted use of organo zinc halides with sulfinimines (**5a-g**) was failed to get any required products.

Prepared the chiral sulfinimines (**5a-g**) by the condensation of aldehydes (**3a-g**) with R(+)-*tert*-butanesulfinamide (**4**) using titanium tetraethoxide as water scavenger. Addition of Grignard reagent isobutylmagnesium bromide from isobutyl bromide and magnesium to the sulfinimines (**5a-g**) undergo diastereoselectively to give sulfinylamines (**6a-g**), which were not isolated and taken further for acidic hydrolysis and followed by treating with base gave the chiral amines (**2a-g**), in all cases S-isomer were the major product. Similarly the addition of organolithium reagent prepared from isobutyl bromide and lithium to the sulfinimines (**5a-g**) gave the insitu formation of sulfinylamines (**7a-g**), which were further cleaved under acidic condition and followed by treating with base gave the chiral amines (**8a-g**) with R-isomer as major product. These results are summarized in Table-1.

It was significant that no product was formed when-**5e** and **5f** and as a reagents either in Grignard or lithium reagent.

To verify the versatility of the diastereofacial selectivity we have also studied further synthesis of S-chiral amine (**2a**) by



Scheme-I

TABLE-1
DIASTEREOSELECTIVE REACTION OF SULFINIMINES (**5a-g**) WITH ORGANO METALLIC REAGENTS

S. No.	R	R'	Reagent	Product	Chiral HPLC (%)		Yield (%)
					S	R	
1		-H	iBuMgBr	2a	95.02	4.98	33.7
2		-H	iBuLi	8a	21.38	78.6	55.6
3	-H	-H	iBuMgBr	2b	60.43	39.50	38.6
4	-H	-H	iBuLi	8b	16.48	83.52	51.0
5	-Cl	-H	iBuMgBr	2c	53.51	46.49	44.4
6	-Cl	-H	iBuLi	8c	19.13	80.97	61.6
7	-CH ₃	-H	iBuMgBr	2d	44.34	55.66	37.8
8	-CH ₃	-H	iBuLi	8d	37.75	62.25	40.3
9		-H	iBuMgBr	2e	-	-	-
10		-H	iBuLi	8e	-	-	-
11	-OCH ₃	-H	iBuMgBr	2f	-	-	-
12	-OCH ₃	-H	iBuLi	8f	-	-	-
13	-H		iBuMgBr	2g	65.28	34.72	35.5
14	-H		iBuLi	8g	29.5	70.5	41.5

taking *S*(-)-*tert*-butanesulfinamide (**9**) and condensed with 2-piperidin-1-ylbenzaldehyde (**3a**) using titanium tetraethoxide gave sulfinimine (**10**). The addition of Grignard reagent isobutylmagnesium bromide to sulfinimine (**10**) gave *R*-isomer (**8a**). Similarly the addition of isobutyl lithium reagent to the sulfinimine (**10**) gave the required *S*-chiral amine (**2a**). These reaction are briefly summarized in **Scheme-II** and the results are summarized in Table-2.

To prove the confirmation of the product of (*S*)-chiral amine (**2a**) obtained from the above route method, we have prepared the repaglinide drug (**1**) by condensing (*S*)-amine

(**2a**) with 3-ethoxy-4-ethoxycarbonyl phenylacetic acid (**13**) gave (*S*)-2-ethoxy-4-*N*-(1-(2-piperidinophenyl)-3-methyl-1-butyl)aminocarbonylmethyl]benzoic acid ethyl ester (**14**) and followed by basic hydrolysis. The isolated product repaglinide, which was matching in all respect with the reported repaglinide. These reaction are briefly summarized in **Scheme-III**.

Conclusion

An efficient asymmetric synthetic method for the preparation of series of hitherto unknown chiral amine (**2b-g** and **8b-g**) and known (*S*)-3-methyl-1-(2-piperidin-1-yl-phenyl)-

