Supporting Information

ENANTIOSELECTIVE CYCLOADDITIONS BETWEEN ALIPHATIC NITRILE OXIDES AND 2-HYDROXYSTYRENES CATALYZED BY CHIRAL AMINE-UREA

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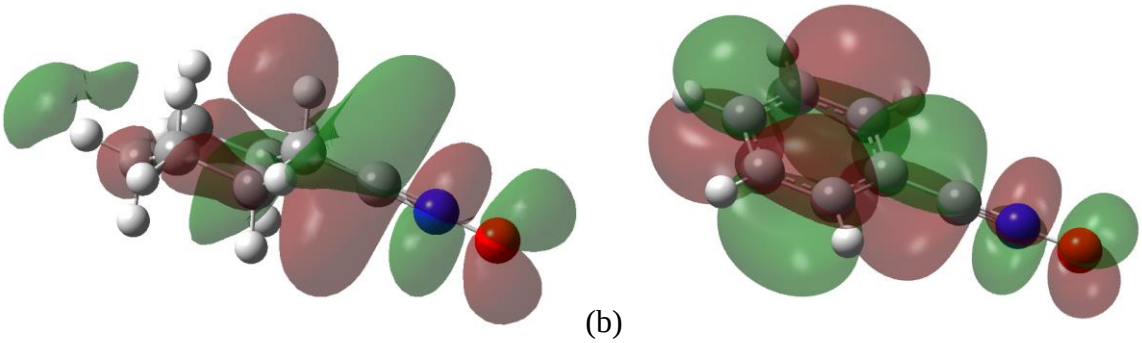
Section I: Computational Details

DFT calculations

Quantum mechanical calculations were performed using Gaussian 09 (Revision E.01).[1] All geometries were optimized using the M06-2X density functional,[2,3] the 6-31G(d) basis set and an ultrafine integration grid within the IEFPCM model.[4] Single point energies were calculated using M06-2X, the polarized, triple-ζ valence quality def2-TZVPP basis set of Weigend and Ahlrichs and an ultrafine integration grid within the IEFPCM model.[5] The free energy corrections were calculated at 1 atm and 298.15 K.



(a) (b)

Figure S1. (a) Cyclohexanecarbonitrile oxide (**5a**: LUMO+2). (b) Benzonitrile oxide (**5b**: LUMO).

Cyclohexanecarbonitrile oxide (5a)

M06-2X/def2tzvpp//M06-2x/6-31G(d), scrf = (iefpcm, solvent = toluene)

	a.u.	eV	kcal mol^{-1}
LUMO+2	0.06939	1.88821	43.54288
HOMO-1	-0.31668	-8.61737	-198.71971

M06-2X/6-31G(d)-IEFPCM(toluene) Energy = -403.082029956 a.u.

M06-2X/6-31G(d)-IEFPCM(toluene) Gibbs Energy = -402.939685 a.u.

M06-2X/def2-TZVPP-IEFPCM(toluene) Energy = -403.244808762 a.u.

Number of Imaginary Frequencies = 0

M06-2X/6-31G(d)-IEFPCM(toluene) Geometry

1	C	11.635	-3.077	3.383
2	C	10.106	-3.091	3.426
3	C	-9.537	-1.670	3.431
4	C	10.105	-0.857	4.596
5	C	11.634	-0.828	4.561
6	C	12.199	-2.261	4.563
7	H	-8.444	-1.700	3.487
8	H	-9.776	-3.618	4.332
9	H	-9.721	-3.656	2.572
10	H	-11.978	-2.616	2.447
11	H	-12.037	-4.094	3.412
12	H	-9.775	-1.301	5.545
13	H	-9.718	0.167	4.575
14	H	-12.034	-0.271	5.414
15	H	-11.977	-0.320	3.650
16	H	-11.896	-2.751	5.499
17	H	-9.796	-1.175	2.486
18	C	-13.670	-2.245	4.534
19	N	-14.826	-2.211	4.472
20	O	-16.043	-2.180	4.414

Benzonitrile oxide (5b)

M06-2X/def2tzvpp//M06-2x/6-31G(d), scrf = (iefpcm, solvent = toluene)

	a.u.	eV	kcal mol^{-1}
LUMO	-0.02632	-0.71621	-16.51605
HOMO	-0.29823	-8.11532	-187.14216

M06-2X/6-31G(d)-IEFPCM(toluene) Energy = -399.469132132 a.u.

