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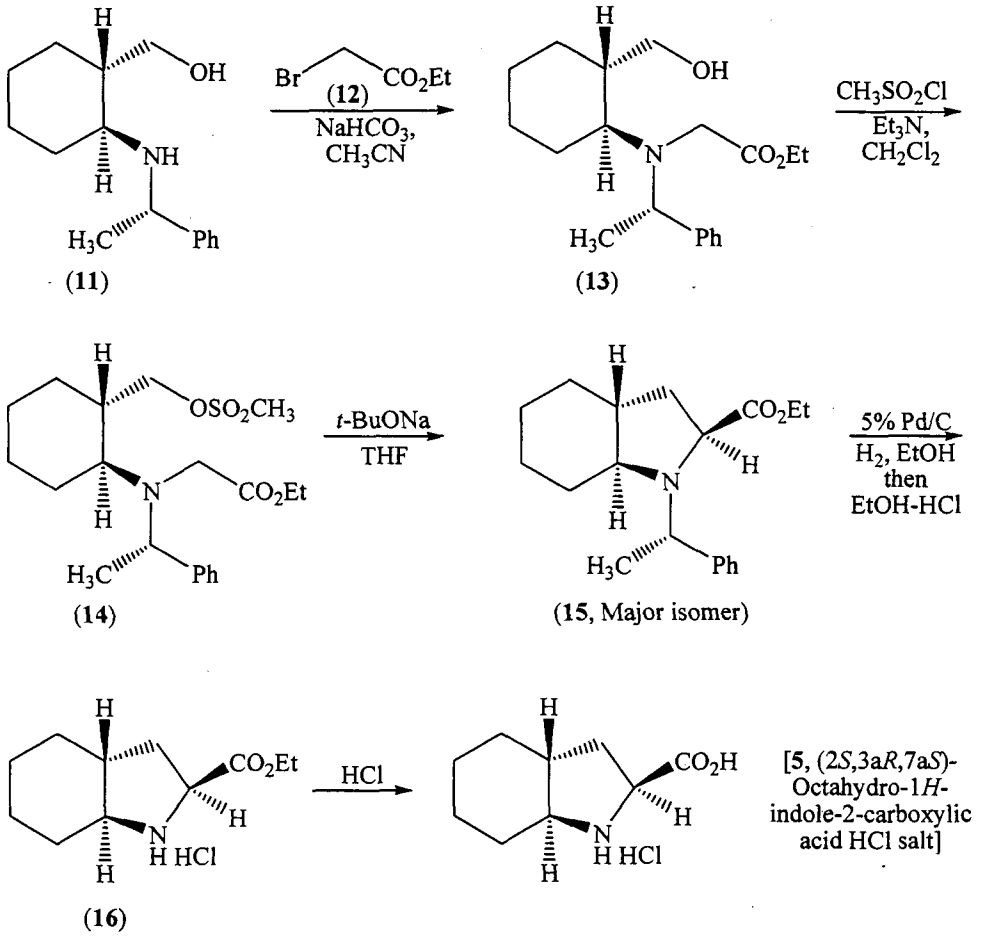
ABSTRACT

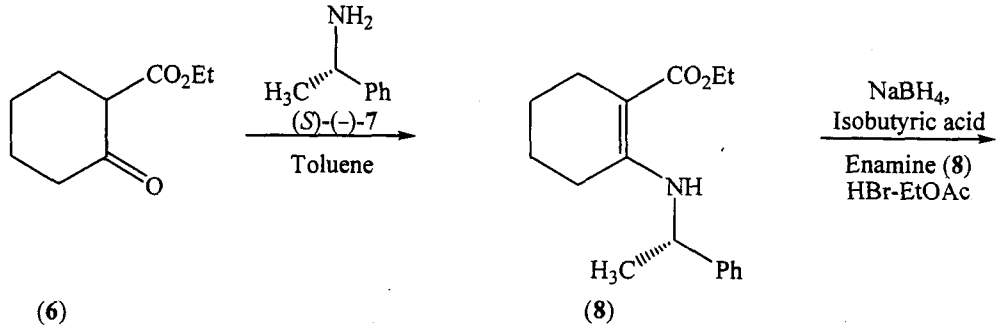
A process for the preparation of (2*S*, 3a*R*, 7a*S*)-octahydro-1*H*-indole-20carboxylic acid hydrochloride.

CLAIMS

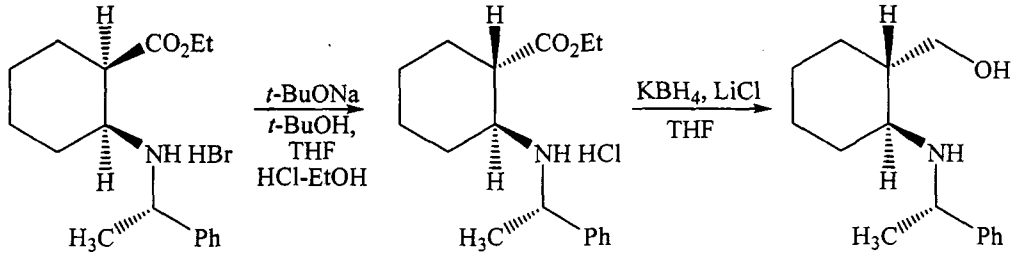
1. A process for preparing (2S,3aR,7aS)-Octahydro-1H-indole-2-carboxylic acid hydrochloride (**5**) comprising the steps of:



2. The process of claim 1, wherein the process of making (1S,2S)-2-[(S)-1-phenylethyl amino]cyclohexyl)methanol (**11**) comprises the steps of:

