Efficient diastereoselective synthesis of (1R,2R)-1-alkyl-1-phenyl-2-methylamino propanes and study of their stereochemical aspects

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Abstract
A concise and novel approach for the synthesis of (1R,2R)-1-alkyl-1-phenyl-2-methylaminopropanes by dehydroxylation of corresponding (1S,2R)-1-phenyl-1-alkyl-2-methylamino propan-1-ols, which were prepared by the asymmetric induction through Grignard reaction of optically active α-aminoketones. These efficient preparations resulted in compounds with very good yields and high diastereoselectivity. The stereochemistry involved in the synthesis was described with justification on absolute configuration of the compounds.

Keywords: Dehydroxylation, α-aminoketones, α-amino chlorides, asymmetric induction, methamphetamine analogues, hydrodehalogenation

Introduction
Chiral drugs have become progressively more popular in recent years and the market is rapidly growing for this segment of drugs. These compounds now represent almost one-third of all drug sales worldwide due to which there is a spurt in demand for chiral building blocks, key intermediates and chemicals. Though there are many ways to prepare chiral compounds, the best would be stereoselective synthesis, as it minimizes the formation of an unwanted isomer. Stereoselective synthesis of several such chiral compounds was attempted in this work. Derivatives of ephedrine available commercially in the market exhibit psycostimulant activity, to name a few, 1-phenyl-2-methylaminopropane 2,1,2 methylenedioxymethamphetamine3 (MDMA) 3, MDEA4 4, benzamphetamine 5, etc. Earlier studies revealed that substitution of an alkyl or aryl group at the benzylic carbon of ephedrine increases the pharmacological activity with
greatly reduced toxicity. Further, derivatives of α-aminopropane with propargyl group substitution on nitrogen (Selegiline 6) is extensively useful in the early stage of Parkinson’s disease. Likewise Famprofazone 7, a non steroidal anti-inflammatory agent (NSAID) is also a prodrug of 1-phenyl-2-methylaminopropane structure. Another new generation analgesic belonging to the family of α-alkylated aminopropanes is (1′R,2′R)-3-(3-dimethylamino-1′-ethyl-2′-methylpropyl)phenol (8) hydrochloride (Tapentadol hydrochloride).³⁻¹⁰

![Chemical Structures](image)

**Results and Discussion**

Recognizing the vast potential for chiral active pharmaceutical ingredients, we report here the diastereoselective synthesis of 1-alkyl-1-phenyl-2-methylaminopropanes (α-alkylated methamphetamine) 1 from ephedrine via the intermediacy of corresponding α-alkylephedrines 9 as illustrated in Scheme 1.

![Chemical Structures](image)

The absolute configuration of the dehydroxylated carbon was arrived by chemical analogy as well as X-ray diffraction studies. Various 1-alkyl-1-phenyl-2-methylaminopropanes were prepared from the corresponding amino alcohols as shown in Scheme 1 and tabulated in Table 1.
Scheme 1. Schematic representation of preparation of α-alkylated methamphetamines.

Table 1. 1-Alkyl-1-phenyl-2-methylaminopropanes (1) and the precursor 1,2-aminoalcohols (11)
The starting compounds, α-alkylated-1-phenyl-2-methyaminopropan-1-ol hydrochlorides 11a-g for the study of dehydroxylation were prepared by the Grignard reaction of alkyl magnesium halides with (R)-(+-) 1-phenyl-2-methyaminopropan-1-one 10 (Scheme 2)\textsuperscript{11,12}

\[
\begin{array}{c}
\text{HO} \quad \text{NHMe} \\
\text{Me} \\
\text{H}
\end{array}
\xrightarrow{\text{RMgX}}
\begin{array}{c}
\text{HO} \\
\text{Me} \\
\text{NHMe}
\end{array}
\]

\[9 \xrightarrow{\text{RMgX}} 10 \xrightarrow{\text{RMgX}} 11a-g\]

**Scheme 2.** Optically active 1-alkylated 1-phenyl-2-methyaminopropan-1-ol 11a-g from (1S,2R)-2-methylaminophenylpropan-1-ol (9).

The amino-ketone with known configuration at adjacent carbon was synthesized by the acid-catalyzed oxidation of (1S,2R)-1-phenyl-2-methyaminopropan-1-ol 9.\textsuperscript{13}

As illustrated in Scheme 3, the hydrogen bonding between the hydrogen of the amino function with carbonyl carbon through five-membered cyclic transition state which freezes the conformation of the ketone and facilitates the approach of alkyl anion of the Grignard reagent from the least hindered site (Cram’s rule), leads to formation of the single diastereomer (1S,2R)-α-alkylated-1-phenyl-2-methyaminopropan-1-ol hydrochlorides 11a–g with high optical purity (ee: 100%; dr: >99%)

\[
\begin{array}{c}
\text{HO} \quad \text{NHMe} \\
\text{Me} \\
\text{H}
\end{array}
\xrightarrow{\text{RMgX}}
\begin{array}{c}
\text{HO} \\
\text{Me} \\
\text{NHMe}
\end{array}
\]

\[9 \xrightarrow{\text{RMgX}} 10 \xrightarrow{\text{RMgX}} 11a-g\]

