Extreme halophilic alcohol dehydrogenase mediated highly efficient syntheses of enantiopure aromatic alcohols

Diya Alsafadi, Francesca Paradisi and Safaa Alsalman

Electronic Supplementary Information

Table of Contents

1. Physico-chemical data of the products

(S)-**1a** (1-phenylethanol): $[\alpha]^{20}_D$ = –41.6 (c 1.1, $CHCl_3$), Lit. (1): $[\alpha]^{20}_D$ = –39.6 (c 2.46 $CHCl_3$). ^{1}H NMR (500 MHz, $CDCL_3$) δ 1.54(3H, d, *J* = 6.4 Hz, CH_3), 2.06 (1H, br, s, OH), 4.93 (1H, q, *J* = 6.4 Hz, CH), 7.28-7.40(5H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 0.6 ml/min and 25°C. Retention time for (S)-1-phenylethanol was 9.7 min.

(S)-**2a** (1-phenyl-2-propanol): $[\alpha]^{20}_D$ = +14.0 (c 1.1, $CHCl_3$), Lit. (2): $[\alpha]^{20}_D$ = +42.0 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCL_3$) δ 1.23 (3H, d, *J* = 6.3 Hz, CH_3), 1.96 (1H, br, s, OH), 2.77-2.65 (2H, m, CH_2), 4.01-3.97 (1H, m, CH), 7.32-7.17 (5H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 1.0 ml/min and 25°C. Retention time for (S)-1-phenyl-2-propanol was 10.6 min.

(S)-**3a** (4-phenyl-2-butanone): $[\alpha]^{20}_D$ = +8 (c 1.3, $CHCl_3$), Lit. (3): $[\alpha]^{20}_D$ = +17.4 (c 1.8, CHCl3). 1H NMR (500 MHz, $CDCL_3$) δ 1.23-1.20 (3H, d, J= 7.1 Hz, CH_3), 2.00 (1H, br, s, OH), 2.64(2H, m, CH_2), 2.71(2H, m, *J* = 7.1 Hz, CH_2), 3.53(1H, m, CH), 7.44- 7.132 (5H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 97:3, 1.0 ml/min and 25°C. Retention time for (S) 4-phenyl-2-butanol was 8.8 min.

(S)-**4a** (α–methyl-2-naphthalenemthanol): $[\alpha]^{20}_D$ = –19.0 (c 1.5, ethanol), Lit. (4): $[\alpha]^{20}_D$ = –40.0 (c 5.0, ethanol). ^{1}H NMR (500 MHz, $CDCL_3$) δ 1.55 (3H, d, *J*= 6.4 Hz, CH_3), 1.88 (1H, br, s, OH), 5 (1H, m, CH), 7.58-7.49 (3H, m, Ar), 7.87-7.80 (4H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 1.0 ml/min and 25°C. Retention time for (S) α–methyl-2-naphthalenemthanol was 8.90 min.

(S)-**6b** (1-(4'-chlorophenyl)ethanol): $[\alpha]^{20}_D$ = –29.0 (c 0.3, $CHCl_3$), Lit. (1): $[\alpha]^{20}_D$ = –50.1 (c 7.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50(3H, d, J= 6.1 Hz, CH_3), 2.07 (1H, br, s, OH), 4.91(1H, q, *J* = 6.4 Hz, CH), 7.28 (2H, d, *J* = 8.25 Hz, Ar), 7.34 (2H, d, *J* = 8.25 Hz, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 98:2, 0.5 ml/min and 25°C. Retention time for (S)-1-(4'-chlorophenyl)ethanol was 27.9 min.

(S)-**7b** (1-(4'-fluorophenyl)ethanol): $[\alpha]^{20}_D$ = – 50.0 (c 0.2, $CHCl_3$), Lit. (5): $[\alpha]^{20}_D$ = –78.6 (c 0.2, $CHCl_3$). 1H NMR (500 MHz, $CDCl_3$) δ 1.50(3H, d, *J* = 6.1 Hz, CH_3), 2.07 (1H, br, s, OH), 4.90 (1H, q, *J* = 6.4 Hz, CH), 7.03-7.07 (2H, m, , Ar), 7.35-7.39(2H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 95:5, 0.6 ml/min and 25°C. Retention time for (S)-1-(4'-fluorophenyl)ethanol was 12.8 min.

(S)-**8b** (1-(4'-bromophenyl)ethanol): $[\alpha]^{20}_D$ = – 37.5 (c 0.2, $CHCl_3$), Lit. (1): $[\alpha]^{20}_D$ = –46.2 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49(3H, d, J= 5.9 Hz, CH_3), 2.06(1H, br, s, OH), 4.85(1H, q, *J*= 6.2 Hz, CH), 7.27 (2H, d, *J* = 8.1 Hz, Ar), 7.7.49 (2H, d, *J* = 7.7 Hz, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OD-H column, λ210, hexane: isopropanol 95:5, 1.0 ml/min and 25°C. Retention time for (S)-1-(4'-bromophenyl)ethanol was

9.0 min.

(S)-**9b** (1-(4'-methylphenyl)ethanol): $[\alpha]^{20}_D$ = –81.5 (c 0.3, $CHCl_3$), Lit. (1): $[\alpha]^{20}_D$ = –39.4 (c 2.72, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCL_3$) δ 1.59 (3H, d, *J*= 6.4 Hz, CH_3), 1.76 (1H, br, s, OH), 2.37 (3H, s,CH_3), 4.89 (1H, q, *J* = 6.4Hz, CH), 7.19 (2H, d, *J*=8.00 Hz, Ar), 7.29 (2H, d, *J* =8.05 Hz, Ar. The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane:isopropanol 90:10, 0.6 ml/min and 25°. Retention time for (S)-1-(4'-methylphenyl)ethanol was 9.8 min.

(S)-**10b** (1-(4'-nitrophenyl)ethanol): $[\alpha]^{20}_D$ = –75.7 (c 0.3, $CHCl_3$), Lit. (5): $[\alpha]^{20}_D$ = –25.0 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (3H, d, *J* = 6.5 Hz, CH_3), 2.01 (1H, br, s, OH), 5.04 (1H, q, *J* = 6.5 Hz, CH), 7.57 (2H, d, *J* =8.5 Hz, Ar), 8.23 (2H, d, *J* =8.55 Hz, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ254, hexane: isopropanol 80:20, 0.5 ml/min and 25°C. Retention time for (S)-1-(4'-nitrophenyl)ethanol was 15.5 min.

(S)-**12b** (1-(3'-fluorophenyl)ethanol): $[\alpha]^{20}_D$ = –30.0 (c 0.3, $CHCl_3$), Lit. (5): $[\alpha]^{20}_D$ = –25.6 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (3H, d, *J* = 6.2 Hz, CH_3), 2.06 (1H, br, s, OH), 4.93 (1H, q, *J* = 5.9 Hz, CH), 6.95-6.99 (1H, m, Ar),7.01-7.11 (2H,m,Ar), 7.14-7.35 (1H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 0.6 ml/min and 25°C. Retention time for (S)-1-(3'-fluorophenyl)ethanol was 8.9 min.

(S)-**13b** (1-(3'- bromophenyl)ethanol): $[\alpha]^{20}_D$ = –40.0 (c 0.4, $CHCl_3$), Lit. (1): $[\alpha]^{20}_D$ = –27.6 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51(3H, d, *J* = 6.5 Hz, CH_3), 2.07(1H, br, s, OH), 4.89(1H, q, *J* = 6.4 Hz, CH), 7.22-7.28 (2H,m,Ar), 7.31-7.33 (1H, m, Ar), 7.41-7.56(1H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 0.6 ml/min and 25°C. Retention time for (S)-1-(3'- bromophenyl)ethanol was 10.0 min.

(S)-**14b** (1-(3'-methylphenyl)ethanol): $[\alpha]^{20}_D$ = –41.9 (c 0.3, $CHCl_3$), Lit. (1): $[\alpha]^{20}_D$ –30.2 (c 0.58, EtOH). ^{1}H NMR (500 MHz, $CDCL_3$) δ 1.52 (3H, d, *J* = 6.5 Hz, CH_3), 2.07 (1H, br, s, OH), 2.19 (3H, s, CH_3), 4.90 (1H, q, *J* = 6.45 Hz, CH), 7.1-7.12 (1H, m, Ar), 7.18-7.22 (2H, m, Ar), 7.25-7.28(1H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 0.6 ml/min and 25°C. Retention time for (S)- 1-(3'-methylphenyl)ethanol was 9.0 min.

(S)-**15b** (1-(3'-nitrophenyl)ethanol): $[\alpha]^{20}_D$ = –13.33 (c 0.3, $CHCl_3$), Lit. (5): $[\alpha]^{20}_D$ –22.0 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCL_3$) δ 1.56 (3H, d, *J* = 6.5 Hz, CH_3), 2.06 (1H, br, s, OH) 5.04 (1H, q, *J* = 6.5 Hz), 7.54 (1H, t, *J*= 6.4 Hz), 7.74 (1H, d, *J*= 6.4 Hz), 8.28(s, 1H). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ254, hexane: isopropanol 80:20, 0.6 ml/min and 25°C. Retention time for (S)-1-(3'-nitrophenyl)ethanol was 12.7 min.

(S)-**16b** (1-(3'-aminophenyl)ethanol): $[\alpha]^{20}_D$ = –40.0 (c 0.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCL_3$) δ 1.49(3H, d, *J* = 6.45 Hz, CH_3), 2.07(1H, br, s, OH), 4.83(1H, q, *J* = 6.4 Hz, CH), 6.61-6.63 (1H, m, Ar), 6.75-6.78 (2H, m, Ar), 7.14-7.28 (1H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OD-H column, λ239, hexane: isopropanol 75:25, 0.6 ml/min and 25°C. Retention time for (S)-(1-(3'-aminophenyl)ethanol) was 22.8 min.

(S)-**17c** (2-bromo-1-phenylethanol): $[\alpha]^{20}_D$ = + 33.3 (c 0.4, $CHCl_3$), Lit. (6): $[\alpha]^{20}_D$ + 42.3 (c 1.5, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 2.00 (1H, br, s, OH), 4.09 (2H, m, CH_2) 4.85 (1H, m, CH), 7.46-7.60 (5H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 0.6 ml/min and 25°C. Retention time for (S)-2-bromo-1-phenylethanol was 13.8 min.

(S)-**18c** (2-fluoro-1-phenylethanol): $[\alpha]^{20}_D$ = +14.3 (c 0.3, $CHCl_3$), Lit. (7): $[\alpha]^{20}_D$ +55.6 (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 2.01 (1H, br, s, OH), 4.37-4.59 (2H, m CH_2) 4.59-5.09 (1H, m, CH), 7.28-7.43(5H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 90:10, 0.6 ml/min and 25°C. Retention time for (S)-2-fluoro-1-phenylethanol was 15.3 min.

(S)-**19c** (2-chloro-1-phenylethanol): $[\alpha]^{20}_D$ = + 37.9 (c 0.3, $CHCl_3$), (R)-**19** Lit. (4): $[\alpha]^{20}_D$ + 43 (c 2.8, cyclohexane). ^1H NMR (500 MHz, $CDCL_3$) δ 2.69 (1H, s, OH), 3.65-3.8(2H, m, CH_2), 4.92-4.95 (1H, m, CH), 7.60-7.28 (5H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 95:5, 0.6 ml/min and 25°C. Retention time for (S)-2-chloro-1-phenylethanol was 20.1 min.

(S)-**20c** (2-chloro-1-(4'-fluorophenyl)ethanol): $[\alpha]^{20}_D$ = +47.6 (c 0.2, $CHCl_3$), Lit. (8): $[\alpha]^{20}_D$ + 52.8 (c 1.0, $CHCl_3$).^1H NMR (500 MHz, $CDCl_3$) δ 2.19 (1H, br, s, OH), 3.66 (1H, m, CH_2), 3.76 (1H, m, CH_2), 4.83 (1H, m, CH), 7.09(1H, m, Ar), 7.36 (1H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OB-H column, λ210, hexane: isopropanol 95:5, 1.0 ml/min and 25°C. Retention time for (S)-2-chloro-1-(4'-fluorophenyl)ethanol was 14.4 min.

(S)-**21c** (2-chloro-1-(2',4'-difluorophenyl)ethanol): $[\alpha]^{20}_D$ = +78.3 (c 0.2, $CHCl_3$), Lit. (8): $[\alpha]^{20}_D$= +38.0 (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 2.02 (1H, br, s, OH), 3.57-3.70 (2H, m, CH_2), 5.2 (1H, m,CH), 6.81-6.84 (1H, m, Ar), 6.85-7.28(1H, m, Ar) , 7.52-7.58 (1H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OD-H column, λ210, hexane: isopropanol 99:1, 0.5 ml/min and 25°C. Retention time for (S)-2-chloro-1-(2',4'-difluorophenyl)ethanol was 48.0 min.

(S)-**22d** (3-hydroxy-3-phenylpropanenitrile): $[\alpha]^{20}_D$ = –24.1 (c 0.3, $CHCl_3$), Lit. (8): $[\alpha]^{20}_D$= –61.3 (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.96 (1H, br, s, OH), 2.67-2.69 (2H, m, CH_2) 4.93(1H, t, *J*= 6.1 Hz, CH), 7.23-7.47(5H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OD-H column, λ210, methanol: isopropanol 90:10, 0.4 ml/min and 25°C. Retention time for (S)-3-hydroxy-3-phenylpropanenitrile was 8.2 min.

