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

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Abstract

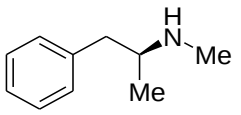
A concise and novel approach for the synthesis of (1*R*,2*R*)-1-alkyl-1-phenyl-2-methyl-aminopropanes by dehydroxylation of corresponding (1*S*,2*R*)-1-phenyl-1-alkyl-2-methylamino-propan-1-ols, which were prepared by the asymmetric induction through Grignard reaction of optically active α-aminoketones. 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] methylenedioxymethamphetamine[3] (MDMA) **3**, MDEA[4] **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.[5] 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**,[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).[8-10]



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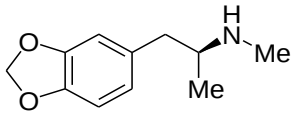

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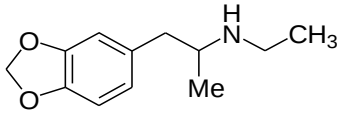

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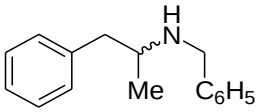

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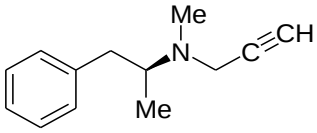

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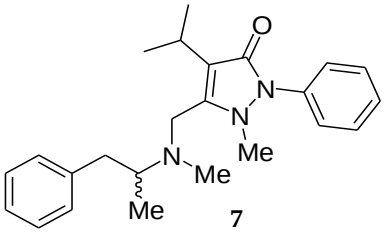

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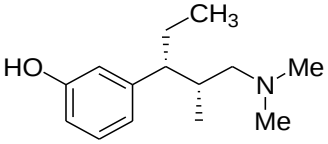

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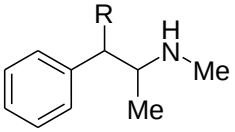
Results and Discussion

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



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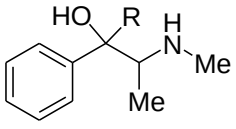

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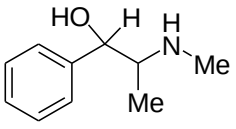

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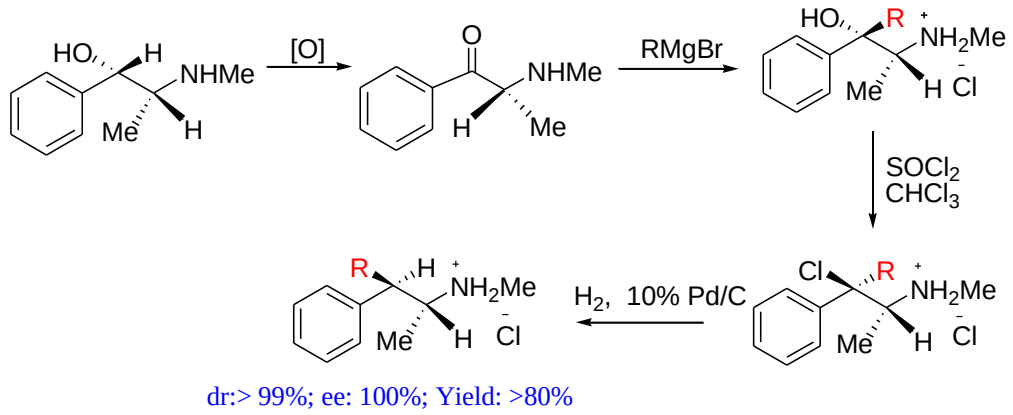
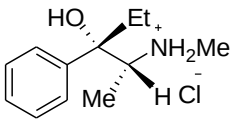
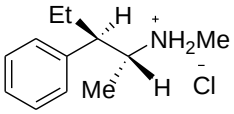
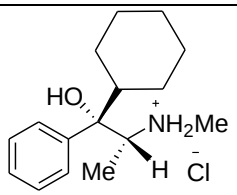
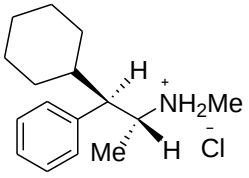
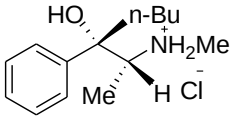
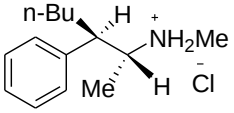
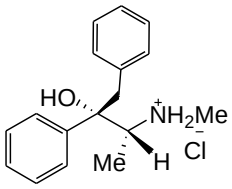
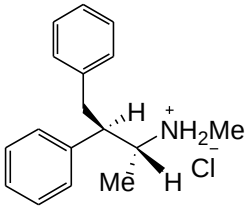
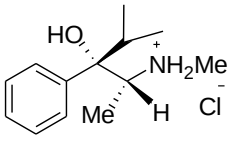
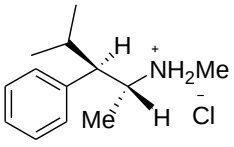
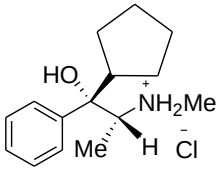
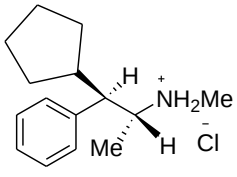
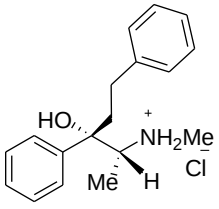
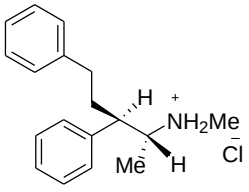
The absolute configuration of the dehydroxylated carbon was arrived by chemical analogy as well as X-ray diffraction studies. Various 1-alkyl-1-phenyl-2-methylaminopropanes were prepared from the corresponding amino alcohols as shown in Scheme 1 and tabulated in Table 1.