**Scheme 3.** Schematic representation of the formation of a single diastereomer via a five-membered transition state.

The absolute configuration of α-alkylated-1,2-aminoalcohol 11a-g is that predicted with the help of Cram’s rule and molecular models, which is confirmed by single crystal X-ray diffraction study. The ORTEP diagram of (1S,2R)-1-(2-phenylethyl)-1-phenyl-2-methyaminopropan-1-ol hydrochloride (11g) is shown in Figure 1.\textsuperscript{21}
According to the envisaged strategy, $\alpha$-alkyl-1-chloro-1-phenyl-2-methylaminopropane hydrochlorides 13a-g were synthesized by chlorinating the $\alpha$-alkylated-1-phenyl-2-methylaminopropan-1-ol hydrochlorides 11a-g using thionyl chloride. As a well-known fact, in the presence of amino functionality, chlorination of alcohols proceeds through S$_{N}$2 mechanism$^{14}$ rather than S$_{N}$i mechanism. Thus, chlorination of $(1S,2R)$-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride 11a-g at C-1 is expected to undergo via S$_{N}$2 mechanism resulting in inversion of configuration at the reaction center to obtain corresponding $(1R,2R)$-1-alkyl-1-chloro-1-phenyl-2-methylaminopropane hydrochloride 13a-g (Table 2).

The possible formation of aziridinium ion$^{15-17}$ by intramolecular rearrangement of amino chloride is inhibited as the chlorination is performed with the quaternary salt of the 1,2-aminoalcohol where the lone pair on nitrogen is not available for the cyclization to yield an aziridinium ion. Further, catalytic hydrodehalogenation of the chloro intermediates brings about another inversion,$^{18}$ leading to overall retention of configuration at C-1 (Scheme 4).

![Figure 1. ORTEP representation of $(1S,2R)$-1-(2-phenylethyl)-1-phenyl-2-methylaminopropan-1-ol hydrochloride (11g).](image)

**Scheme 4.** Schematic representation of 1-alkylated 1-phenyl-2-methylaminopropane formation via the chloro intermediates 13.
Table 2. Physical properties of α-alkyl-1-chloro-1-phenyl-2-methylaminopropane hydrochlorides synthesized in the present work

<table>
<thead>
<tr>
<th>Amino alcohol</th>
<th>1-Alkyl-1-chloro-1-phenyl-2-methylaminopropane hydrochloride</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>Entry</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>11a</td>
<td>Ethyl (1S,2R)</td>
<td>13a</td>
</tr>
<tr>
<td>11b</td>
<td>n-Butyl (1S,2R)</td>
<td>13b</td>
</tr>
<tr>
<td>11c</td>
<td>Isopropyl (1S,2R)</td>
<td>13c</td>
</tr>
<tr>
<td>11d</td>
<td>Cyclopentyl (1S,2R)</td>
<td>13d</td>
</tr>
<tr>
<td>11e</td>
<td>Cyclohexyl (1S,2R)</td>
<td>13e</td>
</tr>
<tr>
<td>11f</td>
<td>Benzyl (1S,2R)</td>
<td>13f</td>
</tr>
<tr>
<td>11g</td>
<td>Phenylethyl (1S,2R)</td>
<td>13g</td>
</tr>
<tr>
<td>14c &amp; 14e</td>
<td>Isopropyl (1R,2S)</td>
<td>15c &amp; 15e</td>
</tr>
</tbody>
</table>

The absolute configuration of the product at C-1 is inferred as ‘R’ by the application of Cahn-Ingold-Prelog (CIP) priority rules and from the molecular models and by chemical analogy. A range of 1-alkyl-1-phenyl-2-methylaminopropane hydrochlorides prepared in the present work is furnished in Table 3 along with their physical properties, diasteromeric ratio and ee.

Similarly (1S,2S)-1-isopropyl-1-phenyl-2-methylaminopropane 16c, (1S,2S)-1-cyclohexyl-1-phenyl-2-methylaminopropane 16b were synthesized from the respective (1R,2S)-α-alkylated aminoalcohol 14c & 14e via the chloro intermediacy 15c & 15e using similar method. The optical rotation, HPLC purity and Ee along with their retention times are correlated with their corresponding (1R,2R) products in Table 3.

A second major area of work involves the study of stereochemical aspects at C-1 by carrying out the dehydroxylation of (1S,2R)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol 11a-g by diverse routes. This was envisaged by inhibiting the inversion in the first step by transforming the OH group of 1,2-aminoalcohol to trifluoroacetyl (Scheme-5) and subsequent hydrogenation.
Scheme 5. Dehydroxylation by trifluoracetate derivative of amino alcohol leading to diastereomer of the title compounds.

