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Chiral α-alkylation/arylation in 1-phenyl-2-(1-pyrrolidinyl)-1-propanol through Grignard reactions

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ABSTRACT

Complete asymmetric induction has been achieved during Grignard alkylations/arylations resulting in (1*S*,2*R*)- and (1*R*,2*R*)-1-phenyl-1-alkyl/aryl-2-(1-pyrrolidinyl)-1-propanols which are isolated as hydrochlorides.

1. Introduction

Ephedrine, (1*R*,2*S*)-(−)-1-phenyl-2-methylamino-1-propanol, pseudoephedrine and (1*S*,2*S*)-(+)-1-phenyl-2-methylamino-1-propanol are used in the pharmaceutical industry as decongestants, analgesics, bronchodilators and mydriatics.[1] The ketone, (*R*)-(+) ephedrone, obtained upon oxidation of (1*S*,2*R*)-ephedrine contains one stereogenic carbon at the β-position. Suter and Weston have prepared racemic ephedrone hydrochloride and obtained α-alkylephedrines via Grignard reactions of the keto function.[2] These authors observed, on physiological studies of these racemic α-alkylephedrines, that the presence of an alkyl group at the α-position of ephedrine lowers the toxicity without significant loss of therapeutic activity. The α-alkylated ephedrines studied by these authors are racemic mixtures. Herein we report the preparation of chiral α-alkylated/arylated ephedrine derivatives from optically active (*R*)-(+)-1-phenyl-2-(1-pyrrolidinyl)-1-propanone through Grignard reactions. These newly obtained α-alkylated/arylated ephedrine derivatives are expected to exhibit manifold pharmaceutical activities with lesser toxicity, as is well established in the case of active pharmaceutical ingredients.[3–5]

2. Results and discussion

(1*S*,2*R*)-(+)-1-Phenyl-2-aminopropanol-1[6] was treated with 1,4-dibromobutane in the presence of sodium carbonate to obtain (1*S*,2*R*)-(+)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol. The pyrrolidinyl compound was oxidised to the corresponding ketone isolated as the hydrochloride (Scheme 1). All Grignard reactions have been performed with the ketone, (*R*)-(+)-1-phenyl-2-(1-pyrrolidinyl)-1-propanone. The Grignard reactions were carried out with the base liberated from the hydrochloride salt (Scheme 2). The specific rotation of the hydrochloride of the ketone was +64.6. The various compounds prepared using these Grignard reactions are given in Table 1.

The physical properties of all the 1-phenyl-1-alkyl/aryl-2-(1-pyrrolidinyl)-1-propanol hydrochlorides are reported in Table 2.

It can be observed that all the synthesised alkyl/arylpropanol hydrochlorides are found to be laevo-rotatory except for the α-phenylethyl and naphthyl derivatives which are found to be dextro-rotatory. During Grignard synthesis with 1-phenyl-2-(1-pyrrolidinyl)-1-propanone, asymmetry is expected to be induced at the reaction site due to the presence of a stereogenic carbon at the β-position with respect to the phenyl ring.

Chiral induction during Grignard reactions has been reported during the synthesis of 1,2-diphenyl-3-methyl-4-dimethylamino-2-butanol.[3,4,5]

3. Stereochemical aspects

The expected asymmetric induction at the α-carbon of the Grignard reaction product leads to one of the possible diastereomers. The absolute configuration of the new stereogenic centre formed through the Grignard reaction can be predicted with the help of Cram's rule[7] as applied to the Grignard synthesis of 1-phenyl-1-ethyl-2-(1-pyrrolidinyl)-1-propanol (Scheme 3) and also by experimental analogy (Scheme 6).

It should be noted that at carbon-1, where asymmetry is induced, the absolute configuration, as inferred by Cram's rule, is '*S*' and the product is an *erythro* isomer. The enantiomeric purity of this Grignard product is 100% as observed from the HPLC chromatogram using a chiral column with a retention time of 5.43 (Table 3). The driving force for the exclusive formation of the *erythro* isomer appears to be the ability of the magnesium cation of the Grignard reagent to complex with the electron-rich

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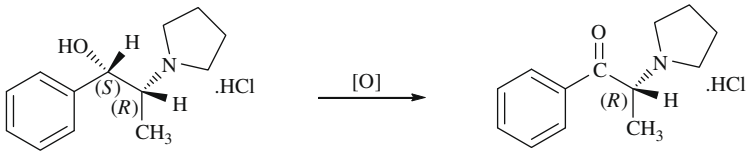
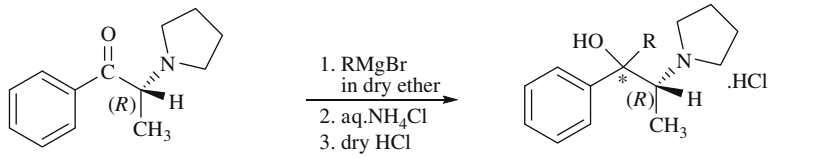


(1*S*,2*R*)-(+)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride

(*R*)-(+)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanone hydrochloride

Scheme 1.



(*R*)-(+)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanone

α-Alkylated/arylated-1-phenyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride

Scheme 2. (*Absolute configuration to be ascertained)

Table 1
List of Grignard products prepared and isolated as hydrochlorides

Compound No.	R
1	Methyl
2	Ethyl
3	2-Propyl
4	1-Butyl
5	2-Methylpropyl
6	Benzyl
7	Phenylethyl
8	3-Methoxyphenyl
9	1-Naphthyl

carbonyl oxygen and nitrogen serving as bidentate ligands. This complexation (Schemes 3 and 4) freezes the conformation of the ketone, facilitating attack of the alkyl/aryl anions of the Grignard reagent from the less hindered side leading to the exclusive formation of the Grignard product with an (*S*)-configuration at carbon-1. The preferred diastereomer of the Grignard product is *erythro*-(1*S*,2*R*)-(−)-1-phenyl-1-ethyl-2-(1-pyrrolidinyl)-1-propanol.