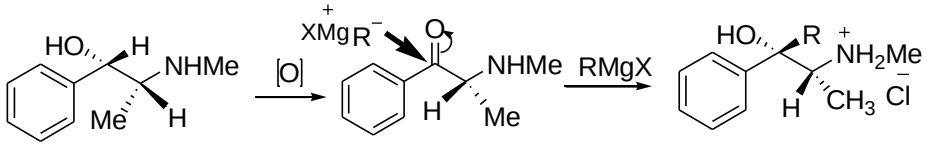
dr:> 99%; ee: 100%; Yield: >80%

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**)

Entry	Substrate	Product	Entry	Substrate	Product
1	 **11a**	 **1a**	**5**	 **11 e**	 **1 e**
2	 **11 b**	 **1b**	**6**	 **11 f**	 **1 f**
3	 **11c**	 **1 c**			
4	 **11 d**	 **1 d**	**7**	 **11g**	 **1g**

The starting compounds, α-alkylated-1-phenyl-2-methylaminopropan-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-methylaminopropan-1-one **10** (Scheme 2).[11,12]

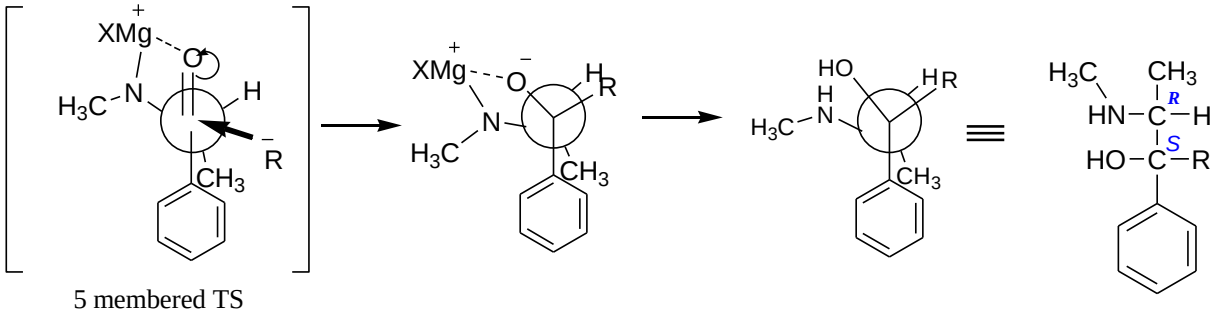


9 **10** **11a-g**

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

The amino-ketone with known configuration at adjacent carbon was synthesized by the acid-catalyzed oxidation of (1*S*,2*R*)-1-phenyl-2-methylaminopropan-1-ol **9**.[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 (1*S*,2*R*)-α-alkylated-1-phenyl-2-methylaminopropan-1-ol hydrochlorides **11a**–**g** with high optical purity (ee: 100%; dr: >99%)



5 membered TS
(Least hindered side)

dr : 99:1

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 (1*S*,2*R*)-1-(2-phenylethyl)-1-phenyl-2-methylaminopropan-1-ol hydrochloride (**11g**) is shown in Figure 1.[21]

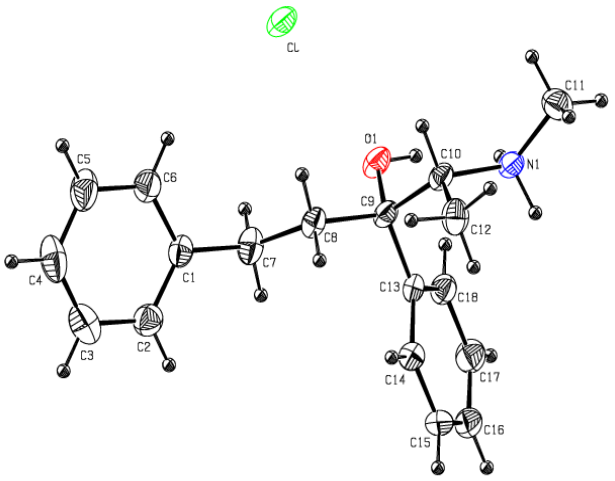
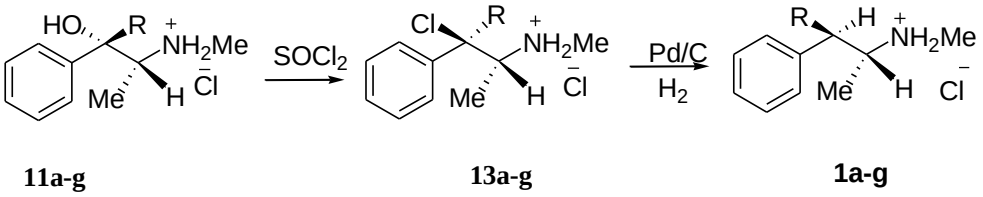


Figure 1. ORTEP representation of (1*S*,2*R*)-1-(2-phenylethyl)-1-phenyl-2-methylaminopropan-1-ol hydrochloride (**11g**).

