A PRACTICAL SYNTHESIS, OPTICAL RESOLUTION AND DETERMINATION OF ABSOLUTE CONFIGURATION OF ENANTIOMERICALLY PURE 1S,2R-(+)- and 1R,2S-(-)-CIS-2-(1-PYRROLIDINYL)CYCLOHEXYLAMINES: IMPORTANT PRECURSORS FOR A NEW CLASS OF SIGMA-RECEPTOR LIGANDS AND ANTICONVULSANT DRUGS

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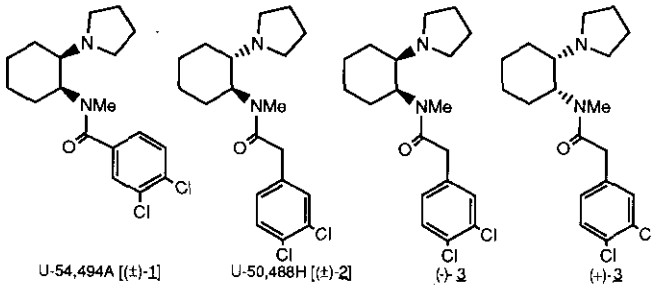
Abstract- Enantiomerically pure (+)- and (-)-cis-2-(1-pyrrolidinyl) cyclohexylamines ((+)- and (-)-4) were prepared starting with (±)-trans-2-aminocyclohexanol ((±)-5). The key step in the generation of the cis stereochemistry of (+)- and (-)-4 employed catalytic hydrogenation of the enamine mixture generated from condensation of pyrrolidine with (±)-2-(benzamido)cyclohexanone ((±)-7). An efficient optical resolution of (±)-4 was achieved through two recrystallizations of the mandelate salts. The absolute configuration of (+)- and (-)-4 was assigned as 1S,2R and 1R,2S, respectively, based on conversion of (-)-4 to and comparison with the N-methyl derivative (-)-13 of known 1R,2S absolute configuration.

In response to the increasing demand for an anticonvulsant with high efficacy and low toxicity, (±)-cis-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzamide ((±)-1) was recently developed by the Upjohn company as a non-opioid, non-phencyclidine (PCP) related anticonvulsant with high therapeutic index.[1] This compound is of interest since it bears a structural resemblance to (±)-trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzacetamide (U50,488) ((±)-2), a highly potent and selective kappa opioid receptor agonist.[2] In a study of the effects of changes in the stereochemistry of (±)-2 on receptor binding activity, we recently reported the synthesis, absolute configuration and evaluation of optically pure forms of the cis diastereomers, (+)-and (-)-3; unlike (±)-2, these compounds possessed high affinity and selectivity at the sigma receptor and very low affinity for kappa opioid receptors.[3]



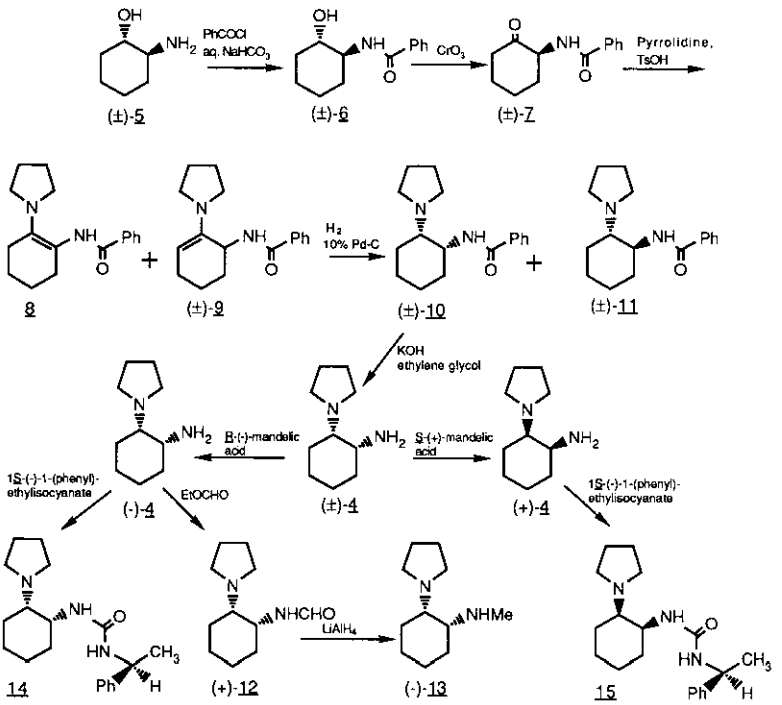
Sigma receptors have recently gained much importance because of their association with the psychotomimetic effects that occur after administration of certain (+)-benzomorphans[4] as well as PCP;[5] activation of sigma receptors has also been implicated as the origin of dystonia, a movement disorder precipitated by administration of antipsychotic drugs.[6] Because it is well appreciated that the enantiomers in a racemic mixture can have different, and in some cases opposite effects at receptors, it is imperative for us to examine individual enantiomers in these receptor studies.[7]