In order to derive additional evidence towards the absolute configuration at carbon-1 in the Grignard product, the Grignard reactions using ethyl magnesium bromide with (*S*)-(−)-1-phenyl-2-(1-pyrrolidinyl)-1-propanone and the corresponding (*SR*)-ketone were also carried out. Scheme 4 shows that the attack of the C_2H_5 anion from the least hindered side as per the Cram's rule provides the *erythro*-(1*R*,2*S*)-(+)-1-phenyl-1-ethyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride with the (*S*)-(−)-ketone.

Table 2
Physical properties of 1-phenyl-1-alkyl/aryl-2-(1-pyrrolidinyl)-1-propanol hydrochlorides (compounds **1**–**9**)

Compound	Melting point (°C)	Yield (%)	Purity by HPLC (%)	$[\alpha]_D^{25}$	Enantiomeric purity %
1	193–195	64	99.5	−12.5	100
2	214–218	74	99.5	−18.4	100
3	208–210	74	98.9	−6.6	100
4	194–198	77	96.0	−9.1	100
5	194–196	51	99.5	−6.9	100
6	228–232	55	96.0	−71.8	100
7	200–202	60	98.0	+29.2	100
8	210–212	73	97.2	−58.4	100
9	268–270	57	99.5	+135.3	100

It was observed that the Grignard products formed from the enantiomeric ketones are mirror images as can be expected. The stereochemical consequence of the Grignard product from (*SR*)-(±)-1-phenyl-2-(1-pyrrolidinyl)-1-propanone is given in Scheme 5. Similar observations were also made in the case of benzyl, phenethyl and 1-naphthyl in Grignard reagents Table 3.

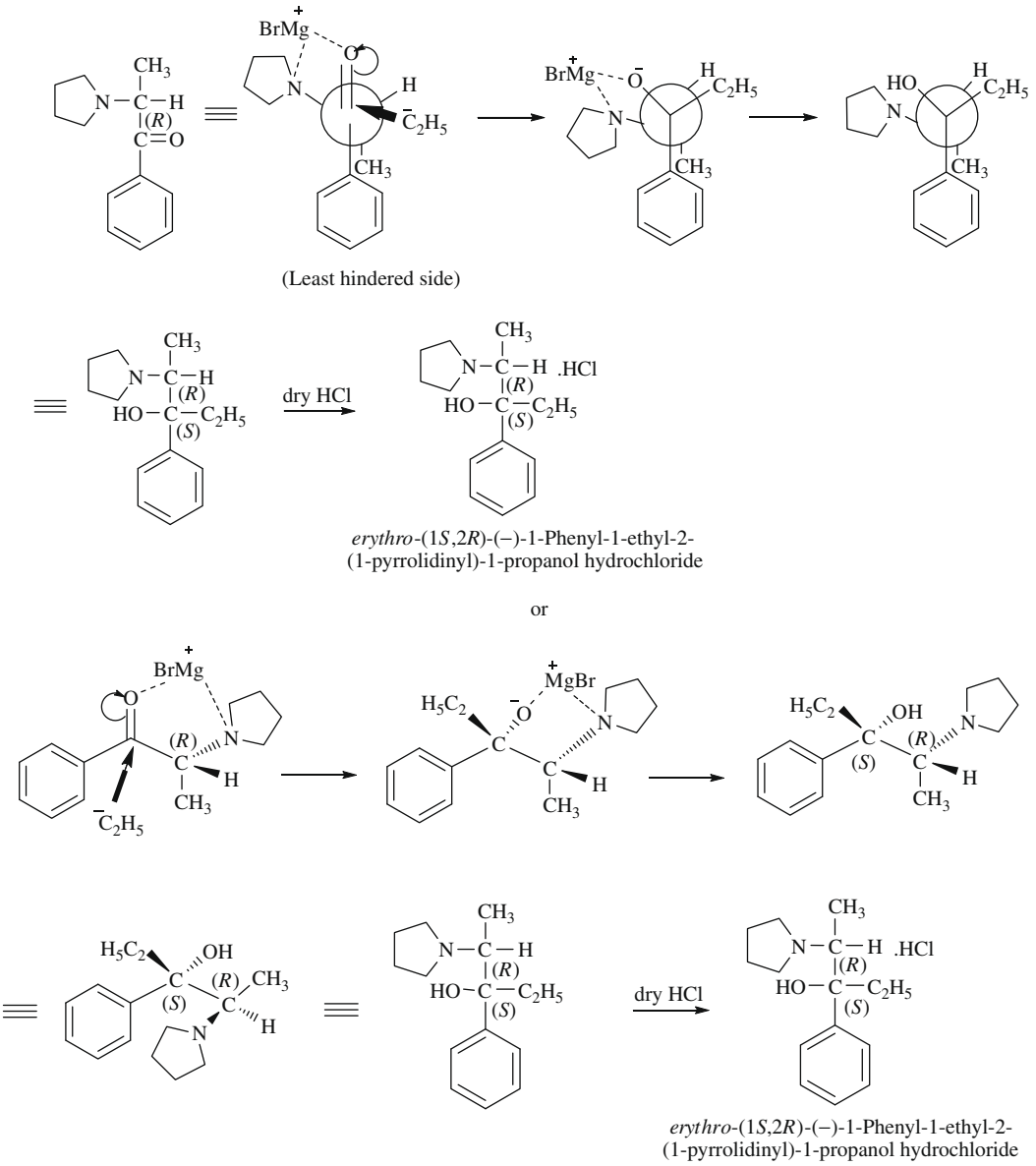
In order to provide an additional evidence for the proposed (*S*)-configuration at carbon-1 in the Grignard product through chemical analogy, the Grignard alkylations of (*R*)- and (*S*)-1-phenyl-2-methylamino-1-propanone[8] with methylmagnesium bromide have been undertaken. The specific rotation, enantiomeric purities and ee values of the Grignard products are shown in Table 4. It can be seen that the Grignard products obtained from the (2*S*)- and (2*R*)- ketones are mirror images as shown by their specific rotations. The configurations at carbon-1 in (1*S*,2*R*) and (1*R*,2*S*) Grignard products have been inverted (Walden) via reported procedures,[9] the results of which are given in Table 4. It can again be noticed that the two Walden-inverted products are mirror images as shown by their specific rotations. These two products will have (1*R*,2*R*) and (1*S*,2*S*) configurations (Scheme 6). Hence, the configuration at carbon-1 of the Grignard products can be concluded to be (*S*) which matches with the configuration inferred through molecular modelling.