According to the envisaged strategy, α-alkyl-1-chloro-1-phenyl-2-methylaminopropane hydrochlorides **13a-g** were synthesized by chlorinating the α-alkylated-1-phenyl-2-methylamino-propan-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_N2 mechanism[14] rather than S_Ni mechanism. Thus, chlorination of (1*S*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride **11a-g** at C-1 is expected to undergo via S_N2 mechanism resulting in inversion of configuration at the reaction center to obtain corresponding (1*R*,2*R*)-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).



11a-g **13a-g** **1a-g**

Scheme 4. Schematic representation of 1-alkylated 1-phenyl-2-methylaminopropane formation *via* the chloro intermediates **13.**

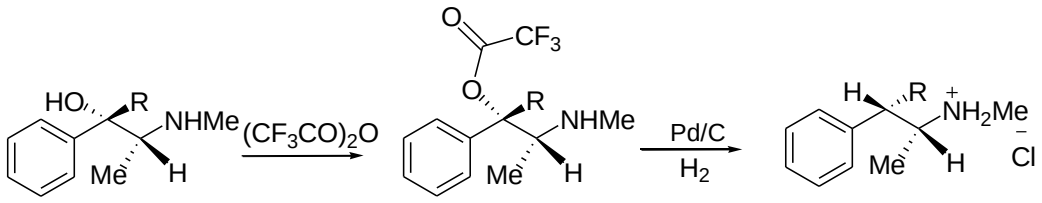
Table 2. Physical properties of α-alkyl-1-chloro-1-phenyl-2-methylaminopropane hydrochlorides synthesized in the present work

Amino alcohol		1-Alkyl-1-chloro-1-phenyl-2-methylaminopropane hydrochloride				
Entry	R-Group (config)	Entry	Yield (%)	Config.	$[\alpha]_D^{25}$ (1% in H_2O)	Purity (%)
11a	Ethyl (1S,2*R*)	**13a**	78.2	(1*R*,2*R*)	+15.2 °	98.27
11b	*n*-Butyl (1S,2*R*)	**13b**	82.3	(1*R*,2*R*)	+2.1°	97.65
11c	Isopropyl (1S,2*R*)	**13c**	76.8	(1*R*,2*R*)	+33.5°	98.95
11d	Cyclopentyl (1S,2*R*)	**13d**	85.2	(1*R*,2*R*)	+12.4°	98.57
11e	Cyclohexyl (1S,2*R*)	**13e**	85.4	(1*R*,2*R*)	+27.9°	99.04
11f	Benzyl (1S,2*R*)	**13f**	88.7	(1*R*,2*R*)	−86.5°	98.19
11g	Phenylethyl (1S,2*R*)	**13g**	89.2	(1*R*,2*R*)	+44.4°	98.31
14c	Isopropyl (1*R*,2*S*)	**15c**	80.1	(1*S*,2*S*)	−33.9°	98.71
14e	Cyclohexyl (1*R*,2*S*)	**15e**	87.2	(1*S*,2*S*)	−28.1°	98.46

The absolute configuration of the product at C-1 is inferred as '*R*' by the application of Cahn-Ingold-Prelog (CIP) priority rules[19] 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 e*e*.

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



11c&e **17c&e** **1c'&e'**

Scheme 5. Dehydroxylation by trifluoracetate derivative of amino alcohol leading to diastereomer of the title compounds.

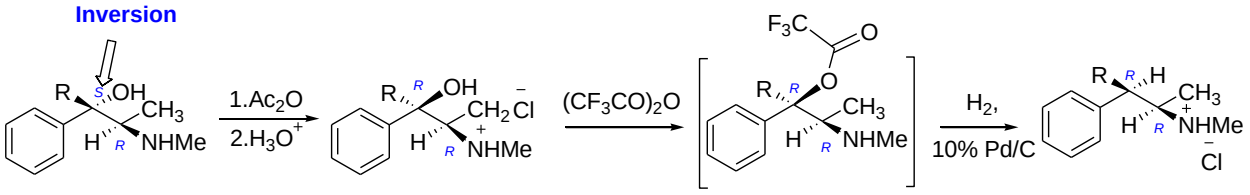
Table 3. Physical properties of 1-Alkyl-1-phenyl-2-methylaminopropane hydrochloride synthesized