The purpose of this study was to develop a practical synthesis of optically pure (+)- and (-)-cis-2-(1-pyrrolidinyl)cyclohexylamine ((+)-4 and (-)-4) (Scheme 1) of defined absolute configuration which would serve as precursors for investigating the SAR of the N-alkyl group of (+)- and (-)-3 as well as related compounds. The synthetic route employed in the present study was based upon a modification of our previously reported method for obtaining enantiomeric (+)- and (-)-cis-2-(1-pyrrolidinyl)-N-methylcyclohexylamines.[3] Previously reported syntheses of (±)-1 and (+)- and (-)-3 can only afford N-methyl analogs.[3]

This synthetic route (Scheme 1) commenced with (±)-trans-2-aminocyclohexanol ((±)-5).[8] Selective N-benzoylation of (±)-5 to give (±)-6 in 90% yield was achieved by treatment of a solution of (±)-5 in chloroform-aqueous $NaHCO_3$ with excess benzoyl chloride. Crystalline (±)-6 could be filtered directly from the reaction mixture, thus saving a purification step. Jones oxidation[9] of (±)-6 proceeded smoothly to give crystalline (±)-2-(N-benzamido)cyclohexanone ((±)-7) in 86% yield. Treatment of (±)-7 with excess pyrrolidine in refluxing benzene containing a trace of *p*-toluenesulfonic acid resulted in a 91% yield of enamines (8 and (±)-9).[10] The ratio of 8 to (±)-9 was 3 : 1 as determined by ^{1}H-nmr comparison of the olefinic proton of (±)-9 at 4.73 ppm to the combined aromatic protons at 7.32-7.76 ppm for the enamine mixture. Interestingly, our previously reported synthesis of the enamine mixture from (±)-2-(N-t-butyloxycarbonyl) cyclohexanone and pyrrolidine under identical conditions resulted in a 97 : 3 ratio of tetra- to tri- substituted enamines.[3] Catalytic hydrogenation of enamine

mixture (8 and (±)-9) in ethyl acetate in the presence of 10% Pd-C resulted in a quantitative yield of a 3 : 1 ratio of (±)-cis-2-pyrrolidinyl-N-(benzoyl)cyclohexyl amine ((±)-10) to (±)-trans-2-(1-pyrrolidinyl)-N-(benzoyl)cyclohexylamine ((±)-11).

Scheme 1



Changing the catalyst from 10% Pd-C to PtO_2 did not change the ratio of (±)-10 to (±)-11; this effect of changing the catalyst is different from that observed in our previous study of the 97 : 3 enamine mixture formed from reaction of pyrrolidine with (±)-2-(N-t-butyloxycarbonyl)cyclohexanone.[3] Hydrogenation of this over 10% Pd-C afforded a 99 : 1 ratio of cis- to trans-isomers while over PtO_2, an 88 : 12 ratio of cis- to trans-products was formed. These results suggest that the distribution of cis to trans products is dependent on the proportion of trisubstituted enamine in the mixture. As would be expected, only the trisubstituted enamine forms the trans product.