The Walden inversion with 1-phenyl-1-methyl-2-(1-pyrrolidinyl)-1-propanol cannot be performed because of the requirement of a hydrogen on the amino function for the procedure adopted for the Walden inversion.[9] Hence the absolute configuration at carbon-1 of the Grignard products has been inferred as (*S*) by drawing an analogy from the *N*-methyl compounds (Scheme 6).

In order to ascertain that the chirality at carbon-2 remains unaffected during the oxidation of the hydroxyl group at carbon-1, the (1*S*,2*R*)-(+)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol and its (1*R*,2*R*)-isomer[10] were oxidised under the same conditions. The two oxidised products show nearly same specific rotations (Table 5) with very high ee values.

4. Conclusion

(*R*)-(+)-1-Phenyl-2-(1-pyrrodinyl)-1-propanone has been alkylated/arylated via a Grignard addition. During these reactions, the C-1 carbon, the reaction centre experiences near total chiral induction. The driving force for this observation can be attributed to the fact that magnesium cation, both in the reactant and in the prod-

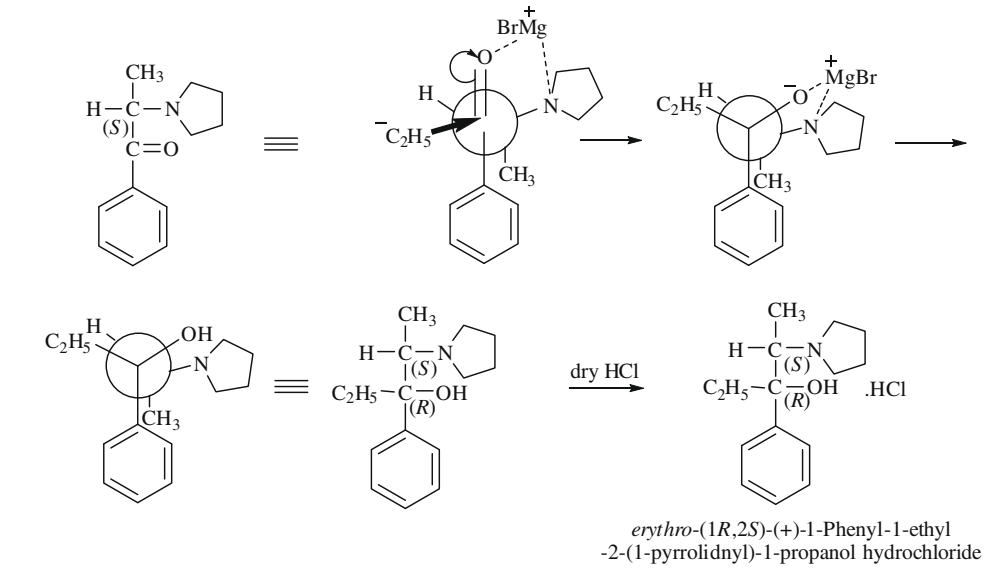


Scheme 3.

Table 3
Retention times with optical purities of (*S,R*), (*R,S*) and (*S,R* and *R,S*) isomers of 1-phenyl-1-alkyl- and (1-naphthyl)-2-(1-pyrrolidinyl)-1-propanol hydrochloride given in parentheses

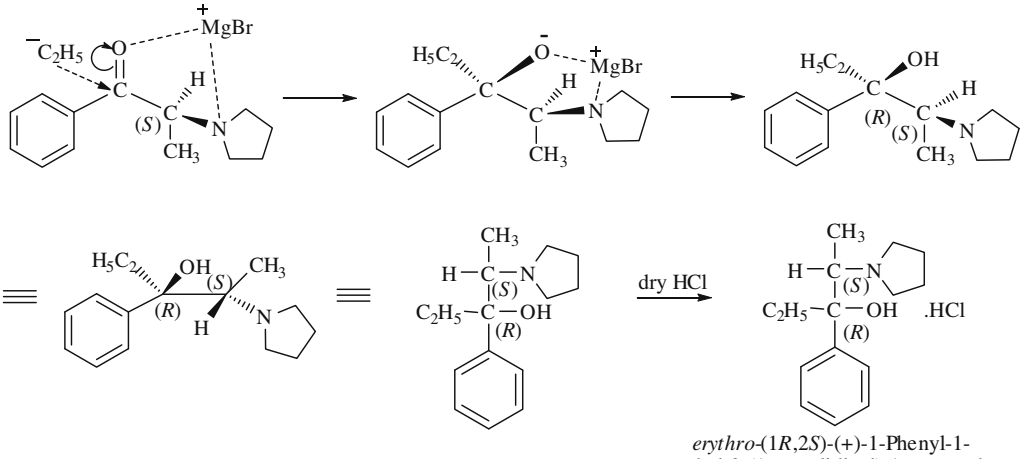
Compound	Alkyl group	(1*S*,2*R*)-isomer	(1*R*,2*S*)-isomer	(1*SR*,2*RS*)-racemic mixture		
		Retention time, $[\alpha]_D^{25}$, (enantiomeric purity %)	Retention time, $[\alpha]_D^{25}$, (enantiomeric purity %)	Retention time, (enantiomeric purity %)		$[\alpha]_D^{25}$
2	Ethyl	5.43 −18.44 (100)	5.19 +17.8 (100)	5.58 (47)	5.13 (53)	0
6	Benzyl	6.23 −71.7 (100)	4.51 +69.2 (97)	6.31 (51)	4.52 (49)	0
7	Phenethyl	5.01 +29.92 (100)	4.62 −29.2 (100)	5.03 (48)	4.59 (52)	0
9	1-Naphthyl	6.63 (1S, 2S) isomer +135.3 (100)	7.14 (1R, 2R) isomer −132.0 (100)	6.63 (50)	7.21 (50)	0

