Supplementary Information for:

TITLE:

Replication of chiral α-hydroxy acid *via* induction and amplification through an enantioenriched cyanohydrin conglomerate

AUTHORS:

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CONTENTS:

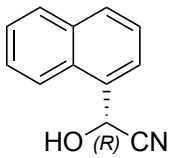
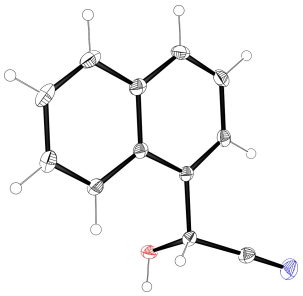
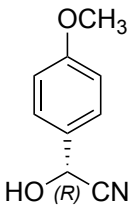
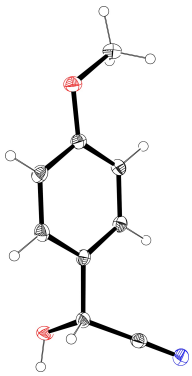
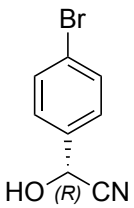
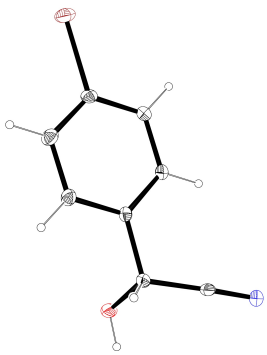
GENERAL COMMENTS

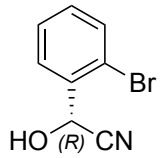
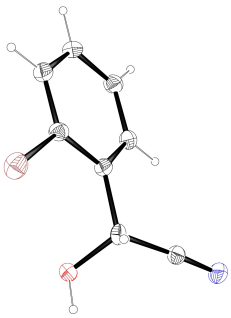
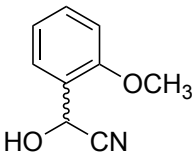
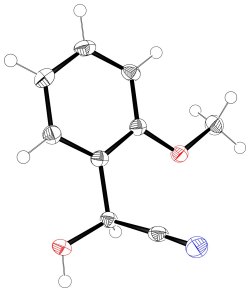
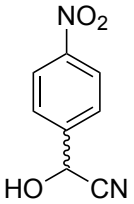
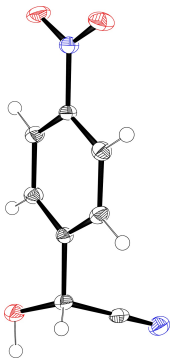
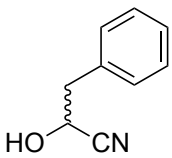
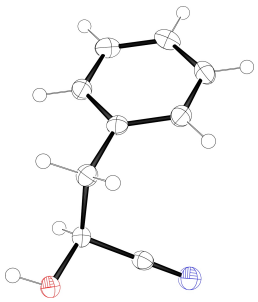
All solvents and chemicals were purchased from commercial sources. 1-Naphthaldehyde, DBU, and solvents were used after distillation. **CAUTION**: Hydrogen cyanide (HCN) was generated from H_2SO_4 and NaCN or KCN in water and isolated by the distillations. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA500II, ECZ400S and JNM-ESC300 FT NMR spectrometers. The chemical sifts (δ) are given in parts per million (ppm) relative to TMS (δ_H 0.00 ppm) and methanol-d_4 (δ_C 49.00 ppm) as an internal standard. Single-crystal X-ray diffraction data were collected using a Rigaku R-axis Rapid II imaging plate diffractometer equipped with a Cu Kα rotating anode X-ray source. Data collection, integration, and scaling were carried out with Rigaku RAPID AUTO. Optical rotations were measured on a JASCO P-2200 digital polarimeter, and specific rotations ($[\alpha]_D$) are reported in $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$. Melting points were determined on an AS ONE ATM-01 or a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco FT/IR-4600 spectrometer, with absorbance frequencies reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained using a JEOL AccuTOF JMS-T100LP mass spectrometer with electrospray ionization (ESI).

SINGLE-CRYSTAL STRUCTURES OF CYANOHYDRINS

Synthesis of racemic cyanohydrins: To a mixture of the corresponding aldehyde (25 mmol) and DBU (18 μL, 0.12 mmol, Et_3N can be used instead of DBU) was added HCN (1.0 mL, 25.4 mmol) at 0 °C. The reaction mixture was then stirred at room temperature overnight. The reaction was quenched with 1 M aqueous HCl and extracted with Et_2O (× 3). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography. To stabilize **1**, small amount of acetic acid (*ca*. 1–2 vol%) was added to the eluent. For example, **1a** was purified using a mixed solvent of hexane/Et_2O/AcOH (50:10:1, *v*/*v*/*v*).

Table S1

Structure	Ortep drawing	Single-crystal data
		CCDC 2543998, toluene, $C_{12}H_9NO$, *M* 183.21, *R*3, *a* 24.5800(13), *b* 24.5800(13), *c* 4.05490(12), *α* 90, *β* 90, *γ* 120, *V* 2121.65(17), *Z* 9, *ρ* 1.290, *R* 0.0267 (1579), *wR*2 0.0697 (1618), Flack 0.00(8).
		CCDC 2543999, toluene, $C_9H_9NO_2$, *M* 163.18, $P2_12_12_1$, *a* 4.1037(4), *b* 7.5234(8), *c* 26.123(3), *α* 90, *β* 90, *γ* 90, *V* 806.52(15), *Z* 4, ρ 1.344, *R* 0.0347 (1424), *wR*2 0.0896 (1466), Flack 0.15(14).
		CCDC 2544000, toluene/hexane (liquid–liquid diffusion), C_8H_6BrNO, *M* 212.05, $P2_12_12_1$, *a* 4.1087(3), *b* 7.2751(5), *c* 27.201(2), α 90, β 90, γ 90, *V* 813.06(10), *Z* 4, ρ 1.732, *R* 0.0317 (1352), *wR*2 0.0677 (1464). Flack 0.009(13).

		CCDC 2544001, toluene, C_8H_6BrNO, *M* 212.05, $P2_12_12_1$, *a* 4.0898(6), *b* 7.4104(11), *c* 26.361(4), α 90, β 90, γ 90, *V* 798.9(2), *Z* 4, ρ 1.763, *R* 0.0390 (920), *wR*2 0.0687 (1448). Flack 0.07(3).
		CCDC 2544002, toluene, $C_9H_9NO_2$, *M* 163.17, $P2_1/n$, *a* 7.4048(3), *b* 8.0992(4), *c* 14.0215(7), *α* 90, *β* 96.227(7), *γ* 90, *V* 835.87(7), *Z* 4, *ρ* 1.297, *R* 0.0339 (1440), *wR*2 0.0907 (1516).
		CCDC 2544003, toluene, $C_8H_6N_2O_3$, *M* 178.15, *P*–1, *a* 6.1702(3), *b* 7.6597(4), *c* 9.0213(5), α 77.760(6), β 69.976(5), γ 87.076(6), *V* 391.37(4), *Z* 2, ρ 1.012, *R* 0.0367 (1278), *wR*2 0.1007 (1400).
		CCDC 2544004, toluene, C_9H_9NO, *M* 147.17, $P2_1/c$, *a* 6.0176(2), *b* 7.4684(3), *c* 17.5398(7), α 90, β 96.968(7), γ 90, *V* 782.45(5), *Z* 4, ρ 1.249, *R* 0.0367 (1345), *wR*2 0.0979 (1405).

RACEMIZATION HALF-LIFE ($t_{1/2}$) OF CYANOHYDRINS

Cyanohydrin 1a: To a solution of (*S*)-**1a** (98% ee, 4.0 mg, 0.022 mmol) in toluene (1.0 mL) was added DBU (1,8-diazabicyclo[5.4.0]-7-undecene, 2 μL, 0.013 mmol) at room temperature. The change in ee was monitored by sampling a portion of the solution, which was passed through a short-path silica gel column chromatography using Et_2O (containing *ca*. 1 vol% acetic acid) as the eluent to remove DBU. The ee was determined by HPLC using a chiral stationary phase.