Amino Chloride		1-Alkyl-1-phenyl-2-methylaminopropane hydrochloride					
Entry	R-Group (config)	Entry	Yield (%)	Config.	$[\alpha]_D^{25}$ (1%H_2O)	Dr (%)	ee (%)
13a	Ethyl (1R,2R)	**1a**	80.9	(1R,2R)	+3.2°	99.1 : 0.9	100
13b	n-Butyl (1R,2R)	**1b**	82.7	(1R,2R)	−4.14°	99.2 : 0.8	100
13c	Isoproyl (1R,2R)	**1c**	86.4	(1R,2R)	+19.1°	99.3 : 0.7	100
13d	Cyclopentyl (1R,2R)	**1d**	83.2	(1R,2R)	+9.2°	99.2 : 0.7	100
13e	Cyclohexyl (1R,2R)	**1e**	85.7	(1R,2R)	+18.6°	99.1 : 0.89	100
13f	Benzyl (1R,2R)	**1f**	88.4	(1R,2R)	−56.3°	99.2 : 0.8	100
13g	Phenylethyl (1R,2R)	**1g**	86.2	(1R,2R)	−10.7°	99.1 : 0.9	100
15c	Isopropyl (1S,2S)	**16c**	88.0	(1S,2S)	−20.6°	99.0 : 1.0	100
15e	Cyclohexyl (1S,2S)	**16e**	84.7	(1S,2S)	−17.9°	99.0 : 1.0	100

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 (1*S*,2*R*)-1-isopropyl-2-(methylamino)-1-phenylpropyltrifluoroacetate **17c** and (1*S*,2*R*)-1-cyclohexyl-2-(methylamino)-1-phenylpropyltrifluoroacetate **17e** from the corresponding 1,2-aminoalcohol, *viz.* **(**1*S*,2*R*)-1-isopropyl-1-phenyl-2-methylaminopropan-1-ol **11c** and (1*S*,2*R*)-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 (1*S*,2*R*)-1-isopropyl-1-phenyl-2-methylaminopropane **1c′** and (1*S*,2*R*)-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, (1*S*,2*R*)-1-isopropyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride **11c** on Walden inversion at C-1 by known procedures[20] afforded (1*R*,2*R*)-1-isopropyl-1-phenyl-2-(methylamino)propan-1-ol hydrochloride **18c** which was derivatized using trifluoroacetic anhydride to obtain (1*R*,2*R*)-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 (1*R*,2*R*)-1-isopropyl-1-phenyl-2-methylaminopropane hydrochloride **1c.**



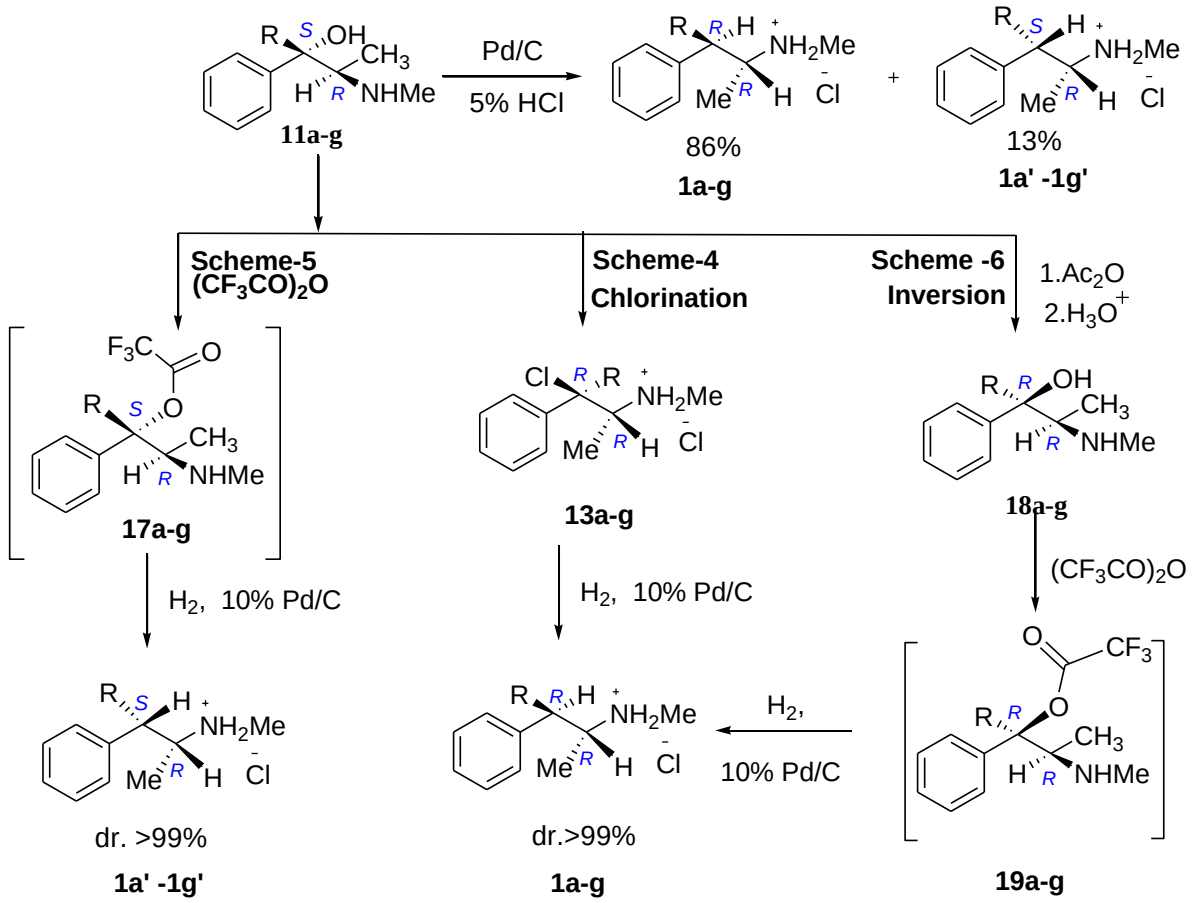
Scheme 6. Synthesis of (1*R*,2*R*)-1-alkyl-1-phenyl-2-(methylamino)propane hydrochloride through double stereoinversions.