uct, complexes with the nitrogen of the pyrrolidinyl moiety and the carbonyl oxygen forcing the formation of a particular diastereomer. These alkylated/arylated compounds are expected to reveal higher therapeutic values with reduced toxicity.



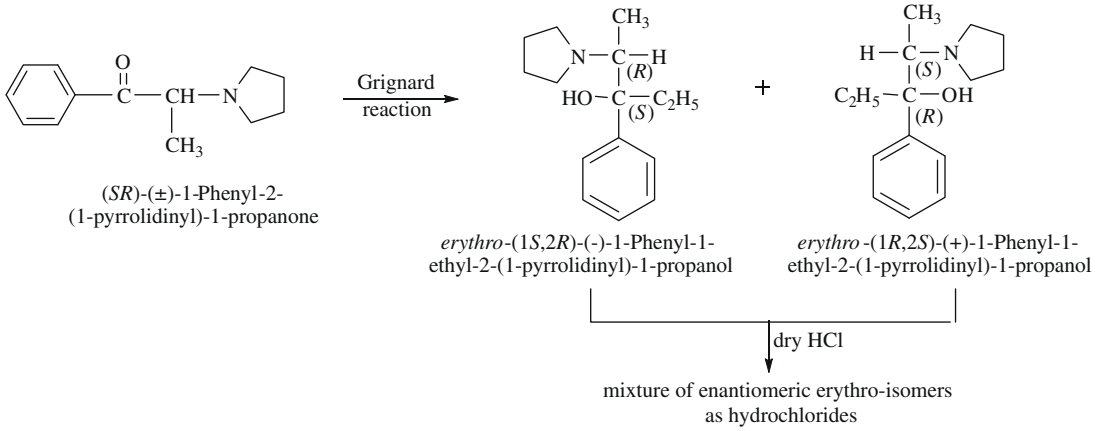
erythro-(1*R*,2*S*)-(+)-1-Phenyl-1-ethyl
-2-(1-pyrrolidnyl)-1-propanol hydrochloride

or



erythro-(1*R*,2*S*)-(+)-1-Phenyl-1-
ethyl-2-(1-pyrrolidinyl)-1-propanol
hydrochloride

Scheme 4.



(*SR*)-(±)-1-Phenyl-2-
(1-pyrrolidinyl)-1-propanone

erythro-(1*S*,2*R*)-(-)-1-Phenyl-1-
ethyl-2-(1-pyrrolidinyl)-1-propanol

erythro-(1*R*,2*S*)-(+)-1-Phenyl-1-
ethyl-2-(1-pyrrolidinyl)-1-propanol

mixture of enantiomeric erythro-isomers
as hydrochlorides

Scheme 5.

Table 4
Physical properties of the stereoisomers of 1-phenyl-1-methyl-2-methylamino-1-propand hydrochloride

Compound	Melting point (°C)	Enantiomeric purity by HPLC (%)	$[\alpha]_D^{25}$ (2%, H_2O)	ee (%)
(1*S*,2*R*)-1-Phenyl-1-methyl-2-methylamino-1-propanol	210–214	99.92	+15.6	99.84
(1*R*,2*S*)-1-Phenyl-1-methyl-2-methylamino-1-propanol	210–213	98.52	−16.5	97.92
(1*R*,2*R*)-1-Phenyl-1-methyl-2-methylamino-1-propanol	263–265	100.00	−54.15	100.00
(1*S*.2*S*)-1-Phenyl-1-methyl-2-methylamino-1-propanol	260–263	100.00	+53.15	100.00

Table 5
Physical properties of stereoisomers of 1-phenyl-2-(1-pyrrolidinyl)-1-propanone hydrochloride

Compound	Oxidised from	Melting point (°C)	Purity by HPLC (%)	$[\alpha]_D^{25}$	ee
(*R*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanone	(1*S*,2*R*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol	182–184	100	+64.6	99.47
(*S*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanone	(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol	182–185	100	−62.4	97.92
(*R*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanone	(1*R*,2*R*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol	181–184	99.0	+62.9	99.70
(*RS*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanone	(1*SR*,2*RS*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol	182–185	99.0	0	—