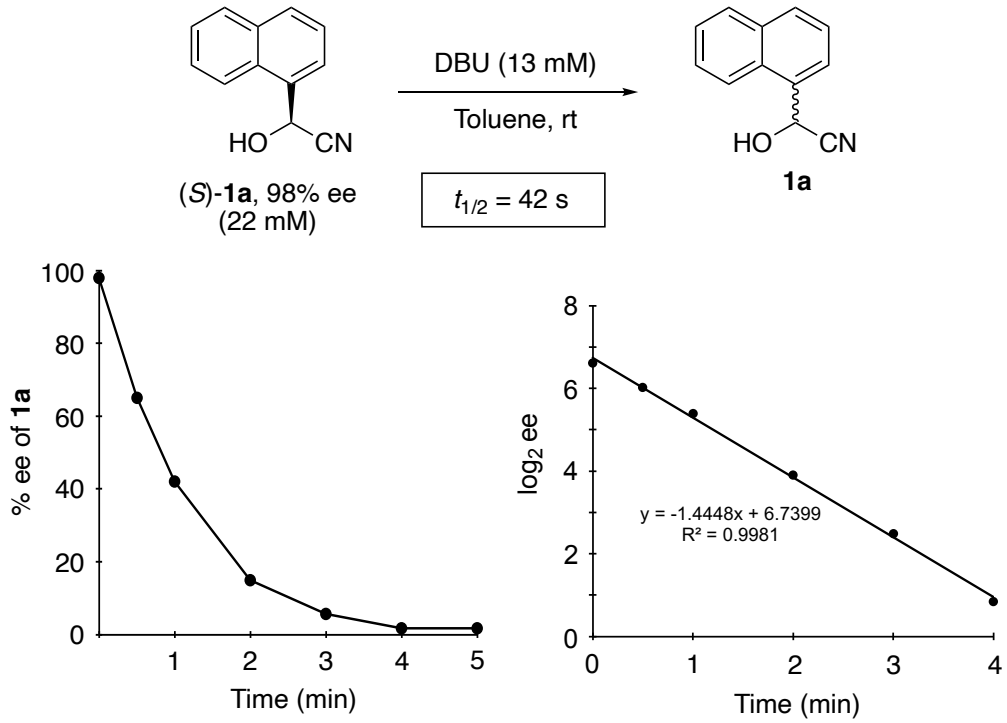


Figure S1. Racemization half-life ($t_{1/2}$) of **1a** promoted by DBU.

Cyanohydrin 1b: To a solution of (*R*)-**1b** (95% ee, 10 mg, 0.061 mmol) in toluene (1.0 mL) was added DBU (1 μL, 0.0067 mmol) at room temperature. The change in ee was monitored by sampling a portion of the solution, which was passed through a short-path silica gel column chromatography using hexane/AcOEt (1/1, *v*/*v*) (containing *ca*. 1 vol% acetic acid) as the eluent. The ee was determined by HPLC using a chiral stationary phase. The racemization half-life $t_{1/2}$ was calculated to be 9.1 s.

Cyanohydrin 1b in the presence of HCN: To a solution of (*S*)-**1b** (94% ee, 100 mg, 0.61 mmol) and HCN (12 μL, 0.31 mmol) in toluene (10 mL) was added DBU (10 μL, 0.067 mmol) at room temperature. The change in ee was monitored by sampling a portion of the solution, which was passed through a short-path silica gel column chromatography using hexane/AcOEt (1/1, *v*/*v*) (containing *ca*. 1 vol% acetic acid) as the eluent. The ee was determined by HPLC using a chiral stationary phase. The racemization half-life $t_{1/2}$ was calculated to be 4.5 s.

Cyanohydrin 1c: To a solution of (*R*)-**1c** (99% ee, 13 mg, 0.061 mmol) in toluene (1.0 mL) was added DBU (1 μL, 0.0067 mmol) at room temperature. The change in ee was monitored by sampling a portion of the solution, which was passed through a short-path silica gel column chromatography using hexane/EtOAc (1:1, *v*/*v*) (containing *ca*. 1 vol% acetic acid) as the eluent. The ee was determined by HPLC using a chiral stationary phase. The racemization half-life $t_{1/2}$ was calculated to be 17.5 s.

SPONTANEOUS ABSOLUTE ASYMMETRIC SYNTHESIS

Experimental procedure: To a solution of 1-naphthaldehyde (706 μL, 5.2 mmol) and DBU (2 μL, 0.013 mmol) in toluene (2.0 mL) was added HCN (210 μL, 5.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for > 5 h, after which it was cooled with liquid N_2 to induce precipitation of **1a**. DBU (2 μL, 0.013 mmol) was then added to the resulting suspension at room temperature, and the mixture was heated to *ca*. 35–40 °C until approximately 80–90% of the solid had dissolved (as judged visually). The mixture was subsequently cooled gradually to room temperature. This temperature cycling was repeated. For example, after two cycles, the solid was collected by filtration to give (*R*)-**1a** (344 mg, 1.88 mmol) in 36% yield with 88% ee. The collected solid was purified by silica-gel column chromatography (hexane/ethyl acetate = 1:3, *v*/*v*, containing a small amount of acetic acid for stabilization) prior to chiral HPLC analysis.

Table S2. Numerical data corresponding to the histogram shown in Figure 2.

Entry	Cyanohydrin **1a**			Temperature cycling (times)
	Config.	ee (%)[a]	Yield (%)[b]	
1	*S*	96	34	3
2	*R*	88	36	2
3	*R*	9	ND	5
4	*S*	93	32	3
5	*R*	14	34	3
6	*S*	96	30	3
7	*R*	95	32	3
8	*S*	86	36	3
9	*R*	71	ND	3
10	*R*	36	19	6
11	*S*	54	ND	2
12	*R*	76	9	9
13	*S*	98	42	5
14	*S*	76	14	9
15	*R*	91	10	9
16	*S*	39	7	6
17	*R*	99	23	7
18	*R*	96	10	6
19	*R*	92	19	4
20	*S*	99	6	8
21	*R*	99	24	6
22	*S*	83	37	13
23	*S*	63	41	11
24	*R*	82	16	5

25	*R*	4	20	8
26	*S*	73	9	6
27	*R*	3	ND	9
28	*S*	97	19	6
29	*S*	79	29	6
30	*S*	40	22	6
31	*R*	96	29	7
32	*S*	99	28	3
33	*S*	92	36	7
34	*R*	76	50	8
35	*R*	98	38	8
36	*S*	98	38	5
37	*R*	91	20	4
38	*R*	67	31	8

[a] Determined using HPLC on a chiral stationary phase.

[b] Isolated yield of solid **1a** after filtration. ND: not determined.

ASYMMETRIC AMPLIFICATION OF CYANOHYDRINS

To a suspension of (*R*)-cyanohydrin **1b** (4.4% ee, 870 mg, 5.3 mmol) in toluene (2.0 mL) was added DBU (2 μL, 0.013 mmol). The suspension was then heated to 30 °C until *ca*. 80–90% of the solid had dissolved, and subsequently cooled gradually to 22 °C. After this thermal cycling was repeated five times, the solid phase was collected by filtration and purified by silica gel column chromatography (hexane/EtOAc = 1:1, *v*/*v*, containing a small amount of acetic acid for stabilization) to afford (*R*)-**1b** (426 mg, 2.6 mmol) in 49% yield with 96% ee as a white solid.

Table S3. Numerical data for Figures 3a and 3b.

	Enantiomeric excess (ee)			
	(*R*)-**1a**	(*S*)-**1a**	(*R*)-**1b**	(*S*)-**1b**
Initial	BDL	BDL	4	3
After run 1	21	BDL	29	44
After run 2	90	11	59	92
After run 3	99	35	70	96
After run 4	–	86	96	–
After run 5	–	93	–	–

BDL: Below the detectable level.

ENANTIOSELECTIVE REACTIVE CRYSTALLIZATION

To a solution *rac*-**1b** (100 mg, 0.61 mmol) and DBU (4 μL, 0.027 mmol) in toluene (0.5 mL) was added (*S*)-**1b** (99% ee, 100 mg, 0.61 mmol) at room temperature. To this suspension were added *p*-anisaldehyde (2.3 mL, 18.9 mmol), HCN (1.1 mL, 28.0 mmol), toluene (4.0 mL) and DBU (35 μL, 0.22 mmol) in eight separate portions at intervals of > 2 h. After cooling the reaction mixture to 15 °C, the solid product **1b** was collected by the filtration and passed through a short-path silica gel column chromatography (hexane/EtOAc = 1:1, *v*/*v*, containing *ca*. 1 vol% acetic acid for stabilization) to give (*S*)-**1b** (1.65 g, 10.1 mmol) in 50% yield with 94% ee as a white solid.