Similar reactions are repeated with (1*S*,2*R*)-1-cyclohexyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride **11e** to obtain the respective compound (1*S*,2*R*)-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 **1c′**. Similar observation was noted for the compounds **1e** 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 (1*S*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride. It can be noticed that 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

Scheme	Compound No.	Configuration	$[\alpha]_D^{25}$	Diastereomeric purity (%)	RT (min)
Scheme 4	**1c**	1*R*,2*R*	+19.1	99.34	12.3
Scheme 5	**1c′**	1*S*,2*R*	−10.1	99.3	15.1
Scheme 6	**1c**	1*R*,2*R*	+19.9	99.0	12.4
Scheme 4	**1e**	1*R*,2*R*	+18.6	99.1	10.1
Scheme 5	**1e′**	1*S*,2*R*	−8.8	99.2	9.0
Scheme 6	**1e**	1*R*,2*R*	+18.1	99.0	10.2



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 (1*R*,2*R*)-1-cyclohexyl-1-phenyl-2-methylaminopropane hydrochloride (**1e**) which confirms the assigned configuration.[21]

The exceptional selectivity was observed during dehydroxylation of (1*S*,2*R*)-α-alkylated-1-phenyl-2-methylaminopropan-1-ol hydrochlorides **11a–g** at the benzylic carbon. In either ways i.e via chloro or triflluoro intermediacy, the exclusive formation of single diasteroisomer 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[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.

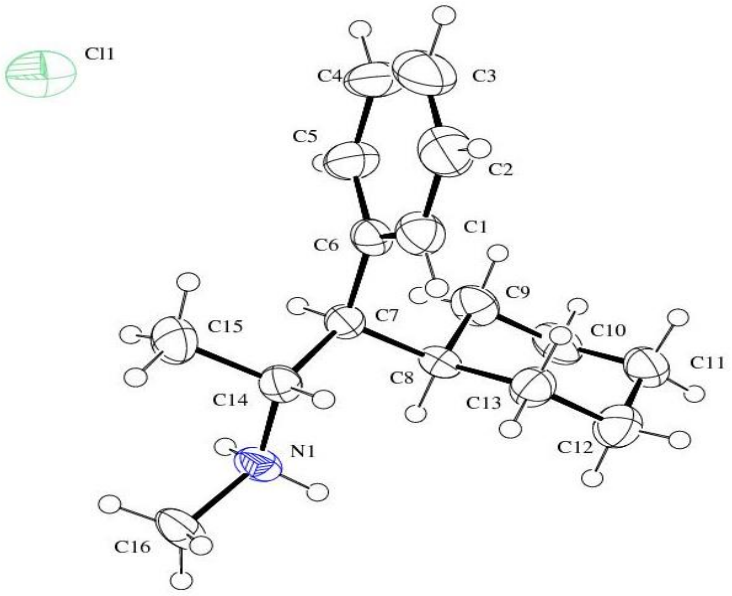


Figure 2. X-ray structure of (1*R*,2*R*)-1-cyclohexyl-1-phenyl 2-methylaminopropane hydrochloride **1e** (ORTEP view).

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

General Procedures

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

General method for the preparation of (1*R*,2*R*)-1-chloro-1-alkyl-1-phenyl-2-methylamino-propan-1-ol hydrochloride (13a-g). Thionyl chloride (0.16 mol) was slowly added to a solution of (1*S*,2*R*)-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 (1*R*,2*R*)-1-chloro-1-alkyl-1-phenyl-2-methylaminopropan-1-ol hydrochloride as a white crystalline solid.