5. Experimental

5.1. Oxidation of (+)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol

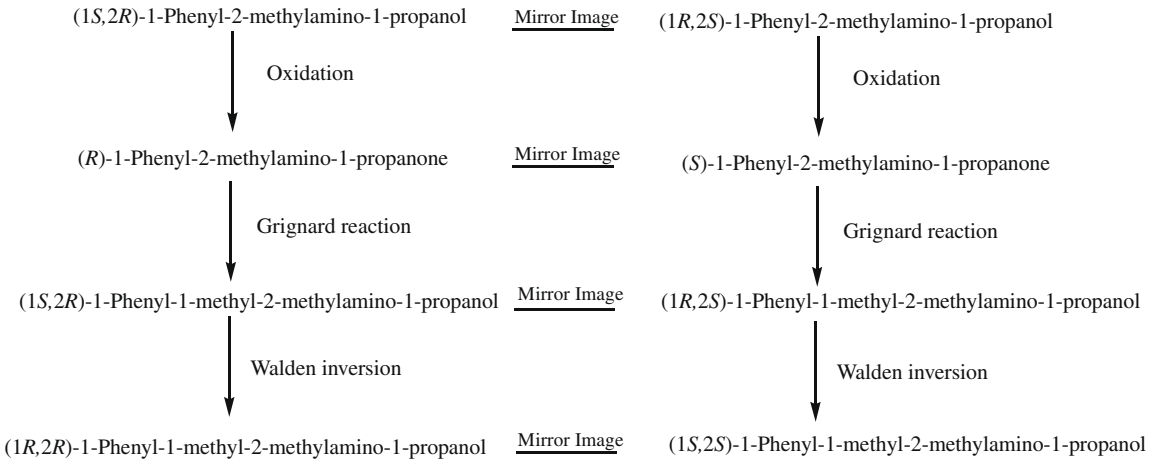
To a solution of 10 g (0.04 mol) of (1*S*,2*R*)-(+)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride in 30 mL of water, 10.5 g (0.107 mol) of sulfuric acid was added dropwise at 15–20 °C. Next, 12.5 g (0.04 mol) of sodium dichromate dissolved in 12.5 mL of water was added to the reaction mass over a period of 20 min. While maintaining the temperature between 15 and 20 °C, the reaction mass was stirred for 12 h at the same temperature. To this reaction mixture, 10 mL of water and 25 mL of toluene were added while maintaining the temperature at 5 °C. The pH of the mixture was adjusted to 10.5 by adding 50% of sodium hydroxide and the temperature was kept below 20 °C. The undissolved chromate salts were filtered through hyflo and the salts were washed with 10 mL of toluene. The organic layer was separated from the filtrate and washed with 20 mL of water. The organic layer was acidified with dilute hydrochloric acid to a pH of 2.0. The product was extracted into the aqueous layer which was concentrated under reduced pressure, until an oily residue was obtained. Acetone (25 mL) was added to the residue, when (+)-1-phenyl-2-(1-pyrrolidinyl)-1-propanone hydrochloride crystallised. The mixture was cooled further and the crystals were filtered to obtain the keto-product. 8.4 g (84%): HPLC purity 99.64%; mp (acetone): 182–84 °C; $[\alpha]_D^{25} = +64.6$ (*c* 1.0, H_2O).

5.2. General procedure for the Grignard reactions of (+)-1-phenyl-2-(1-pyrrolidinyl)-propanone-1 with alkyl/ aryl magnesium bromides

The Grignard reagents (alkyl/aryl magnesium bromides in ether) were prepared from 0.14 mol of magnesium in 25 mL of diethyl ether and 0.14 mol of alkyl/ aryl bromide. To a stirred solution of the Grignard reagent in ether, (+)-1-phenyl-2-(1-pyrrolidinyl)-propanone-1 base (prepared from 10.0 g, 0.04 mol of the hydrochloride salt of the ketone and sodium hydroxide solution) in 25 mL of ether was added slowly keeping the temperature between 20 and 25 °C. The reaction mixture was stirred for 12 h at 20–25 °C. The progress of the reaction was monitored by TLC. The reaction mixture was quenched, at the end of the reaction, with 20 mL of saturated solution of ammonium chloride in water keeping the temperature below 20 °C. The ether layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield an oil. The oily product was dissolved in 20 mL of acetone and was acidified to a pH of 2.0–3.0 by bubbling dry HCl gas. The precipitated product was filtered, washed with acetone and recrystallised from 2-propanol.

5.3. General procedure for Walden inversion

(1*S*,2*R*)- and (1*R*,2*S*)-*erythro*-1-Phenyl-1-methyl-2-methylamino-1-propanol hydrochloride 5 g (0.0232 mol) and 12.0 mL of acetic



Scheme 6.

anhydride were heated to 120–130 °C for 1 h. The reaction mass was concentrated under reduced pressure to yield an oil. To the oily residue, 20 mL of 10% hydrochloric acid was added and heated at reflux for 3 h. The reaction mass was concentrated under reduced pressure to yield an oily residue, which was triturated with acetone to obtain a white precipitate. The precipitated product was filtered and washed with acetone to obtain (1*R*,2*R*)- and (1*S*,2*S*)-*threo*-1-phenyl-1-methyl-2-methylamino-1-propanol hydrochlorides.

5.3.1. (1*S*,2*R*)-(−)-1-Phenyl-1-methyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride 1

Compound **1** (6.76 g, 63.8%): $[\alpha]_D^{25} = -12.5$ (*c* 1.0, H_2O); mp (2-propanol): 193–195 °C; IR (KBr, cm^{-1}): 3200 (OH), 2646 (N–H); ^1H NMR (300 MHz, DMSO-d_6) δ_H 0.98 (d, *J* = 6.7 Hz, 3H, CH–CH_3), 1.71 (s, 3H, C(OH)–CH_3), 1.75–1.87 (m, 4H, NH–CH$_2$–CH_2–CH_2), 2.90 (m, 1H, NH–CH_e)[11], 3.31 (m, 2H, H_aC–N–CH_a), 3.68 (m, 1H, H_eC–NH), 3.82 (q, *J* = 6. 5 Hz, 1H, CH$_3$–C*H*), 6.10 (br s, 1H,O*H*), 7.25–7.52 (m, 5H, Harom), 9.76 (br s, 1H, N*H*); ^{13}C NMR (DMSO-d_6): 8.6, 23.0, 24.4, 28.7, 48.5, 55.0, 67.0, 74.3, 125.3, 126.8, 127.9, 145.4; MS (CI, CH_3OH), *m/z* (rel. intens.): 220 (M+H$^+$, 100), 202 (16), 98 (17). Anal. Calcd for $C_{14}H_{21}NO{\cdot}HCl$: C, 65.74; H, 8.67; N, 5.47. Found: C, 66.23; H, 8.64; N, 5.50. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% diethylamine, 1.0 mL/min) t_R (1*S*,2*R*) = 6.4 min (100%).