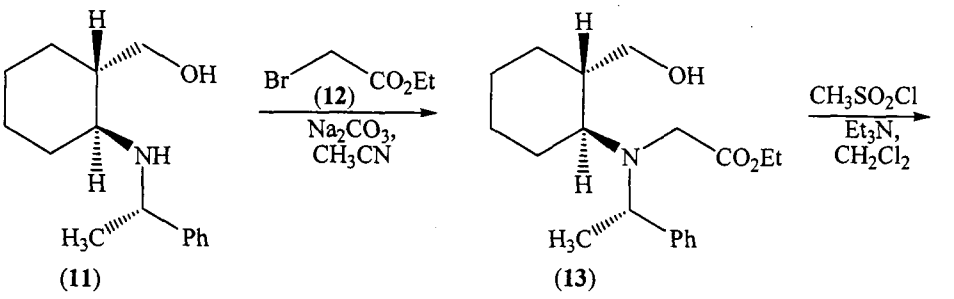


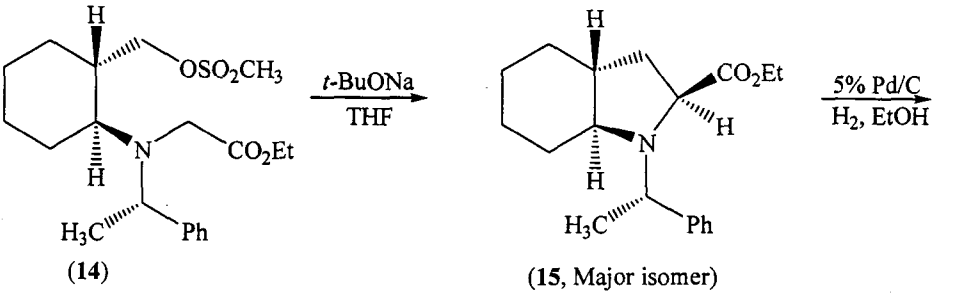
(**6**) (**8**)

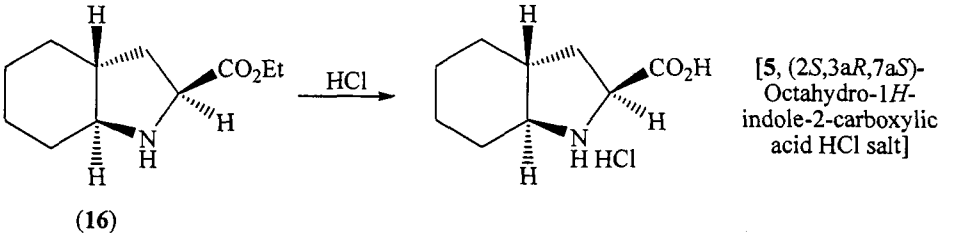


(**9**) (**10**) (**11**)

3. A process for preparing (2S,3aR,7aS)-Octahydro-1H-indole-2-carboxylic acid hydrochloride (**5**) comprising the steps of:

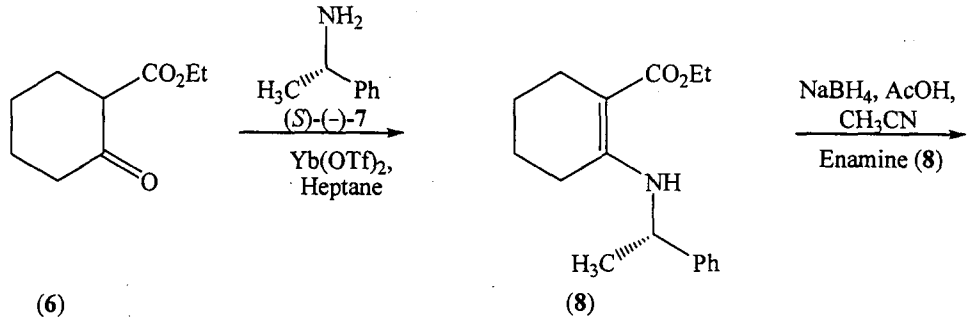




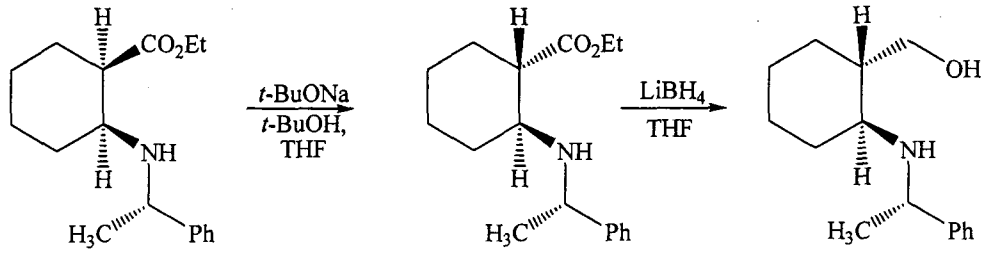


[**5**, (2*S*,3a*R*,7a*S*)-Octahydro-1*H*-indole-2-carboxylic acid HCl salt]

4. The process of claim 1, wherein the process of making (1S,2S)-2-[(S)-1-phenylethyl amino]cyclohexyl)methanol (**11**) comprises the steps of:

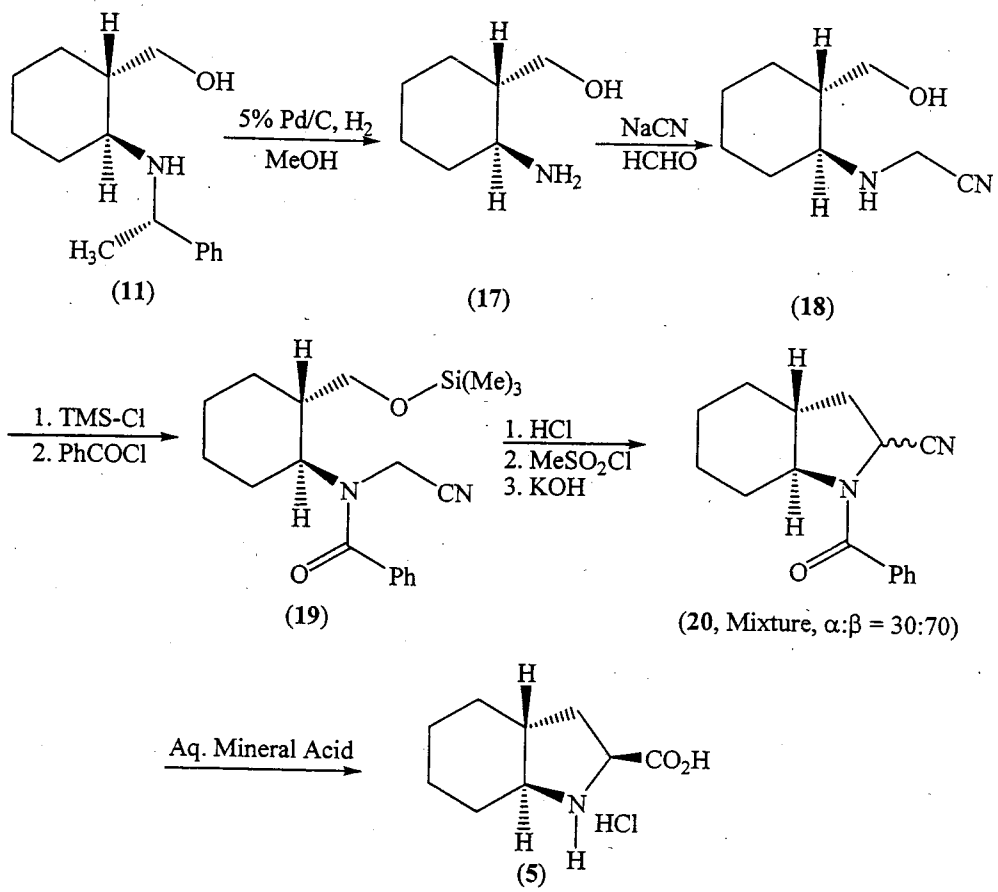


(**6**) (**8**)



