Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Steric *vs* electronic effects in the *Lactobacillus brevis* ADH-catalyzed bioreduction of ketones

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1. General

Acetophenone (**1a**), propiophenone (**2a**), butyrophenone (**3a**), α-chloroacetophenone (**5a**), α-bromoacetophenone (**6a**), α,α-difluoroacetophenone (**7a**), α,α,α-trifluoroacetophenone (**11a**), α-hydroxyacetophenone (**14a**), α-methoxyacetophenone (**15a**), benzoylacetonitrile (**17a**), α-nitroacetophenone (**19a**), methyl benzoylformate (**21a**), ethyl benzoylformate (**22a**), ethyl benzoylacetate (**24a**), 1-phenylethanol (**1b**), 1-phenylpropanol (**2b**), 1-phenylbutanol (**3b**), 1-phenyl-1,2-ethanediol (**14b**), and ethyl mandelate (**22b**) were obtained from Fluka-Sigma-Aldrich and were used without further purification. α-Fluoroacetophenone (**4a**),[1] α,α,α-trichloroacetophenone (**12a**),[2] α,α,α-tribromoacetophenone (**13a**),[3] and 2,2,2-tribromo-1-phenylethanol (**13b**)[4] have been prepared as previously described. α-Acetoxyacetophenone (**16a**) and *N*-(2-oxo-2-phenylethyl)acetamide (**20a**) were obtained under simple acetylation conditions (acetic anhydride and *N*,*N*-dimethylaminopyridine in dichloromethane) starting from commercially available α-hydroxyacetophenone and α-aminoacetophenone, respectively. All other reagents and solvents were of the highest quality available.

2. Experimental procedures

*2.1. Synthesis of α,α-dichloroacetophenone (**8a**)*[5]

To a solution of acetophenone (1.5 g, 12.5 mmol) in 8 mL of acetonitrile, *N*-chlorosuccinimide (3.33 g, 25.4 mmol) and *p*-toluenesulfonic acid (2.37 g, 12.5 mmol) were added. The reaction mixture was stirred for 12 h at 50˚C. After that time the solvent was evaporated under reduced pressure. Then a water solution of saturated $NaHCO_3$ (20 mL) was added and the solution was extracted with dichloromethane (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel) using hexanes/CH_2Cl_2 (9:1) as an eluent. Isolated yield: 2.10 g (89.1%). This compound exhibited physical and spectral data in agreement with those reported.[5]

*2.2. Synthesis of α-bromo-α-chloroacetophenone (**9a**)*[6]

To a solution of α-chloroacetophenone (0.5 g, 3.23 mmol) in 2 mL of acetonitrile, *N*-bromosuccinimide (0.27 g, 4.85 mmol) and *p*-toluenesulfonic acid (0.61 g, 3.23 mmol) were added. The reaction mixture was stirred for 24 h at 50˚C. After that time the solvent was evaporated under reduced pressure. Then, a water solution of saturated $NaHCO_3$ (10 mL) was added and the solution was extracted with dichloromethane (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel) using hexanes/CH_2Cl_2 (9:1) as an eluent. Isolated yield: 0.28 g (37.1%). This compound exhibited physical and spectral data in agreement with those reported.[6]

*2.3. Synthesis of α,α-dibromoacetophenone (**10a**)*[7]

To a solution of acetophenone (1.5 g, 12.5 mmol) in 8 mL of acetonitrile, *N*-bromosuccinimide (4.43 g, 25.4 mmol) and *p*-toluenesulforic acid (2.37 g, 12.5 mmol) were added. The reaction mixture was stirred for 12 h at 50˚C. After that time the solvent was evaporated under reduced pressure. Then a water solution of saturated $NaHCO_3$ (20 mL) was added and the solution was extracted with dichloromethane (3 x 20 mL). The organic layers

were combined and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel) using hexanes/CH_2Cl_2 (9:1) as an eluent. Isolated yield: 3.02 g (87.0%). This compound exhibited physical and spectral data in agreement with those reported.[7]