Preparation of (1*R*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropane hydrochlorides (**1a-g**). (1*R*,2*R*)-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 syrupy 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 **15 c** and **15e** which were prepared from 1,2-aminoalcohols **14c** and **14e**

(1*R*,2*R*)-(+)-1-Ethyl-1-phenyl-2-methylaminopropane hydrochloride (**1a**). (9.5g, 80.9%); $[\alpha]_D^{25}$ = +3.2° (C = 1.0, H_2O); 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 KH_2PO_4 pH 3.0 with orthophosphoric acid and 5% CH_3CN, 1mL/min), t_R (1*R*,2*R*) 12.17 min (99.11%) and (1*S*,2*R*) 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; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ_H) 0.63-0.66 (3H, t, *J* 7.2, CH_2-C<u>H</u>$_3$), 0.80-0.83 (3H, d, *J* 6.4, CH-C<u>H</u>$_3$), 0.98-0.99 (3H, d, *J* 6.4, CH-C<u>H</u>$_3$), 1.61–1.91 (2H, m, C<u>H</u>$_2$-CH_3), 2.50 (3H, s, NH-C<u>H</u>$_3$), 2.92-2.97 (1H, m, C<u>H</u>-CH-CH_3), 3.37-3.40 (1H, m, C<u>H</u>-CH-CH_3), 7.25-7.37 (5H, m, H_{arom}), 8.98 (bs, 2H, NH_2^+) ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 11.77 (CH_2-<u>C</u>H$_3$), 12.76 (CH-<u>C</u>H$_3$), 24.52 (<u>C</u>H$_2$-CH_3), 29.82(NH-C<u>H</u>$_3$), 48.94 (<u>C</u>H-CH-CH_3), 57.66 (CH-<u>C</u>H-CH_3), 126.94-139.32 (aromatic carbons). Mass spectrum (ESI, (+)-mode) $[M+H]^+$ at *m/z* 178 (100). Anal. Calcd for $C_{12}H_{19}N$. HCl : C, 67.43; H, 9.43; N, 6.59. Found: C, 67.22; H, 9.45; N, 6.53.

(1*R*,2*R*)-(-)-1-(1-Butyl)-1-phenyl-2-methylaminopropane hydrochloride (**1b**). (11.0g, 82.7%); $[\alpha]_D^{25}$ = −4.14 ° (C=1.0, H_2O); 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 KH_2PO_4 pH 3.0 with orthophosphoric and 5% CH_3CN, 1mL/min) t_R (1*R*,2*R*) 8.67 min (99.24%) and (1*S*,2*R*) 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; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 0.76 (3H, t, *J* 7.2, CH_2-C<u>H</u>$_3$), 0.98-0.99 (3H, d, *J* 6.8, CH-C<u>H</u>$_3$), 1.13-1.29 (2H, m, C<u>H</u>$_2$-CH_3), 1.61-1.85 (2H, m, CH_2-C<u>H</u>$_2$-CH_2-CH_3), 2.50 (3H, s, NH-C<u>H</u>$_3$), 3.04-3.09 (1H, m, CH-C<u>H</u>-CH_3), 3.33-3.40 (3H, m, C<u>H</u>-CH-CH_3 and C<u>H</u>$_2$-CH_2-CH_2-CH_3), 7.25-7.36 (5H, m, Harom), 8.50-9.60 (bs, 2H, NH_2^+). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 12.62 (CH_2-<u>C</u>H$_3$), 13.79 (CH-<u>C</u>H$_3$), 21.83 (<u>C</u>H$_2$-CH_3), 29.06 (CH_2-<u>C</u>H$_2$-CH_2-CH_3), 29.86 (NH-<u>C</u>H$_3$), 31.12 (<u>C</u>H-CH_3), 47.05 (<u>C</u>H$_2$-CH_2-CH_2-CH_3), 57.86 (<u>C</u>H-CH-CH_3), 126.91-139.54 (aromatic carbons). Mass spectrum (ESI, (+)-mode) $[M+H]^+$ at *m/z* 206 (100). Anal. Calcd for $C_{14}H_{23}N$.HCl: C, 69.54; H, 10.0 and N, 5.79. Found: C, 69.45 ; H,9.98; N, 5.77 %.

(1*R*,2*R*)-(+)-1-Isopropyl-1-phenyl-2-methylaminopropane hydrochloride (**1c**). (10.8 g, 86.4%); $[\alpha]_D^{25}$ = +19.1° (C = 1.0, H_2O); 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 KH_2PO_4 pH 3.0 with orthophosphoric acid and 5% CH_3CN, 1mL/min) t_R (1*R*,2*R*) 12.28 min (99.34%) and (1*S*,2*R*) 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-d_6, 400 MHz) (δ_H) 0.64 (3H, d, *J* 6.4, CH_3-CH-C$\underline{H}_3$), 0.92 (3H, d, *J* 6.4, C$\underline{H}_3$-CH-CH_3), 1.09 (3H, d, *J* 6.8, CH-C$\underline{H}_3$), 2.13-2.21 (1H, m, CH_3-C$\underline{H}$-CH_3), 2.47 (3H, s, NH-C$\underline{H}_3$), 2.92-2.96 (1H, m, C$\underline{H}$-CH-CH_3), 3.57 (1H, m, CH-C$\underline{H}$-CH_3), 7.27-7.37 (5H, m, H^{arom}), 8.09 and 9.60 (two bs, 2H, NH_2^+)**.** ^{13}C NMR (DMSO-d_6, 100 MHz) (δ_c) 11.36 (CH_3-CH-C$\underline{H}_3$), 20.36 (C$\underline{H}_3$-CH-CH_3), 20.78 (CH-C$\underline{H}_3$), 27.68 (CH_3-C$\underline{H}$-CH_3), 30.34 (NH-C$\underline{H}_3$), 53.25 (C$\underline{H}$-CH-CH_3), 55.09 (CH-C$\underline{H}$-CH_3), 126.97-137.40 (aromatic carbons). Mass spectrum (ESI, (+)-mode) $[M+H]^+$ at *m/z* 192 (100). Anal. Calcd for $C_{13}H_{21}N.HCl$: C, 68.55; H, 9.74 ; N, 6.15 Found: C, 68.38; H,9.77; N, 6.13 %.