5.3.2. (1*S*,2*R*)-(−)-1-Phenyl-1-ethyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride 2

Compound **2** (8.24 g, 73.6%): $[\alpha]_D^{25} = -18.4$ (*c* 1.0, H_2O); mp (2-propanol) 214–218 °C; IR (KBr, cm^{-1}): 3271 (OH), 2718 (N–H); ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.77 (t, 3H, CH$_2$–CH_3) 1.25 (d, *J* = 6.5 Hz, 3H, CH–CH_3), 1.68 (m, 1H, HO–C–CH^1H^2–CH$_3$), 1.89 (m, 1H, HO–C–CH$^1H^2$–CH$_3$, H^1 and H^2 are diastereotopic protons), 2.02–2.36 (m, 5H, NH–CH_e–CH_2–CH_2), 3.16 (m, 2H, H_aC–NH–CH_a), 4.08 (q, *J* = 6.4 Hz, 1H, *H*C–CH$_3$), 4.33 (m, 1H, H_eC–N), 5.63 (br s, 1H, O*H*), 7.26–7.60 (m, 5H, Harom), 10.29 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ_C 7.5, 9.4, 23.9, 25.5, 31.9, 48.7, 56.4, 70.3, 77.6, 126.9, 127.4, 128.4, 139.9; MS (EI) *m/z* (rel. intens.): 233 (M$^+$), 98 (100), 56 (8). Anal. Calcd for $C_{15}H_{23}NO{\cdot}HCl$: C, 66.77; H, 8.96; N, 5.19. Found: C, 66.89; H, 8.85; N, 5.16. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% diethylamine, 1.0 mL/ min) t_R (1*S*,2*R*) = 5.4 min (100%).

5.3.3. (1*S*,2*R*)-(−)-1-Phenyl-1-(2-propyl)-2-(1-pyrrolidinyl)-1-propanol hydrochloride 3

Compound **3** (10.37 g, 73.7%): $[\alpha]_D^{25} = -6.6$ (*c* 1.0, H_2O); mp (2-propanol) 208–210 °C; IR (KBr, cm^{-1}): 3276 (OH), 2703 (N–H); ^1H NMR (300 MHz, DMSO-d_6) δ_H 0.67 (d, 3H, HO–C–CH–CH^a_3), 1.02 (d, 3H, HO–C–CH–CH^b_3, CH$^a_3$ and CH$^b_3$ are diastereotopic methyl groups), 1.28 (d, *J* = 6.3 Hz, 3H, CH–CH_3), 1.62 (m, 1H, H$^a_3$C–CH–CH$^b_3$), 1.73–2.23 (m, 4H, NH–CH$_2$–CH_2–CH_2), 2.34–2.52 (m, 2H, H_aC–NH–CH_e), 3.16 (m, 1H, H$_2$C–NH–CH_a), 3.74 (m, 1H, H_eC–NH–CH$_2$), 3.95 (q, *J* = 6.4 Hz, 1H, *H*C–CH$_3$), 5.85 (br s, 1H, O*H*), 7.36–7.64 (m, 5H, Harom), 9.18 (br s, 1H, N*H*); ^{13}C NMR (300 MHz, DMSO-d_6) δ_c 8.1, 15.9, 17.3, 22.9, 24.4, 32.9, 47.8, 55.6, 66.7, 78.5, 126.8, 127.3, 127.9, 140.5; MS (CI,CH_3OH), *m/z* (rel. intens.): 248 (M+H$^+$, 100), 230 (8), 98 (14). Anal. Calcd for $C_{16}H_{25}NO{\cdot}HCl$: C, 67.46; H, 9.55; N, 4.91. Found: C, 67.74; H, 9.28; N, 4.98. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% diethylamine, 1.0 mL/min) t_R (1*S*,2*R*) = 3.9 min (100%).

5.3.4. (1*S*,2*R*)-(−)-1-Phenyl-1-butyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride 4

Compound **4** (9.50 g, 76.6%): $[\alpha]_D^{25} = -9.1$ (*c* 1.0, H_2O); mp (2-propanol) 194–198 °C; IR (KBr, cm^{-1}): 3316 (OH), 2644 (N–H); ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.82 (t, 3H, CH$_2$–CH_3), 1.25 (d, *J* = 6.4 Hz, 3H, CH–CH_3), 1.38 (m, 2H, CH_2–CH$_3$), 1.64 (m, 1H, HO–C–CH^1H^2), 1.90 (m, 1H, HO–C–CH$^1H^2$, H^1 and H^2 are diastereotopic protons), 2.00–2.31 (m, 7H, NH–CH$_2$–CH_2–CH_2, –CH_2–CH$_2$–CH$_3$, NH–CH_e), 3.02 (m, 2H, H_aC–NH–CH_a), 4.06 (q, *J* = 6.6 Hz, 1H, C*H*–CH$_3$), 4.34 (m, 1H, H_eC-NH), 5.69 (br s, 1H, O*H*), 7.27–7.60 (m, 5H, Harom), 10.30 (br s, 1H, N–*H*); ^{13}C NMR (300 MHz, $CDCl_3$) δ_c 9.4, 14.1, 22.9, 23.9, 25.0, 25.5, 38.8, 48.6, 56.5, 70.5, 77.2, 126.8, 127.4, 128.4, 139.9; MS (EI) *m/z* (rel. intens.) 261 (M$^+$), 98 (100), 56 (6). Anal. Calcd for $C_{17}H_{27}NO{\cdot}HCl$: C, 68.55; H, 9.47; N, 4.70. Found: C, 69.12; H, 9.48; N, 4.63. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% dimethylamine, 1.0 mL/ min) t_R (1*S*,2*R*) = 4.0 min (100%).