*2.4. Synthesis of α-azidoacetophenone (**18a**)*[8]

To a solution of α-bromoacetophenone (500 mg, 2.5 mmol) in dry THF (8 mL), sodium azide (244 mg, 3.75 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred for 24 h at 50˚C. After that time the solvent was evaporated under reduced pressure. Then, water (10 mL) was added and the solution was extracted with dichloromethane (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel) using hexanes/ethyl acetate (95:5) as an eluent. Isolated yield: 245 mg (60.8%). This compound exhibited physical and spectral data in agreement with those reported.[9]

*2.5. Synthesis of methyl benzoylacetate (**23a**)*[10]

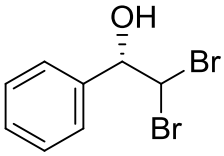
To a solution of ethyl benzoylacetate (1.59 g, 8.3 mmol) in methanol (20 mL), three drops of concentrated hydrochloric acid were added. The reaction mixture was stirred for 24 h under reflux. After that time the solvent was evaporated under reduced pressure. Then, water (10 mL) was added and the solution was extracted with dichloromethane (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel) using hexanes/ethyl acetate (95:5) as an eluent. Isolated yield: 887 mg (60.0%). This compound exhibited physical and spectral data in agreement with those reported.[10]

α,α,α-Tribromoacetophenone (**13a**),[11] 2-oxo-2-phenylethyl acetate (**16a**),[12] and *N*-(2-oxo-2-phenylethyl)acetamide (**20a**),[13] exhibited physical and spectral data in agreement with those reported.

2.6. General procedure for the synthesis of the racemic alcohols

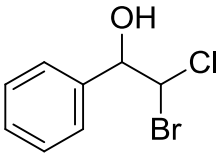
To a solution of the corresponding ketone (4.0 mmol) in methanol (5 mL) at 0˚C, sodium borohydride (1.2 mmol) was added. When the reduction was completed (according to the TLC) a few drops of 1M HCl were added. The solvent was evaporated under reduced pressure. Then, water (10 mL) was added and the solution was extracted with dichloromethane (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel) using mixtures of hexanes/ethyl acetate as eluents. Isolated yields: 39.0-92.5%.

2-Fluoro-1-phenylethanol (**4b**),[14] 2-Chloro-1-phenylethanol (**5b**),[8] 2-bromo-1-phenylethanol (**6b**),[15] 2,2-difluoro-1-phenylethanol (**7b**),[16] 2,2-dichloro-1-phenylethanol (**8b**),[17] 2,2-dibromo-1-phenylethanol (**10b**),[18] 2,2,2-trifluoro-1-phenylethanol (**11b**),[19] 2,2,2-trichloro-1-phenylehanol (**12b**),[20] 2-methoxy-1-phenylethanol (**15b**),[21] 2-hydroxy-2-phenylethyl acetate (**16b**),[22] 3-hydroxy-3-phenylpropanenitrile (**17b**),[8] 2-azido-1-phenylethanol (**18b**),[8] 2-nitro-1-phenylethanol (**19b**),[23] *N*-(2-hydroxy-2-phenylethyl)acetamide (**20b**),[24] methyl mandelate (**21b**),[25] methyl 3-hydroxy-3-phenylpropanoate (**23b**),[26] and ethyl 3-hydroxy-3-phenylpropanoate (**24b**),[27] exhibited physical and spectral data in agreement with those reported.



$[\alpha]_D^{20}$ = +24.7 (*c* 2.2, $CHCl_3$).

2-Bromo-2-chloro-1-phenylethanol (**9b**)



m.p. 57.5-59.8˚C; IR (NaCl): 3583, 3054, 1453, 1422, 1265, 1187, 896, 740, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of diastereoisomers 3:1): δ 2.91 (1H, br s), 4.98 (major, 1H, d, $^3J_{HH}$ = 5.4 Hz), 5.10 (minor, 1H, d, $^3J_{HH}$ = 5.0 Hz), 5.87 (major, 1H, d, $^3J_{HH}$ = 5.4 Hz), 5.89

(minor, 1H, d, $^{3}J_{HH}$ = 6.0 Hz), 7.44-7.40 (5H, m); ^{13}C NMR (75 MHz): δ 64.6 (minor), 65.8 (major), 78.9 (major), 79.0 (minor), 126.9 (major), 127.0 (minor), 128.5, 129.0, 137.6.