(1*R*,2*R*)-(+)-1-Cyclopentyl-1-phenyl-2-methylaminopropane hydrochloride (**1d**). (11.6 g, 83.2 %); $[\alpha]_D^{25}$ = +9.2 ° (C = 1.0, H_2O); 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 KH_2PO_4 pH 3.0 with orthophosphoric acid and 5% CH_3CN, 1mL/min) t_R (1*R*,2*R*) 13.78 min (99.25%) and (1*S*,2*R*) 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-d_6, 400 MHz) (δ_H) 0.81-0.84 (1H, m, $CH_a\underline{H}_b$-CH_2-CH-CH_2-CH_2), 1.15 (3H, d, *J* 6.8 Hz, CH-CH-C$\underline{H}_3$), 1.18 – 1.23 (1H, m, 1H, m, C$\underline{H}_a$$H_b$-$CH_2$-CH-$CH_2$-$CH_2$), 1.34-1.55 (4H, m, CH_2-CH_2-CH-C$\underline{H}_2$-C$\underline{H}_2$), 1.63-1.85 (2H, m, $CH_a$$H_b$-C$\underline{H}_2$-CH-$CH_2$-$CH_2$), 2.27- 2.38 (1H, m, CH_2-CH_2-C$\underline{H}$-CH_2-CH_2), 2.45 (3H, s, NH-C$\underline{H}_3$), 3.09-3.13 (1H, d of d, J_1 4.0 Hz, J_2 4.0 Hz, C$\underline{H}$-CH-CH_3), 3.37 (1H, m, CH-C$\underline{H}$-CH_3), 7.28-7.37 (5H, m, H_{arom}), 7.80 and 9.50 (two bs, 2H, NH_2^+).^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 10.48 (C$\underline{H}_2$-CH_2-CH-CH_2-CH_2), 24.13 (CH-CH-C$\underline{H}_3$), 24.86 (CH_2-C$\underline{H}_2$-CH-CH_2-CH_2), 30.55 (CH_2-CH_2-CH-CH_2-C$\underline{H}_2$), 30.80 (CH_2-CH_2-CH-C$\underline{H}_2$-CH_2), 31.41 (CH_2-CH_2-C$\underline{H}$-CH_2-CH_2-CH_2), 40.67 (NH-C$\underline{H}_3$), 51.89 (C$\underline{H}$-CH-CH_3), 56.80 (CH-C$\underline{H}$-CH_3),126.95-137.98 (aromatic carbons). Mass spectrum (ESI, (+)-mode) $[M+H]^+$ at *m/z* 218 (100). Anal. Calcd for $C_{15}H_{23}N.HCl$: C, 70.98; H, 9.53; N, 5.52 Found: C, 70.84 ; H, 9.51; N, 5.54 %.

(1*R*,2*R*)-(+)-1-Cyclohexyl-1-phenyl-2-methylaminopropane hydrochloride (**1e**). (12.2 g, 85.7%); $[\alpha]_D^{25}$ = +18.6 ° (C = 1.0, H_2O); 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 KH_2PO_4 pH 3.0 with orthophosphoric acid and 5% CH_3CN, 1mL/min) t_R (1*R*,2*R*) 10.14 min (99.11%) and (1*S*,2*R*) 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-d_6, 400 MHz**)** (δ_H) 0.61-0.83 (2H, m, CH_2-CH_2-CH-CH_2-CH_2-C$\underline{H}_2$), 1.07-1.09 (3H, d, *J* 6.8Hz, CH-CH-C$\underline{H}_3$), 1.14-1.38 (2H, m, C$\underline{H}_2$-CH_2-CH-CH_2-CH_2-CH_2), 1.50-1.85 (4H, m, CH_2-C$\underline{H}_2$-CH-C$\underline{H}_2$-CH_2-CH_2), 2.47- 2.51 (4H, m, CH_2CH_2-C$\underline{H}$-CH_2-CH_2-CH_2 and NH-C$\underline{H}_3$), 3.00– 3.04 (1H, m, C$\underline{H}$-CH-CH_3), 3.37-3.59 (1H, m CH-C$\underline{H}$-CH_3), 7.28-7.36(5H, m, H_{arom}), 8.00 and 9.40 (two bs, 2H, NH_2^+). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 11.39 (CH_2-CH_2-CH-CH_2-CH_2-C$\underline{H}_2$), 25.20 (CH-CH-C$\underline{H}_3$), 25.50 (C$\underline{H}_2$-CH_2-CH-CH_2 -CH_2 -CH_2), 25.90 (CH_2-CH_2-CH-CH_2-CH_2-C$\underline{H}_2$), 30.01 (CH_2-CH_2-CH-C$\underline{H}_2$-CH_2-CH_2), 30.39 (CH_2-C$\underline{H}_2$-CH-CH_2-CH_2-CH_2), 30.60 (NH-C$\underline{H}_3$), 36.86 (CH_2-CH_2-C$\underline{H}$-CH_2-CH_2-CH_2), 52.12 (C$\underline{H}$-CH-CH_3), 54.40 (CH-C$\underline{H}$-CH_3), 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 %.