To a solution *rac*-**1b** (1.0 g, 6.1 mmol) and DBU (43 μL, 0.288 mmol) in toluene (5 mL) was added (*R*)-**1b** (94% ee, 1.0 g, 6.1 mmol) at room temperature. To this suspension were added *p*-anisaldehyde (18 mL, 0.15 mol), HCN (9.0 mL, 0.23 mol), toluene (35 mL) and DBU (304 μL, 2.04 mmol) in seven separate portions at intervals of > 2 h. After cooling the reaction mixture to 15 °C, the solid product **1b** was collected by the filtration and passed through a short-path silica gel column chromatography (hexane/EtOAc = 4:1, *v*/*v*, containing *ca*. 1 vol% acetic acid) to give (*R*)-**1b** (10.9 g, 66.8 mmol) in 41% yield with 92% ee as a pale-yellow solid.

HYDROLYSIS OF CYANOHYDRIN TO HYDROXY ACID

Cyanohydrin (*S*)-**1a** (556 mg, 3.0 mmol) was treated with conc. hydrochloric acid (9.5 mL) at room temperature. The reaction mixture was stirred overnight, and completion of the reaction was confirmed by TLC. The mixture was then diluted with brine and extracted with EtOAc (×3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by recrystallization from toluene/methanol (99:1, *v*/*v*) to afford (*S*)-**3a** (553 mg, 2.75 mmol,) in 91% yield with 99% ee as a white solid.

Hydroxyamide (*S*)-**3a** (150 mg, 0.75 mmol) was added to a mixture of Et_2O and 5 M sulfuric acid (3:5, mL/mL). The reaction mixture was stirred at 40 ℃ for 3 days. The mixture was then diluted with brine and extracted with Et_2O (×3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by recrystallization from hexane/$CHCl_3$ to give (*S*)-**2a** (142 mg, 0.70 mmol) in 94% yield in 99% ee as a white solid.

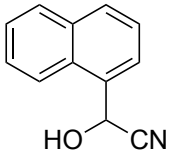
ASYMMETRIC INDUCTION AND AMPLIFICATION

Hydroxy acid (*S*)-**2a** (53 mg, 0.26 mmol) was dissolved in 1 M aqueous NaOH (0.26 mL), and the solvent was removed *in vacuo*. To the resulting residue were added toluene (2.0 mL), DBU (2 μL, 0.013 mmol), 1-naphthaldehyde (0.71 mL, 5.2 mmol), and HCN (0.21 mL, 5.2 mmol). After stirring for 5 h, DBU (2 μL, 0.013 mmol) and HCN (0.21 mL, 5.2 mmol) were added, and the reaction mixture was cooled with liquid N_2 to induce precipitation. The mixture was then stirred at room temperature for 1 day (incubation period), after which the temperature cycling was carried out repeatedly. For example, after six cycles, the solid was collected by filtration to give (*S*)-**1a** (362 mg, 2.0 mmol) in 38% yield with 98% ee as white solid.

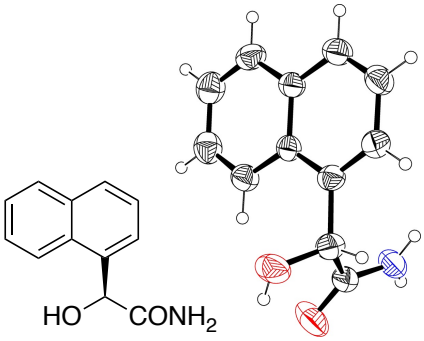
To a solution of (*R*)-**3a** (52 mg, 0.26 mmol), DBU (2 μL, 0.013 mmol) and 1-naphthaldehyde (0.71 mL, 5.2 mmol) in toluene (2.0 mL) was added HCN (0.21 mL, 5.2 mmol). After stirring for 5 h, the reaction mixture was cooled with liquid N_2 to induce precipitation. DBU (2 μL, 0.013 mmol) was then added, and the mixture was stirred for 3 h (incubation period), after which temperature cycling was carried out repeatedly. For example, after three cycles, the solid was collected by filtration to afford (*R*)-**1a** (110 mg, 0.6 mmol) in 12% yield with 98%.

CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

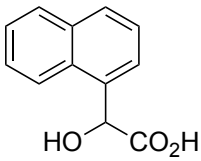
2-Hydroxy-2-(naphthalen-1-yl)acetonitrile[S1] **:** Colorless needle. m.p. 69.8–71.0 °C (racemate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (1H, d, J = 7.3 Hz), 6.19 (1H, d, J = 7.3 Hz), 7.50–7.66 (3H, m), 7.84–7.86 (1H, m), 7.93–7.97 (2H, m), 8.15–8.18 (1H, m). HPLC: Daicel Chiralpak IA-3 (250 × 4.6 mm ID), hexane/IPA = 90/10 (*v*/*v*), flow rate: 1.0 mL/min, 220 nm UV detector, t_R = 8.8 min for (*S*)-isomer, 9.6 min for (*R*)-isomer.



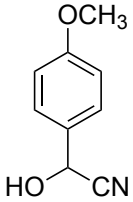
2-Hydroxy-2-(naphthalen-1-yl)acetamide: m.p. 111.2-111.9 °C (racemate), 115.4–116.4 °C (99% ee). Specific rotatory: $[\alpha]_D^{22}$ –116.0 (*c* 0.50, $CHCl_3$, (*R*)-isomer with 83% ee), $[\alpha]_D^{22}$ +156.2 (*c* 0.50, $CHCl_3$, (*S*)-isomer with 96% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (1H, s), 5.53 (1H, s), 5.66 (1H, s), 5.83 (1H, s), 7.46–7.59 (4H, m), 7.87–789 (2H, m), 8.14–8.16 (1H, m). ^{13}C NMR (126 MHz, methanol-d_4): δ 73.6, 125.5, 126.2, 126.7, 127.1, 129.6, 129.9, 132.8, 135.5, 137.4, 178.8. HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{11}NNaO_2$ 224.0688; found 224.0679. IR (ATR, solid): 3392, 3156, 1737, 1681, 1660 cm^{-1}. HPLC: Daicel Chiralpak ID (250 × 4.6 mm ID), hexane/IPA/TFA = 90:10:0.1 (*v*/*v*/*v*), flow rate 1.5 mL/min, 220 nm UV detector, t_R = 21.0 min for (*S*)-isomer, 25 min for (*R*)-isomer. X-ray single-crystal structure: CCDC 2544005, MeOH/toluene, μ (Mo Kα) 0.71075, *C*2/*c*, *a* 32.423(13), *b* 5.8134(17), *c* 11.070(4), α 90, β 105.377(16), γ 90, *V* 2011.9(12), *Z* 8, ρ 1.329, *R* 0.648 (990), *wR*2 0.1927 (2307).



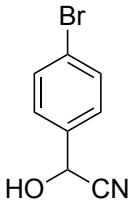
2-Hydroxy-2-(naphthalen-1-yl)acetic acid[S2]: Colorless solid. Specific rotatory: $[\alpha]^{22}_D$ –185.1 (*c* 0.5, $CHCl_3$, (*R*)-isomer with >99.5% ee), $[\alpha]^{22}_D$ +192.6 (*c* 0.5, $CHCl_3$, (*S*)-isomer with >99.5% ee). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.34 (1H, s), 5.92 (1H, s), 7.46–7.59 (4H, m), 7.87–7.91 (2H, m), 8.16–8.18 (1H, m). HPLC: Daicel Chiralpak ID (250 × 4.6 mm ID), hexane/IPA/TFA = 90:10:0.1 (*v*/*v*/*v*), flow rate: 1.5 mL/min, 220 nm UV detector, t_R = 8.6 min for (*R*)-isomer, 10.5 min for (*S*)-isomer.