3. Steady-state kinetics

Table S1. Steady-state kinetic parameters of LBADH for substrates **1-24a**

ketone	k_{cat} (s^{-1})	K_M (mM)	k_{cat}/K_M (M^{-1} s^{-1})
1a	20.3	1.3	16,100
2a	6.5	1.4	4,700
3a	<0.1	n.d.	n.d.
4a	92.4	0.18	512,200
5a	32.8	0.09	378,900
6a	35.5	0.4	87,900
7a	68.5	0.55	125,400
8a	38.9	0.51	75,800
9a	17.5	0.69	25,600
10a	1.4	0.12	11,800
11a	8.6	2.6	3,300
12a	0.6	0.15	4,200
13a	n.d.	n.d.	n.d.
14a	2.3	3.0	800
15a	<0.1	n.d.	n.d.
16a	n.d.	n.d.	n.d.
17a	0.9	2.4	400
18a	4.6	8.1	600
19a	n.d.	n.d.	n.d.
20a	<0.1	n.d.	n.d.
21a	0.8	0.17	4,300
22a	0.5	0.02	26,500
23a	<0.1	n.d.	n.d.
24a	<0.1	n.d.	n.d.

n.d. not determined

4. Molecular volume calculations

Table S2. Measured ketone volumes using the solvent-excluded molecular volume ($VSES_{R=1.4}$) and the van der Waals molecular volume (V_{mol}) methods.

ketone	**$VSES_{R=1.4}$ (Å^3)**	**V_{mol} (Å^3)**
1a	123.94	117.49
2a	142.44	134.08
3a	160.96	150.60
4a	129.20	122.35
5a	139.34	131.66
6a	144.08	136.08
7a	134.49	127.24
8a	154.65	145.81
9a	159.32	150.23
10a	163.97	154.60
11a	139.69	132.06
12a	169.32	159.59
13a	183.42	172.67
14a	132.33	125.62
15a	153.58	143.21
16a	173.26	161.73
17a	142.30	134.54
18a	150.91	141.32
19a	149.94	140.67
20a	175.04	164.37
21a	154.75	146.02
22a	172.94	162.50
23a	172.12	161.31
24a	194.62	177.87

5. LBADH-catalyzed reduction of ketones

5.1. Bioreductions under standard and minimal conditions

In Table S3 are summarized the conversions and enantiomeric excess of the LBADH-catalyzed bioreductions with 2-PrOH.

Table S3. Bioreduction of acetophenone derivatives with LBADH using 5% v v^{-1} or 2.5 equiv. of 2-propanol (*t*= 48 h).

entry	**ketone**	**conv. (%)**[a]	**conv. (%)**[b]	***ee* (%)**[c]
Alkylated acetophenone derivatives				
1	**1a**	92	49	>99 (*R*)
2	**2a**	93	45	>99 (*R*)
3	**3a**	4	n.d.	n.d.
α-Halogenated acetophenone derivatives				
4	**4a**	>99	92	>99 (*S*)
5	**5a**	>99	>99	>99 (*S*)
6	**6a**	>99	>99	>99 (*S*)
7	**7a**	>99	90	>99 (*S*)
8	**8a**	>99	63 (>99)[d]	>99 (*S*)
9	**9a**	97	75 (93)[d]	>99 (*S*)[e]
10	**10a**	>99	>99	>99 (*S*)
11	**11a**	>99	86	>99 (*S*)
12	**12a**	25	18	n.d.
13	**13a**	<1	n.d.	n.d.
α-Oxygenated acetophenone derivatives				
14	**14a**	>99	90	>99 (*S*)
15	**15a**	<1	n.d.	n.d.
16	**16a**	8	n.d.	n.d.