(S)-**23d** (3-(4-bromophenyl)-3-hydroxypropanenitrile): $[\alpha]^{20}_D$ = –22.2 (c 0.3, $CHCl_3$), Lit. (8): $[\alpha]^{20}_D$= –46.3 (c 1.0, $CHCl_3$). (3-hydroxy-3-phenylpropanenitrile): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (1H, d, *J* = 4.0 Hz CH), 2.78 (2H, d, *J* = 6.4 Hz CH_2), 5.05-5.06 (1H, m, OH), 7.28-7.35 (2H, m, Ar), 7.55-7.56 (2H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OD-H column, λ210, methanol: isopropanol 85:15, 0.6 ml/min and 25°C. Retention time for (S)-3-(4-bromophenyl)-3-hydroxypropanenitrile was 5.5 min.

(S)-**24e** 1-(3,5-bis(trifluoromethyl)phenyl)ethanol: $[\alpha]^{20}_D$ = –33.3 (c 0.5, $CHCl_3$), (R)-1-(3,5-bis(trifluoromethyl)phenyl) ethanol Lit. (9): $[\alpha]^{20}_D$ = +22.7 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCL_3$) δ 1.52-1.51(3H, d, *J* = 6.5 Hz, CH_3), 1.99 (1H, br, s, OH), 5.04-5.00 (1H, q, *J* = 6.5 Hz, CH), 7.92- 7.78 (3H, s, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OD-H column, λ210, hexane: isopropanol 98:2, 0.5 ml/min and 25°C. Retention time for (S)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol was 18.7 min.

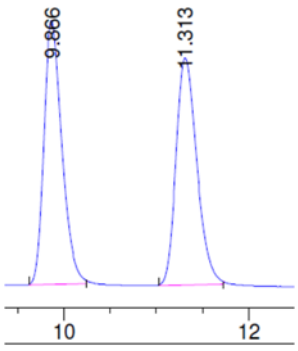
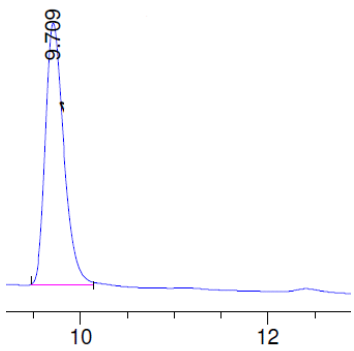
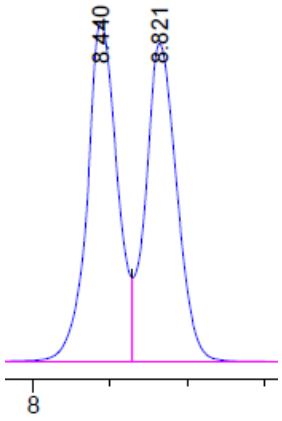
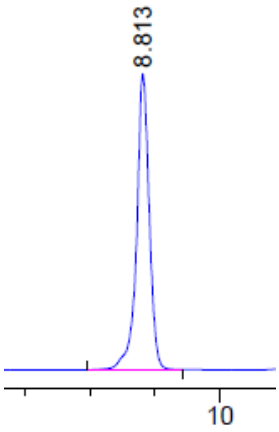
(S)-**26f** 1-(pyrazin-2-yl)ethanol: $[\alpha]^{20}_D$ = –40.7 (c 0.2, $CHCl_3$), Lit. (8): $[\alpha]^{20}_D$ = –29.4 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49(3H, d, J= 5.8 Hz, CH_3), 2.00 (1H, br, s, OH), 4.92(1H, m, CH), 8.68 (2H, m, Ar), 9.14 (1H, s, Ar). The enantiomeric excess (% e.e) was determined by HPLC using OD-H column, λ210, hexane: isopropanol 80:20, 0.6 ml/min and 25°C. Retention time for (S)-1-(pyrazin-2-yl)ethanol was 12.8 min.

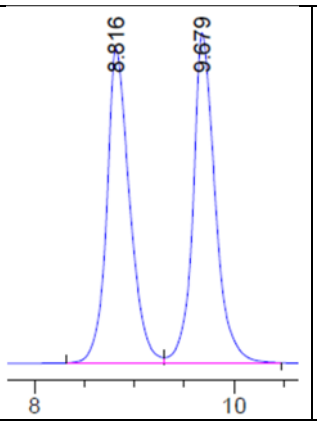
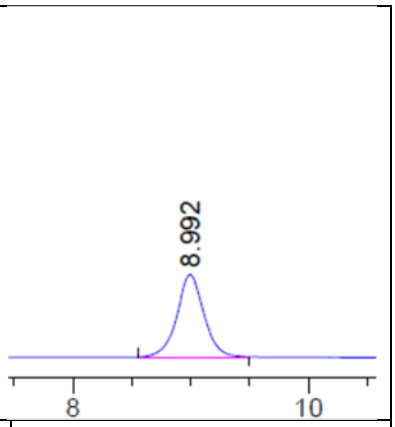
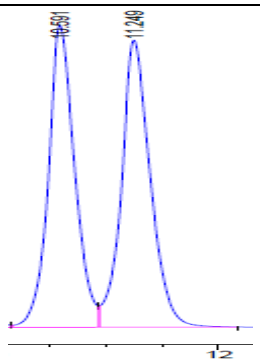
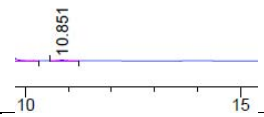
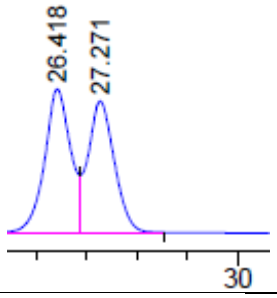
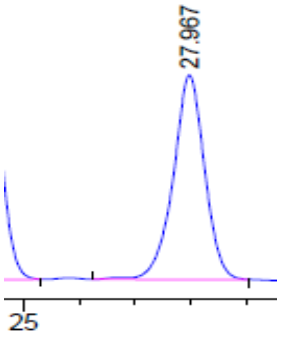
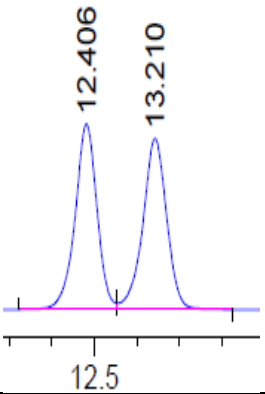
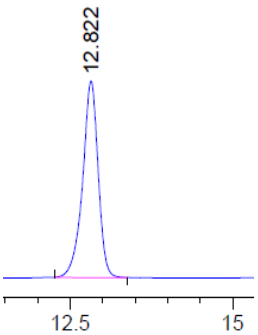
(S)-**27f** 1-(3-methylpyrazin-2-yl)ethanol: $[\alpha]^{20}_D$ = –55.5 (c 0.2, $CHCl_3$), Lit. (8): $[\alpha]^{20}_D$ –86.9 (c 1.0, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40(3H, d, *J* = 6.4 Hz, CH_3), 2.52(3H, s, CH_3), 1.98 (1H, br, s, OH), 4.99 (1H, m, CH), 8.42 (1H, m, Ar), 8.53 (1H, m, Ar). The enantiomeric excess (% e.e) was determined by HPLC using Chiralcel OD-H, λ210, hexane: isopropanol 95:5, 0.6 ml/min and 25°C. Retention time for (S)-1-(3-methylpyrazin-2-yl)ethanol was 16.3 min.

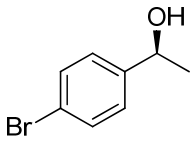
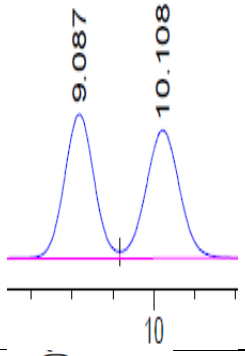
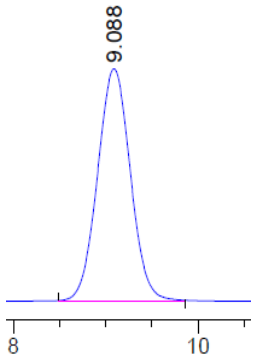
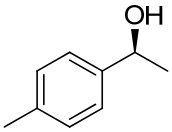
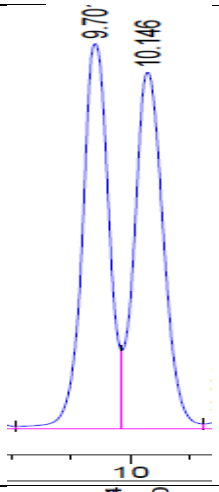
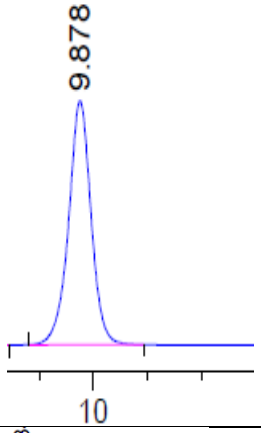
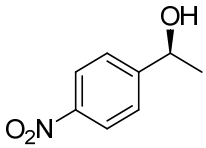
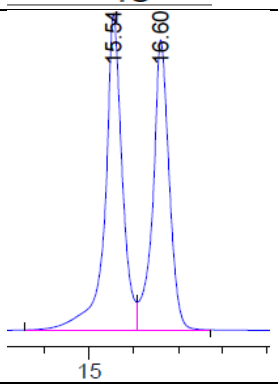
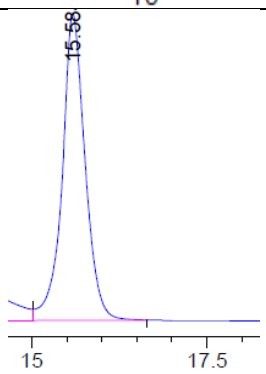
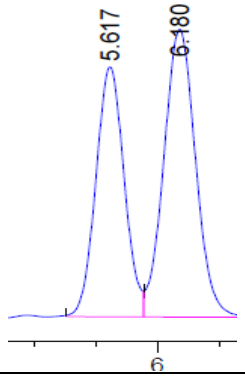
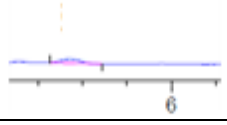
2. HPLC chromatograms

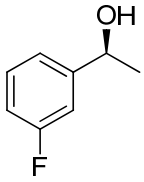
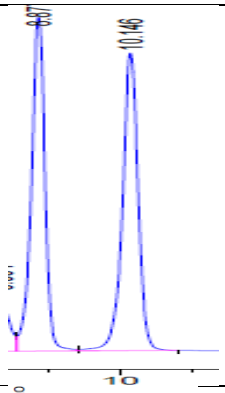
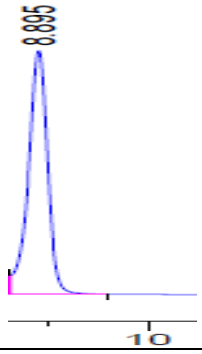
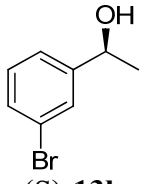
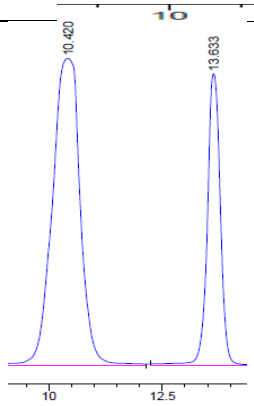
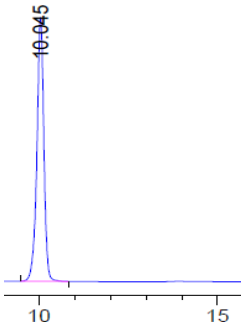
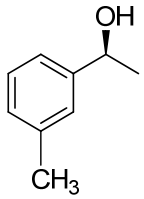
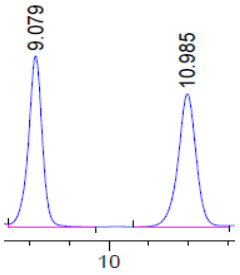
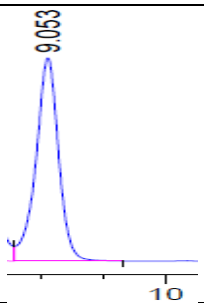
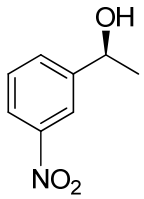
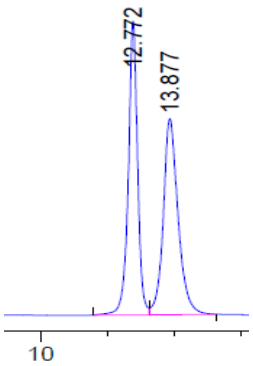
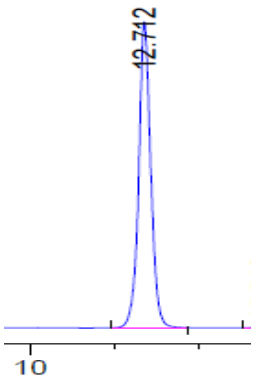
The HPLC chromatograms for *rac*-alcohols and the biocatalyzed alcohols using *Hv*ADH2 are presented in Table S1.