5.3.5. (1*S*,2*R*)-(−)-1-Phenyl-1-(2-methylpropyl)-2-(1-pyrrolidinyl)-1-propanol hydrochloride 5

Compound **5** (7.56 g, 51.2%): $[\alpha]_D^{25} = -6.9$ (*c* 1.0, H_2O); mp (2-propanol) 194–196 °C; IR (KBr, cm^{-1}): 3292 (OH), 2716 (N–H); ^1H NMR (300 MHz, DMSO-d_6) δ_H 0.56 (d, 3H, CH$_3$–CH–CH_3), 0.89 (d, 3H, CH_3–CH–CH$_3$, the two methyl groups of the isobutyl function appear to be diastereotopic), 1.06 (d, *J* = 6.2 Hz, 3H, HO–C–CH–CH_3), 1.48 (m, 1H, H$_3$C–C*H*–CH$_3$), 1.80 (m, 4H, NH–CH$_2$–CH_2–CH_2–), 1.85 (d of d, *J* = 6.1, 1.0 Hz, 1H, HO–C–CH^1H^2–CH–CH$_3$), 2.02 (d of d, *J* = 6.0, 1.2 Hz, 1H, HO–C–CH$^1H^2$–CH–CH$_3$, H^1 and H^2 are diastereotopic protons), 2.48 (m, 1H, H_eCH$_a$–NH), 2.69 (m, 1H, H$_e$CH$_a$–NH–CH$_e$H$_a$–CH$_2$), 3.14 (m, 1H, H$_e$CH$_a$–NH), 3.65 (m, 1H, H$_e$CH$_a$–NH–CH$_e$H$_a$), 3.78 (q, *J* = 6.3 Hz, 1H, –C*H*–CH$_3$), 5.86 (br s, 1H, O*H*), 7.27–7.54 (m, 5H, Harom), 9.29 (br s, 1H, N–*H*); ^{13}C NMR (300 MHz, DMSO-d_6) δ_c 8.6, 22.8, 23.6, 24.0, 24.2, 39.4, 46.3, 48.2, 55.5, 69.0, 77.2, 126.3, 127.0, 127.8, 141.5; MS(CI, CH_3OH) *m/z* (rel. intens.) 262 (M+H$^+$, 100), 244 (10), 98 (11). Anal. Calcd for $C_{17}H_{27}NO{\cdot}HCl$: C, 68.55; H, 9.47; N, 4.70. Found: C, 68.20; H, 9.50; N, 4.75. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% dimethylamine, 1.0 mL/ min) t_R (1*S*,2*R*) = 3.8 min (100%).

5.3.6. (1*S*,2*R*)-(−)-1-Phenyl-1-benzyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride 6

Compound **6** (7.62 g, 55.2%): $[\alpha]_D^{25} = -71.8$ (*c* 1.0, H_2O); mp (2-propanol) 228–232 °C; IR (KBr, cm^{-1}): 3183 (OH), 2675 (N–H); ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.29 (d, *J* = 6.1 Hz, 3H, CH–CH_3), 1.63–2.17 (m, 4H, NH–CH$_2$–CH_2–CH_2), 2.58 (m, 1H, NH–CH_e), 2.99 (m, 1H, NH–CH_a), 3.21 (m, 1H, H_aC–NH), 3.45 (d, 1H, *J* = 1.5 Hz, HO–C–CH^1H^2–C$_6$H$_5$), 3.70 (d, 1H, *J* = 1.5 Hz, HO–C–CH$^1H^2$–C$_6$H$_5$, H^1 and H^2 are diastereotopic protons), 4.12 (q, *J* = 6.3 Hz, NH–C*H*–CH$_3$), 4.24 (m, 1H, H_eC–NH), 4.99 (br s, 1H, C–O*H*), 7.08–7.52 (10H, m, Harom), 10.50 (br s, 1H, N–*H*); ^{13}C NMR (300 Hz, $CDCl_3$) δ_c 9.6, 23.8, 25.4, 44.9, 48.9, 56.2, 69.1, 77.6, 126.5, 126.8, 127.7, 128.3, 131.0, 135.1, 140.2; MS(EI) *m/z* (rel. intens.) 295 (M+), 98 (100), 56 (7). Anal. Calcd for $C_{20}H_{25}NO{\cdot}HCl$: C, 72.38; H, 7.90; N, 4.22. Found: C, 72.14; H, 7.88; N, 4.26. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% dimethylamine, 1.0 mL/min) t_R (1*S*,2*R*) = 6.2 min (100%).