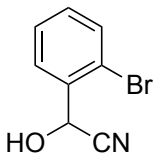
2-Hydroxy-2-(4-methoxyphenyl)acetonitrile[S3]: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.56 (1H, m), 3.84 (3H, s), 5.49 (1H, d, J = 7.3 Hz), 6.94–6.97 (2H, m), 7.44–7.47 (2H, m).



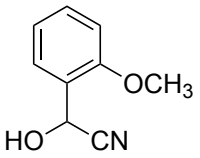
2-(4-Bromophenyl)-2-hydroxyacetonitrile[S4]**:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64–2.73 (1H, m), 5.53 (1H, d, J = 6.9 Hz), 7.42–7.43 (2H, m), 7.58–7.60 (2H, m).



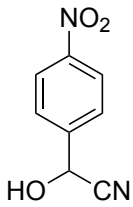
2-(2-Bromophenyl)-2-hydroxyacetonitrile[S4]**:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.94 (1H, s), 5.87 (1H, s), 7.32–7.33 (1H, m), 7.43–7.46 (1H, m), 7.63–7.65 (1H, m), 7.73–7.75 (1H, m).



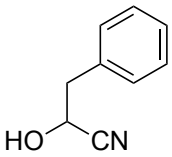
2-Hydroxy-2-(2-methoxyphenyl)acetonitrile[S 5] : ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.44 (1H, d, J = 9.1 Hz), 3.96 (3H, s), 5.56 (1H, d, J = 9.1 Hz), 6.97–7.04 (2H, m), 7.38–7.43 (2H, m).



2-Hydroxy-2-(4-nitrophenyl)acetonitrile[S6]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (1H, s), 5.71 (1H, s), 7.74–7.77 (2H, m), 8.33–8.34 (2H, m).

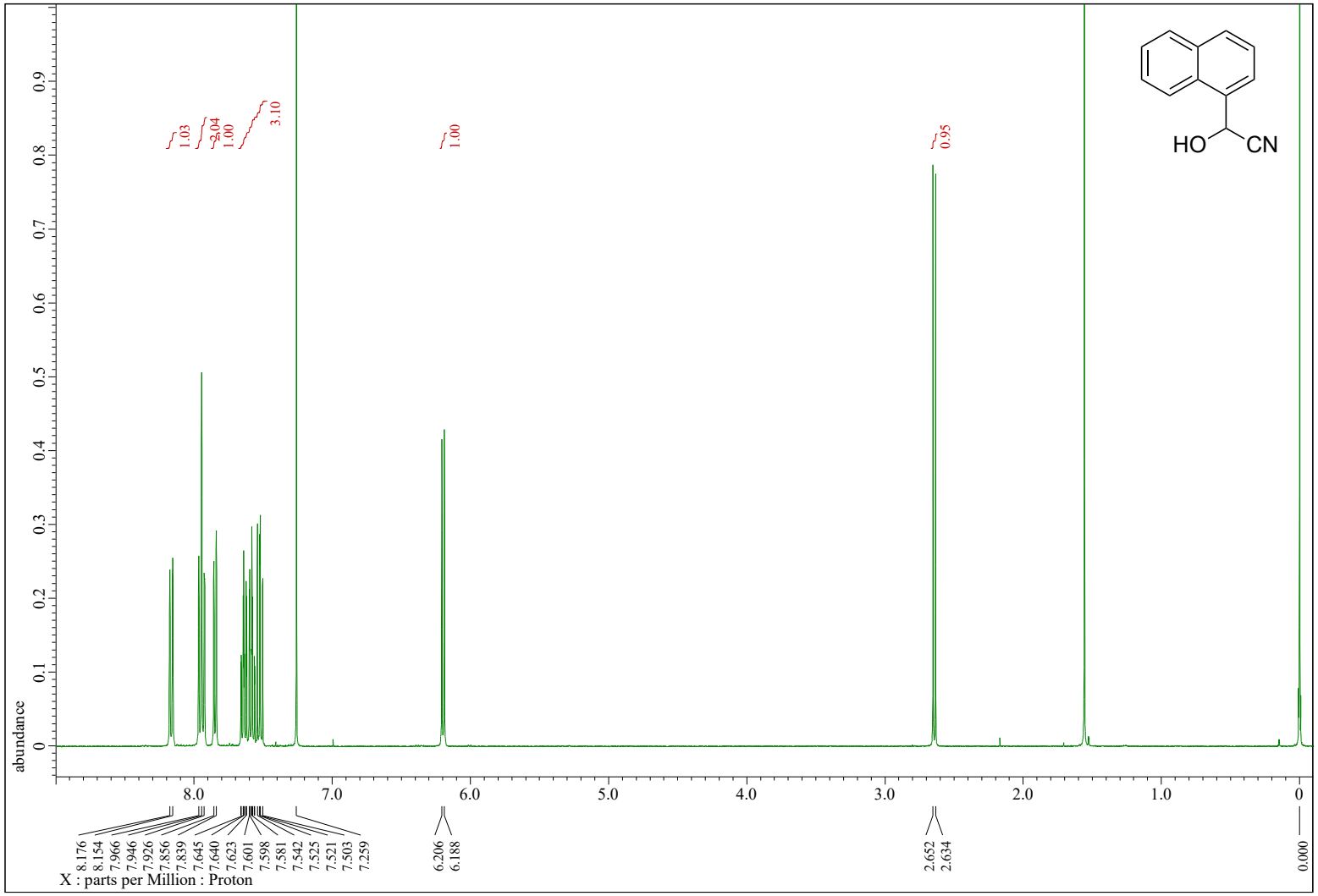


2-Hydroxy-3-phenylpropanenitrile[S6]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.14 (2H, d, J = 6.34 Hz), 4.69 (1H, t, J = 6.34 Hz), 7.28–7.42 (5H, m).