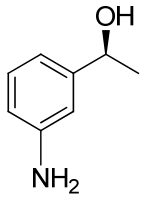
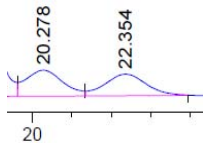
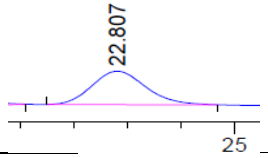
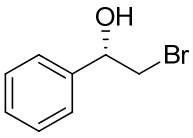
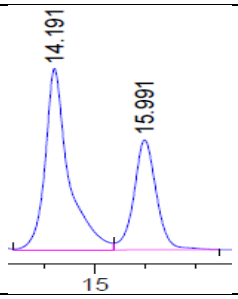
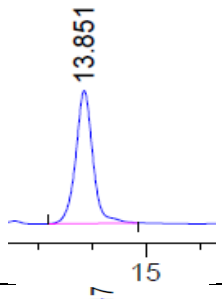
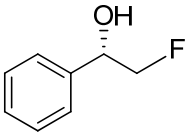
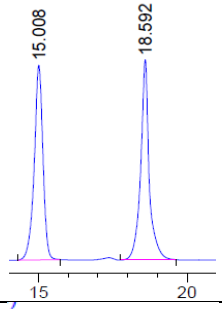
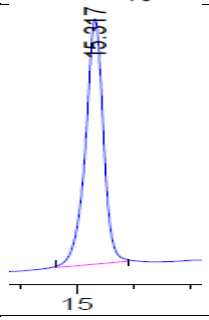
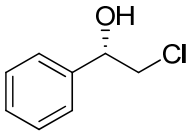
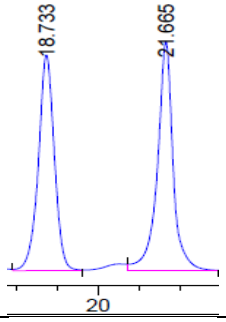
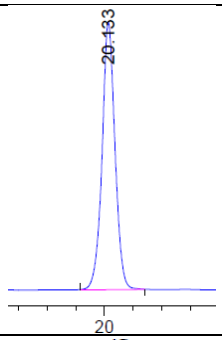
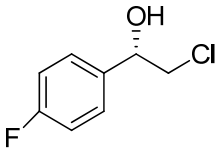
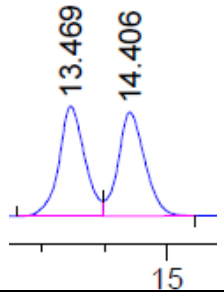
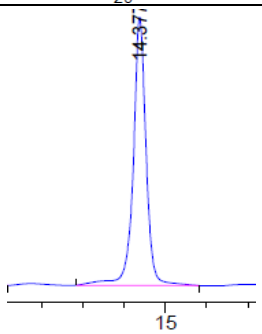
Table S1. The HPLC chromatograms for *rac*-alcohols and the biocatalyzed alcohols using *Hv*ADH2

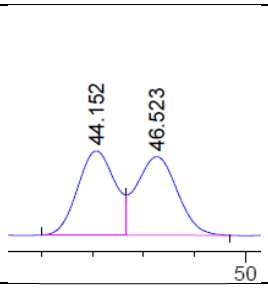
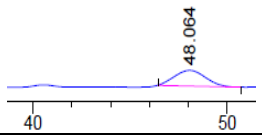
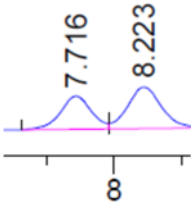
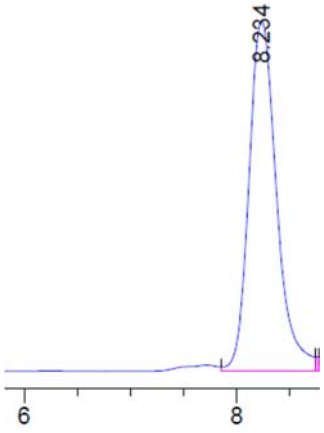
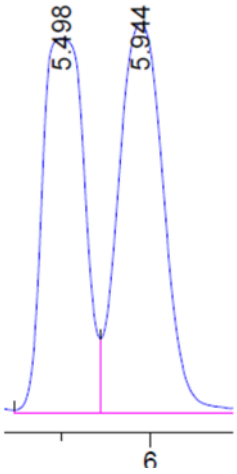
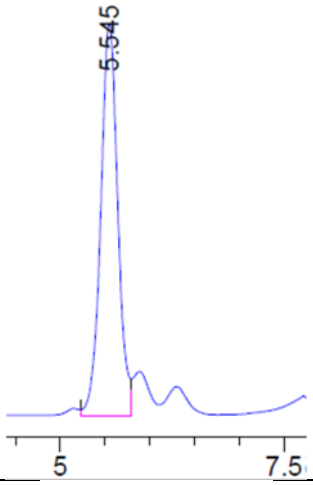
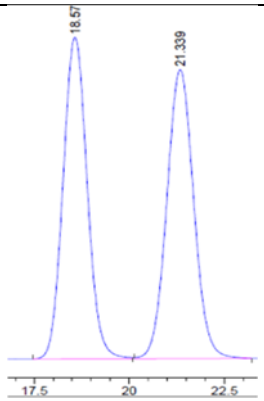
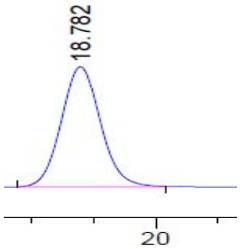
Substrate	**Product**	***rac*-alcohol**	**Biocatalyzed alcohol using *Hv*ADH2**
1	(S)-**1a**		
2	(S)-**2a**		
3	(S)-**3a**		
Substrate	**Product**	***rac*-alcohol**	**Biocatalyzed alcohol using *Hv*ADH2**

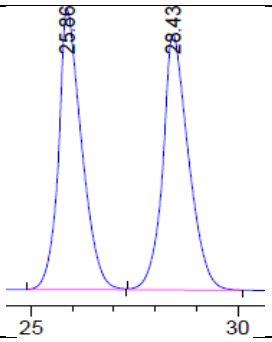
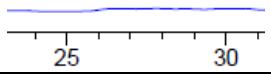
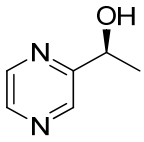
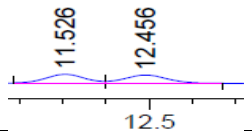
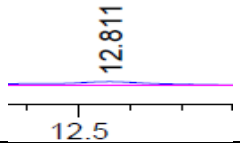
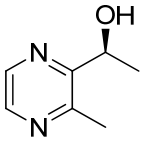
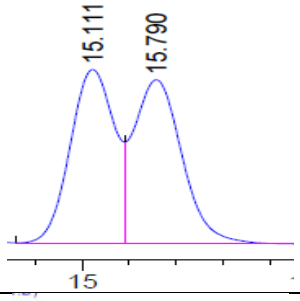
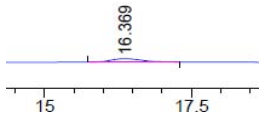
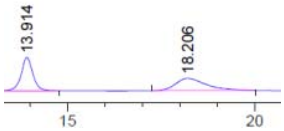
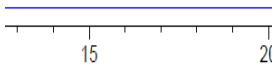
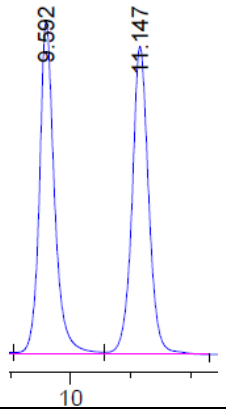
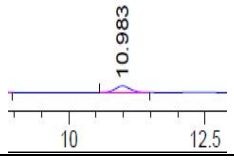
4	(S)-**4a**		
5	------		
6	(S)-**6b**		
7	(S)-**7b**		
Substrate	**Product**	***rac*-alcohol**	**Biocatalyzed alcohol using *Hv*ADH2**

8	 (S)-**8b**		
9	 **(S)-9b**		
10	 **(S)-10b**		
11	--------		
Substrate	**Product**	***rac*-alcohol**	**Biocatalyzed alcohol using *Hv*ADH2**

12	 **(S)-12b**		
13	 (S)-**13b**		
14	 (S)-**14**		
15	 (S)-**15b**		
Substrate	**Product**	***rac*-alcohol**	**Biocatalyzed alcohol using *Hv*ADH2**

16	 (S)-**16b**		
17	 (S)-**17c**		
18	 (S)-**18c**		
19	 (S)-**19c**		
20	 (S)-**20c**		
Substrate	**Product**	***rac*-alcohol**	**Biocatalyzed alcohol using *Hv*ADH2**

21	(S)-**21c**		
22	(S)-**22d**		
23	(S)-**23d**		
24	(S)-**24e**		
Substrate	**Product**	***rac*-alcohol**	**Biocatalyzed alcohol using *Hv*ADH2**

25	----------		
26	 (S)-**26f**		
27	 (S)-**27f**		
28	------		
29	--------		

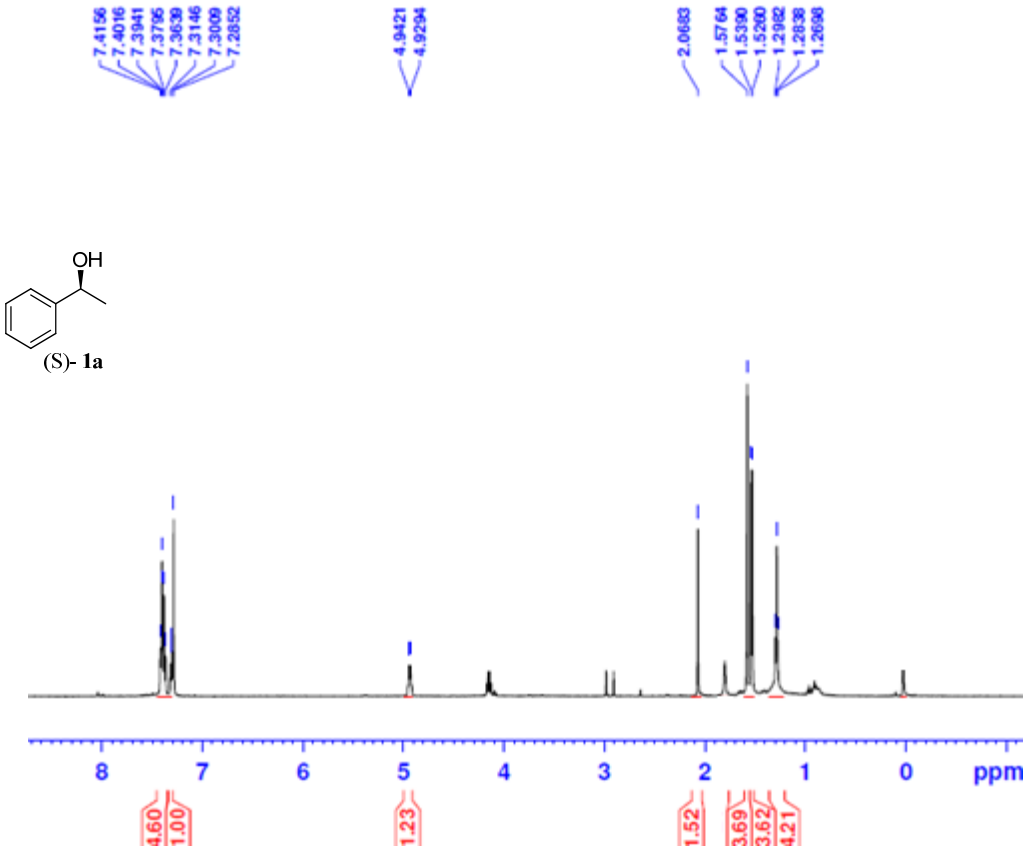
3. IR spectroscopy study

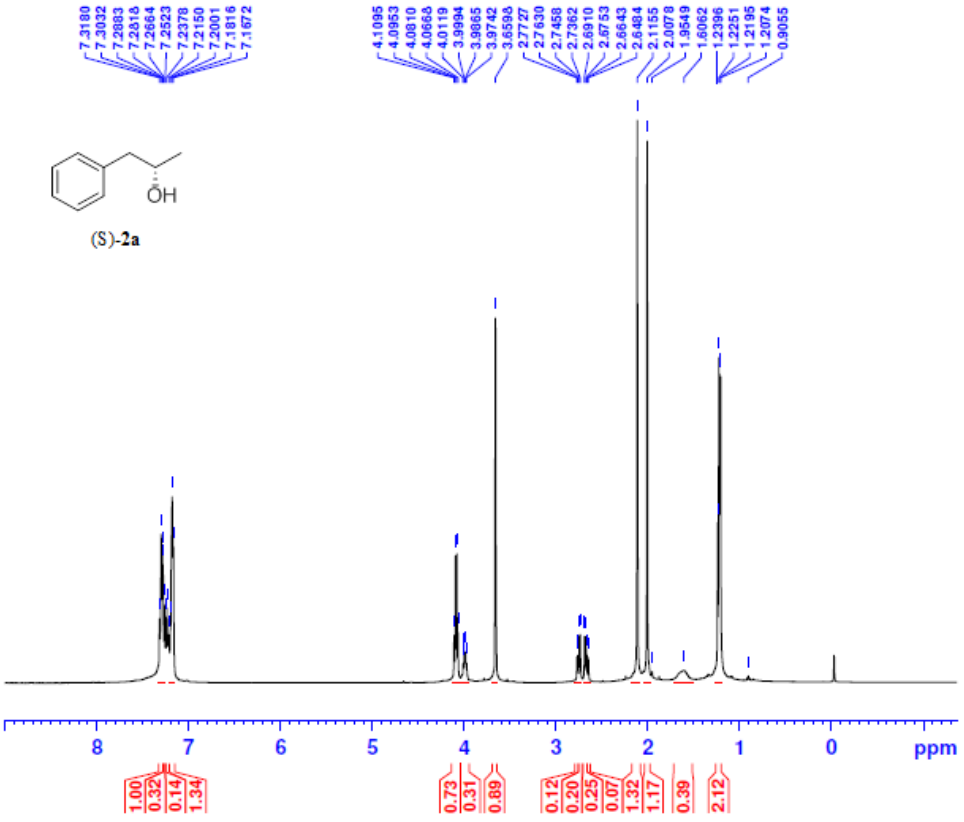
IR absorption spectra of the ketones were recorded on fourier transform infrared (FT-IR) spectra using KCl disc.