The presence of (±)-11 in the product mixture did not present a problem since (±)-10 and (±)-11 were readily separated through one crystallization of their hydrochloride salt from 2-propanol. Thus no attempt was made to further optimize the ratio of (±)-10 formed. Attempts to effect optical resolution of (±)-10 through fractional crystallization of several diastereomeric mixtures of salts were unsuccessful. Thus, (±)-10 was hydrolysed by refluxing with KOH in ethyleneglycol to give (±)-cis-2-pyrrolidinylcyclohexylamine ((±)-4) in 96% yield. Two recrystallizations of the bis-R-(-)-mandelate salt of (±)-4 afforded an 81% yield of enantiomerically pure (-)-4. The mother liquor was converted back to the free base by partitioning between 30% sodium hydroxide and chloroform; evaporation of the chloroform layer and high vacuum distillation of the residue afforded optically enriched (with the opposite enantiomer) base. Two recrystallizations of the bis-S-(+)-mandelate salt of the recovered base afforded 83% yield of enantiomerically pure (see below) (+)-4. The absolute configuration of (+)-4 and (-)-4 was established by the sequence of N-formylation of (-)-4 with refluxing ethyl formate to give (+)-12, followed by LAH reduction to give 1R,2S-(-)-13 identical to the previously reported cis-(-)-2-pyrrolidinyl-N-methyl cyclohexylamine of known (1R,2S) absolute configuration[3] by tlc, ^{1}H-nmr and optical rotation comparison. The optical purity of 1R,2S-(-)-4 and 1S,2R-(+)-4 was established by hplc analysis of the diastereomeric ureas 14 and 15 formed by reaction of these amines with enantiomerically pure 1S-(-)-1-(phenyl) ethylisocyanate[11] in dry chloroform (Scheme 1). Diamines ((-)-4 and (+)-4) were greater than 99.5% enantiomerically pure as determined by this method.

EXPERIMENTAL

Materials

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Specific rotation determinations at the sodium-D line were obtained in a 1 dM cell using a Perkin-Elmer 241-MC polarimeter (automatic). Gas chromatographic (gc) analysis was performed on a Hewlett-Packard 5880A instrument fitted with a 30 M SE-30 capillary column and a flame ionization detector. High performance liquid chromatography (hplc) was performed using a Gilson model 303 with a solvent mixer (model 811) and a Data Master (model 620). Elemental analyses were performed at Atlantic Microlabs, Atlanta, GA. Chemical-ionization mass spectra (CIms) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization mass spectra (EIms) and high resolution mass measurements (HRms) were obtained using a VG-Micro Mass 7070F mass spectrometer. ^{1}H-Nmr spectra were obtained using a Varian XL-300 spectrometer. Thin layer chromatography (tlc) was performed on 250 μM Analtech GHLF silica gel plates. Tlc system A corresponds to $CHCl_3$-MeOH-conc.

aq. NH_3 (90 : 9 : 1); tlc system B corresponds to $CHCl_3$-MeOH-conc. aq. NH_4OH (80 : 18 : 2).

(±)-trans-2-(Benzamido)cyclohexanol ((±)-6). To a mechanically stirred solution of (±)-trans-2-aminocyclohexanol (240.67 g, 2.09 mol) in a mixture of chloroform (2000 ml), water (2000 ml) and sodium bicarbonate (351.6 g, 4.18 mol) was added dropwise during 30 min, benzoyl chloride (351.6 g, 267.5 ml, 2.50 mol). Stirring was continued for 1 h or until reaction was complete by tlc (solvent system A). The crystalline product was isolated by filtration of the reaction mixture. The filter cake was pressed dry and washed with enough distilled water to give a neutral silver nitrate test. The crystalline product was dried overnight in vacuo at 80 °C to afford 312.5 g (68%) of analytically pure (±)-6: mp 172-173 °C as feathery needles. The yield could be increased to 90% by separation and evaporation of the chloroform layer in vacuo. ^{1}H-Nmr ($CDCl_3$): δ 1.24-1.43 (m, 4H), 1.74-1.79 (m, 2H), 2.09-2.14 (m, 2H), 3.43-3.52 (m, 2H, CH-N, CH-O), 3.85 (br s, 1H, OH), 6.12 (br s, 1H, NH), 7.41-7.52 (m, 3H, ArH)), 7.76-7.79 (m, 2H, ArH). CIms: MH^+ (calcd for $C_{13}H_{17}NO_2$) = 220, MH^+(found) = 220. Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39; Found: C 71.33, H 7.80, N 6.45.