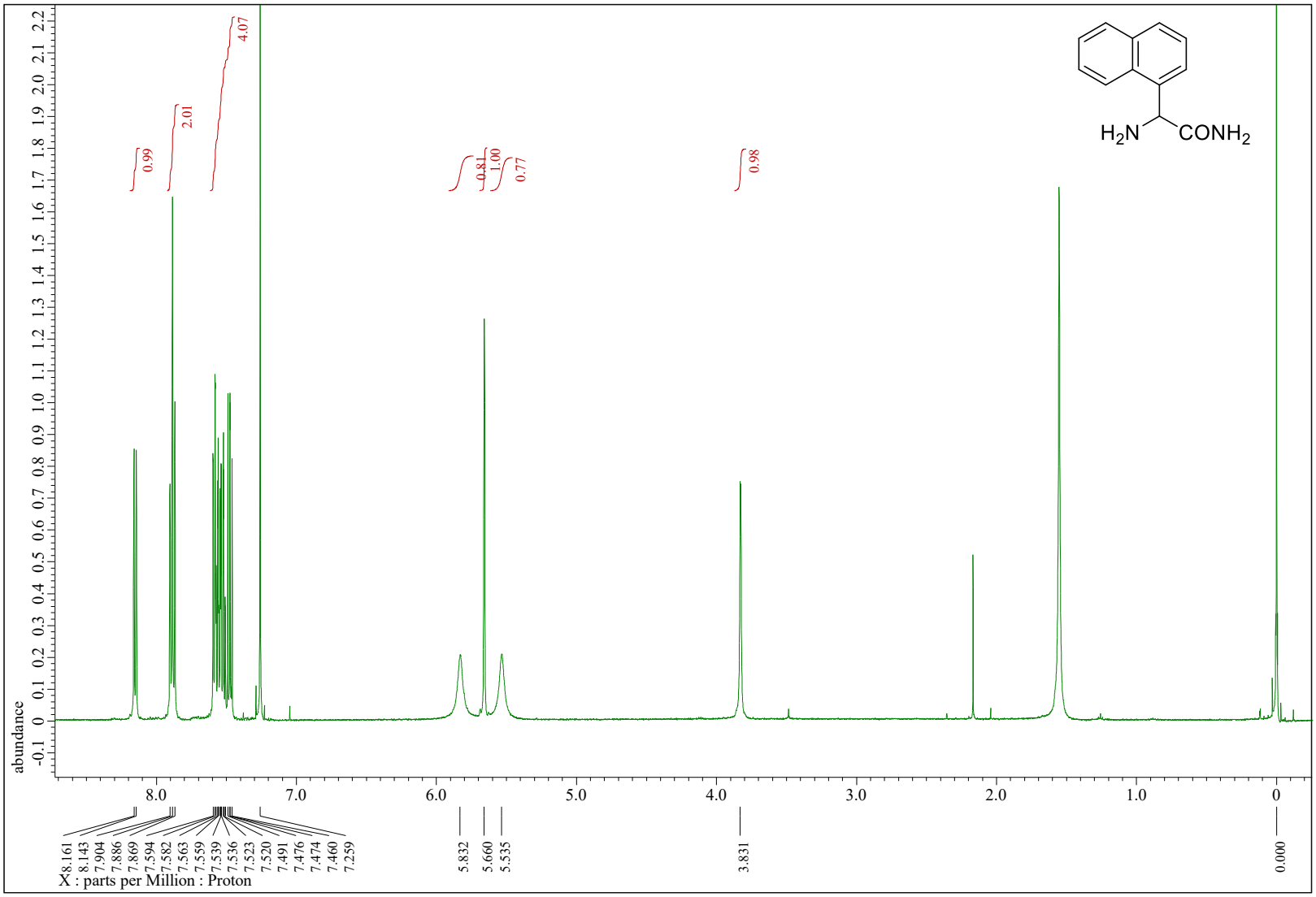


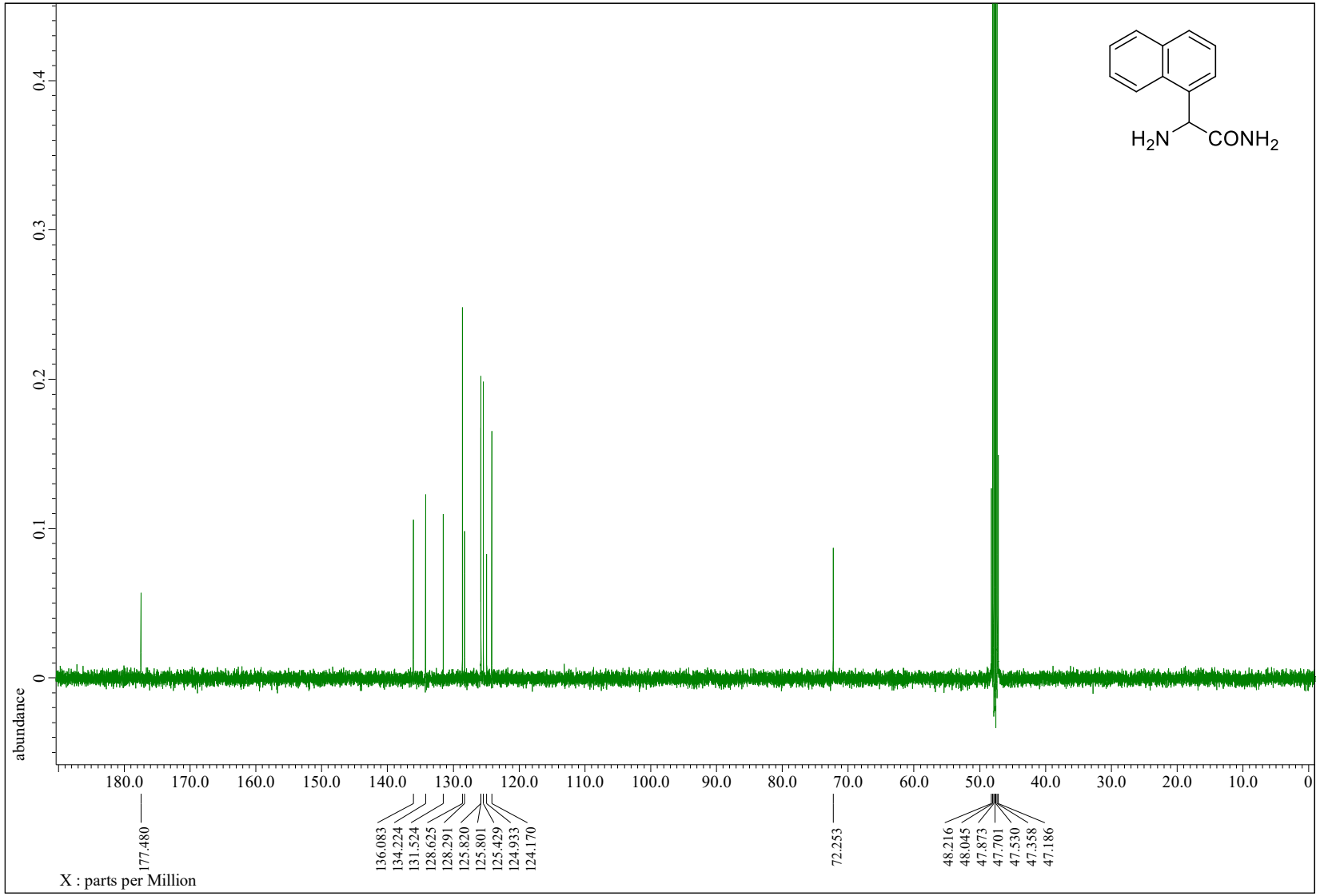
COPIES OF ^{1}H NMR AND ^{13}C NMR SPECTRA