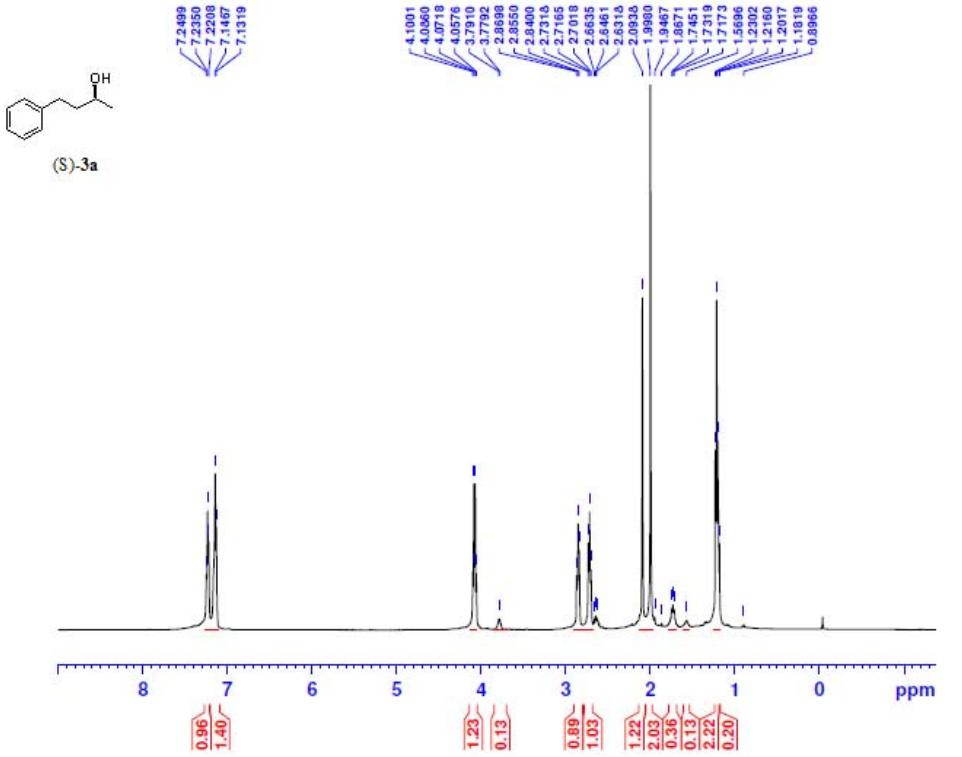
Substrate	C=O band/cm^{-1}
1	1681.9
2	1712.7
3	1712.8
4	1666.5
5	1681.9
6	**1685.8**
7	**1681.9**
8	**1674.2**
9	**1678.1**
10	**1689.6**
11	**1647.0**
12	**1685.7**
13	**1681.9**
14	**1681.9**
15	**1685.9**
16	**1649.9**
17	1689.6
18	1705.1
19	1685.8
20	1697.4
21	1701.2
22	1681.8
23	1678.1

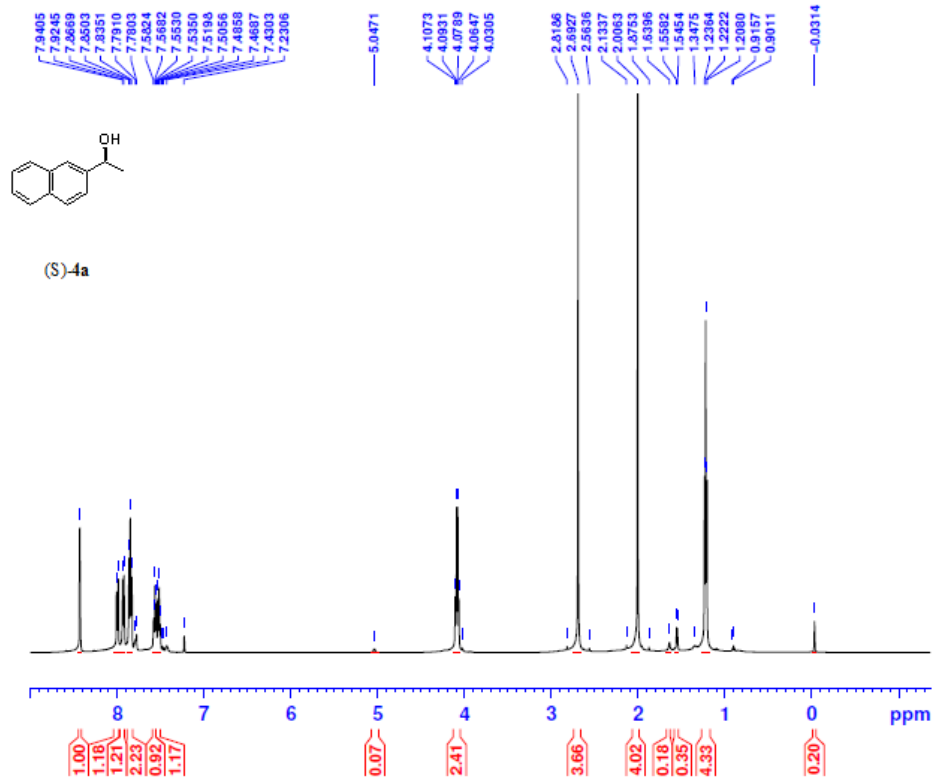
4. Supporting references

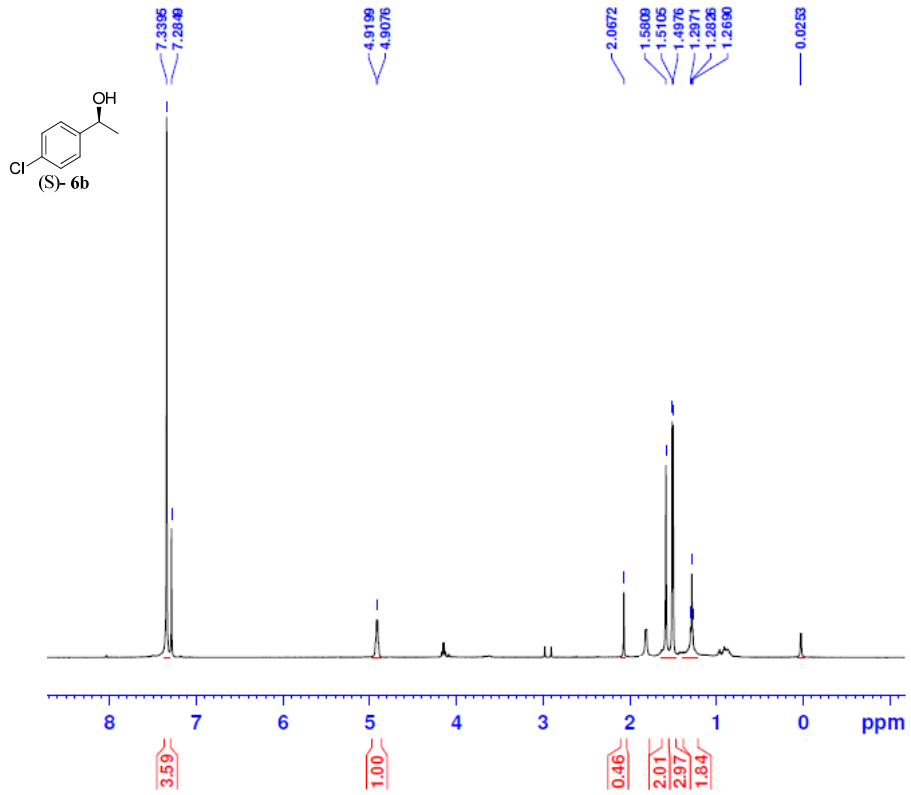
1 M. L. Kantam, S. Laha, J. Yadav, P. R. Likhar, B. Sreedhar, S. Jha, S. Bhargva, M. Udaykiran and B. Jagadeesh, *Org. Lett.,* 2008, **10**, 2979–2982.
2 B. Erdélyi, A. Szabó, G. Seres, L. Birincsik, J. Ivanics, G. Szatzker and L. Poppe, *Tetrahedron: Asymmetry*, 2006, **17**, 268-274.
3 K. Nakamura, Y. Inoue, T. Matsuda and I Misawa, *J. Chem. Soc. Perkin. Trans*., 1999, **1**, 2397–2402.
4 Sigma aldrich catalog, www.sigmaaldrich.com
5 M. L. Contente, I. Serra, L. Palazzolo, C. Parravicini, E. Gianazza, I. Eberini, A. Pinto, B. Guidi, F. Molinari and D. Romano, *Org. Biomol. Chem*., 2016, **14**, 3404–3408.
6 D. M. Du, T. Fang, J. X. Xu and S. W. Zhang, *Org. Lett*., 2006, **8**, 1327–1330.
7 T. W. Shaw, J. A. Kalow and A. G. Doyle, *Organic syntheses*, 2012, **89**, 9-18.
8 A. S. Rowan, T. S. Moody, R. M. Howard, T. J. Underwood, I. R. Miskelly, Y. He and B. Wang, *Tetrahedron: Asymmetry*, 2013, **24**, 1369-1381.
9 W.-P. Liu, M.-L. Yuan, X.-H. Yang, K. Li, J.-H. Xie and Q.-L. Zhou, *Chem. Commun.*, 2015, **51**, 6123–6125.