Table 3. Physical properties of 1-Alkyl-1-phenyl-2-methylaminopropane hydrochloride synthesized

<table>
<thead>
<tr>
<th>Amino Chloride</th>
<th>1-Alkyl-1-phenyl-2-methylaminopropane hydrochloride</th>
<th>Yield (%)</th>
<th>Config.</th>
<th>[α]D 25 (1%H2O)</th>
<th>Dr (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 13a Ethyl (1R,2R)</td>
<td>1a</td>
<td>80.9</td>
<td>(1R,2R)</td>
<td>+3.2°</td>
<td>99.1 : 0.9</td>
<td>100</td>
</tr>
<tr>
<td>13b n-Butyl (1R,2R)</td>
<td>1b</td>
<td>82.7</td>
<td>(1R,2R)</td>
<td>−4.14°</td>
<td>99.2 : 0.8</td>
<td>100</td>
</tr>
<tr>
<td>13c Isopropyl (1R,2R)</td>
<td>1c</td>
<td>86.4</td>
<td>(1R,2R)</td>
<td>+19.1°</td>
<td>99.3 : 0.7</td>
<td>100</td>
</tr>
<tr>
<td>13d Cyclopentyl (1R,2R)</td>
<td>1d</td>
<td>83.2</td>
<td>(1R,2R)</td>
<td>+9.2°</td>
<td>99.2 : 0.7</td>
<td>100</td>
</tr>
<tr>
<td>13e Cyclohexyl (1R,2R)</td>
<td>1e</td>
<td>85.7</td>
<td>(1R,2R)</td>
<td>+18.6°</td>
<td>99.1 : 0.89</td>
<td>100</td>
</tr>
<tr>
<td>13f Benzyl (1R,2R)</td>
<td>1f</td>
<td>88.4</td>
<td>(1R,2R)</td>
<td>−56.3°</td>
<td>99.2 : 0.8</td>
<td>100</td>
</tr>
<tr>
<td>13g Phenylethyl (1R,2R)</td>
<td>1g</td>
<td>86.2</td>
<td>(1R,2R)</td>
<td>−10.7°</td>
<td>99.1 : 0.9</td>
<td>100</td>
</tr>
<tr>
<td>15c Isopropyl (1S,2S)</td>
<td>16c</td>
<td>88.0</td>
<td>(1S,2S)</td>
<td>−20.6°</td>
<td>99.0 : 1.0</td>
<td>100</td>
</tr>
<tr>
<td>15e Cyclohexyl (1S,2S)</td>
<td>16e</td>
<td>84.7</td>
<td>(1S,2S)</td>
<td>−17.9°</td>
<td>99.0 : 1.0</td>
<td>100</td>
</tr>
</tbody>
</table>

Thus obtained, 1-alkyl-1-phenyl-2-methylaminopropane hydrochlorides are compared with the compounds obtained via the chloro intermediates (Scheme-4). Accordingly, for the study, we synthesized (1S,2R)-1-isopropyl-2-(methylamino)-1-phenylpropyltrifluoroacetate 17c and (1S,2R)-1-cyclohexyl-2-(methylamino)-1-phenylpropyltrifluoroacetate 17e from the corresponding 1,2-aminoalcohol, viz. (1S,2R)-1-isopropyl-1-phenyl-2-methylaminopropan-1-ol 11c and (1S,2R)-1-cyclohexyl-1-phenyl-2-methylaminopropan-1-ol 11e by reaction with trifluoro-
acetic anhydride (Scheme 5) in THF. Further, hydrogenolysis of the trifluoroacetoxy compounds 17c and 17e intermediate using palladium on carbon yielded (1S,2R)-1-isopropyl-1-phenyl-2-methylaminopropane 1c' and (1S,2R)-1-cyclohexyl-1-phenyl-2-methylaminopropane 1e' respectively, both isolated as hydrochlorides. In this sequence of reactions, the trifluoroacetylation reaction proceeded with retention of configuration and reduction resulted in inversion and hence overall configuration at C-1 is inferred as “S” by the application of CIP rule.

Again, (1S,2R)-1-isopropyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride 11c on Walden inversion at C-1 by known procedures\(^{20}\) afforded (1R,2R)-1-isopropyl-1-phenyl-2-(methylamino)propan-1-ol hydrochloride 18c which was derivatized using trifluoroacetic anhydride to obtain (1R,2R)-1-isopropyl-2-(methylamino)-1-phenylpropyltrifluoroacetate 19c (Scheme 6) with retention of configuration as described above. The hydrogenation of the trifluoroacetate derivative with palladium on carbon gave (1R,2R)-1-isopropyl-1-phenyl-2-methylaminopropane hydrochloride 1c.

**Scheme 6.** Synthesis of (1R,2R)-1-alkyl-1-phenyl-2-(methylamino)propane hydrochloride through double stereoinversions.