(**9**, Major isomer) (**10**, Major isomer) (**11**)

5. A process for preparing (2S,3aR,7aS)-Octahydro-1H-indole-2-carboxylic acid hydrochloride (**5**) comprising the steps of:



Dated this 16/01/2012

HRISHIKESH RAY CHAUDHURY
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

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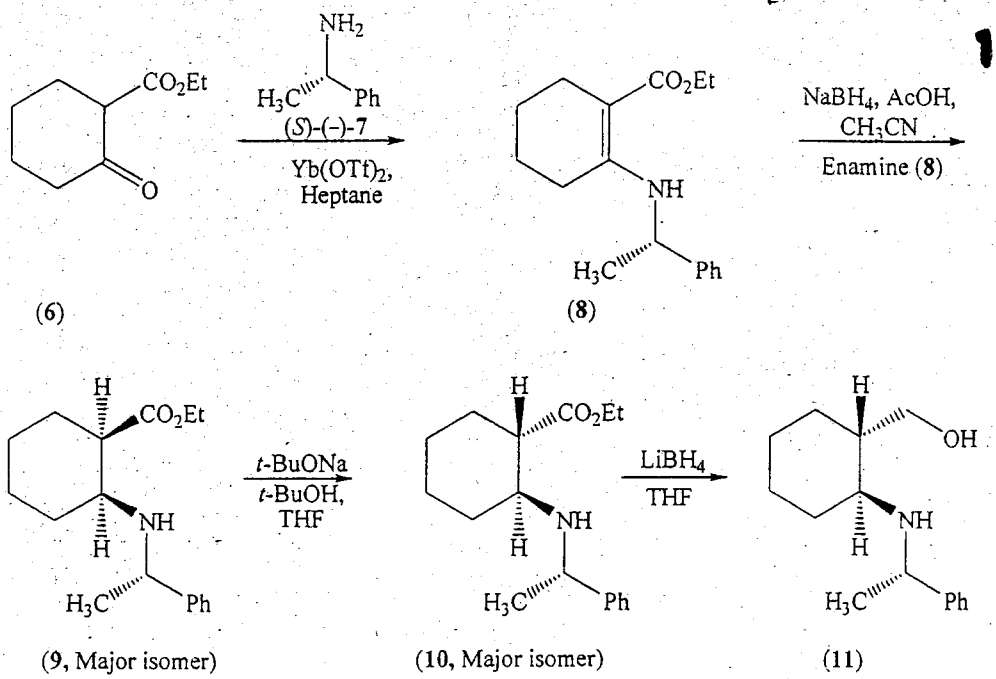
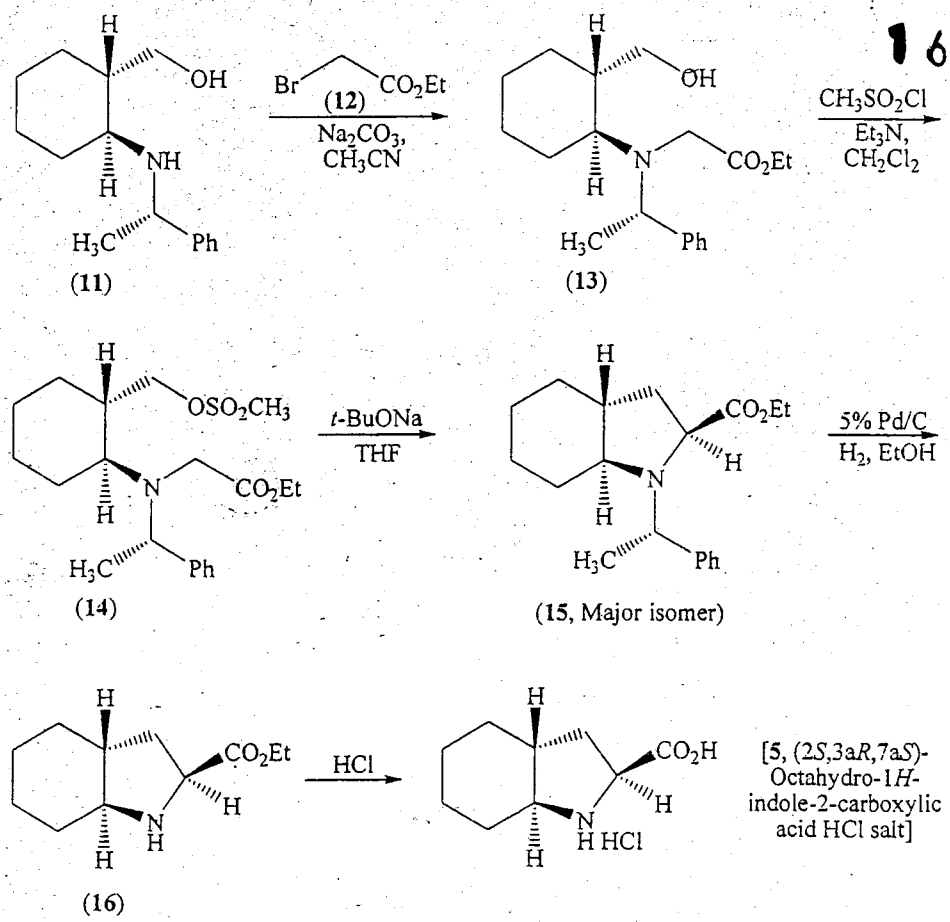
FIGURE 1