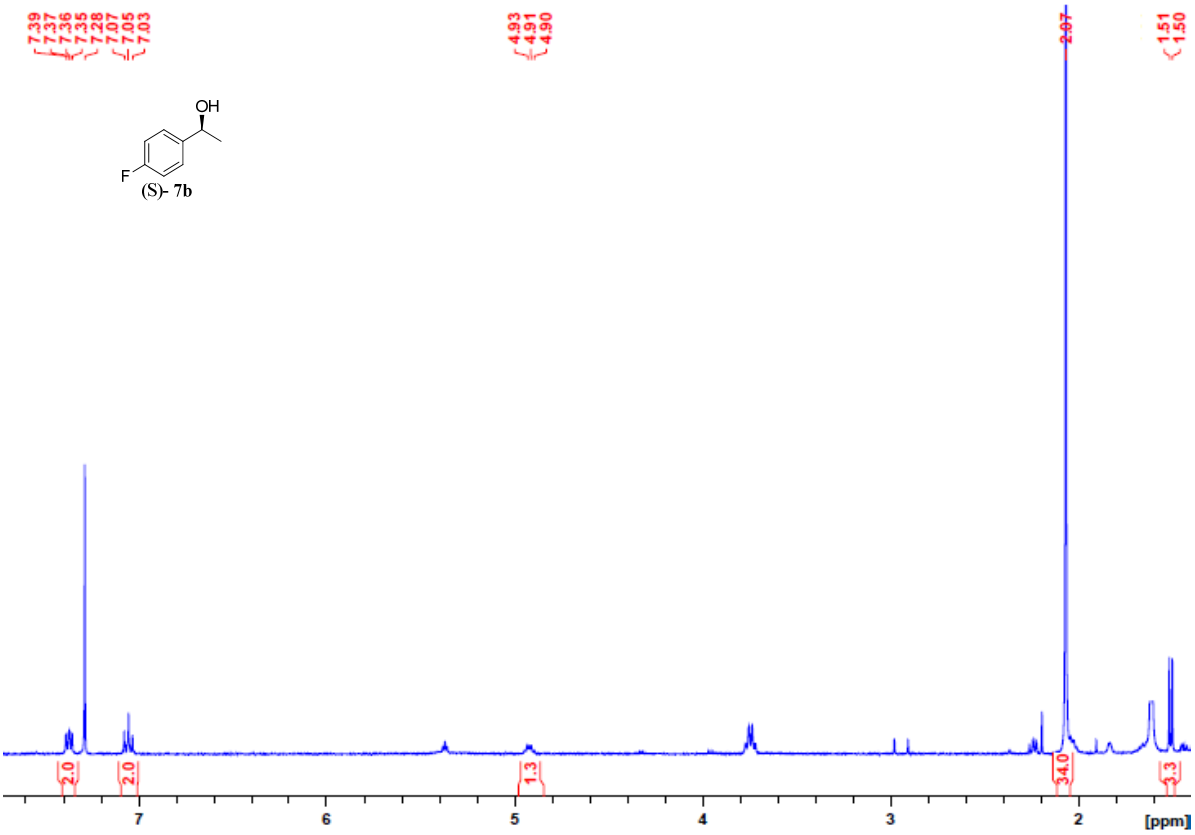

OH
(S)- 1a
ppm

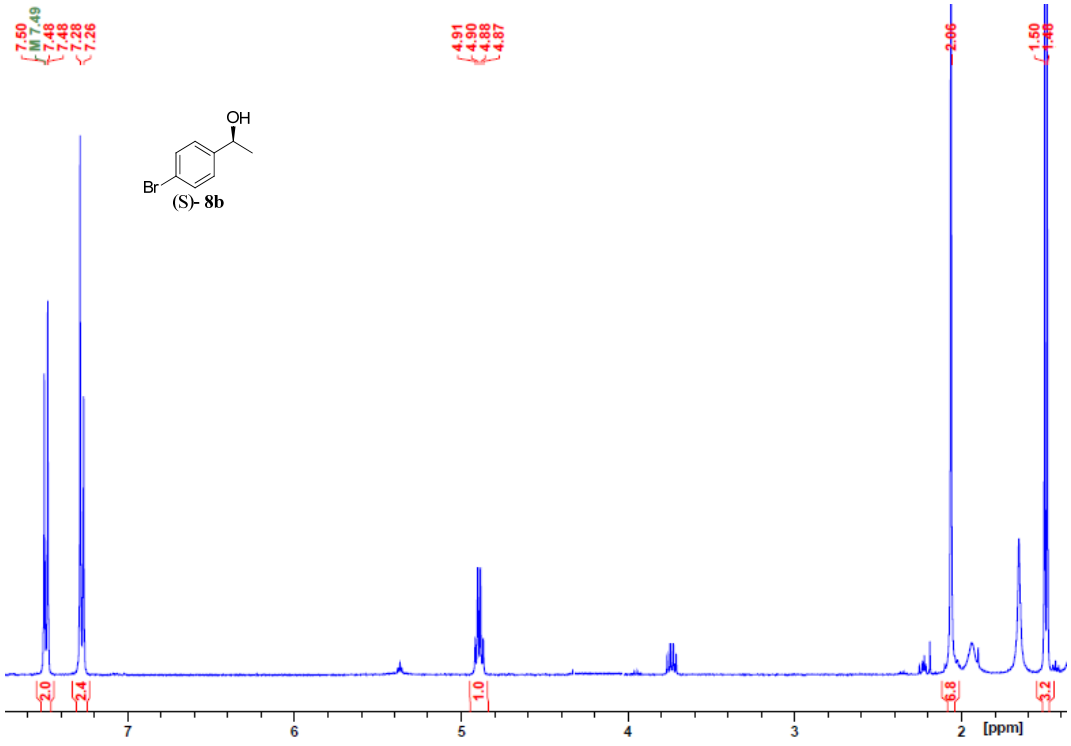

OH
(S)-2a
ppm

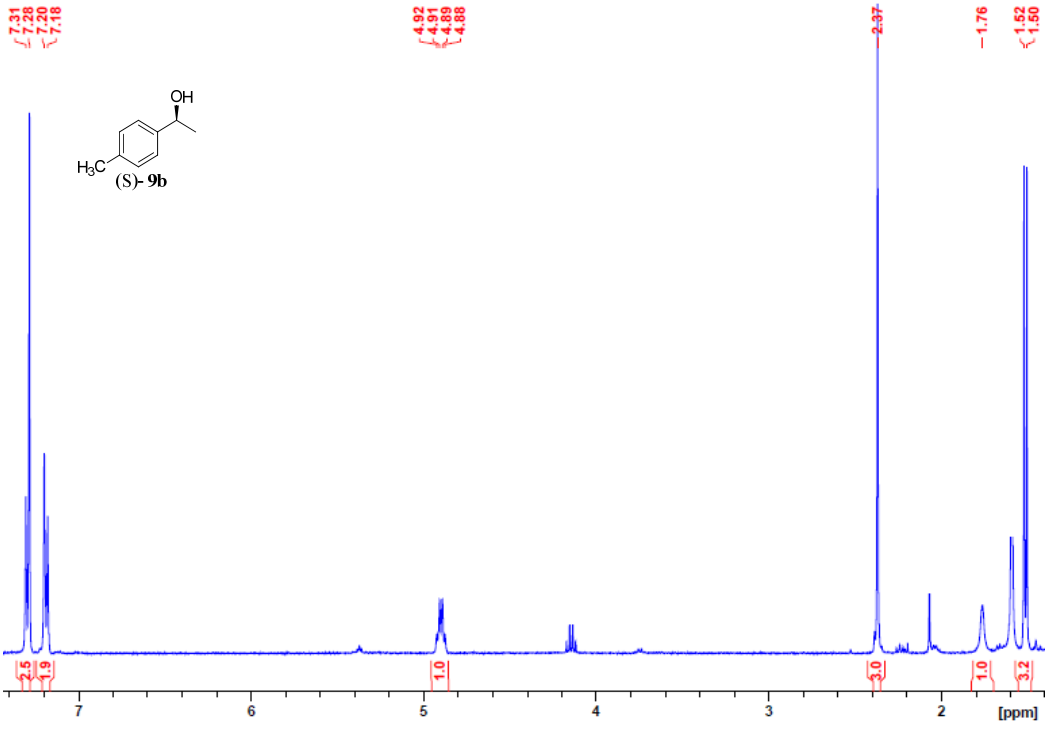

OH
(S)-3a
7.2499
7.2350
7.2208
7.1467
7.1319
4.1001
4.0860
4.0718
4.0576
3.7910
3.7792
2.8698
2.8550
2.8400
2.7316
2.7165
2.7018
2.6635
2.6461
2.6318
2.0938
1.9980
1.9467
1.8671
1.7451
1.7319
1.7173
1.5696
1.2302
1.2160
1.2017
1.1819
0.9966
8
7
6
5
4
3
2
1
0
ppm
0.96
1.40
1.23
0.13
0.89
1.03
1.22
2.03
0.36
0.13
2.22
0.20

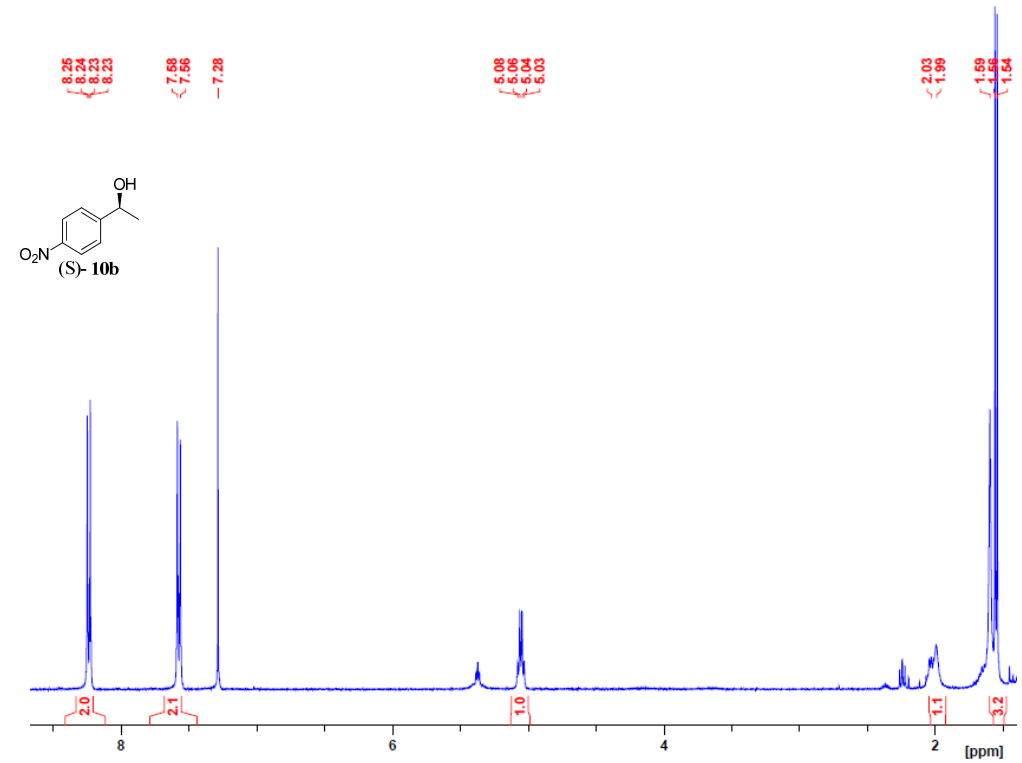

OH
(S)-4a
7.9405
7.9245
7.8669
7.8503
7.8351
7.7910
7.7803
7.5824
7.5682
7.5530
7.5350
7.5194
7.5056
7.4858
7.4687
7.4303
7.2306
5.0471
4.1073
4.0931
4.0789
4.0647
4.0305
2.6186
2.6027
2.5636
2.1337
2.0063
1.8753
1.6396
1.5582
1.5454
1.3475
1.2364
1.2222
1.2080
0.9157
0.9011
-0.0314
8
7
6
5
4
3
2
1
0
ppm
1.00
1.18
1.21
2.23
0.92
1.17
0.07
2.41
3.66
4.02
0.18
0.35
4.33
0.20

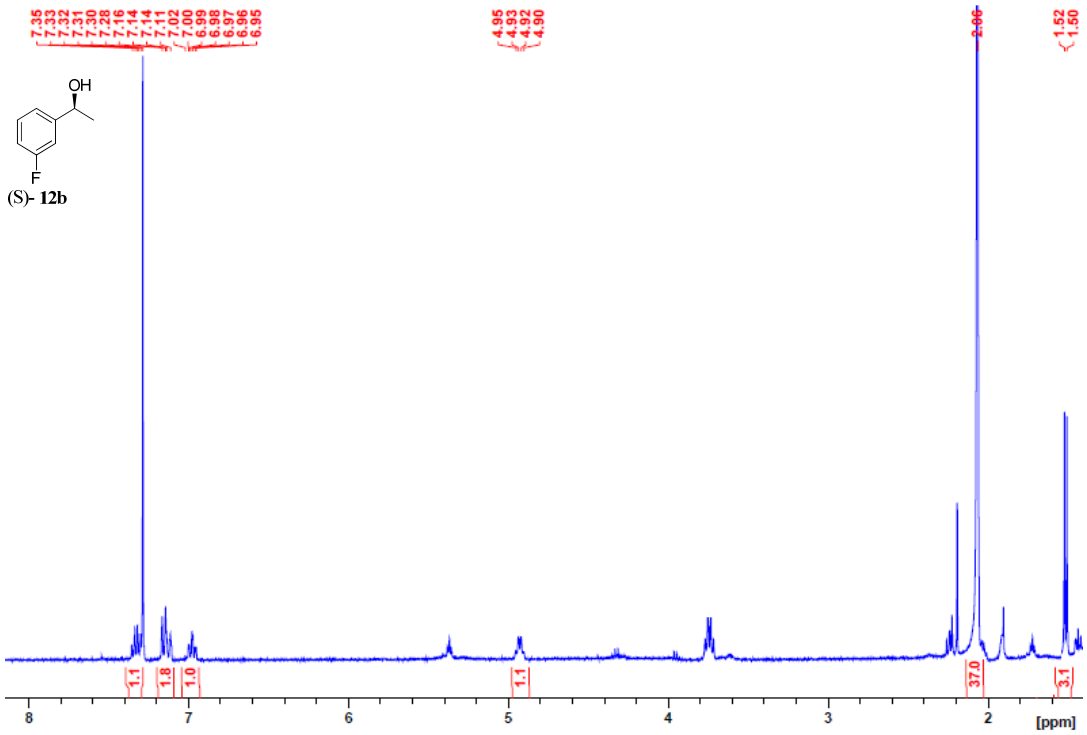

7.3395
7.2849
4.9199
4.9076
2.0672
1.5809
1.5105
1.4976
1.2971
1.2826
1.2690
0.0253
OH
Cl
(S)- 6b
8
7
6
5
4
3
2
1
0
ppm
3.59
1.00
0.46
2.01
2.97
1.84