Similar reactions are repeated with (1S,2R)-1-cyclohexyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride 11e to obtain the respective compound (1S,2R)-1-cyclohexyl-1-phenyl-2-methylaminopropane hydrochloride 18e. It is to be noted (Scheme 7 and Table 4) that absolute configuration at C-1 for the products 1c obtained in two different routes Scheme 6 and Scheme 4 is similar but differed for the product 1e'. Similar observation was noted for the compounds 1c and 1e'. This study confirms the absolute configuration of the dehydroxylated product in the present work to be \( R \) at C-1.

This is in agreement with the proposed configuration of diastereomer during dehydroxylation of (1S,2R)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride. It can be noticed that the Scheme 7, Table 4 compounds synthesized 1-alkyl-1-phenyl-2-methylaminopropanes from Scheme 4 and 5 having diastereomeric relationship. Whereas compound obtained from Scheme 4 and 6 are having same absolute configuration.
Table 4. Comparison of physical properties of diasteromeric 1-alkyl-1-phenyl-2-aminopropane hydrochlorides

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Compound No.</th>
<th>Configuration</th>
<th>[α]$_D^{25}$</th>
<th>Diasteromeric purity (%)</th>
<th>RT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 4</td>
<td>1c</td>
<td>1R,2R</td>
<td>+19.1</td>
<td>99.34</td>
<td>12.3</td>
</tr>
<tr>
<td>Scheme 5</td>
<td>1c'</td>
<td>1S,2R</td>
<td>-10.1</td>
<td>99.3</td>
<td>15.1</td>
</tr>
<tr>
<td>Scheme 6</td>
<td>1c</td>
<td>1R,2R</td>
<td>+19.9</td>
<td>99.0</td>
<td>12.4</td>
</tr>
<tr>
<td>Scheme 4</td>
<td>1e</td>
<td>1R,2R</td>
<td>+18.6</td>
<td>99.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Scheme 5</td>
<td>1e'</td>
<td>1S,2R</td>
<td>-8.8</td>
<td>99.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Scheme 6</td>
<td>1e</td>
<td>1R,2R</td>
<td>+18.1</td>
<td>99.0</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Scheme 7. Overview of the synthesis of 1-alkyl-1-phenyl-2-methylaminopropane by diverse routes.

Moreover, the tentative assignment of configuration at C-1 was eventually corroborated by single crystal X-ray diffraction analysis. Presented in Figure 2 is the ORTEP view of the
compound (1R,2R)-1-cyclohexyl-1-phenyl-2-methylaminopropane hydrochloride (1e) which confirms the assigned configuration.\textsuperscript{21}

The exceptional selectivity was observed during dehydroxylation of (1S,2R)-α-alkylated-1-phenyl-2-methylaminopropan-1-ol hydrochlorides 11a–g at the benzylic carbon. In either ways i.e via chloro or trifluoro intermediacy, the exclusive formation of single diastereisomer is due to the potential displacement of leaving group as nucleophile, which intern, depends on state of hybridization of benzyl carbon, and the electronic interaction on chemisorption through phenyl residue.

The same series of compounds 11a–g, when hydrogenated directly, resulted in products 1a–g with partial racemisation. As an example, compound 11a is hydrogenated in acidic medium\textsuperscript{22} at 60°C in the presence of palladium on carbon for 16hrs. The compound obtained 1a, was analysed by HPLC, showed mixture of diastereomers in the ratio of 86:13.

![Figure 2. X-ray structure of (1R,2R)-1-cyclohexyl-1-phenyl 2-methylaminopropane hydrochloride 1e (ORTEP view).](image)

**Conclusions**

We have demonstrated diasteroselective synthesis of substituted methamphetamine series from α-alkylated-1-phenyl-2-methylaminopropan-1-ol hydrochlorides. The process adopted in the synthesis is very useful to obtain desired enantiomer with excellent diasteroselectivity in good yield and tolerate broad range of substrates. Various stereochemical aspects involved in the synthesis are discussed to arrive at the absolute configuration and are justified by synthesizing
the diasteromers by diverse routes. The absolute configuration of intermediate amino alcohol and of alkyl aminopropane was confirmed by X-ray crystallography. The success of this synthetic method opens up new perspectives in the construction of biological and pharmaceutically active candidates.

**Experimental Section**

**General.** $^1$H NMR spectra were recorded on Brucker Avance 400 MHz and $^{13}$C NMR spectra were recorded on Brucker Avance 400 MHz/100 MHz in CDCl$_3$. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as internal reference standard. Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), q (quartet), bs (broad spectrum) or m (multiplet). IR spectra were recorded on a Shimadzu IR-460 FT-IR spectrometer and only major bands are reported in cm$^{-1}$. Melting points were determined on a microscopic apparatus Veego (VMP-PM). All the compounds were further characterized by Mass spectrum (ESI). The X-ray diffraction measurements are carried out on a Bruker AXS Kappa APEX 2 CCD diffractometer equipped with graphite monochromatic. Elemental analysis for all the compounds synthesized was carried out at Ashko Laboratories Ltd. Hyderabad. All the reagents used are commercial grade without further purification. (1S,2R)-1-Phenyl-2-methylaminopropan-1-ol hydrochloride and (1R,2S)-1-phenyl-2-methylaminopropan-1-ol hydrochloride were obtained from Malladi Drugs and Pharmaceuticals Ltd., Chennai.