Table S3. *(cont.)*

α-Nitrogenated acetophenone derivatives				
17	**17a**	74	11 (57)[d]	>99 (*S*)
18	**18a**	>99	85	>99 (*S*)
19	**19a**	13	3	n.d.
20	**20a**	<1	n.d.	n.d.
α- and β-Keto esters				
21	**21a**	99	72	>99 (*S*)
22	**22a**	75	74	>99 (*S*)
23	**23a**	<1	n.d.	n.d.
24	**24a**	<1	n.d.	n.d.

[a] Conversion using an excess of 2-propanol, measured by GC. [b] Conversion using 2.5 equiv. of 2-propanol, measured by GC. [c] Measure by chiral GC. [d] With 2% v v^{-1} of DMSO. [e] As a mixture of diastereoisomers. n.d. not determined.

5.2. Time-frame study with selected ketones using 2.5 equiv. of 2-PrOH

In a 1.5 mL Eppendorf vial, LBADH (3U) was added in 50 mM Tris-HCl buffer pH 7.5 (600 µL, 1 mM NADPH, 1 mM $MgCl_2$) and mixed with 2-propanol (3 µL, 2.5 equiv.) and the corresponding ketone (30 mM, 1 equiv.). Reactions were shaken at 30ºC and 250 rpm and samples were taken at different times (see Table S4) and extracted with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na_2SO_4. Conversions of the corresponding alcohols were determined by GC.

Table S4. LBADH-catalyzed bioreductions of several ketones within the time.

ketone	**conv. (%)**[a]					
	1h	**2h**	**4h**	**8h**	**24h**	**48h**
1a	49	53	51	51	49	54
5a	43	65	80	>99	>99	>99
14a	12	35	53	92	90	92
18a	13	29	37	44	65	85
22a	15	22	40	47	60	74

[a] Measured by GC analysis.

5.3. LBADH thermostability study

Protocol 1

In a 1.5 mL Eppendorf vial, LBADH (3U) was added in 50 mM Tris-HCl buffer pH 7.5 (600 µL, 1 mM NADPH, 1 mM $MgCl_2$). Reactions were shaken for 24 h at 30ºC and 250 rpm. After that, 2-propanol (32 µL, 5% v v^{-1}) and acetophenone (30 mM) were added and then the reactions were shaken for other 24 h at 30ºC and 250 rpm. Then, reactions were extracted with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na_2SO_4. Conversion of 1-phenylethanol (91%) was determined by GC.

Protocol 2

In a 1.5 mL Eppendorf vial, LBADH (3U) was added in 50 mM Tris-HCl buffer pH 7.5 (600 µL, 1 mM NADPH, 1 mM $MgCl_2$) and with 2-propanol (32 µL, 5% v v^{-1}). Reactions were shaken for 24 h at 30ºC and 250 rpm. After that, acetophenone (30 mM) was added and then the reactions were shaken for other 24 h at 30ºC and 250 rpm. Then, reactions were extracted with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na_2SO_4. Conversion of 1-phenylethanol (90%) was determined by GC.

6. IR spectroscopy study

IR spectra were recorded on a standard IR spectrophotometer using NaCl plates dissolving the compounds with a drop of CH_2Cl_2.

Table S5. IR carbonyl stretching values of ketones.

ketone	**$\upsilon_{C=O}$ value (cm^{-1})**
1a	1685.9
2a	1685.4
3a	1686.1
4a	1709.8
5a	1690.1
6a	1683.9
7a	1711.0
8a	1708.1
9a	1705.7
10a	1701.5
11a	1720.3
12a	1713.0
13a	1700.1
14a	1689.5
15a	1699.9
16a	1706.1
17a	1701.9
18a	1698.5
19a	1707.4
20a	1670.9
21a	1691.1
22a	1690.1
23a	1686.2
24a	1686.2

7. Analytics

7.1. Determination of conversions by achiral GC

The following columns were used: Column **A**: Varian Chirasil Dex CB (25 m x 0.25 mm x 0.25 µm, 12.2 psi N_2); Column **B**: Hewlett Packard HP1 (30 m x 0.32 mm x 0.25 µm, 12.2 psi N_2).