(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

FIGURE 2



(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

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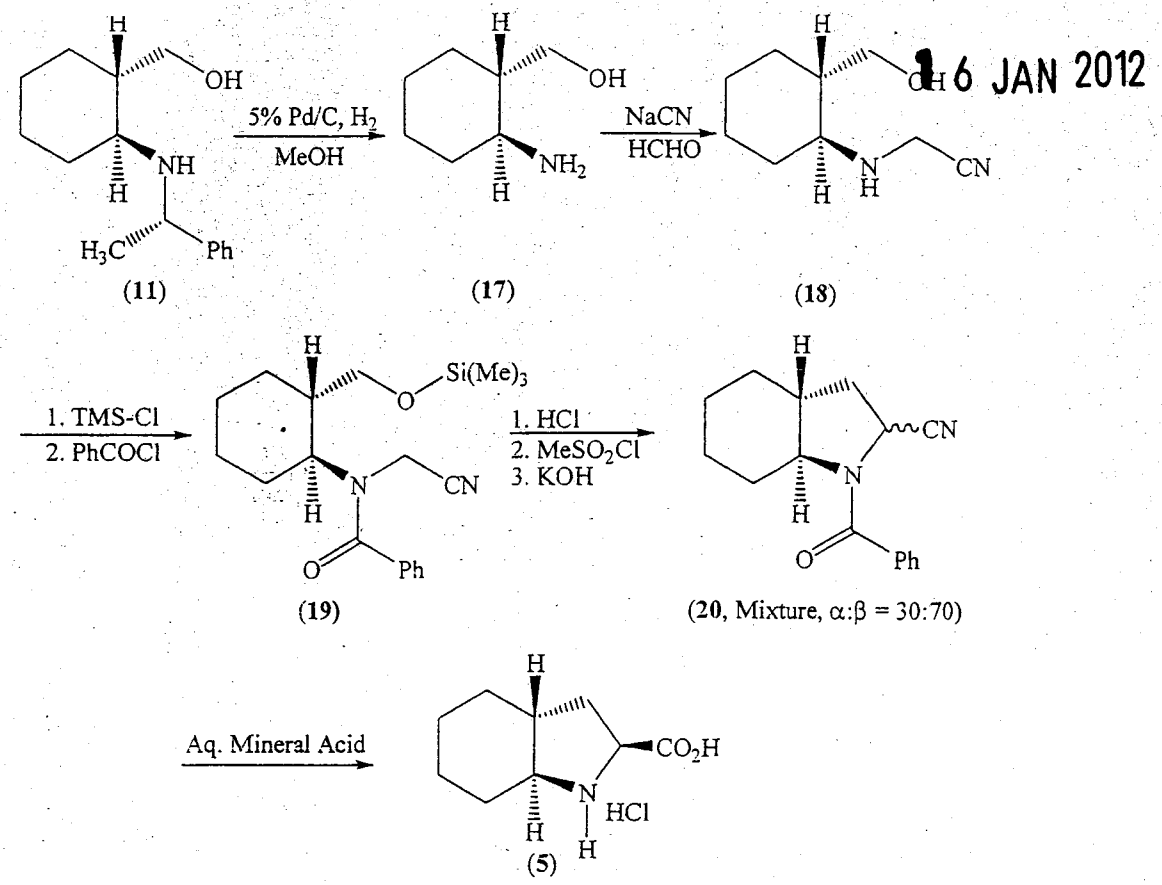
FIGURE 3



(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

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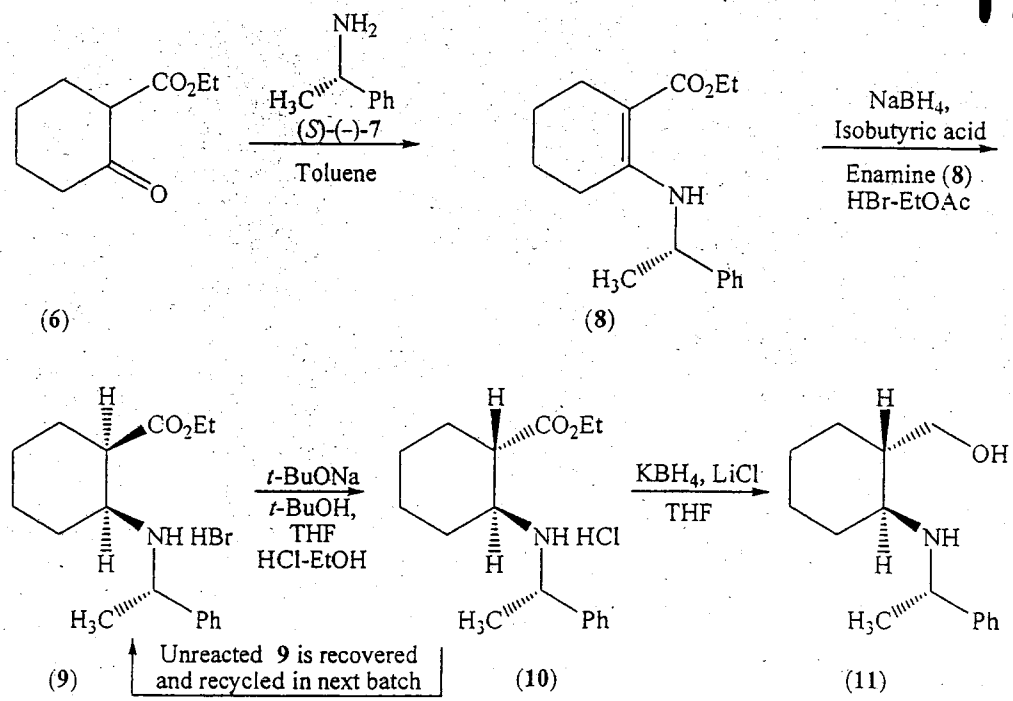
FIGURE 4