**General Procedures**

**Preparation of (1S,2R)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride and (1R,2S)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride.** Prepared by the reported procedure$^{12}$ from (1S,2R)-1-phenyl-2-methylaminopropan-1-ol hydrochloride and (1R,2S)-1-phenyl-2-methylaminopropan-1-ol hydrochloride.

**General method for the preparation of (1R,2R)-1-chloro-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride (13a–g).** Thionyl chloride (0.16 mol) was slowly added to a solution of (1S,2R)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride (11a–g, 0.08 mol) in chloroform (50 mL) at 50-55 °C over a period of 2 h under nitrogen atmosphere. The mixture was then stirred at 50-55 °C for another 2 h. Solvent and excess thionyl chloride was removed under reduced pressure. The resulted residue was triturated with acetone to afford (1R,2R)-1-chloro-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride as a white crystalline solid.

**Preparation of (1R,2R)-1-alkyl-1-phenyl-2-methylaminopropane hydrochlorides (1a–g).** (1R,2R)-1-Chloro-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride 13a–g (0.055 mol) was placed in a round bottomed flask under nitrogen atmosphere and methanol 100 mL was added. The resulting solution was hydrogenated at room temperature for 2 hours at 2.0 bar hydrogen pressure in the presence 10% palladium on carbon (1.0 g). The catalyst was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with water 50
mL and washed with toluene (20 mL). The aqueous layer was concentrated under reduced pressure, and the syrup mass was crystallized using isopropyl alcohol to afford (1R,2R)-1-alkyl-1-phenyl-2-methylamino propane hydrochloride 1a-g as white crystalline solid.

Similarly compounds 16c and 16e were prepared starting from corresponding chloro derivatives 15c and 15e which were prepared from 1,2-aminoalcohols 14c and 14e.

(1R,2R)-(++)-1-Ethyl-1-phenyl-2-methylaminopropane hydrochloride (1a). (9.5g, 80.9%); [α]D 25 = +3.2° (C = 1.0, H2O); mp 204-205 °C (2-propanol); The diastereomeric purity was determined by HPLC to be 99.11% (Inertsil Phenyl 250 × 4.6 mm, 95% of 0.1M KH2PO4 pH 3.0 with orthophosphoric acid and 5% CH3CN, 1mL/min), tr (1R,2R) 12.17 min (99.11%) and (1S,2R) 11.14 min (0.85%). The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 98% n-hexane, 1% 2-propanol, 1% absolute ethanol, 0.1% diethylamine, 1mL/min, 210 nm). IR (KBr, cm−1): 2720, 1603, 1472, 1352, 756, 698; 1H NMR (DMSO-d6, 400 MHz) (δH) 0.63-0.66 (3H, t, J 7.2, CH2-CH3), 0.80-0.83 (3H, d, J 6.4, CH3-CH3), 0.98-0.99 (3H, d, J 6.4, CH-CH3), 1.61-1.91 (2H, m, CH2-CH3), 2.50 (3H, s, NH-CH3), 2.92-2.97 (1H, m, CH-CH-CH3), 3.37-3.40 (1H, m, CH-CH-CH3), 7.25-7.37 (5H, m, Harom), 8.98 (bs, 2H, NH2+). 13C NMR (DMSO-d6, 100 MHz) δc 11.77 (CH2-CH3), 12.76 (CH-CH3), 24.52 (CH-CH3), 29.82(NH-CH3), 48.94 (CH-CH-CH3), 57.66 (CH-CH-CH3), 126.94-139.32 (aromatic carbons). Mass spectrum (ESI, (+)-mode) [M+H]+ at m/z 178 (100). Anal. Calcd for C12H19N. HCl : C, 67.43; H, 9.43; N, 6.59. Found: C, 67.22; H, 9.45; N, 6.53.