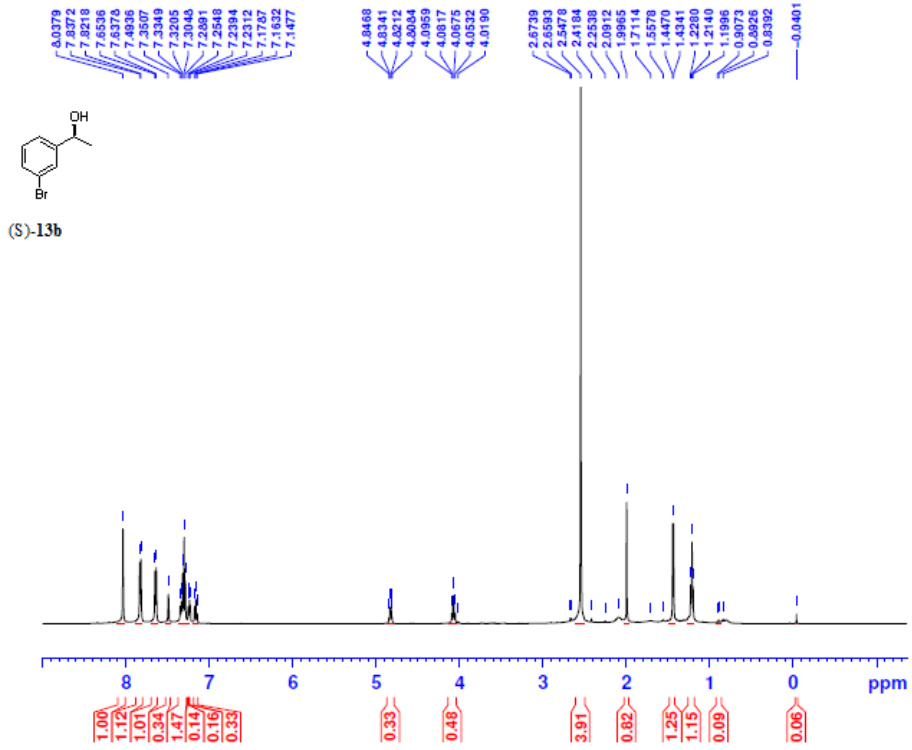

7.39
7.37
7.36
7.35
7.28
7.07
7.05
7.03
4.93
4.91
4.90
2.07
1.51
1.50
OH
F
(S)- 7b
2.0
2.0
1.3
34.0
3.3
7
6
5
4
3
2
[ppm]

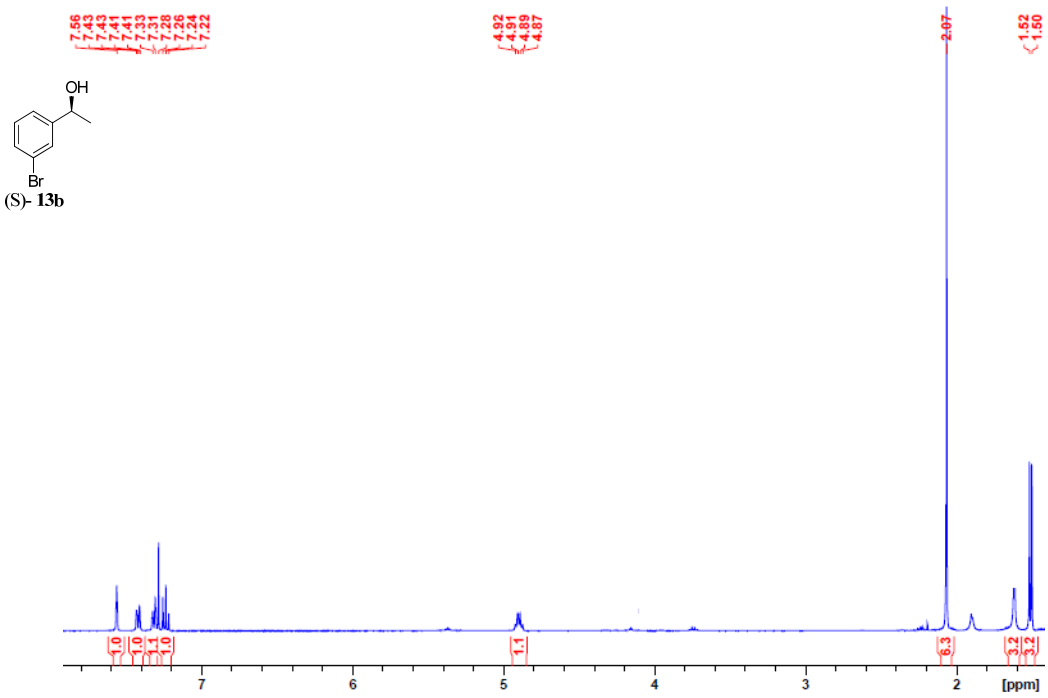

7.50
M 7.49
7.48
7.48
7.28
7.26
4.91
4.90
4.88
4.87
2.06
1.50
1.48
OH
Br
(S)- 8b
2.0
2.4
1.0
6.8
3.2
7
6
5
4
3
2
[ppm]


7.31
7.28
7.20
7.18
4.92
4.91
4.89
4.88
2.37
1.76
1.52
1.50
OH
H3C
(S)- 9b
2.5
1.9
1.0
3.0
1.0
3.2
7
6
5
4
3
2
[ppm]

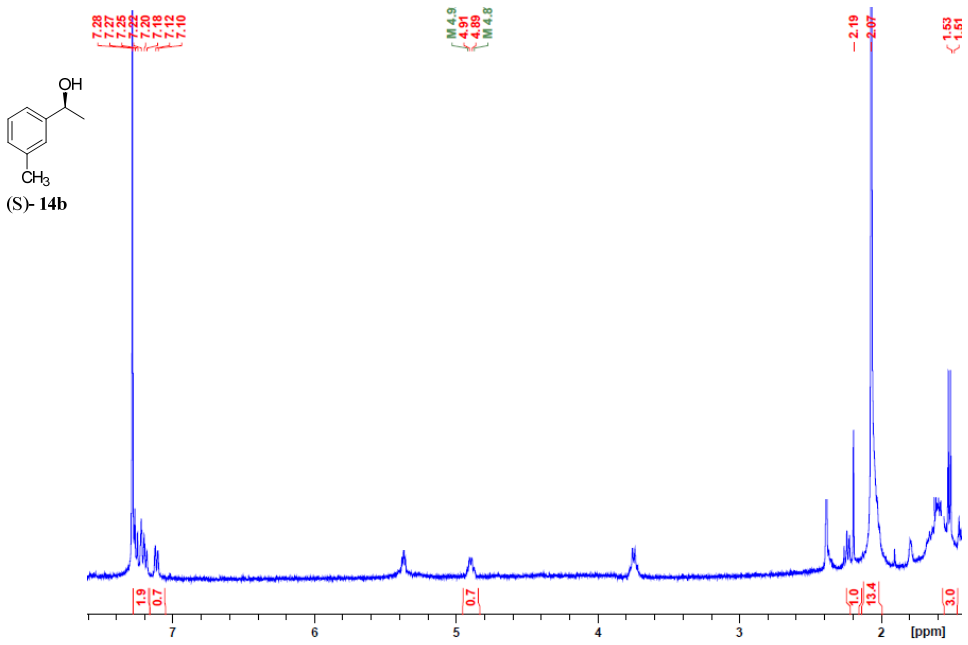

8.25
8.24
8.23
8.23
7.58
7.56
7.28
5.08
5.06
5.04
5.03
2.03
1.99
1.59
1.56
1.54
OH
O2N
(S)- 10b
2.0
2.1
1.0
1.1
3.2
8
6
4
2
[ppm]


OH
F
(S)- 12b
[ppm]

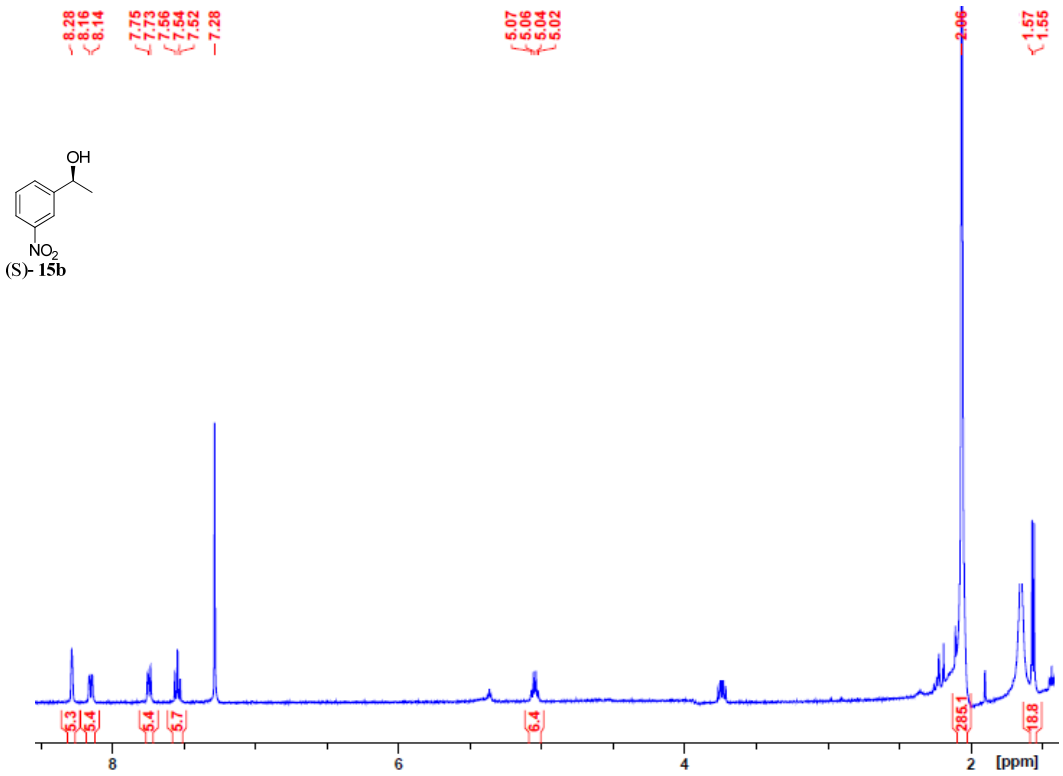

OH
Br
(S)-13b
ppm

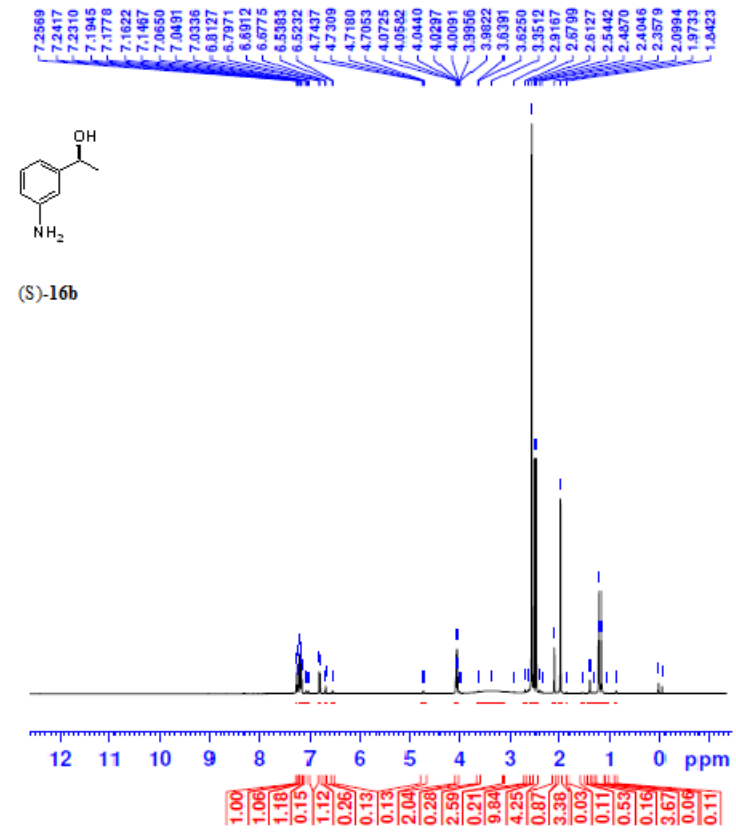

OH
Br
7.56
7.43
7.43
7.41
7.41
7.33
7.31
7.28
7.26
7.24
7.22
4.92
4.91
4.89
4.87
2.07
1.52
1.50
4.0
1.0
1.1
1.0
1.1
6.3
2.2
3.2
7
6
5
4
3
2
[ppm]