(±)-2-(Benzamido)cyclohexanone ((±)-7). To a mechanically stirred and cooled (ice-bath to keep reaction mixture at room temperature) suspension of (±)-6 (260.0 g, 1.19 mol) in acetone (3000 ml) was added dropwise during 30 min, 962 nl (1.19 mol) of a solution of Jones reagent (prepared by adjusting a solution of ,40 g of CrO_3 in 122 ml of conc. H_2SO_4 to 1135 ml with distilled water). After the addition was complete, the reaction became homogeneous. The reaction was stirred for a further 1 h when tlc (solvent system A) indicated that the reaction was complete. The reaction mixture was neutralized (with stirring) by careful addition of a 20% solution of K_2CO_3 in distilled water until there was no further evolution of CO_2. The clear upper layer was evaporated in vacuo to afford a crystalline solid. The inorganic salts that remained on the bottom of the reaction flask were triturated with ethyl acetate (2 x 500 ml). The ethyl acetate triturate was added to residue remaining after evaporation of the reaction mixture, and a further 2000 ml of ethyl acetate added to produce a near homogeneous solution. The organic phase was extracted with water (4 x 500 ml) and saturated brine (500 ml). Evaporation of the solvent afforded the crude ketone as a white crystalline solid. Recrystallization of the crude product from 800 ml of aqueous 2-propanol (1 : 1) afforded 221.5 g (86 %) of (±)-7: mp 126-127 °C. ^{1}H-Nmr ($CDCl_3$): δ 1.38-1.55 (m, 1H), 1.10-2.00 (m, 3H), 2.13-2.24 (m, 1H), 2.40-2.55 (m, 1H), 2.55-2.65 (m, 1H), 2.78-2.90 (m, 1H), 4.60-4.74 (m, 1H), 7.20 (br s, 1H), 7.40-7.55 (m, 3H), 7.82 (d, J=6.8 Hz, 2H). CIms: MH^+ (calcd for $C_{13}H_{15}NO_2$) = 218; MH^+ (found) = 218. Anal. Calcd for $C_{13}H_{15}NO_2$: C 71.87, H 6.96, N 6.45; Found: C 71.90, H 6.95, N 6.46.

1-Benzamido-2-(1-pyrrolidinyl)cyclohexene (8) and (±)-3-Benzamido-2-(1-pyrrolidinyl)cyclohexene ((±)-9). A stirred solution of (±)-7 (212.8 g, 0.9806 mol), *p*-toluenesulfonic acid (9.32 g, 0.049 mol) and pyrrolidine (103 ml, 1.24 mol) in benzene (3300 ml) was refluxed for 23 h when gc (200 °C) indicated 11.4% unreacted (±)-7 remaining. A further 103 ml (1.24 mol) of pyrrolidine was added and refluxing continued for a further 24 h; gc (200 °C) indicated that the reaction was 97.8% complete at this stage. Evaporation of the solvent and excess pyrrolidine in vacuo yielded quantitative yield of mixture 8 and (±)-9 as an off-white crystalline solid after high vacuum drying. Elms (m/z, rel. int.): 270 (12, M^+), 217 (18), 149 (94), 105 (100), 77 (87), 70 (33). M^+ (calcd for $C_{17}H_{22}N_2O$): 270.1732; M^+ (found) : 270.1723.