(1R,2R)-(−)-1-(1-Butyl)-1-phenyl-2-methylaminopropane hydrochloride (1b). (11.0g, 82.7%); [α]D 25 = −4.14 ° (C=1.0, H2O); mp 128-129 °C (2-propanol); The diastereomeric purity was determined by HPLC to be 99.24% (Inertsil Phenyl 250 × 4.6 mm, 95% of 0.1M KH2PO4 pH 3.0 with orthophosphoric acid and 5% CH3CN, 1mL/min) tr (1R,2R) 8.67 min (99.24%) and (1S,2R) 7.95 min (0.74%). The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 98% n-hexane, 1% 2-propanol, 1% absolute ethanol, 0.1% diethylamine, 1mL/min, 210 nm). IR (KBr, cm−1): 2735,1585, 1466, 1355, 754, 700; 1H NMR (DMSO-d6, 400 MHz) δH 0.76 (3H, t, J 7.2, CH2-CH3), 0.98-0.99 (3H, d, J 6.8, CH3-CH3), 1.13-1.29 (2H, m, CH2-CH3), 1.61-1.85 (2H, m, CH2-CH=CH2-CH2-CH3), 2.50 (3H, s, NH-CH3), 3.04-3.09 (1H, m, CH-CH-CH3), 3.33-3.40 (3H, m, CH-CH-CH3 and CH2=CH2-CH2-CH3), 7.25-7.36 (5H, m, Harom), 8.50-9.60 (bs, 2H, NH2+). 13C NMR (DMSO-d6, 100 MHz) δc 12.62 (CH2-CH3), 13.79 (CH-CH3), 21.83 (CH2-CH3), 29.06 (CH2-CH=CH2-CH2-CH3), 29.86 (NH-CH3), 31.12 (CH3-CH3), 47.05 (CH2=CH2-CH2-CH3), 57.86 (CH-CH-CH3), 126.91-139.54 (aromatic carbons). Mass spectrum (ESI, (+)-mode) [M+H]+ at m/z 206 (100). Anal. Calcd for C13H23N.HCl: C, 69.54; H, 10.0 and N, 5.79. Found: C, 69.45; H,9.98; N, 5.77 %.

(1R,2R)-(++)-1-Isopropyl-1-phenyl-2-methylaminopropane hydrochloride (1c). (10.8 g, 86.4%); [α]D 25 = +19.1° (C = 1.0, H2O); mp 205-207 °C (2-propanol). The diastereomeric purity was determined by HPLC to be 99.34% (Inertsil Phenyl 250 × 4.6 mm, 95% of 0.1M KH2PO4 pH 3.0 with orthophosphoric acid and 5% CH3CN, 1mL/min) tr (1R,2R) 12.28 min (99.34%) and (1S,2R) 14.16 min (0.58%). The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 98% n-hexane, 1% 2-propanol, 1% absolute ethanol, 0.1% diethylamine, 1mL/min, 210
nm). IR (KBr, cm⁻¹): 2712, 1601, 1476, 1337, 746, 700; ¹H NMR (DMSO-d₆, 400 MHz) (δH) 0.64 (3H, d, J 6.4, CH₃-CH-CH₃), 0.92 (3H, d, J 6.4, CH₃-CH-CH₃), 1.09 (3H, d, J 6.8, CH₃-CH₃), 2.13-2.21 (1H, m, CH₃-CH-CH₃), 2.47 (3H, s, NH-CH₃), 2.92-2.96 (1H, m, CH-CH-CH₃), 3.57 (1H, m, CH-CH-CH₃), 7.27-7.37 (5H, m, H arom), 8.09 and 9.60 (two bs, 2H, NH₂+). ¹³C NMR (DMSO-d₆, 100 MHz) (δC) 11.36 (CH₃-CH-CH₃), 20.36 (CH₃-CH-CH₃), 20.78 (CH-CH₃), 27.68 (CH₃-CH-CH₃), 30.34 (NH-CH₃), 53.25 (CH-CH-CH₃), 55.09 (CH-CH-CH₃), 126.97-137.40 (aromatic carbons). Mass spectrum (ESI, (+)-mode) [M+H]⁺ at m/z 192 (100). Anal. Calcd for C₁₅H₂₂N.HCl: C, 68.55; H, 9.74; N, 6.15 Found: C, 68.38; H, 9.77; N, 6.13 %.