2-Hydroxy-2-(naphthalen-1-yl)acetonitrile

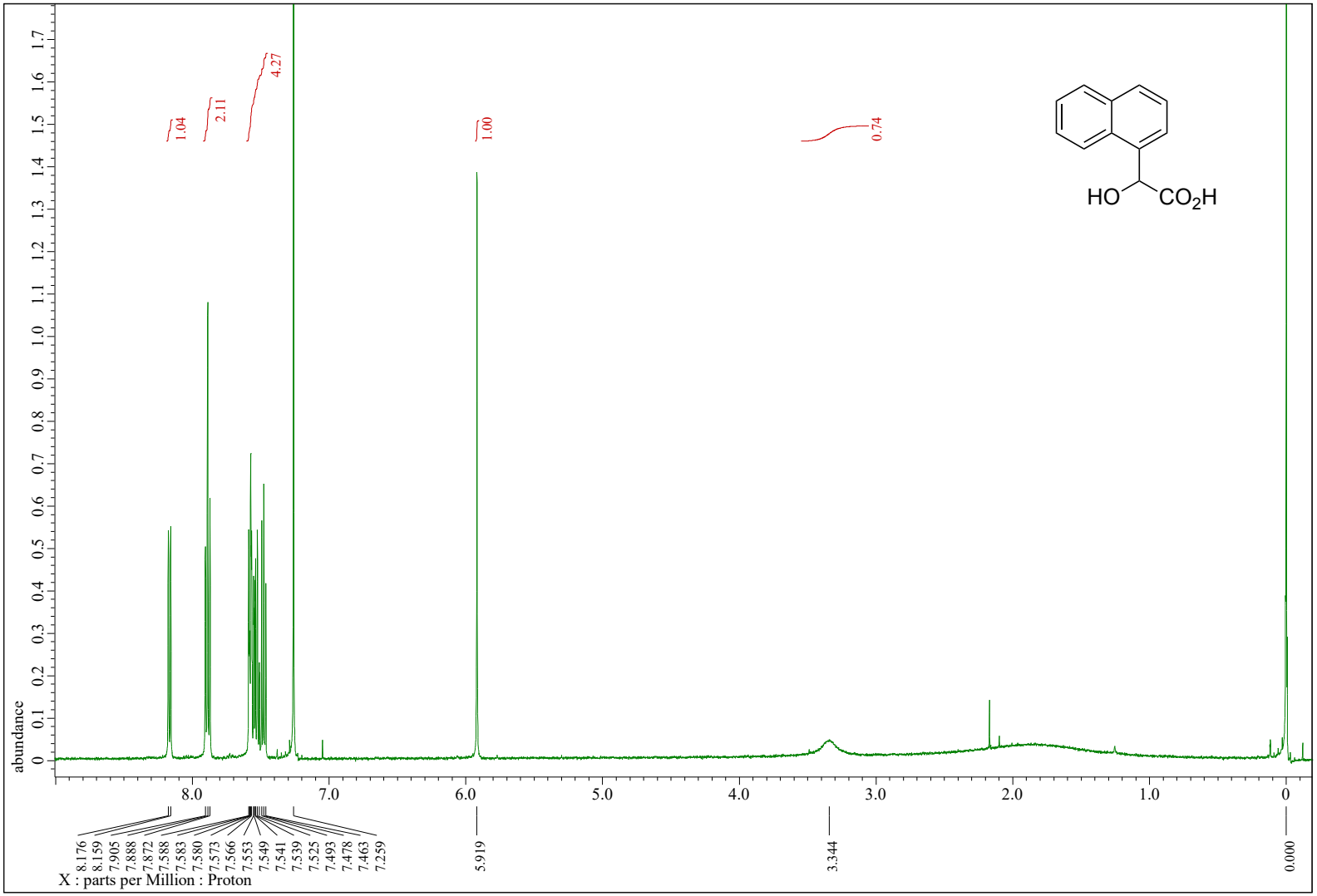


2-Hydroxy-2-(naphthalen-1-yl)acetamide

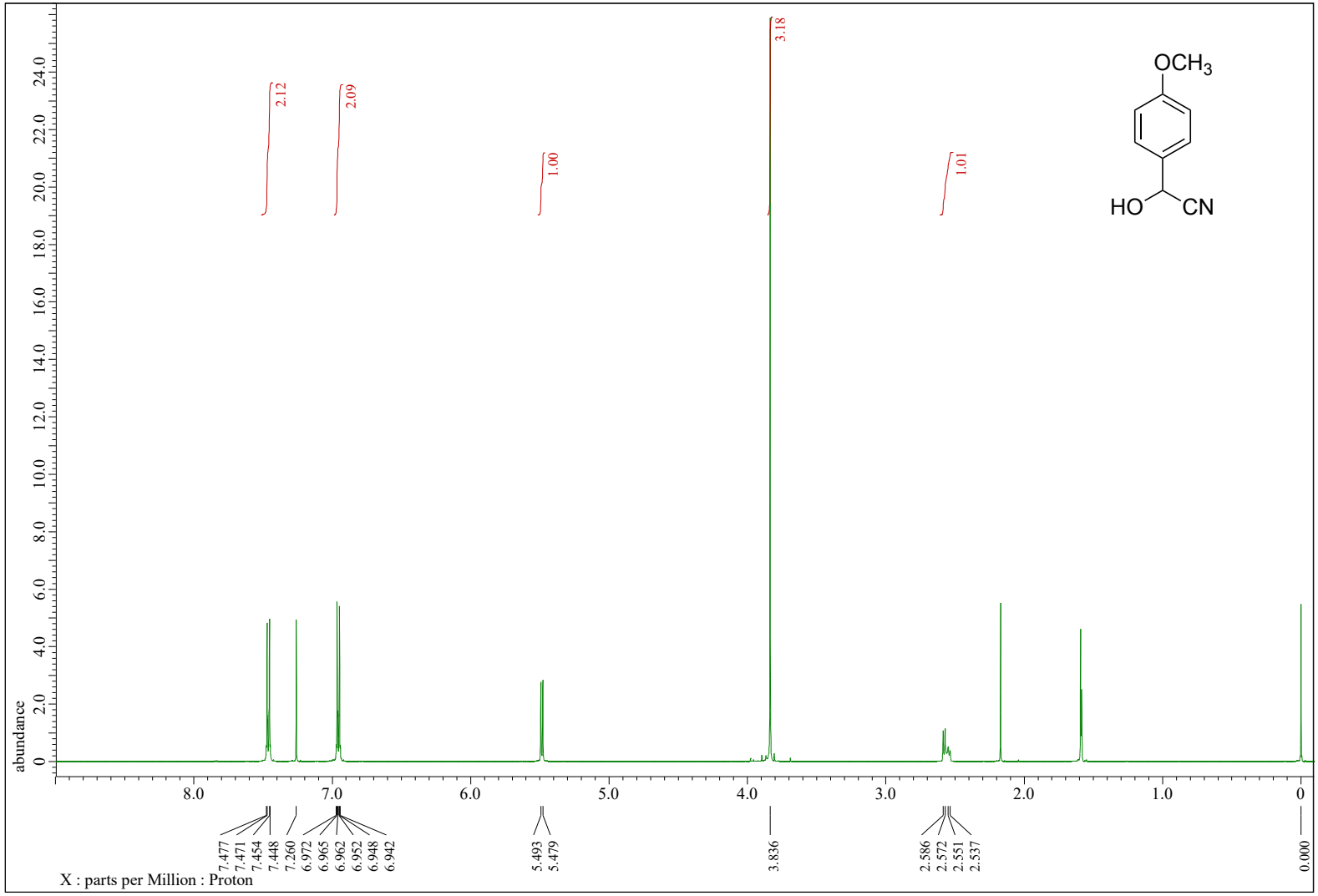



abundance
0.4
0.3
0.2
0.1
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
177.480
136.083
134.224
131.524
128.625
128.291
125.820
125.801
125.429
124.933
124.170
72.253
48.216
48.045
47.873
47.701
47.530
47.358
47.186
X : parts per Million
H2N
CONH2

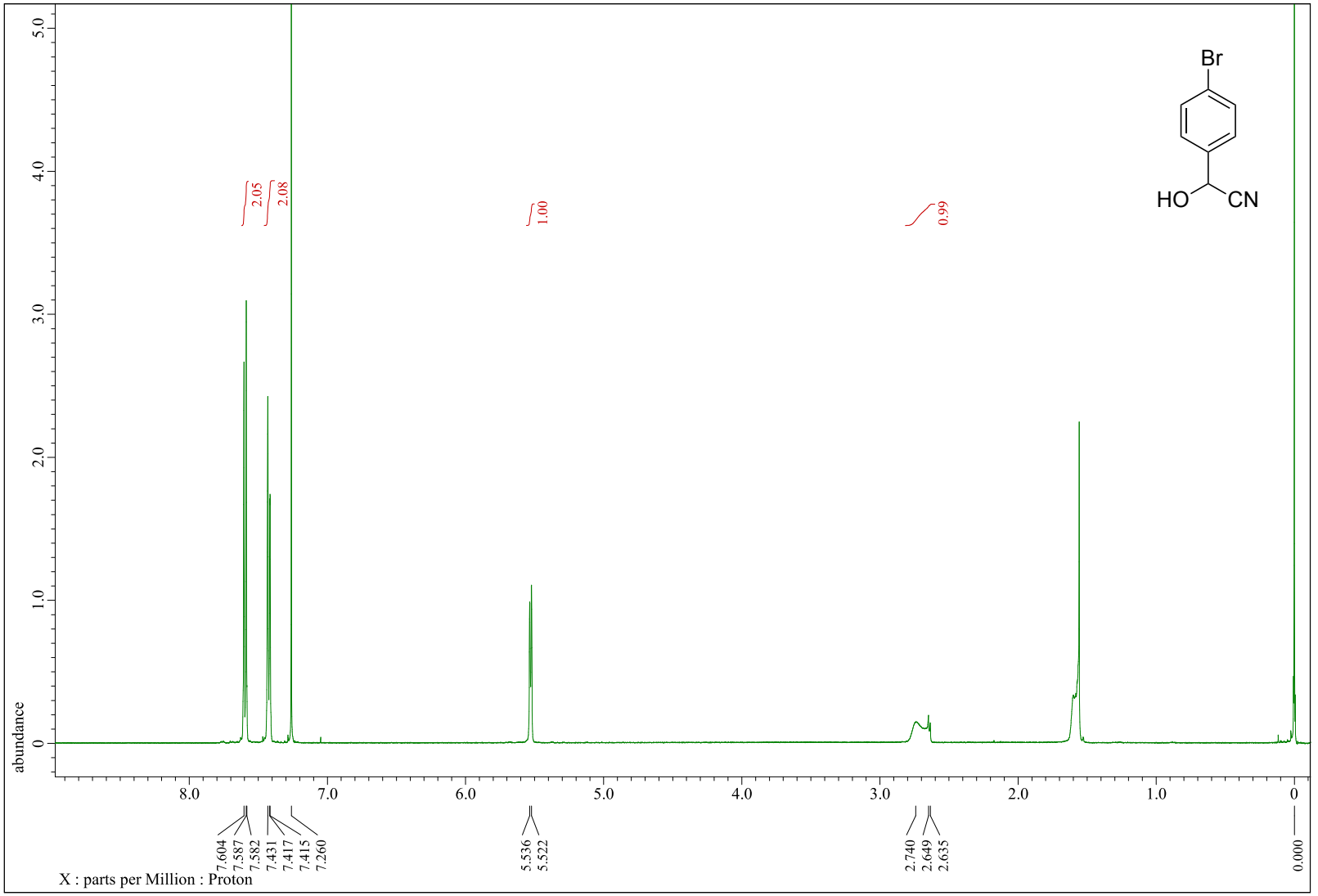
2-Hydroxy-2-(naphthalen-1-yl)acetic acid