(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

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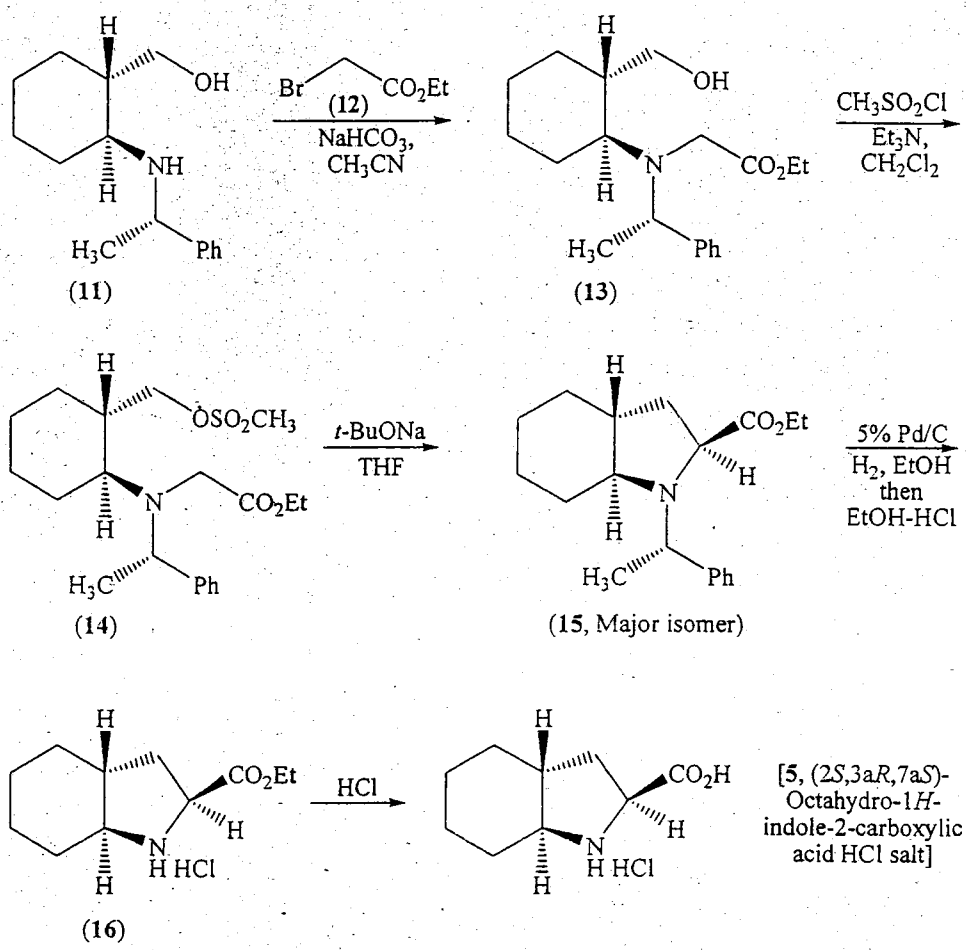
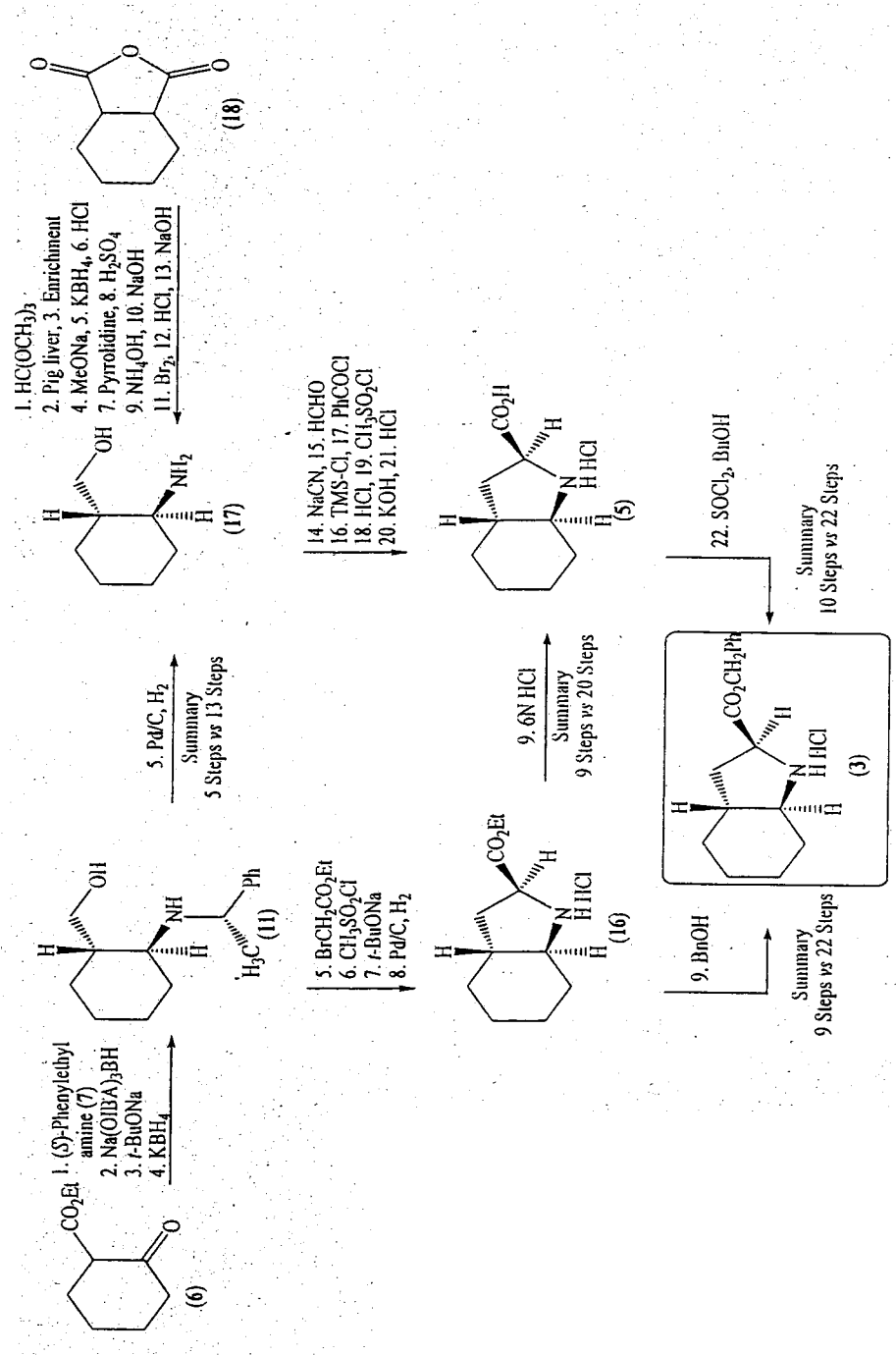
FIGURE 5



(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

FIGURE 6



(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

benzoyl chloride to produce compound (19). Further, compound (19) is subjected to three sequential reactions to produce compound (20) as illustrated in Figure 3. Specifically, compound (19) is first subjected to treatment with hydrochloric acid. Subsequently, methanesulfonyl chloride is added to the reaction mixture. Thereafter, potassium hydroxide is added to the reaction to produce compound (20). After compound (20) is produced, the compound is treated with aqueous mineral acid to produce the hydrochloride salt of compound (5).