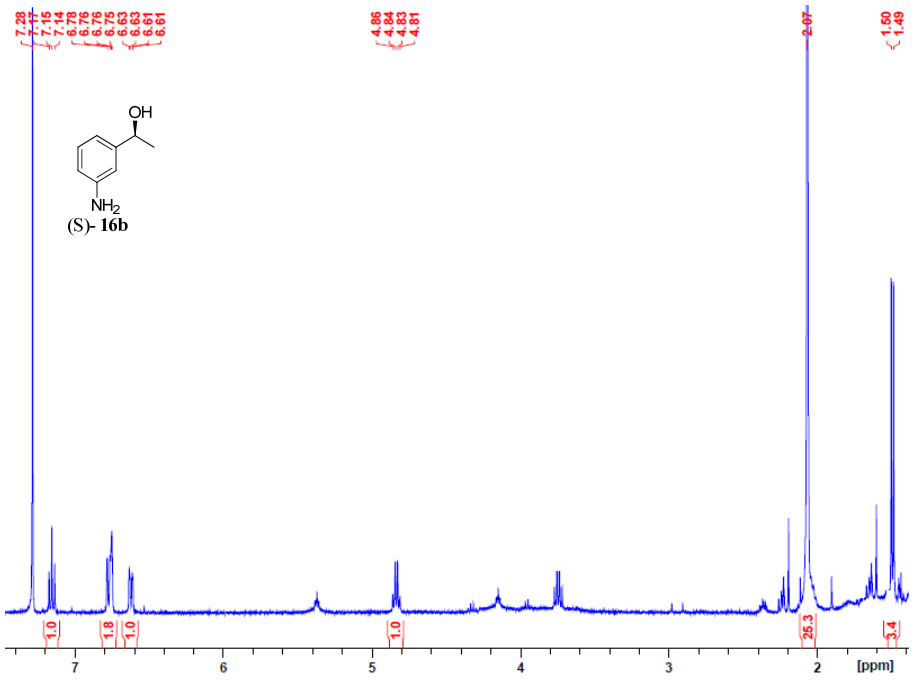
(S)- **13b**

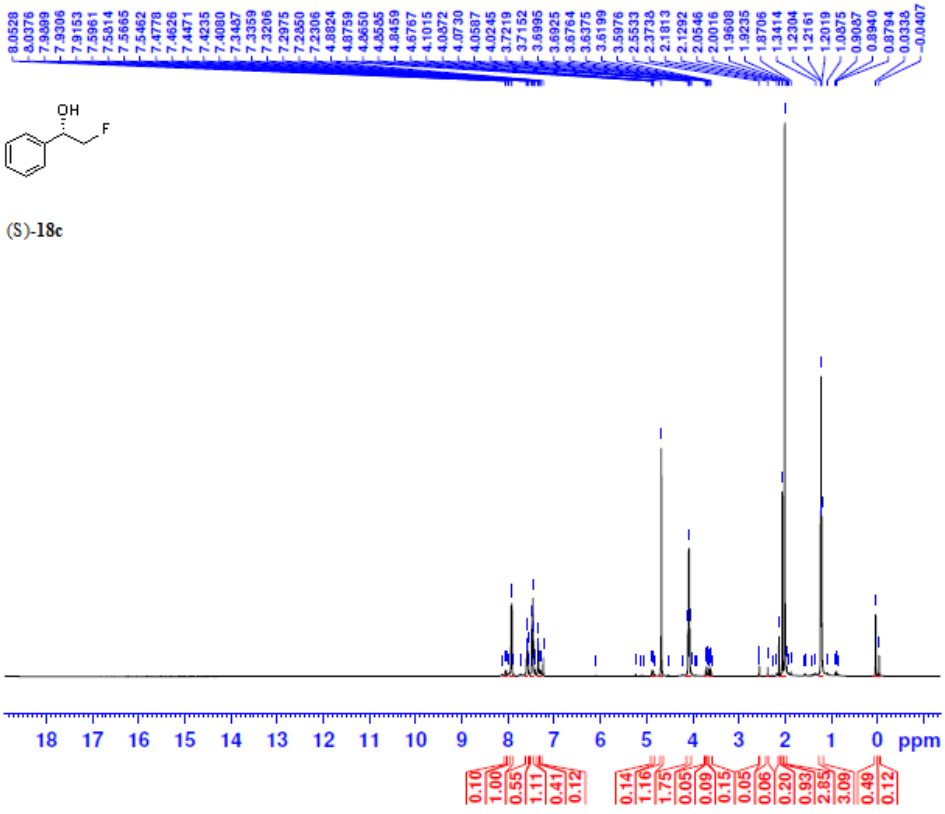

OH
CH3
7.28
7.27
7.25
7.22
7.20
7.18
7.12
7.10
M 4.9
4.91
4.89
M 4.8
2.19
2.07
1.53
1.51
1.9
0.7
0.7
1.0
13.4
3.0
7
6
5
4
3
2
[ppm]

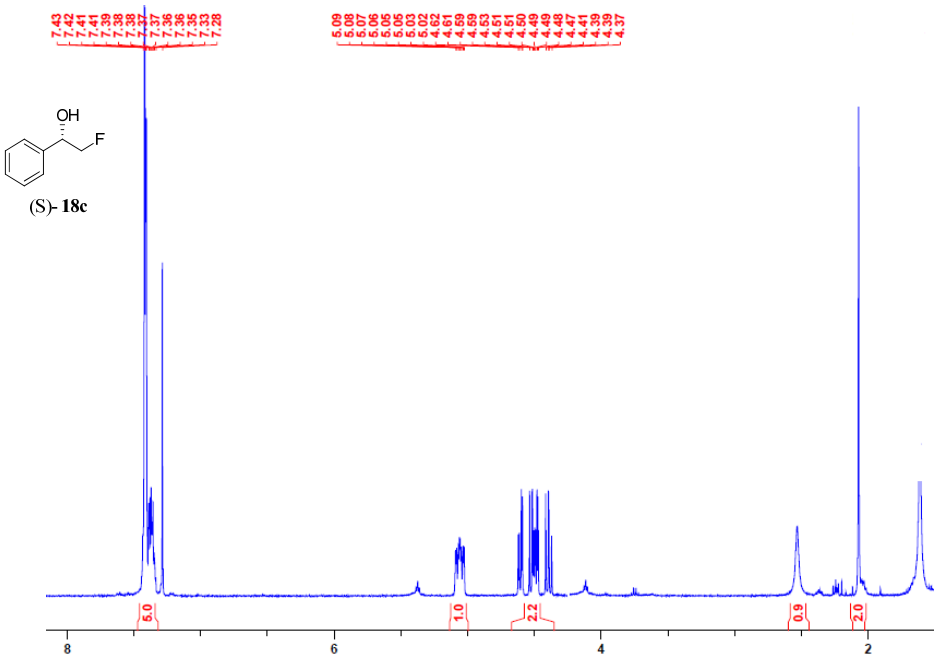
(S)- **14b**

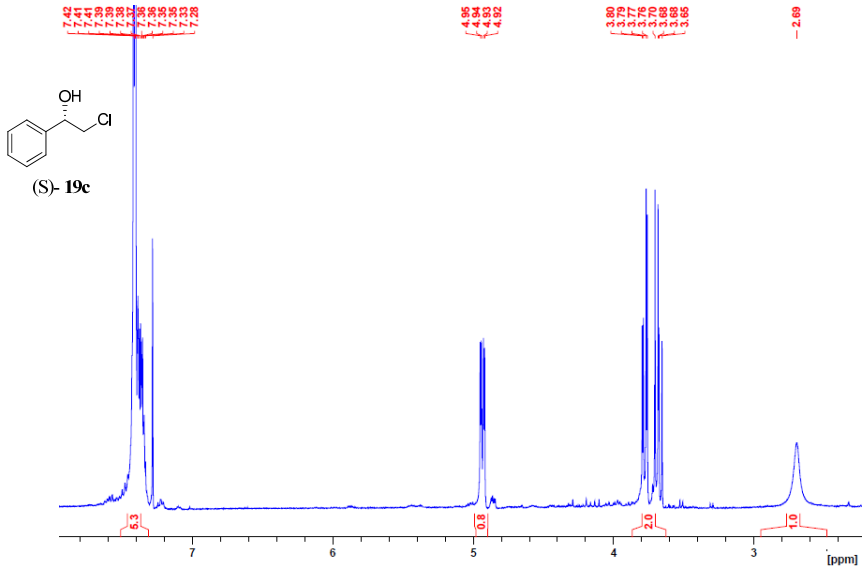

8.28
8.16
8.14
7.75
7.73
7.56
7.54
7.52
7.28
5.07
5.06
5.04
5.02
2.06
1.57
1.55
OH
NO2
(S)- 15b
5.3
5.4
6.4
6.7
6.4
285.1
18.8
8
6
4
2
[ppm]

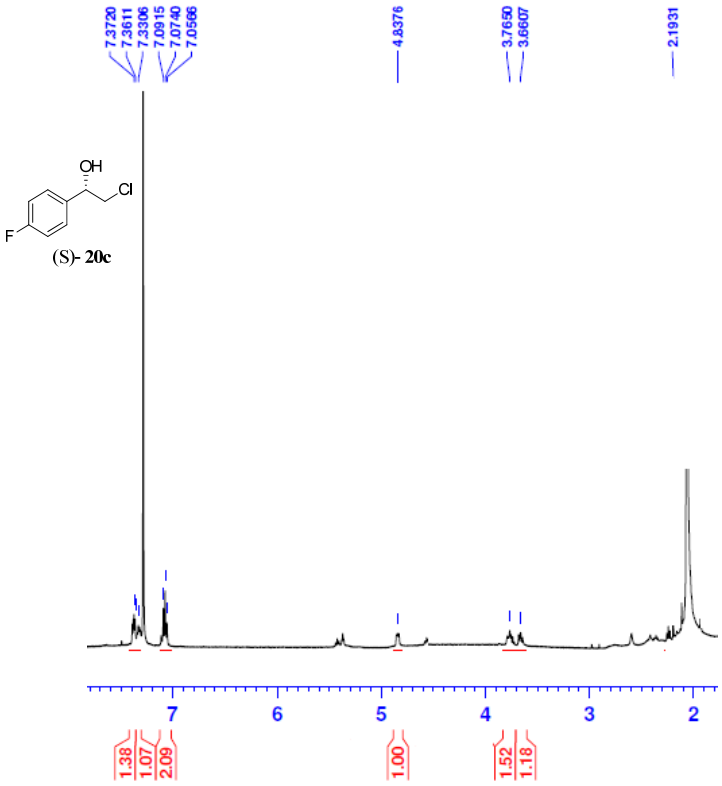

OH
NH2
(S)-16b
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

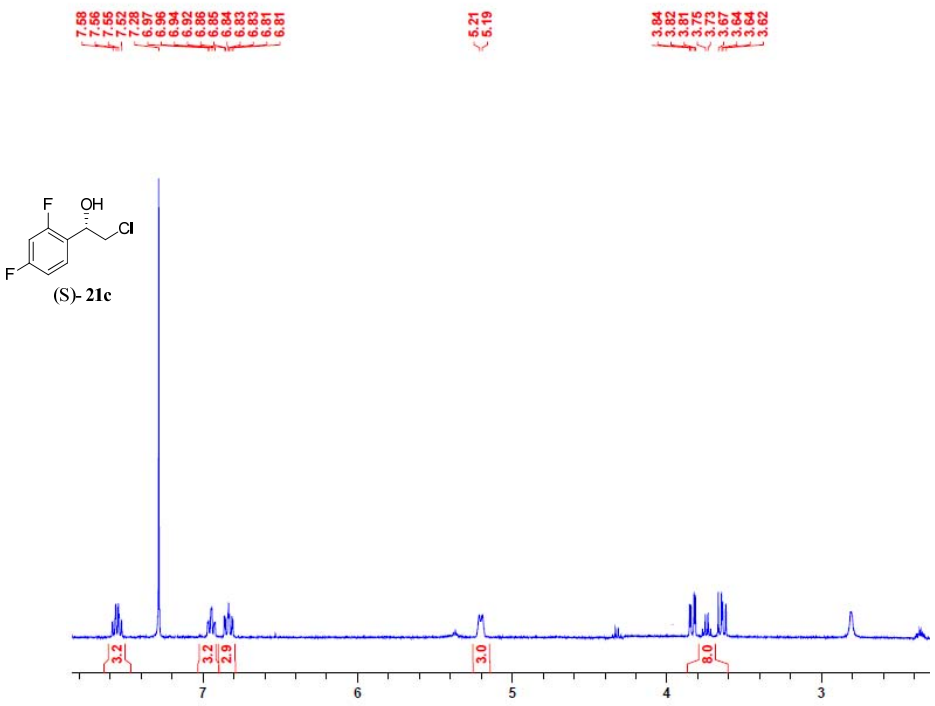

OH
NH2
(S)- 16b
[ppm]