(±)-cis-2-(1-Pyrrolidinyl)-N-benzoylcyclohexylamine ((±)-10) and (±)-trans-2-(1-Pyrrolidinyl)-N-benzoylcyclohexylamine ((±)-11). Enamine mixture (8 and (±)-9) (100 g) in ethyl acetate (200 ml) containing 10.0 g of 10% Pd/C was hydrogenated in a Parr apparatus at 50 p.s.i. for 1.5 h at ambient temperature. Gc analysis (200 °C) of the reaction mixture indicated a 3 : 1 ratio of (±)-10 to (±)-11. The combined reaction mixtures from hydrogenation of a total of 257.2 g of enamine (8 and (±)-9) were filtered through a bed of celite, and the celite was washed well with ethyl acetate. The combined filtrate and washings were evaporated in vacuo. To the residue was added 306 g of citric acid monohydrate followed by water (1300 ml) and the mixture was shaken with CH_2Cl_2 (500 ml) until homogeneous. The aqueous layer was washed well with a further 2 x 500 ml of CH_2Cl_2 and the combined organic extract was discarded. The aqueous layer was basified by addition of excess concentrated aqueous ammonia and extracted with 3 x 500 ml of CH_2Cl_2. Drying of the organic extract by filtration through anhydrous Na_2SO_4 followed by evaporation of the solvent in vacuo afforded 236.0 g (91.1%) of a 3 : 1 ratio of (±)-10 and (±)-11 as a crystalline solid.

Separation of (±)-10 and (±)-11. Amine mixture of 11/12 from above (225.5 g) was converted to its HCl salt by dissolving it in 200 ml of MeOH followed by addition of an excess of anhydrous HCl gas dissolved in MeOH. The solution was adjusted to 700 ml by addition of 2-propanol and the MeOH component was distilled off while keeping the volume constant at 700 ml by addition of 2-propanol. Crystallization occurred after most of the MeOH component had evaporated. The crystallization mixture was set aside to cool slowly to room temperature, and then placed in a refridgerator and further cooled to 4 °C. The mixture was filtered and the filter-bed was washed twice with cold (0 °C) 2-propanol to afford 156.2 g of (±)-10·HCl. Gc (200 °C) indicated that this material contained 2% of (±)-11. One further recrystallization of this material afforded 146.8 g of (±)-10·HCl as small prisms which were 99.5% pure by gc: mp 276-277 °C. Anal Calcd for $C_{17}H_{25}N_2OCl$: C 66.11, H 8.16, N 9.07; Found: C 66.22, H 8.15, N

9.04. Compound (±)-10 (base): mp 103-104 °C. ^{1}H-Nmr ($CDCl_3$): δ 1.22-1.55 (m, 5H), 1.65-1.82 (m, 5H), 1.92-2.00 (m, 1H), 2.17-2.27 (m, 1H), 2.49-2.60 (m, 5H), 4.23 (br s, 1H), 6.77 (br s, 1H), 7.40-7.52 (m, 3H), 7.80 (d, J=7.0 Hz, 2H). Anal. Calcd for $C_{17}H_{24}N_2O$: C 74.96, H 8.88, N 10.28; Found: C 74.85, H 8.87, N 10.31.

(±)-cis-2-(1-Pyrrolidinyl)cyclohexylamine ((±)-4). To a solution of (±)-10 (102 g, 0.375 mol) in ethylene glycol (250 ml) was added KOH pellets (49.5 g, 2.0 eq.) and the solution was refluxed for 48 h under an argon atmosphere. The reaction mixture was cooled to room temperature and diluted to 1500 ml by addition of 1250 ml of water. To the aqueous mixture was added (with ice cooling), 225 g of KOH pellets. When the addition of the KOH was complete, an upper organic layer of the oily base separated out. When the solution had cooled to room temperature, it was extracted with $CHCl_3$ (5 x 300 ml), and the combined organic extract was dried over Na_2SO_4. Evaporation of the $CHCl_3$ phase and distillation of the residue under high vacuum afforded 60.2 g (95.6%) of (±)-4 as a colorless unstable oil.[12] bp: 94 °C / 0.05 mmHg. Ir (film): 3380, 3300, 2940, 1590, 1440, 1125, 835 cm^{-1}. (±)-4·HCl crystallized slowly from 2-propanol as small conglomerates: mp 263-265 °C. ^{1}H-Nmr (free base) ($CDCl_3$): δ 1.00-1.18 (m, 1H), 1.20-1.40 (m, 5H), 1.50-1.68 (m, 6H), 1.74 (t, J=3.5 Hz, 1H), 1.78 (t, J=3.5 Hz, 1H), 2.30- 2.48 (m, 4H), 3.08 (br s, 2H). EIms (m/z, rel. int.): 168 (31, M^+), 110 (100), 97 (42), 84 (92), 70 (33). Anal. Calcd for $C_{10}H_{22}N_2Cl_2$: C 49.79, H 9.19, N 11.62; Found: C 49.82, H 9.19, N 11.67.