Table S6. Determination of conversions by GC.

compound	**column**	**program**[a]	**retention time (min)**	
			a	**b**
1	A	110/0/2.5/120/0/10/200/1	4.9	6.7
2	B	110/0/2.5/120/0/10/200/1	6.2	8.0
3	B	110/0/2.5/120/0/10/200/1	7.3	9.3
4	A	70/4/20/110/0/10/130/0/20/200/2	9.6	10.5
5	B	70/4/20/110/0/10/130/0/20/200/1	7.4	7.2
6	B	70/4/20/110/0/10/130/0/20/200/5	11.7	12.5
7	A	110/3/3/180/1	4.2	14.0
8	B	80/20/20/200/2	14.9	19.0
9	B	80/20/20/200/2	22.1	23.0
10	B	80/20/20/200/2	23.9	24.3
11	B	80/10/20/200/2	1.4	2.7
12	B	80/20/20/200/2	21.6	23.4
13	B	80/20/20/200/5	25.9	26.2
14	B	80/10/20/200/2	7.5	11.4
15	B	80/10/20/200/2	8.7	12.6
16	B	100/20/20/200/2	10.7	5.6
17	B	80/20/20/200/2	21.1	21.9
18	B	70/4/10/100/0/2.5/110/0/20/200/2	11.8	11.6
19	B	80/10/20/200/2	13.7	12.8
20	B	100/20/20/200/2	23.2	23.9
21	A	80/10/20/200/2	15.1	16.0

Table S6. *(cont.)*

22	B	80/20/20/200/2	18.2	15.4
23	A	100/0/5/200/2	5.9	15.9
24	A	100/0/5/200/2	5.9	16.9

[a] Program: initial temp. (°C)/ time (min)/ slope (°C/min)/ temp. (°C)/ time (min)/ slope (°C/min)/ temp. (°C)/ time (min)/ slope (°C/min)/ final temp. (ºC)/ time (min).

7.2. Determination of ee by chiral GC

The following columns were used: Column **A**: Varian Chirasil Dex CB (25 m x 0.25 mm x 0.25 µm, 12.2 psi N_2); column **B**: Restek RT-BetaDEXse (30 m x 0.25 mm x 0.25 µm, 12.2 psi N_2); column **C**: Restek RT-GAMMA DEXsa (30 m x 0.25 mm x 0.25 µm, 12.2 psi N_2).

Table S7. Determination of *ee* by chiral GC.

compound	**column**	**program**[a]	**retention time (min)**	
			R	***S***
1b[b]	A	110/0/2.5/120/0/10/200/1	6.4	6.1
2b[b]	A	110/0/2.5/120/0/10/200/1	7.0	6.8
4b	A	120/20/60/200/1	15.8	14.5
5b[b]	B	110/0/5/160/10/20/180/2	18.0	18.6
6b	B	110/0/5/160/10/20/180/1	18.6	18.0
7b	A	110/3/3/180/2	14.2	13.5
8b	B	90/5/3/180/4	33.5	32.8
10b	B	110/0/5/160/20/20/180/5	32.8	31.8
11b	A	120/20/60/200/1	17.2	16.1
14b	C	90/10/5/160/20/20/180/10	46.3	46.6
17b	B	170/10/2.5/200/0	14.5	13.9
18b[b]	B	90/5/2.5/105/0/5/135/0/2.5/145/20/20/180/2	37.8	38.4
21b	C	110/0/2.5/120/0/10/200/5	13.7	13.9
22b	C	70/4/10/100/0/2.5/110/0/20/200/10	19.4	19.6

[a] Program: initial temp. (°C)/ time (min)/ slope (°C/min)/ temp. (°C)/ time (min)/ slope (°C/min)/ temp. (°C)/ time (min)/ slope (°C/min)/ final temp. (ºC)/ time (min). [b] Measured as acetate derivative.