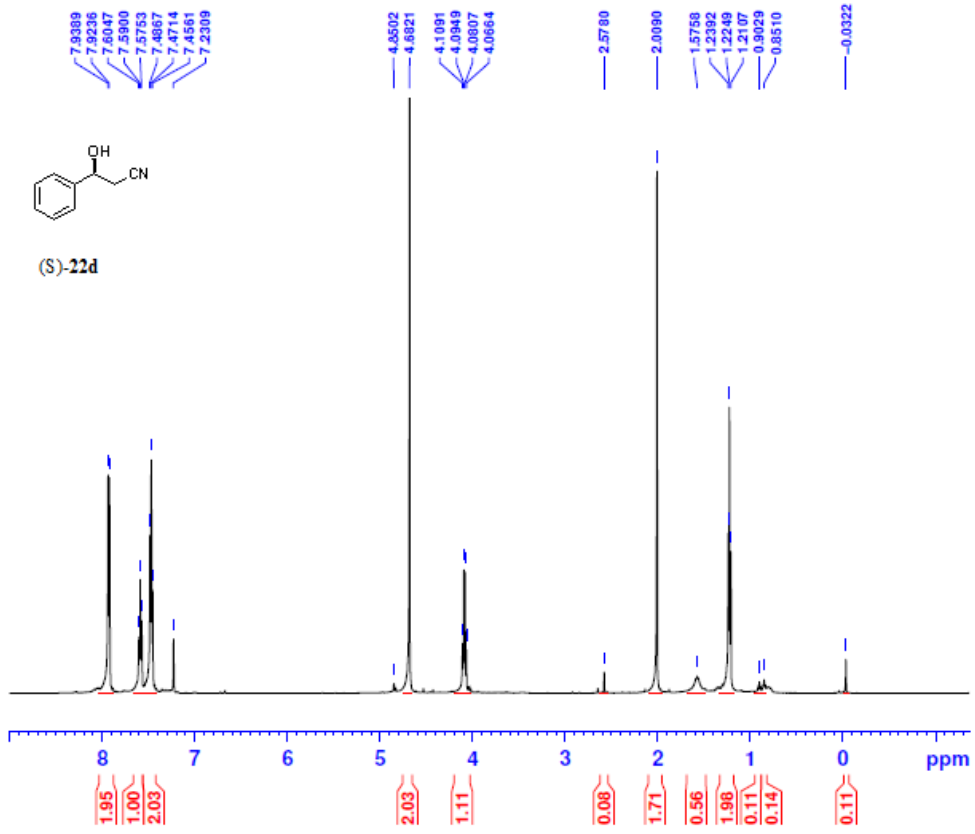

OH
F
(S)-18c
ppm

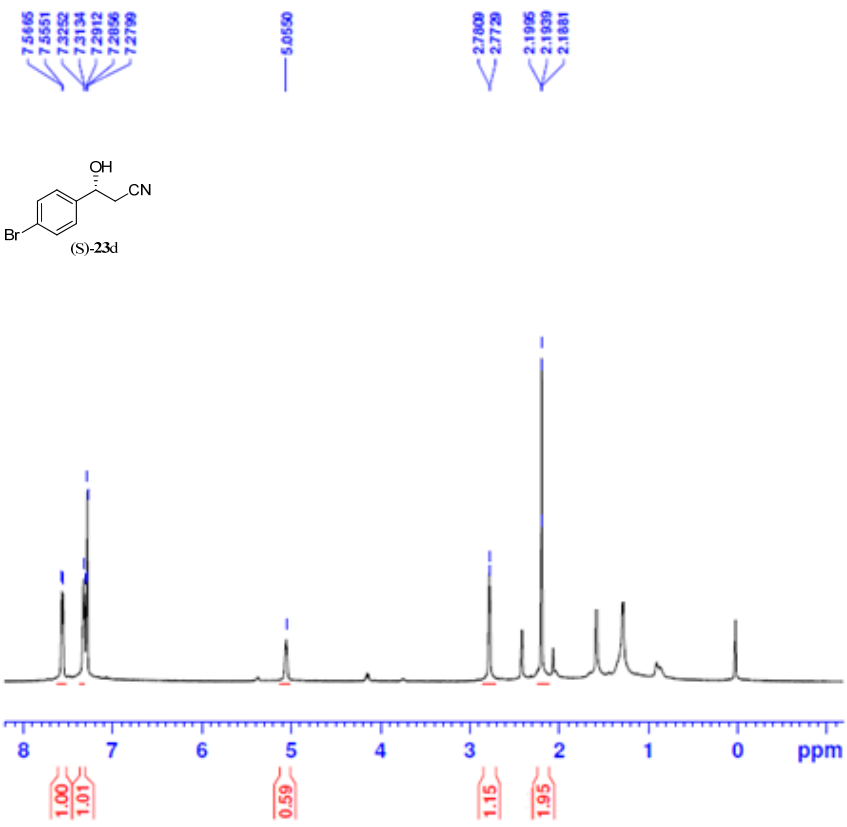

OH
F
(S)- 18c

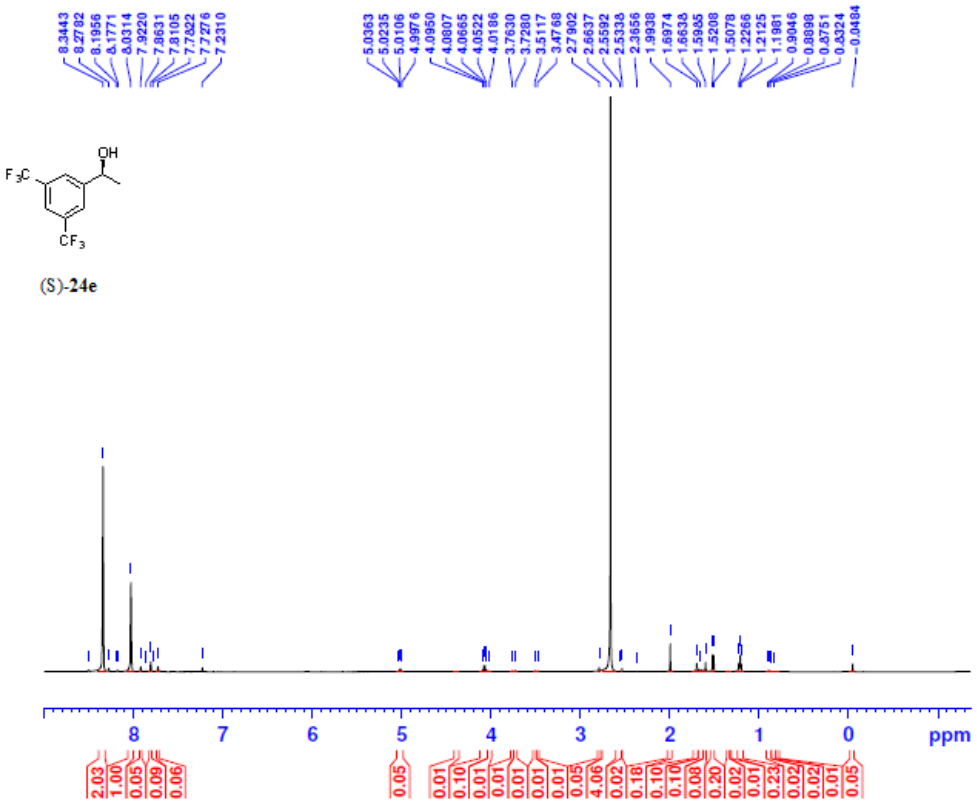

OH
Cl
(S)- 19c
[ppm]

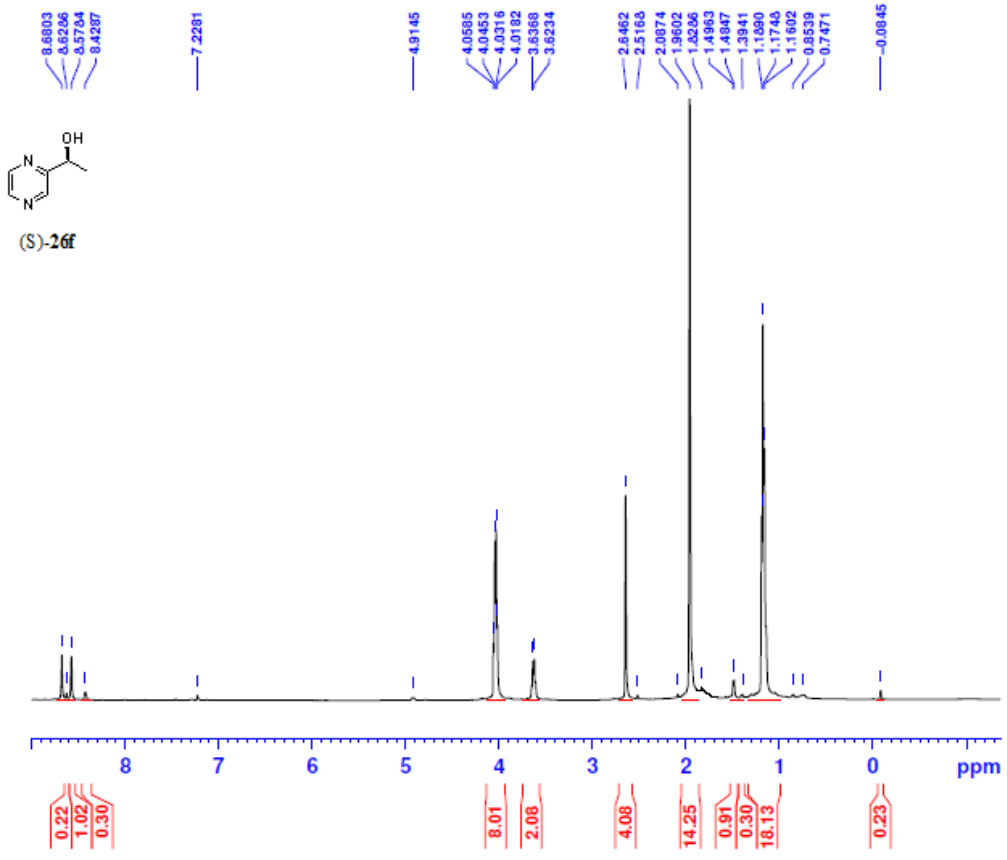

7.3720
7.3611
7.3306
7.0915
7.0740
7.0566
4.8376
3.7650
3.6607
2.1931
OH
Cl
F
(S)- 20c
7
6
5
4
3
2
1.38
1.07
2.09
1.00
1.52
1.18

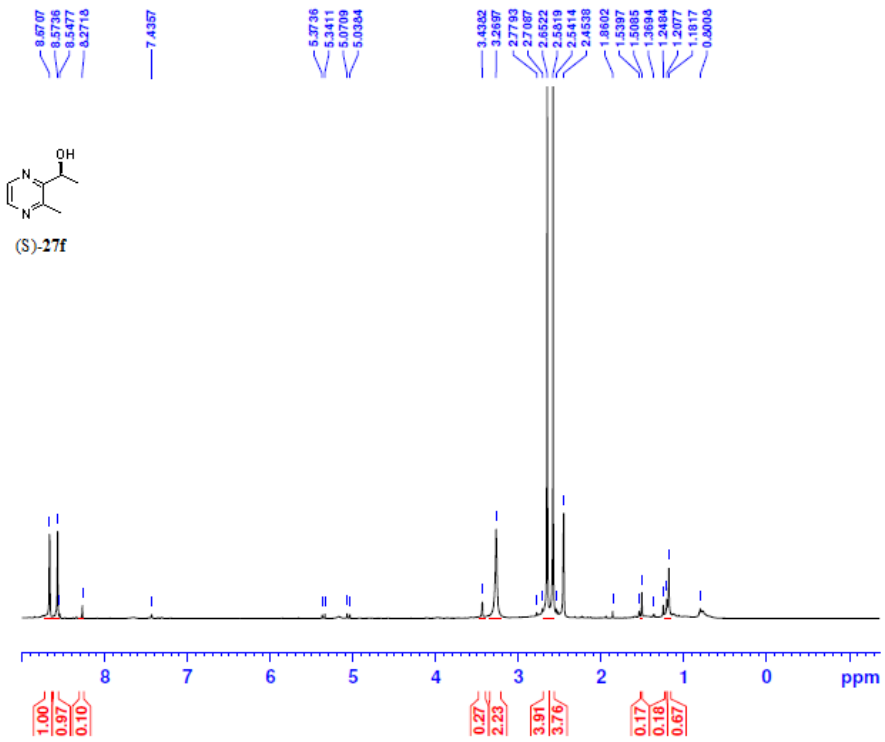

7.58
7.56
7.55
7.52
7.28
6.97
6.96
6.94
6.92
6.86
6.85
6.84
6.83
6.81
6.81
5.21
5.19
3.84
3.82
3.81
3.75
3.73
3.67
3.64
3.64
3.62
F
OH
Cl
F
(S)- 21c
3.2
3.2
2.9
3.0
8.0
7
6
5
4
3


7.9389
7.9236
7.6047
7.5900
7.5753
7.4867
7.4714
7.4561
7.2309
4.6502
4.6821
4.1091
4.0949
4.0807
4.0664
2.5780
2.0990
1.5758
1.2392
1.2249
1.2107
0.9029
0.8510
-0.0322
OH
CN
(S)-22d
8
7
6
5
4
3
2
1
0
ppm
1.95
1.00
2.03
2.03
1.11
0.08
1.71
0.56
1.96
0.11
0.14
0.11


7.5565
7.5551
7.3252
7.3134
7.2912
7.2856
7.2799
5.0550
2.7609
2.7729
2.1995
2.1939
2.1881
OH
CN
Br
(S)-23d
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
0.59
1.15
1.95


8.3443
8.2782
8.1956
8.1771
8.0314
7.9220
7.8631
7.8105
7.7822
7.7276
7.2310
5.0363
5.0235
5.0106
4.9976
4.0950
4.0807
4.0665
4.0522
4.0186
3.7630
3.7280
3.5117
3.4768
2.7902
2.6637
2.5592
2.5338
2.3656
1.9938
1.6974
1.6638
1.5965
1.5208
1.5078
1.2266
1.2125
1.1981
0.9046
0.8898
0.8751
0.8324
-0.0484
OH
F3C
CF3
(S)-24e
8
7
6
5
4
3
2
1
0
ppm
2.03
1.00
0.05
0.09
0.06
0.05
0.01
0.10
0.01
0.01
0.01
0.01
0.01
0.05
4.06
0.02
0.18
0.10
0.10
0.08
0.20
0.02
0.01
0.23
0.02
0.02
0.01
0.05


8.6803
8.6286
8.5704
8.4287
7.2281
4.9145
4.0585
4.0453
4.0316
4.0182
3.6368
3.6234
2.6462
2.5168
2.0874
1.9602
1.8286
1.4963
1.4847
1.3941
1.1890
1.1743
1.1602
0.8539
0.7471
-0.0845
OH
N
N
(S)-26f
8
7
6
5
4
3
2
1
0
ppm
0.22
1.02
0.30
8.01
2.08
4.08
14.25
0.91
0.30
16.13
0.23


8.6707
8.5736
8.5477
8.2718
7.4357
5.3736
5.3411
5.0709
5.0384
3.4382
3.2697
2.7793
2.7087
2.6522
2.5519
2.5414
2.4538
1.8602
1.5397
1.5085
1.3694
1.2484
1.2077
1.1817
0.8008
OH
N
N
(S)-27f
8
7
6
5
4
3
2
1
0
ppm
1.00
0.97
0.10
0.27
2.23
3.91
3.76
0.17
0.18
0.67