(-)-cis-2-(1-Pyrrolidinyl)cyclohexylamine ((-)-4). To a solution of R-(-)-mandelic acid (18.12 g, 119.1 mmol) in 250 ml of ethanol/2-propanol (1 : 4) at 60 °C was added a warm (60 °C) solution of (±)-4 (10.00 g, 59.5 mmol) in 50 ml of ethanol/2-propanol (1 : 4). The solution was allowed to cool slowly to room temperature when copious crystallization started to occur. After 1 h, the suspension of crystals was filtered and the filter cake was washed with 2 x 40 ml of cold (0 °C) ethanol/2-propanol (1 : 4) followed by 40 ml of ether to afford 12.46 g of (-)-4·R-(-)-mandelate. This first crop of crystals was recystallized from 400 ml of ethanol/2-propanol (1 : 4) to afford 11.39 g (81%) of (-)-4·R-(-)-mandelate as small needles: mp 167-169 °C. $[\alpha]_D$ -85.8° (c 0.33, MeOH). Anal. Calcd for $C_{26}H_{36}N_2O_6$: C 66.08, H 7.68, N 5.93; Found: C 66.15, H 7.70, N 5.94. Conversion of 11.00 g of this salt to its free base by partitioning between 100 ml of 30% NaOH and 100 ml of $CHCl_3$ afforded 3.83 g (98%) of enantiomerically pure (-)-4 as a colorless oil[12] which crystallized to form large low melting prisms on standing at room temperature: bp 86 °C / 0.1 mmHg. $[\alpha]_D$ -2.95 ° (c 0.68, MeOH).

(+)-cis-2-(1-Pyrrolidinyl)cyclohexylamine ((+)-4). The mother liquors from the above resolution were combined and evaporated down in vacuo to yield a crystalline residue. The residue was partitioned between 30% aqeous NaOH (100 ml) and $CHCl_3$ (100 ml). The aqueous layer was washed with a further 3 x 50 ml

of $CHCl_3$ and the combined organic layer was evaporated in vacuo. Distillation of the oily residue under high vacuum through a short-path condenser afforded 5.43 g of optically enriched mixed bases. These were dissolved in 50 ml of ethanol/2-propanol (1 : 4) and the solution was warmed to 60 °C. This solution was then added to a 60 °C solution of S-(+)-mandelic acid (9.83 g, 64.6 mmol) in ethanol/2-propanol (1 : 4) (250 ml). Crystallization occurred spontaneously as the solution cooled to ambient temperature. The filter cake was washed with 2 x 40 ml of solvent and 40 ml of ether as above and vacuum dried at 60 °C, yield 12.71 g. Recrystallization of the first crop from 300 ml of hot ethanol/2-propanol (1 : 4) afforded 11.69 g (83%) of (+)-4·S-(+)-mandelate as small needles. mp 167-169 °C. $[\alpha]_D$ +82.7 ° (c 0.32, MeOH). Anal. Calcd for $C_{26}H_{36}N_2O_6$: C 66.08, H 7.68, N 5.93; Found: C 66.14, H 7.73, N 5.93. Conversion of 11.00 g of this salt to the free base as described above for (-)-4 furnished 3.77 g (96%) of enantiomerically pure (+)-4 as a colorless oil[12] which formed large low melting prisms on standing at room temperature: bp 86 °C / 0.1 mmHg. $[\alpha]_D$ +2.21 ° (c 1.02, MeOH).