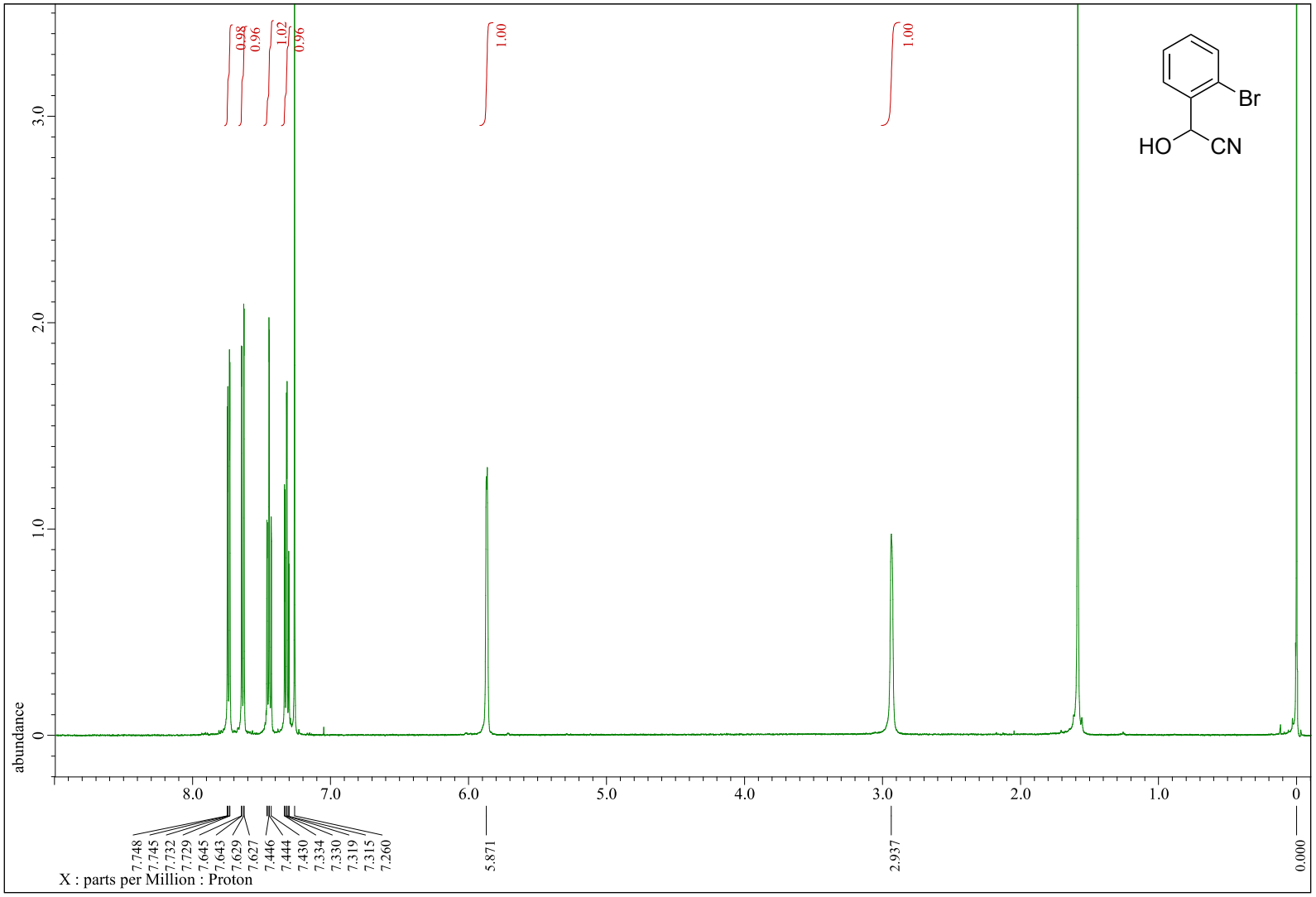
2-Hydroxy-2-(4-methoxyphenyl)acetonitrile