(1*R*,2*R*)-(-)-1-Benzyl-1-phenyl-2-methylaminopropane hydrochloride (**1f**). (13.4 g, 88.4%); $[\alpha]_D^{25} = -56.3$ ° (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 (1*R*,2*R*) 7.54 min (99.23%) and (1*S*,2*R*) 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, 1454, 745, 698; ^{1}H NMR (DMSO-d*6*, 400 MHz) (δ_H) 1.06-1.07, (3H, d, *J* 6.0Hz, CH-CH-C$\underline{H}_3$), 2.51-2.57 (3H, s, NH-C$\underline{H}_3$), 3.27-3.31 (1H, m, C$\underline{H}$-CH-CH_3), 3.43-3.52 (3H, m, CH-C$\underline{H}$-CH_3 and C$\underline{H}_2$-C_6H_5), 7.04-7.35 (10H, m, H_{arom}), 9.13 and 9.14 (two bs, 2H, NH_2^+. ^{13}C NMR (DMSO-d*6*, 100 MHz) (δ_c) 12.58 (CH-CH-$\underline{C}H_3$), 30.10 (NH-$\underline{C}H_3$), 37.61 ($\underline{C}$H-CH-CH_3), 48.80 ($\underline{C}H_2$-C_6H_5), 57.61 (CH-$\underline{C}$H-CH_3), 125.80-139.27 (aromatic carbons). Mass spectrum (ESI, (+)-mode) $[M+H]^+$ at *m/z* 240 (100). Anal. Calcd for $C_{17}H_{21}N.HCl$, : C, 74.03, H, 8.04 , N, 5.08 Found: C, 74.13; H, 7.91; N, 5.03 %.

(1*R*,2*R*)-(-)-1-(2-Phenylethyl)-1-phenyl-2-methylaminopropane hydrochloride (**1g**). (13.7 g, 86.2%); $[\alpha]_D^{25} = -10.7$ ° (C = 1.0, H_2O); mp 162-164 °C (2-propanol); The diastereomeric purity was determined by HPLC to be 99.10% (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 (1*R*,2*R*) 6.95min (99.10 %) and (1*S*,2*R*) 7.96min (0.64%). 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, L/min, λ=210 nm); IR (KBr,cm^{-1}): 2727, 1603, 1454, 1333, 762, 735, 706, 694. ^{1}H NMR (DMSO-d*6*, 400 MHz) (δ_H) 1.01 (3H, d, *J* 6.4Hz, CH-CH-C$\underline{H}_3$), 1.95-2.37 (4H, m, C$\underline{H}_2$-C$\underline{H}_2$-C_6H_5), 2.49 (3H, s, NH-C$\underline{H}_3$), 3.07 (1H, m, C$\underline{H}$-CH-CH_3), 3.43 (1H, m, CH-C$\underline{H}$-CH_3), 7.11-7.42 (10H, m, H_{arom}), 8.60 and 9.30 (two bs, 2H, NH_2^+). ^{13}C NMR (DMSO-d*6*, 100 MHz) δ_C 12.76 (CH-CH–$\underline{C}H_3$), 29.73 ($\underline{C}H_2$-CH_2-C_6H_5), 32.97 (CH_2-$\underline{C}H_2$-C_6H_5), 33.25 (NH-$\underline{C}H_3$), 47.03 ($\underline{C}$H-CH-CH_3), 57.77 (CH-$\underline{C}$H–CH_3), 125.76 – 141.40 (aromatic carbons). Mass spectrum (ESI, (+)-mode) $[M+H]^+$ at *m/z* 254 (100). Anal. Calcd for $C_{18}H_{23}N.HCl$: : C, 74.59, H,8.35 , N, 4.83 Found: C, 74.44; H,8.33 ; N,4.81%.

General method for the preparation (1*S*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropane hydrochloride 1c′ and 1e′ *via* Scheme 5. To a solution of (1*S*,2*R*)-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 (1*S*,2*R*)-1-alkyl-1-phenyl-1-yl-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 (1*S*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropane hydrochloride **1c′**, **1e′** as white crystalline solids.

General method for the preparation of (1*R*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropane-1-ol hydrochloride 1c, 1e (Scheme 6). To a solution of (1*S*,2*R*)-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 (1*R*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropane-1-ol **18c** or **18e** as a syrupy mass. (1*R*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropan-1-ol was treated with trifluoroacetic anhydride in tetrahydrofuran medium to afford (1*R*,2*R*)-trifluoroacetyl derivative **19 c** or **19e**. This on further reduction with palladium on carbon yielded (1*R*,2*R*)-1-alkyl-1-phenyl-2-methylaminopropane hydrochloride **1c** or **1e**.

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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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