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated, as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

Figure 1 illustrates a process for making (1*S*,2*S*)-2-[(*S*)-1-phenylethyl amino]cyclohexyl) methanol (11), comprising the use of ytterbium trifluoromethanesulfonate as a catalyst.

Figure 2 illustrates a first process for making (2*S*,3a*R*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (5), wherein intermediate compound (16) comprises the free base form of the compound.

Figure 3 illustrates the process for making (2*S*,3a*R*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (5) by using (1*S*,2*S*)-2-[(*S*)-1-phenylethyl amino]cyclohexyl) methanol (11) as a starting material.

Figure 4 illustrates a process for making (1*S*,2*S*)-2-[(*S*)-1-phenylethyl amino]cyclohexyl) methanol (11), comprising the use of toluene as a solvent, without the incorporation of a catalyst.

Figure 5 illustrates the process for making (2*S*,3a*R*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (5) wherein intermediate compound (16) comprises the hydrochloride salt form of the compound.

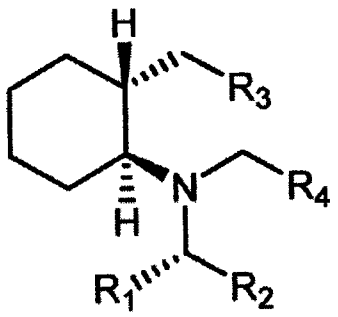
Figure 6 depicts a chart showing the various embodiments of the current invention and how they compare to methods of producing (2*S*,3a*R*,7a*S*)-benzyl octahydro-1*H*-indole-2-carboxylate hydrochloride salt (3) disclosed in the prior art. Specifically, Figure 6 outlines the

3. Process for Generating (2*S*,3a*R*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (5)

a. Under the Catalyst Approach

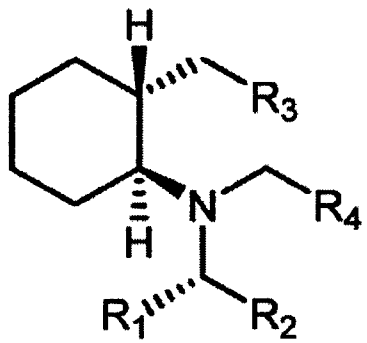
The (1*S*,2*S*)-2-[(*S*)-1-phenylethyl amino]cyclohexyl)methanol (**11**) compound produced by the steps previously described under the catalyst approach may further be incorporated into the process illustrated in Figure 2. Selective *N*-alkylation of (1*S*,2*S*)-2-[(*S*)-1-phenylethyl amino]cyclohexyl) methanol (**11**) with ethyl bromoacetate (**12**) was performed with a base such as, but not limited to, sodium carbonate, sodium bicarbonate, or potassium carbonate, in acetonitrile or tetrahydrofuran to give compound (**13**). The hydroxyl functionality in compound (**13**) was converted to a leaving group, such as, but not limited to, methanesulfonate ester, trifluoromethane sulfonate ester, chloride, bromide, or iodide, to afford compound (**14**). The conversion to a leaving group may be reacted in the presence of triethylamine and dichloromethane.

It should be noted that compound (**14**) as illustrated in Figure 2 comprises the resulting compound when the hydroxyl functional group of compound (**13**) is converted to a methanesulfonate ester. However, compound (**14**) may exist in alternative embodiments without departing from the scope of the current invention. Specifically, compound (**14**) may exist according to following structure:



wherein R1 and R2 are each selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, alkylsulfinyl, and arylsulfinyl, each of which is substituted with aryl, heteroaryl, or cycloalkyl; R3 is a suitable leaving group selected from the group consisting of mesylate, triflate, tosylate, methanesulfonate ester, trifluoromethane sulfonate ester, chloride, bromide, and iodide; and R4 is selected from the group consisting of ester, nitrile, alkenyl, alkynyl, sulfonyl, aryl, and heteroaryl.

It should be noted that compound (**14**) as illustrated in Figure 4 comprises the resulting compound when the hydroxyl functional group of compound (**13**) is converted to a methanesulfonate ester. However, compound (**14**) may exist in alternative embodiments without departing from the scope of the current invention. Specifically, compound (**14**) may exist according to following structure:



wherein R1 and R2 are each selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, alkylsulfinyl, and arylsulfinyl, each of which is substituted with aryl, heteroaryl, or cycloalkyl; R3 is a suitable leaving group selected from the group consisting of mesylate, triflate, tosylate, methanesulfonate ester, trifluoromethane sulfonate ester, chloride, bromide, and iodide; and R4 is selected from the group consisting of ester, nitrile, alkenyl, alkynyl, sulfonyl, aryl, and heteroaryl.

Treatment of compound (**14**) with a base, such as, but not limited to, sodium tert-butoxide, sodium hydride, or lithium diisopropylamide, in solvents, such as, but not limited to, tetrahydrofuran or mixtures of tetrahydrofuran and heptanes, produced a trans-fused octahydroindole ring system (**15**) with the correct stereochemistry at the (2S)-carboxylic ester position, as the major isomer. The yield of (2S)-isomer for compound (**15**) generally ranges from about 90% to about 99%, and the yield of (2R)-isomer generally ranges from about 1% to about 10%. In another embodiment, the ratio of (2S)-isomer to (2R)-isomer of compound (**15**) is approximately 95:5. Additionally, the conversion of compound (**14**) is generally performed at a temperature ranging from approximately 20° C to approximately 65° C, and the reaction is allowed to proceed for a sufficient amount of time, generally not less than one hour.

Compared to prior art methods and the previous embodiments described herein, the production of compound (15) according to this embodiment does not require purification by chromatography, thus providing significant benefits over previous methods. The N-α-methylbenzyl group in (2S,3aR,7aS)-Ethyl 1-((S)-1-phenylethyl)octahydro-1H-indole-2-carboxylate (15) is cleaved by hydrogenolysis using metal catalysts, such as, but not limited to, palladium on carbon or palladium hydroxide on carbon in the presence of hydrogen gas, ethanol, and hydrogen chloride, to afford the hydrochloride salt of compound (16). The overall yield of compound (16) ranges from approximately 35% to approximately 45%, after a five-step process wherein compound (10) is used as the starting material. Incorporating compound (6) as the starting material, and using the solvent approach as described herein, the yield of compound (16) ranges from approximately 15% to approximately 25%, after an eight-step process.