(1R,2R)-(+)1-Cyclopentyl-1-phenyl-2-methylaminopropane hydrochloride (1d). (11.6 g, 83.2 %); [α] D²⁵ = +9.2 ° (C = 1.0, H₂O); mp 201-203 °C (2-propanol); The diastereomeric purity was determined by HPLC to be 99.25% (Inertsil Phenyl 250 × 4.6 mm, 95% of 0.1M KH₂PO₄ pH 3.0 with orthophosphoric acid and 5% CH₃CN, 1mL/min) tR (1R,2R) 13.78 min (99.25%) and (1S,2R) 12.81 min (0.72%). The ee was determined by CSP HPLC to be 100 % (Chiralpak AD-H, 98% n-hexane, 1% 2-propanol, 1% absolute ethanol, 0.1% diethylamine, 1mL/min, 210 nm). IR (KBr, cm⁻¹): 2729, 1595, 1350, 1456, 1351, 754, 704; ¹H NMR (DMSO-d₆, 400 MHz) (δH) 0.81-0.84 (1H, m, CH₃H₅-CH₂-CH₂-CH₂-CH₂), 1.15 (3H, d, J 6.8 Hz, CH-CH-CH₃), 1.18 – 1.23 (1H, m, 1H, m, CH₃H₅-CH₂-CH₂-CH₂-CH₂), 1.34-1.55 (4H, m, CH₂-CH₂-CH₂-CH₂-CH₂), 1.63-1.85 (2H, m, CH₃H₅-CH₂-CH₂-CH₂-CH₂), 2.27-2.38 (1H, m, CH₂-CH₂-CH₂-CH₂-CH₂), 2.45 (3H, s, NH-CH₃), 3.09-3.13 (1H, d of d, J 1, 4.0 Hz, J 2, 4.0 Hz, CH-CH-CH₃), 3.37 (1H, m, CH-CH-CH₃), 7.28-7.37 (5H, m, H arom), 7.80 and 9.50 (two bs, 2H, NH₂+). ¹³C NMR (DMSO-d₆, 100 MHz) δC 10.48 (CH₂-CH₂-CH₂-CH₂-CH₂), 24.13 (CH₂-CH₂-CH₂-CH₂-CH₂), 24.86 (CH₂-CH₂-CH₂-CH₂-CH₂), 30.55 (CH₂-CH₂-CH₂-CH₂-CH₂), 30.80 (CH₂-CH₂-CH₂-CH₂-CH₂), 31.41 (CH₂-CH₂-CH₂-CH₂-CH₂), 40.67 (NH-CH₃), 51.89 (CH₂-CH₂-CH₂-CH₂-CH₂), 56.80 (CH-CH-CH₃), 126.95-137.98 (aromatic carbons). Mass spectrum (ESI, (+)-mode) [M+H]⁺ at m/z 218 (100). Anal. Calcd for C₁₅H₂₂N.HCl: C, 70.98; H, 9.53; N, 5.52 Found: C, 70.84; H, 9.51; N, 5.54 %.

(1R,2R)-(+)1-Cyclohexyl-1-phenyl-2-methylaminopropane hydrochloride (1e). (12.2 g, 85.7 %); [α] D²⁵ = +18.6 ° (C = 1.0, H₂O); mp 230-232 °C (2-propanol); The diastereomeric purity was determined by HPLC to be 99.11% (Inertsil Phenyl 250 × 4.6 mm, 95% of 0.1M KH₂PO₄ pH 3.0 with orthophosphoric acid and 5% CH₃CN, 1mL/min) tR (1R,2R) 10.14 min (99.11%) and (1S,2R) 9.26 min (0.84%). The ee was determined by CSP HPLC to be 100 % (Chiralpak AD-H, 98% n-hexane, 1% 2-propanol, 1% absolute ethanol, 0.1% diethylamine, 1mL/min, 210 nm). IR (KBr, cm⁻¹): 2687, 1593, 1377, 1470, 756, 706; ¹H NMR (DMSO-d₆, 400 MHz) (δH) 0.61-0.83 (2H, m, CH₂-CH₂-CH₂-CH₂-CH₂-CH₂), 1.07-1.09 (3H, d, J 6.8Hz, CH-CH-CH₃), 1.14-1.38 (2H, m, CH₂-CH₂-CH₂-CH₂-CH₂-CH₂), 1.50-1.85 (4H, m, CH₂-CH₂-CH₂-CH₂-CH₂-CH₂), 2.47-2.51 (4H, m, CH₂-CH₂-CH₂-CH₂-CH₂-CH₂ and NH-CH₃), 3.00–3.04 (1H, m, CH-CH-CH₃), 3.37-3.59 (1H, m CH-CH-CH₃), 7.28-7.36(5H, m, H arom), 8.00 and 9.40 (two bs, 2H, NH₂+). ¹³C NMR (DMSO-d₆, 100 MHz) δC 11.39 (CH₂-CH₂-CH₂-CH₂-CH₂), 25.20 (CH-CH-CH₃), 25.50 (CH₂-CH₂-CH₂-CH₂ -CH₂-CH₂), 25.90 (CH₂-CH₂-CH₂-CH₂-CH₂-CH₂), 30.01 (CH₂-CH₂-CH₂-CH₂-CH₂-CH₂), 30.39 (CH₂-CH₂-CH₂-CH₂-CH₂-CH₂), 30.60 (NH-CH₃), 36.86 (CH₂ CH₂-CH₂-CH₂-CH₂), 52.12 (CH₂ CH₂-CH₂-CH₂), 54.40 (CH-CH-CH₃), 126.94-137.38 (aromatic
carbons). Mass spectrum (ESI, (+)-mode) [M+H]^+ at m/z 232 (100). Anal. Calcd for C_{16}H_{25}N.HCl: C, 71.75; H, 9.78; N, 5.23 Found: C, 71.54; H, 9.75; N, 5.21 %.