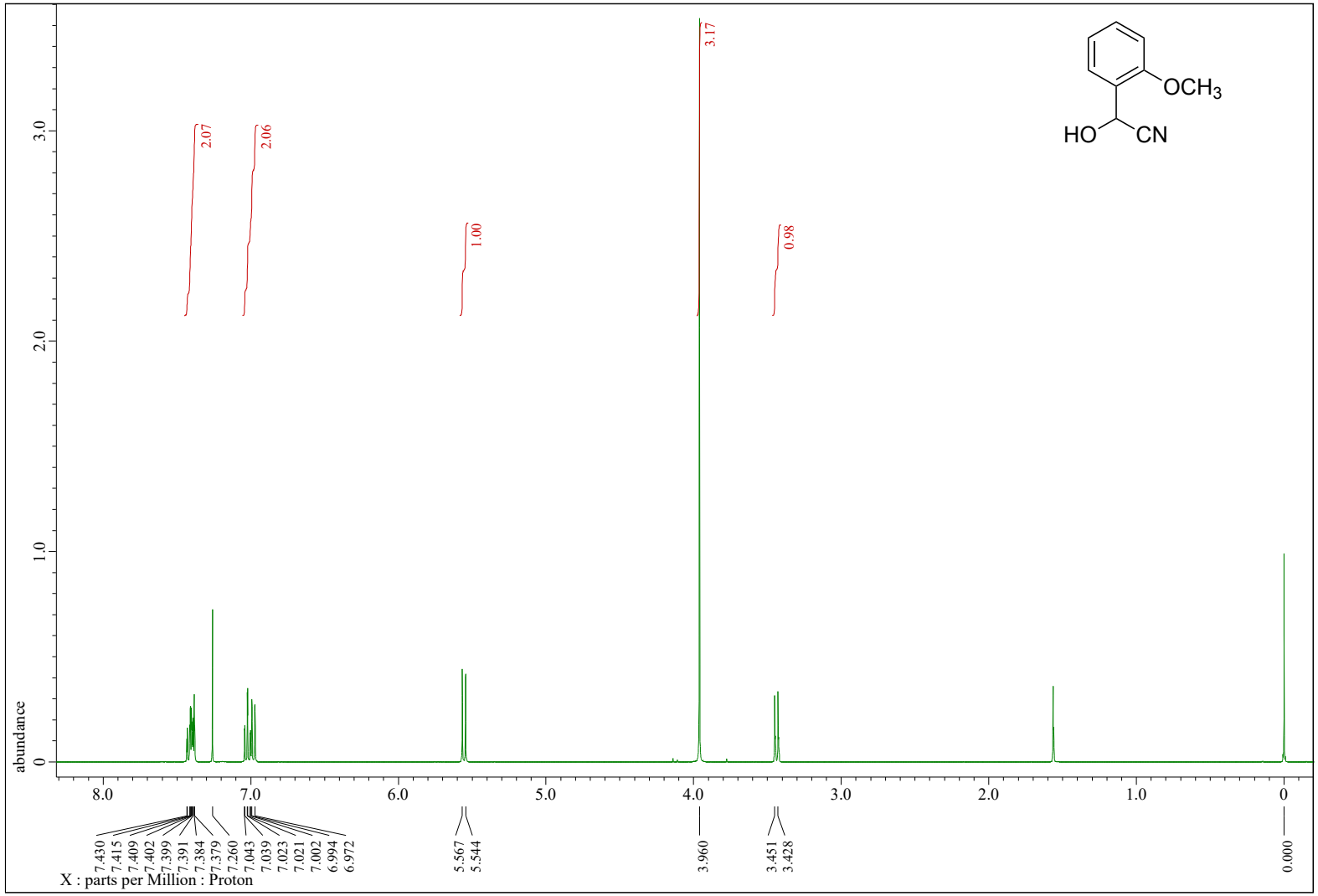
2-(4-Bromophenyl)-2-hydroxyacetonitrile



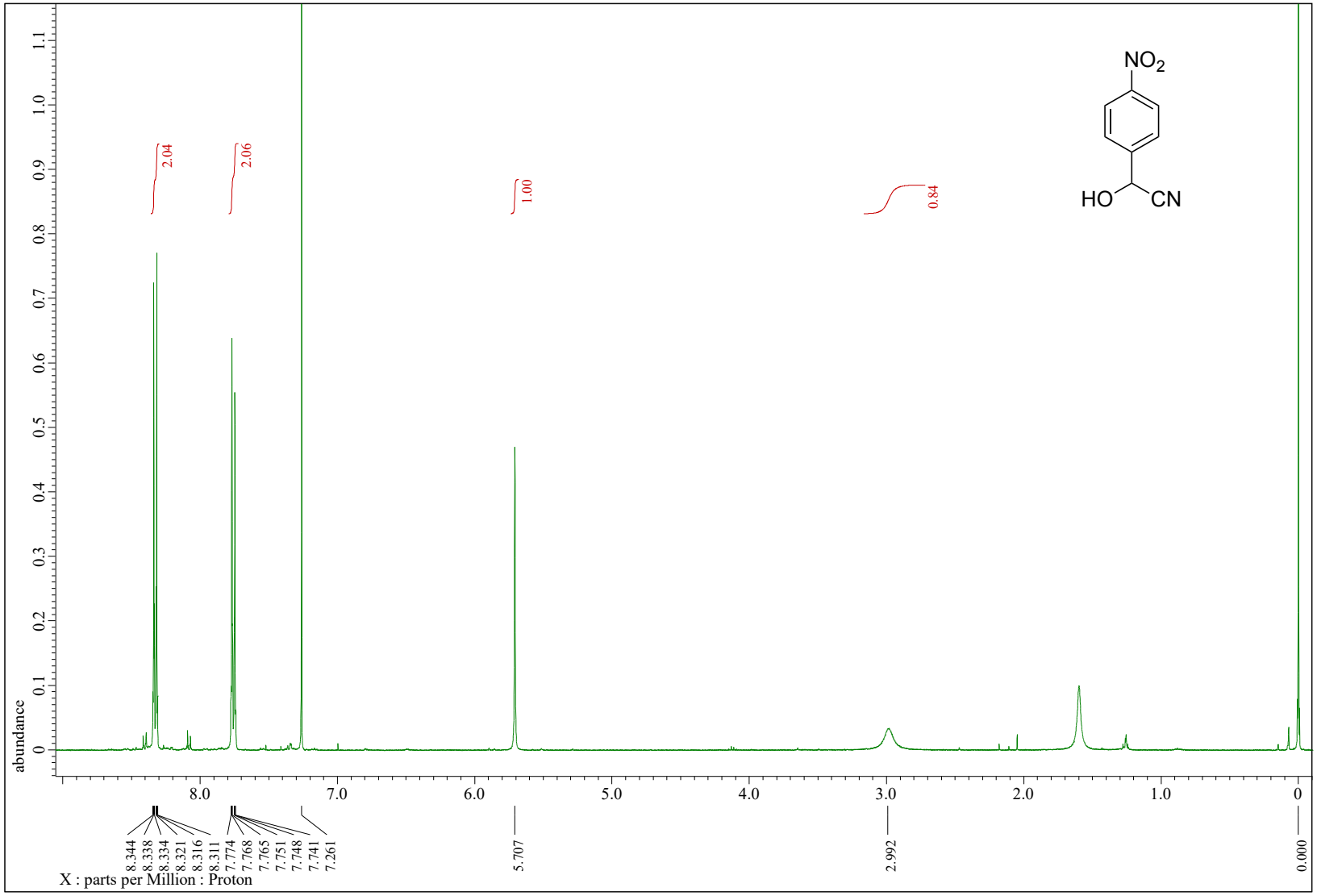
2-(2-Bromophenyl)-2-hydroxyacetonitrile



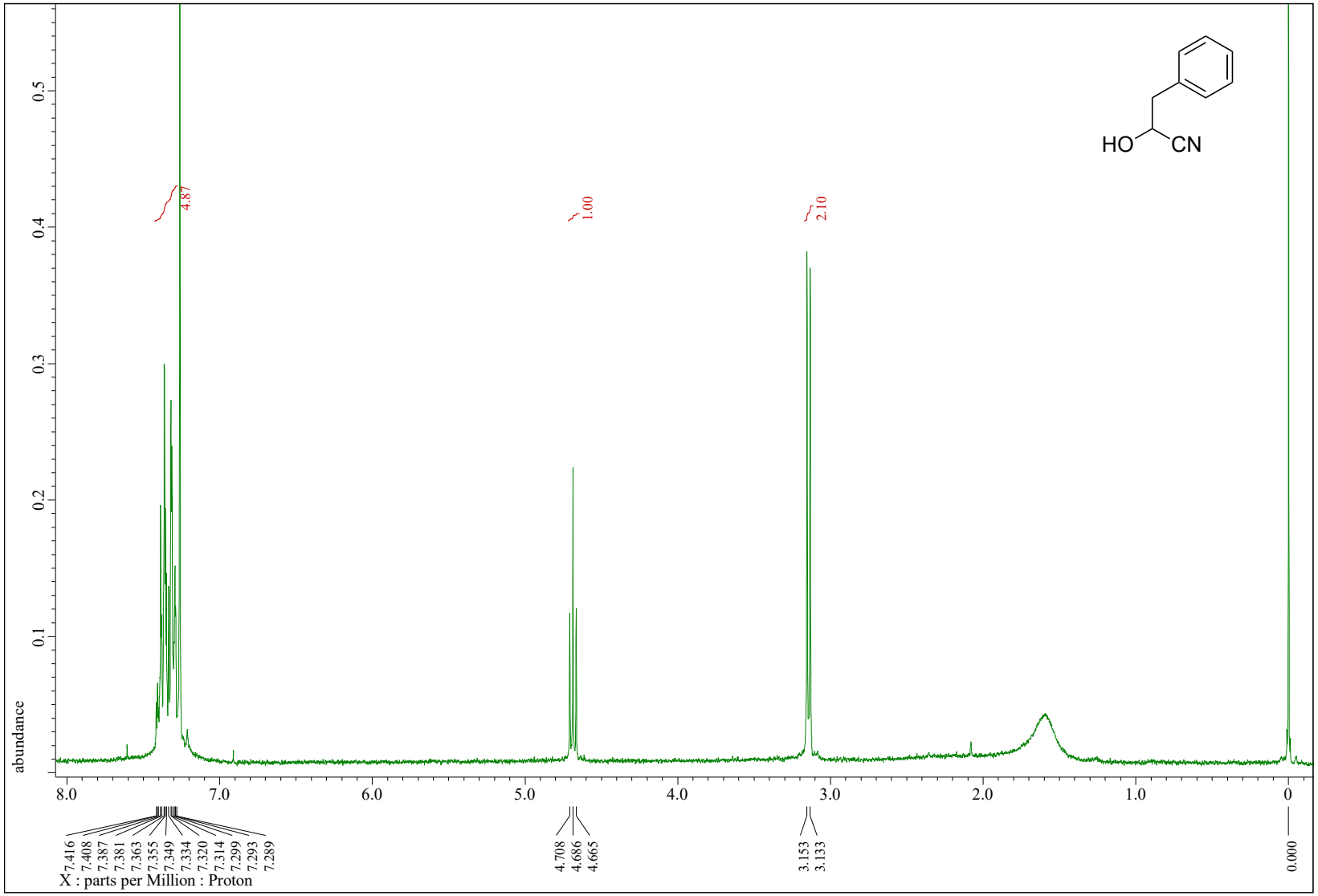
2-Hydroxy-2-(2-methoxyphenyl)acetonitrile



2-Hydroxy-2-(4-nitrophenyl)acetonitrile



2-Hydroxy-3-phenylpropanenitrile



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