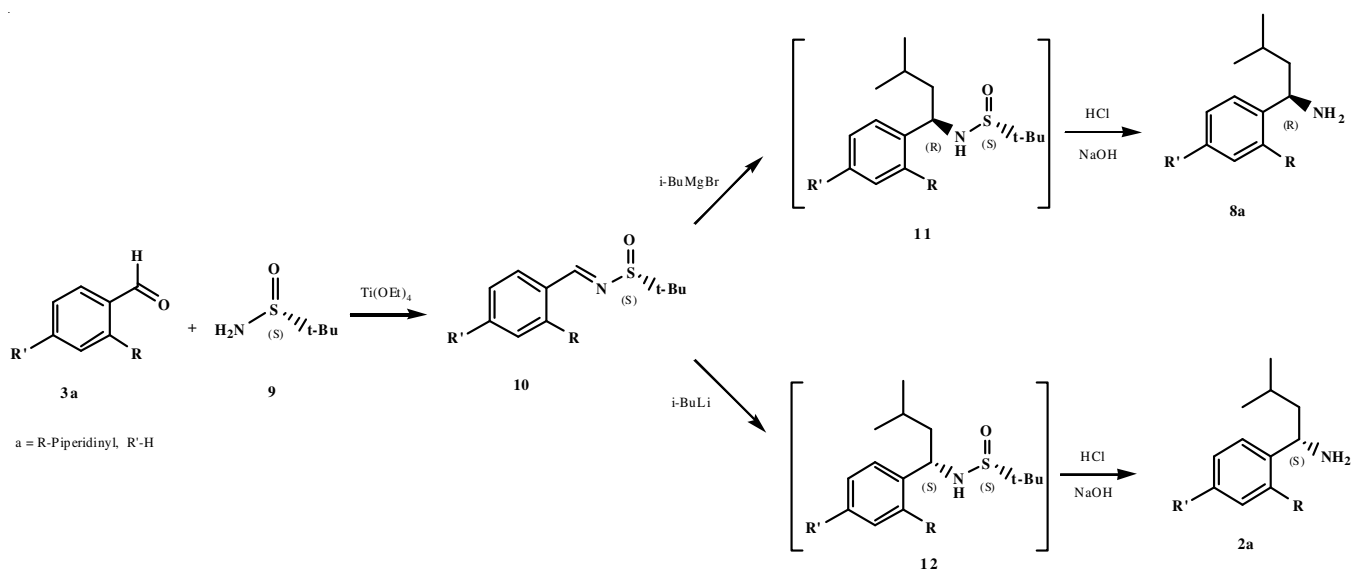
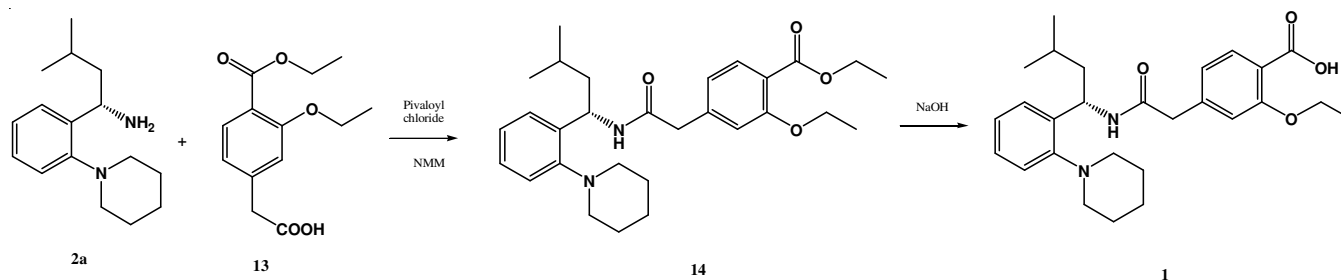


TABLE-2
DIASTEREOSELECTIVE REACTION OF SULFINIMINE (**10**) WITH ORGANO METALLIC REAGENTS

S. No.	R	R'	Reagent	Product	Chiral HPLC (%)		Yield (%)
					S	R	
1		-H	iBuMgBr	8a	6.46	93.54	35.6
2		-H	iBuLi	2a	81.84	18.16	58.3



Scheme-III

butylamine (**2a**) a key intermediate of repaglinide have been developed by diastereoselective addition of Grignard and organo lithium reagent to sulfinimine.

ACKNOWLEDGEMENTS

The authors thank the Management of Suven Life Sciences Limited for permission to publish this work. Cooperation extended by all the colleagues of analytical research and development is highly appreciated.

REFERENCES

- The Merck Index, edn. 14, p. 1402 (2006).
- J.E.F. Reynolds, Martindale: The Extra Pharmacopoeia, edn. 33, p. 334 (2002).
- F.J. Ampudia-Blasco, L. Heinemann, R. Bender, A. Schmidt, T. Heise, M. Berger and A.A.R. Starke, *Diabetologia*, **37**, 703 (1994).
- B.H.R. Wolffenbuttel, L. Nijst, J.P.J.E. Sels, P.P.C.A. Menheere, P.G. Muller and A.C. Nieuwenhuizen Kruseman, *Eur. J. Clin. Pharmacol.*, **45**, 113 (1993).
- J. Gromada, S. Dissing, H. Kofod and J. Frokjaer-Jensen, *Diabetologia*, **38**, 1025 (1995).
- W. Grell, R. Hurnaus, G. Griss, R. Sauter, E. Rupprecht, M. Mark, P. Luger, H. Nar, H. Witneben and P. Muller, *J. Med. Chem.*, **41**, 5219 (1998).
- W. Grel, R. Hurnaus, G. Griss, R. Sauter, M. Reiffen and E. Rupprecht, Phenylacetic Acid Benzylamides, US Patent 6,143,769 (2000).
- M. Veverka, E. Veverkova, J.Klvanova, S. Bombek and M. Merslavic, WO 2010/046360 (2010).
- R. Heck, M. Justus, R. Muller, T. Otten and M. Rettig, Method for preparing phenyl acetic acid derivatives, US Patent 0123564 (2007).
- U.R. Kalkote, M.K. Gurjar, S.V. Joshi, S.M. Kadam and H.K. Mondkar, US Patent 0192921 (2004).
- J.A. Ellmann, M.T. Robak and M.A. Herbage, *Chem. Rev.*, **110**, 3600 (2010).