5.3.7. (1*S*,2*R*)-(+)-1-Phenyl-1-phenylethyl-2-(1-pyrrolidinyl)-1-propanol hydrochloride 7

Compound **7** (8.68 g, 60.3%): $[\alpha]_D^{25} = +29.2$ (*c* 1.0, H_2O); mp (2-propanol) 200–202 °C; IR (KBr, cm^{-1}): 3275 (OH), 2656 (N–H); ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.24 (d, *J* = 6.6 Hz, 3H, CH–CH_3), 1.65 (m, 1H, HO–C–CH^1H^2–CH$_2$–C$_6$H$_5$), 1.91 (m, 2H, HO–C–CH^{1}H^2–CH_2–C$_6$H$_5$), 2.01 (m, 1H, HO–C–CH$^1H^2$–CH$_2$–C$_6$H$_5$, H^1 and H^2 are diastereotopic protons), 2.23 (m, 4H, NH–CH$_2$–CH_2–CH_2), 2.62 (m, 1H, NH–CH_e), 2.92 (m, 3H, H_aH_eC-NH-CH_a), 4.12 (1H, q, *J* = 6.4 Hz, NH–C*H*–CH$_3$), 6.08 (br s, 1H, C–O*H*), 7.11–7.69 (10H, m, Harom), 10.44 (br s, 1H, N–*H*), ^{13}C NMR (300 MHz, $CDCl_3$) δc

9.3, 24.0, 25.6, 29.5, 40.9, 48.6, 56.6, 70.8, 77.1, 125.6, 127.0, 127.7, 128.2, 128.5, 128.6, 139.4, 142.3; MS(CI, CH_3OH) *m/z* (rel. intens.) 310 ($M+H^+$, 100), 293 (9), 98 (9). Anal. Calcd for $C_{21}H_{27}NO{\cdot}HCl$: C, 72.92; H, 8.15; N, 4.05. Found: C, 73.13; H, 8.18; N, 4.06. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% dimethylamine, 1.0 mL/min) t_R (1*S*,2*R*) = 5.01 min (100%).

5.3.8. (1*R*,2*R*)-(−)-1-Phenyl-1-(3-methoxyphenyl)-2-(1-pyrrolidinyl)-1-propanol hydrochloride 8

Compound **8** (10.38 g, 72.6%): $[\alpha]_D^{25} = -58.4$ (*c* 1.0, H_2O); mp (2-propanol) 210–213 °C; IR (KBr, cm^{-1}): 3258 (OH), 2668 (N–H); ^1H NMR (300 MHz, DMSO-d_6) δ_H 1.20 (d, *J* = 6.1 Hz, 3H, CH–CH_3), 1.79 (m, 4H, $\overset{+}{N}H$–CH_2–CH_2–CH_2), 3.02 (m, 1H, H_eC–$\overset{+}{N}H$–CH_2), 3.22–3.33 (m, 3H, H_aC–$\overset{+}{N}H$–C$H_a$$H_e$), 3.75 (s, 3H, C_6H_4–O–CH_3), 5.00 (q, *J* = 6.3 Hz, 1H, C*H*–CH_3), 6.76 (br s, 1H, C_6H_5–C–O*H*), 6.83–7.56 (m, 9H, Harom), 8.89 (br s, 1H, $\overset{+}{N}$–*H*); ^{13}C NMR (300 MHz, DMSO-d_6) δ_c 11.7, 22.7, 22.9, 51.6, 54.8, 55.0, 65.2, 79.0, 111.8, 112.3, 118.0, 125.3, 126.7, 128.0, 129.4, 145.3, 146.5, 159.2; MS(CI, CH_3OH) *m/z* (rel. intens.) 312 ($M+H^+$, 100), 295 (15), 98 (19). Anal. Calcd for $C_{20}H_{25}NO_2{\cdot}HCl$: C, 69.06; H, 7.48; N, 4.03. Found: C, 68.31; H, 7.74; N, 3.99. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/2-propanol/0.1% dimethylamine, 1.0 mL/ min) t_R (1*R*,2*R*) = 7.9 min (100%).

5.3.9. (1*R*,2*R*)-(+)-1-Phenyl-1-(1-naphthyl)-2-(1-pyrrolidinyl)-1-propanol hydrochloride 9

Compound **9** (8.60 g, 56.6%): $[\alpha]_D^{25} = +135.25$ (*c* 1.0, 7:3 of dimethylacetimide and H_2O); mp (7:3 of CH_3OH and H_2O) 268–270 °C; IR (KBr, cm^{-1}): 3124 (OH), 2784 ($\overset{+}{N}$–H); ^1H NMR (300 MHz, $CDCl_3$+CF_3COOD) δ_H 1.38 (d, *J* = 6.0 Hz, 3H, CH–CH_3), 1.98 (m, 4H, $\overset{+}{N}H$–CH_2–CH_2–CH_2), 2.95 (m, 1H, H_eC–$\overset{+}{N}H$–CH_2), 3.23 (m, 1H, H_aC–$\overset{+}{N}H$–CH_2), 3.42 (m, 1H, H_2C–NH–CH_a), 4.16 (m, 1H, H_2C–$\overset{+}{N}H$–CH_e), 4.74 (q, *J* = 6.3 Hz, 1H, C*H*–CH_3), 7.18–7.93 (m, 12H, Harom), the OH and N–H protons have disappeared on exchange with D from CF_3COOD; ^{13}C NMR (300 MHz, $CDCl_3$+CF_3COOD) δ_c 10.6, 23.2, 25.1, 50.6, 57.3, 67.7, 79.6, 123.3, 124.2, 126.3, 126.4, 126.6, 126.8, 128.7, 128.8, 129.5, 130.7, 131.3, 135.8, 136.5, 140.6; MS(CI, CH_3OH) *m/z* (rel. intens.) 332 ($M+H^+$, 100), 315 (83), 233 (12), 98 (31). Anal. Calcd for $C_{23}H_{25}NO{\cdot}HCl$: C, 75.08; H, 7.12; N, 3.81. Found: C, 75.13; H, 7.21; N, 3.84. The ee was determined by CSP HPLC to be 100% (Chiralpak AD-H, 1% *n*-hexane/ 2-propanol/0.1% dimethylamine, 1.0 mL/ min) t_R (1*R*,2*R*) = 7.1 min (100%).

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10. The (1*R*,2*R*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol was prepared from the (1*S*,2*R*)-isomer through a process involving Walden inversion at C-1.
11. The pyrrolidinyl ring protons and carbons appear to be experiencing magnetic anisotropy being in the vicinity of a chiral environment.