(+)-cis-2-(1-Pyrrolidinyl)-N-formylcyclohexylamine ((+)-12). A solution of (-)-4 (2.00 g, 11.90 mmol) in 20 ml of ethyl formate was boiled under reflux for 10 min when tlc (solvent system A) indicated that the reaction was complete. The solvent was evaporated in vacuo to give a quantitative yield of (+)-12 which crystallized to a waxy solid on standing. Crystallization of the fumarate salt from 2-propanol afforded 3.05 g (82%) of analytically pure (+)-12·fumarate: mp 187-188 °C. $[\alpha]_D$ +2.1 ° (c 0.96, MeOH). ^{1}H-Nmr (on free base) ($CDCl_3$): δ 1.20-1.40 (m, 4H), 1.48 (m, 1H), 1.75 (m, 5H), 1.92 (m, 1H), 2.10 (m, 1H), 2.30 (m, 1H), 2.52 (m, 4H), 4.18 (br s, 1H), 6.10 (br s, 1H), 8.24 (s, 1H). CIms MH^+ (Calcd for $C_{11}H_{20}N_2O$): 197, MH^+ (found): 197. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C 57.68, H 7.74, N 8.97; Found: C 57.67, H 7.77, N 8.95.

1R,2S-(-)-cis-2-(1-Pyrrolidinyl)-N-methylcyclohexylamine ((-)-13). To 16 ml of a 1.0 M solution of LAH in THF was added, dropwise with stirring, a solution of (+)-12 (1.52 g, 7.75 mmol) in dry THF (10 ml) and the solution was boiled under reflux for 1 h. The solution was treated dropwise at 0 °C with 0.6 ml of water, 0.6 ml of 15% NaOH followed by 1.8 ml of water. The reaction mixture was filtered and the inorganic salts washed with 10 ml of ether. The filtrate was evaporated in vacuo, and the oily residue was distilled under high vacuum to afford 1.25 g (89%) of (-)-13. bp 76 °C / 1.1 mmHg (lit.[3] bp 79 °C / 1.2 mmHg). $[\alpha]_D$ -31.7 ° (c 3.32, MeOH) {lit.[3] $[\alpha]_D$ -31 ° (c 1.49, MeOH)}.

N-(cis-1S-(1-Pyrrolidinyl)-2R-cyclohexyl)-N'-(1S-(phenyl)ethyl)urea (14). To a stirred solution of (-)-4 (100 mg, 0.59 mmol) in dry chloroform (1.0 ml) was added, via syringe, optically pure[11] 1S-(-)-phenylethylisocyanate (93.8 µl, 10% excess). The solution was stirred for 5 min at ambient temperature or until reaction was complete by tlc (solvent system A), and the solvent was evaporated

in vacuo to afford a quantitative yield of 14 as a crystalline solid. ^{1}H-Nmr ($CDCl_3$): δ 0.90-1.28 (m, 5H), 1.33 (d, J=6.9 Hz, 3H), 1.50 (m, 1H), 1.57-1.70 (m, 5H), 1.90-2.08 (m, 2H), 2.40 (br s, 4H), 3.85 (br s, 1H), 4.18 (m, 1H), 5.00 (br s, 1H), 5.17 (br s, 1H), 7.10-7.24 (m, 5H).

N-(cis-1R-(1-Pyrrolidinyl)-2S-cyclohexyl)-N'-(1S-(phenyl)ethyl)urea (15). The procedure for 14 above was repeated starting instead with 100 mg (0.59 mmol) of (+)-4. The product was obtained in quantitative yield as a white cystalline solid. ^{1}H-Nmr ($CDCl_3$): δ 1.05-1.28 (m, 5H), 1.32 (d, J=6.9 Hz, 3H), 1.50 (br s, 4H), 1.56-1.64 (m, 1H), 1.64-1.70 (m, 1H), 1.88-1.96 (m, 1H), 1.98-2.09 (m, 1H), 2.29 (m, 4H), 3.83 (br s, 1H), 4.66 (m, 1H), 5.05 (br s, 1H), 5.21 (br s, 1H), 7.10-7.24 (m, 5H).

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