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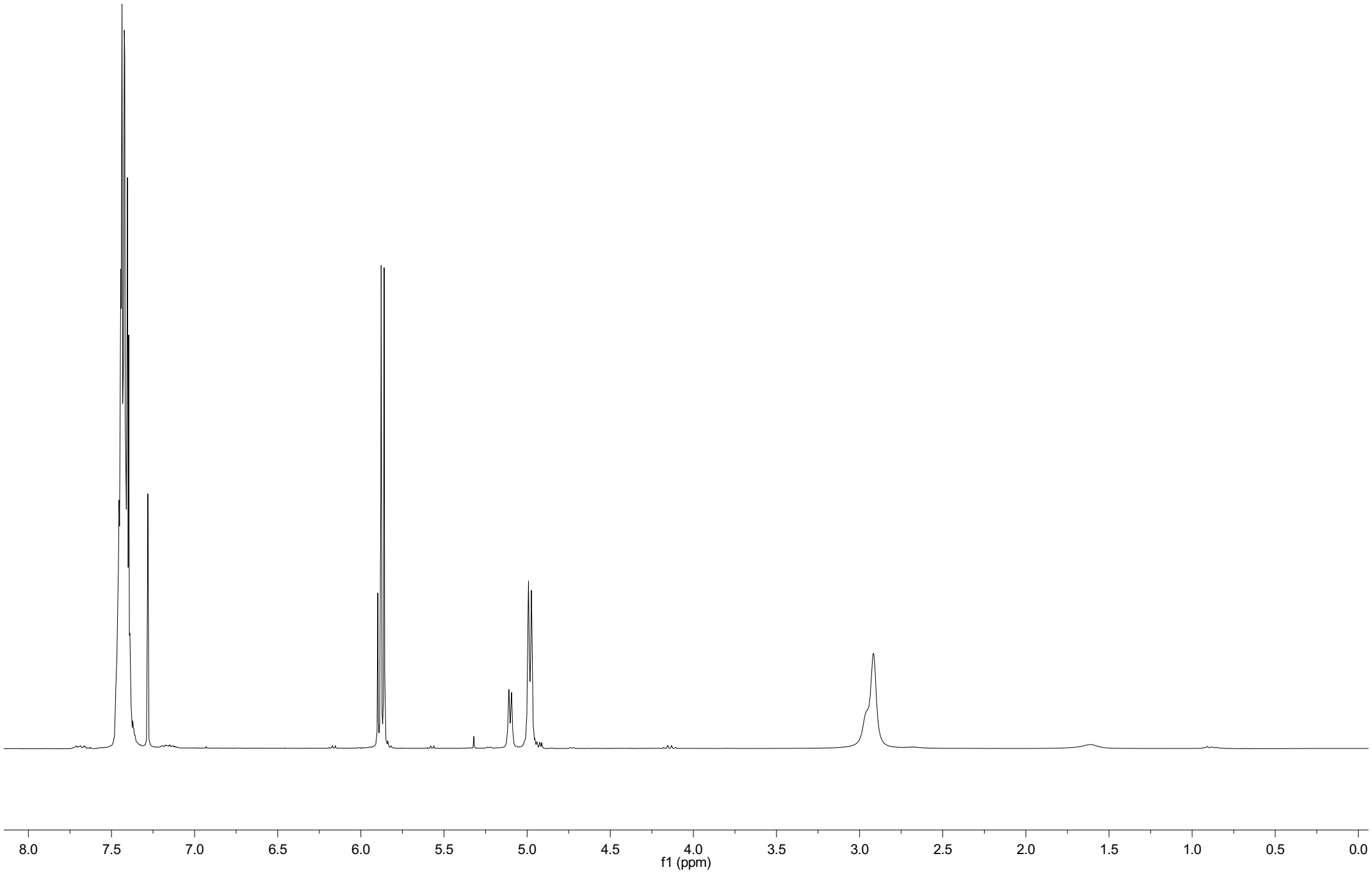
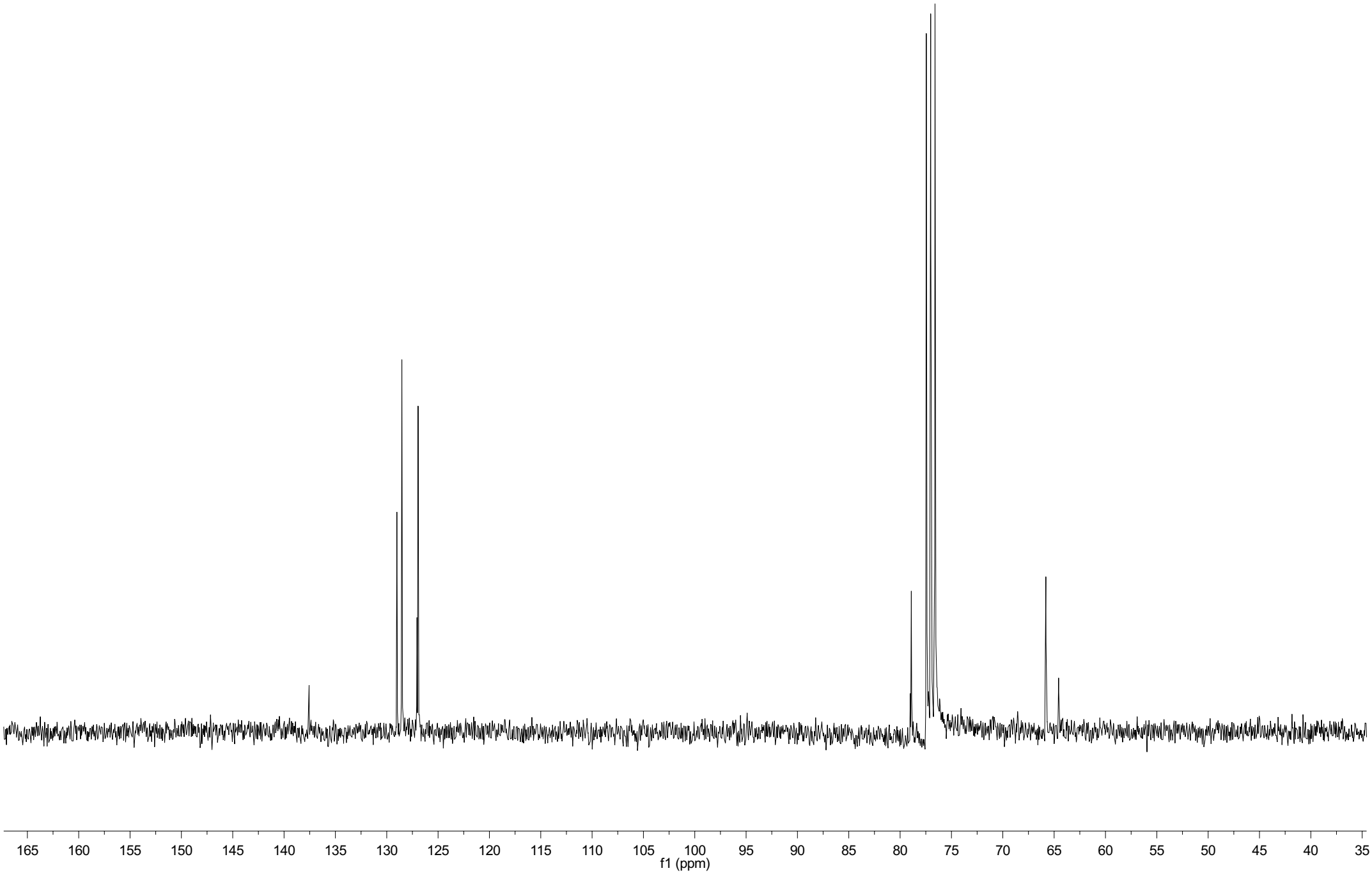
2-bromo-2-chloro-1-phenylethanol
1H NMR (300 MHz)



2-bromo-2-chloro-1-phenylethanol
13 NMR (300 MHz)



2-bromo-2-chloro-1-phenylethanol
DEPT 135 NMR (300 MHz)