Thereafter, the hydrochloride salt of compound (16) is subjected to acid hydrolysis by the incorporation of an acid including, but not limited to, 6 N hydrochloric acid to provide the (2S,3aR,7aS)-octahydro-1H-indole-2-carboxylic acid (5) as its hydrochloride salt in good overall yield (See Figure 5). It should be noted that compound (5) is isolated by crystallization from a solvent including, but not limited to, acetonitrile. Additionally, the yield of the hydrochloride salt of compound (5) compared to the amount of compound (16) ranges from approximately 80% to approximately 90%.

Subsequently, crystallized compound (5) may be subjected to esterification to produce (2*S*,3a*R*,7a*S*)-benzyl octahydro-1*H*-indole-2-carboxylate hydrochloride salt (3), a key intermediate in the production of trandolaprilat and trandolapril. This step final step is known within the art, and generally comprises treatment with esterification agents including, but not limited to, thionyl chloride, benzyl alcohol, and dichloromethane, as disclosed in U.S. Patent No. 4,879,392. Although the conversion of compound (5) to compound (3) is disclosed, the processes for the production of compound (5), as detailed herein are novel and convey significant improvements over the prior art.

Alternatively, it is also possible to convert the hydrochloride salt of (2S,3aR,7aS)-Ethyl 1-((S)-1-phenylethyl)octahydro-1H-indole-2-carboxylate (16) directly into (2*S*,3a*R*,7a*S*)-benzyl octahydro-1*H*-indole-2-carboxylate hydrochloride salt (3) without converting compound (16) to

compound (**5**). This process involves the reaction of compound (**16**) with benzyl alcohol in the presence of heat, and the removal of ethanol.

The cumulative process described in the two previous embodiments for the production of (2S,3aR,7aS)-octahydro-1H-indole-2-carboxylic acid (**5**) from ethyl 2-oxocyclohexane carboxylate (6) provides multiple advantages over the prior act methods. Primarily, the embodiments provide a nine-step process for the production of compound (**5**), which is useful in the production of clinically significant compounds, such as trandolapril, described previously. The reduction in the number of steps provides significant benefits with regard to the efficiencies of production, as well as improving the cost-effectiveness of the production. Additionally, the process requires less solvent compared to previous methods, thereby providing additional cost benefits.

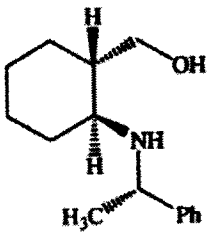
2. Alternative Process for Generating (2*S*,3a*R*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (5) Using the Hoffman Reaction

Additionally, as depicted in Figure 3, the production of (2*S*,3a*R*,7a*S*)-benzyl octahydro-1*H*-indole-2-carboxylate hydrochloride salt (**3**), a key intermediate in the production of trandolaprilat and trandolapril, may be produced using a starting material of crystalline ((1*S*,2*S*)-2-((*S*)-1-phenylethylamino) cyclohexyl)methanol (**11**). The first step of the process involves reaction with a catalyst including, but not limited to, palladium on carbon or palladium hydroxide on carbon in the presence of an alcohol such as methanol to produce ((1*S*,2*S*)-2-aminocyclohexyl)methanol (**17**). The remaining steps in the conversion of compound (**17**) to the hydrochloride salt, and eventual conversion to (2*S*,3a*R*,7a*S*)-benzyl octahydro-1*H*-indole-2-carboxylate hydrochloride salt (**3**) are based upon the teachings of U.S. Patent No. 4,879,392, which is fully incorporated herein by reference. Generally, the remaining steps can be described as follows. Compound (**17**) is subjected to treatment with sodium cyanide in the presence of formaldehyde to produce compound (**18**), as illustrated in Figure 3. Subsequently, compound (**18**) is first reacted with trimethylsilyl chloride, and then the product of that reaction is treated with benzoyl chloride to produce compound (**19**). Further, compound 19 is then subjected to three sequential reactions to produce compound (**20**) as illustrated in Figure 3. Specifically, compound (**19**) is first subjected to treatment with hydrochloric acid. Subsequently, methanesulfonyl chloride is added to the reaction mixture. Thereafter, potassium hydroxide is added to the reaction to produce compound (**20**). After compound (**20**) is produced, the

Tetrahydrofuran (1.25 L) was charged to a reactor followed by *t*-butanol (150 mL), and sodium *t*-butoxide (313 g) under nitrogen at ambient temperature. Additional tetrahydrofuran (1.0 L) was added and then the contents were cooled to <10° C. A solution of (1*R*,2*S*)-ethyl 2-((*S*)-1-phenylethylamino)cyclohexane carboxylate (**9**, 243.9 g) in tetrahydrofuran (300 mL) was added in NLT 30 minutes, while maintaining the temperature between 6-12° C. After the addition was complete, the mixture was warmed to 22° C in NLT 30 minutes and further mixed for NLT 4 hours under nitrogen. The contents were cooled to <10° C and the reaction was quenched with a solution of ammonium chloride (269.3 g) and water in NLT 30 minutes, while maintaining the temperature between 6-12° C. The lower aqueous layer was separated and extracted with 750 mL of heptanes. The upper organic layer was concentrated to about 0.8 L volume and extracted with the heptanes solution. The aqueous layer was separated and extracted with fresh heptanes (2 × 0.75 L) and the combined organic layers were washed with water (2 × 0.75 L) and 3.5 M aqueous sodium chloride solution (0.75 L), and dried with anhydrous magnesium sulfate. Concentration of the organic layer under vacuum gave 237.9 g of (1*S*,2*S*)-ethyl 2-((*S*)-1-phenylethyl amino)cyclohexane carboxylate (**10**) as a major isomer.