(1R,2R)-(−)-1-Benzyl-1-phenyl-2-methylaminopropane hydrochloride (1f). (13.4 g, 88.4%); [α]_D^{25} = −56.3 ° (C = 1.0, H_2O); mp 227-228 °C (2-propanol); The diastereomeric purity was determined by HPLC to be 99.23% (Inertsil Phenyl 250 × 4.6 mm, 95% of 0.1M KH_2PO_4 pH 3.0 with orthophosphoric acid and 5% CH_3CN, 1mL/min) t_R (1R,2R) 7.54 min (99.23%) and (1S,2R) 8.64 min (0.76%). The ee was determined by CSP HPLC to be 100 % (Chiralpak AD-H, 98% n-hexane, 1% 2-propanol, 1% absolute ethanol, 0.1% diethylamine, 1mL/min, 210 nm); IR (KBr, cm⁻¹): 2691, 1593, 1335, 745, 698; ^1H NMR (DMSO-d_6, 400 MHz) (δ_H) 0.97-1.06 (3H, d, (CH_2)_3), 2.51-2.57 (3H, s, NH-C), 3.27-3.31 (1H, m, CH-CH-Ch), 3.43-3.52 (3H, m, CH-CH-Ch and CH_2-C=O), 5.13-5.23 (10H, m, H_ arom), 9.13 and 9.14 (two bs, 2H, NH_2^+). ^13C NMR (DMSO-d_6, 100 MHz) (δ_C) 12.58 (CH-CH-Ch), 30.10 (NH-C), 37.61 (CH-CH-Ch), 48.80 (CH_2-C=O), 57.61 (CH-CH-Ch), 125.80-139.27 (aromatic carbons). Mass spectrum (ESI, (+)-mode) [M+H]^+ at m/z 240 (100). Anal. Calcd for C_{17}H_{27}N.HCl: C, 74.03; H, 8.35; N, 4.83 Found: C, 74.18; H, 8.33; N, 4.80 %.

General method for the preparation (1S,2R)-1-alkyl-1-phenyl-2-methylaminopropane hydrochloride 1e′ and 1e′ via Scheme 5. To a solution of (1S,2R)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol 11c or 11e (0.08 mol) in tetrahydrofuran (50 mL) was added trifluoroacetic anhydride (0.24 mol) at 40-45 °C over 30 min. The mixture was maintained at same temperature for 30 min. The excess of trifluoroacetic anhydride was evaporated under reduced pressure to afford (1S,2R)-1-alkyl-1-phenyl-1-y1-2-methylaminopropyl trifluoroacetate 17a or 17b as a pale yellow syrupy mass. This mass was further dissolved in tetrahydrofuran 100 mL and hydrogenated at 45 °C for 2 hours at 4.0 bar hydrogen pressure in the presence of 10% palladium on carbon (2.0 g). The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was further diluted with toluene (50 mL) and washed with water (50 mL). The organic layer was acidified to pH 1.0 with hydrochloric acid, concentrated under
reduced pressure and the residue was crystallized by adding isopropyl alcohol to yield (1S,2R)-1-alkyl-1-phenyl-2-methylaminopropane hydrochloride \(1c', 1e'\) as white crystalline solids.

**General method for the preparation of \((1R,2R)-1\)-alkyl-1-phenyl-2-methylaminopropane-1-ol hydrochloride \(1c, 1e\) (Scheme 6).** To a solution of \((1S,2R)-1\)-alkyl-1-phenyl-2-methylaminopropan-1-ol \(11c\) or \(11e\) (0.08 mol) in toluene (50 mL) was added acetic anhydride (0.24 mol) at 40 °C to 45 °C for 30 min. The mixture was further maintained at 40 °C to 45 °C for 30 min. Toluene and excess acetic anhydride were distilled under reduced pressure. To the concentrated residual mass, water 100 mL and sulfuric acid (0.16 mol) were added and mixture was heated to 80 °C and maintained at same temperature for the duration of 90 min. The resulting reaction mixture was neutralized and extracted with toluene. The toluene layer was evaporated under reduced pressure to afford \((1R,2R)-1\)-alkyl-1-phenyl-2-methylaminopropane-1-ol \(18c\) or \(18e\) as a syrupy mass. \((1R,2R)-1\)-alkyl-1-phenyl-2-methylaminopropan-1-ol was treated with trifluoroacetic anhydride in tetrahydrofuran medium to afford \((1R,2R)-\)trifluoroacetyl derivative \(19c\) or \(19e\). This on further reduction with palladium on carbon yielded \((1R,2R)-1\)-alkyl-1-phenyl-2-methylaminopropane hydrochloride \(1c\) or \(1e\).

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13. (1S,2R)-(−)-1-Phenyl-2-methylaminopropan-1-ol HCl and (1R,2S)-(−)-1-phenyl-2-methylaminopropan-1-ol HCl were obtained from Malladi Drugs and Pharmaceuticals Ltd., Chennai.

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21. Crystallographic data for the compounds 11g and 1e in this paper are deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 923505 for compound 11g and CCDC 903467 for compound 1e. Copies can be obtained, free of charge, on request to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

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