Example 4

(1*S*,2*S*)-2-[(*S*)-1-Phenylethyl amino]cyclohexyl)methanol (11)

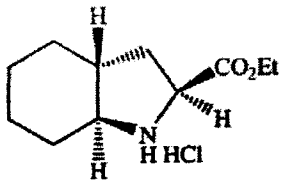


(**11**, Major isomer)

Tetrahydrofuran (1.9 L) was charged to a reactor and cooled to 15° C and lithium borohydride (52.8 g) was added under nitrogen. A solution of (1*S*,2*S*)-Ethyl 2-((*S*)-1-phenylethylamino)cyclohexanecarboxylate (**10**, 237.9 g) in tetrahydrofuran (0.35 L) was added and the reaction mixture was heated to reflux for NLT 12 hours, under nitrogen. The mixture

Example 18

(2*S*,3a*R*,7a*S*)-Ethyl octahydro-1*H*-indole-2-carboxylate Hydrochloride (16)



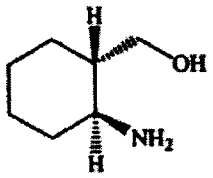
(16)

127 g of Raney Nickel (WR Grace 2800, water slurry) was added to a solution of 127.2 g of (2*S*,3a*R*,7a*S*)-ethyl 1-((*S*)-1-phenylethyl)octahydro-1*H*-indole-2-carboxylate **(15)** in 400 mL ethanol and the solution was mixed at room temperature in a Parr shaker apparatus for 30 min under Argon. The catalyst was filtered off and washed with 400 mL of ethanol. To this pre-treated product solution was added 21.7 g of palladium hydroxide on carbon (Degussa, 50 wt. % water). The mixture was hydrogenated for 1.5 h at 50 °C under 30 psig of hydrogen pressure. The catalyst was filtered and washed with fresh ethanol (100 mL). The hydrogenated product mixture was concentrated under vacuum at NMT 70°C. The resulting oil was added from a dropping funnel over 10-20 min at a temperature range of 25-35 °C to a 500 mL flask containing 263 g of a 14 % ethanolic hydrogen chloride solution. The mixture was stirred for 1 h at ambient temperature then concentrated on a rotary evaporator to remove solvent under vacuum at 50-60 °C. 400 mL of ethyl acetate was added to the residue and the mixture warmed to 35 °C. The mixture was cooled to 22 °C over 30 min to form a precipitate. The slurry was cooled to 0-5 °C and held for 2 h. The solids were collected and washed with 20 mL of 0-5 °C ethyl acetate. The solids were vacuum dried in an oven at 45 °C to afford 34.0 g of (2*S*,3a*R*,7a*S*)-Ethyl octahydro-1*H*-indole-2-carboxylate hydrochloride salt **(16)**. Analytical HPLC (Daicel Chiralpack AD-RH column, Size: 150 × 4.6 mm); 0.02 M Ammonium acetate buffer (pH: 7.7-7.8):Acetonitrile/50:50, 0.3 mL/min, Wave length: 220 nm, Column oven temperature: 55 °C, R_t: 16.21 min, 97.95% (PA); ^{1}H NMR (D_2O, 400 MHz): δ 4.52 (dd, 1 H, J = 11.2, 2.9 Hz), 4.30 (q, 2 H, J = 14.2, 7.16 Hz), 2.94 (dt, 1 H, J = 11.8, 3.6 Hz), 2.42 – 2.34 (m, 1 H), 2.22 – 2.15 (m, 1

Further, (2*S*,3a*R*,7a*S*)-Octahydro-1*H*-indole-2-carboxylic acid hydrochloride (**5**, 25.0 g, 0.122 mol) is converted to the corresponding benzyl ester [(2*S*,3a*R*,7a*S*)-Benzyl octahydro-1*H*-indole-2-carboxylate hydrochloride] using thionyl chloride, benzyl alcohol in dichloromethane in 90.1% yield (32.7 g) and the product was correlated by HPLC and NMR to the to the material prepared according to *US487932 and Tetrahedron Lett.* 1992, *33*, 4889. Analytical HPLC (Daicel Chiralpack AD-RH column, Size: 150 × 4.6 mm); 0.02 M Ammonium acetate buffer (pH: 7.7-7.8):Acetonitrile/50:50, 0.3 mL/min, 220 nm, Column chamber temperature: 55 °C, R_t: 32.6 min, 99.34 % (PA); ^{1}H NMR (D_2O, 400 MHz): δ 7.49 – 7.43 (m, 5 H), 5.37 – 5.28 (q, 2 H, *J* = 23.2, 12.0 Hz), 4.60 (dd, 1 H, *J* = 11.2, 2.9 Hz), 2.95, (dt, 1 H, *J* = 11.8, 3.7 Hz), 2.36 (ddd, 1 H, *J* = 13.1, 6.9, 2.9 Hz), 2.25 – 2.15 (m, 1 H), 2.13 – 2.02 (m, 2 H), 2.03 – 1.96 (m, 1 H), 1.95 – 1.88 (m, 1 H), 1.65 – 1.53 (m, 2 H), 1.32 – 1.12 (m, 3 H); LC-MS (*m/z*): 274.1 $(M+H)^+$.

Example 20

((1*S*,2*S*)-2-Aminocyclohexyl)methanol (17)



(17)

5% Palladium on carbon (0.05 g) was added to a solution of (1*S*,2*S*)-2-[(*S*)-1-phenylethyl amino]cyclohexyl)methanol (**11**, 0.5 g, 0.002 mol) dissolved in methanol (15 mL). The mixture was heated at 60 ° C under hydrogen (14.5 psi) atmosphere for NLT 3 h. The mixture was cooled to room temperature, flushed with nitrogen, the catalyst was filtered and washed with fresh methanol (10 mL). The combined filtrate was concentrated under vacuum to afford 0.28 g of ((1*S*,2*S*)-2-aminocyclohexyl)methanol (**17**) in quantitative yield as a white solid. $[\alpha]^{23}_D$ 9.1 (c, 0.0107 $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.61 – 3.54 (m, 2 H), 2.71 (bs, 3 H), 2.45 (dt, 1 H, *J* = 10.6, 1.2 Hz), 1.85 – 1.78 (m, 1 H), 1.74 – 1.65 (m, 1 H), 1.62 – 1.53 (m, 1 H), 1.40 – 1.30

(m, 1 H), 1.25 – 1.06 (m, 3 H), 0.91 – 0.80 (m, 1 H), ^{13}C NMR ($CDCl_3$): δ 70.2, 57.4, 45.5, 40.1, 28.6, 25.5, 25.5, **For NMR of its enantiomer, ((1R,2R)-2-Aminocyclohexy1) methanol, see Reference J. Am. Chem Soc. 1996, 118, 5502.**