M06-2X/6-31G(d)-IEFPCM(toluene) Gibbs Energy = -399.396473 a.u.

M06-2X/def2-TZVPP-IEFPCM(toluene) Energy = -399.629066257 a.u.

Number of Imaginary Frequencies = 0

M06-2X/6-31G(d)-IEFPCM(toluene) Geometry

1	C	-8.548	1.228	4.337
2	C	-7.159	1.235	4.338
3	C	-6.463	2.443	4.337
4	C	-7.159	3.651	4.336
5	C	-8.548	3.658	4.336
6	C	-9.246	2.443	4.336
7	H	-9.099	0.294	4.338
8	H	-6.618	0.295	4.339
9	H	-5.378	2.443	4.337
10	H	-6.618	4.592	4.336
11	H	-9.099	4.593	4.335
12	C	-10.681	2.444	4.336
13	N	-11.840	2.444	4.336
14	O	-13.055	2.444	4.336

Section II: Experimental Details

General. Melting points were determined on a Yanaco MP-13 melting point apparatus and are uncorrected. IR spectra were taken with a JASCO FT/IR-5300S spectrophotometer. ^{1}H NMR spectra were recorded on a BRUKER AVANCE III Fourier 300 (300 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a BRUKER AVANCE III Fourier 300 (75 MHz) spectrometer using broadband proton decoupling. Chemical shifts are expressed in parts per million using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. Hydrogen multiplicity (C, CH, CH_2, CH_3) information was obtained from carbon DEPT spectrum. High-resolution mass spectra were obtained on a BRUKER micrOTOF II ESI-TOF spectrometer. High performance liquid chromatography was performed on a JASCO PU-2080/UV-2075 system. Optical rotations were recorded with a JASCO P-1010 polarimeter. Fuji Silysia PSQ60B was employed for column chromatography. All reactions were carried out under an argon atmosphere in dried glassware.

Materials. Hydroxystyrene **2**[6] and chiral amin-urea **3**[7] were prepared by the literature procedure. Toluene was purified by distillation first from $CaCl_2$ and then from a sodium benzophenone still under argon atmosphere.

Preparation of hydroximoyl chlorides 1.[8] To a solution of an oxime (1 equiv) in DMF (1.2 M) was added NCS (1.05 equiv) portionwise at 0 °C. After consumption of the starting material as measured by TLC analysis, the mixture was treated with water, and then extracted with Et_2O (x 3). The organic layers were combined, washed with water (x 2) and brine (x 1), dried over Na_2SO_4, and concentrated. The material was subjected to the cycloaddition without further purification.

1a (R^1 = *c*-hexyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12-1.51 (5H, m), 1.66-1.97 (5H, m), 2.47 (1H, tt, *J* = 3.3, 11.4 Hz).

1b (R^1 = *n*-pentyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-0.94 (3H, m), 1.24-1.42 (4H, m), 1.59-1.72 (2H, m), 2.47-2.54 (2H, m), 8.10-8.14 (1H, m).

1c (R^1 = *i*-butyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (5.4H, d, *J* = 6.6 Hz), 1.04 (0.6H, d, *J* = 6.6 Hz), 1.94-2.21 (1H, m), 2.37 (1.8H, d, *J* = 7.2 Hz), 2.43 (0.2H, d, *J* = 6.6 Hz), 7.91-7.93 (1H, m).

1d (R^1 = benzyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (2H, s), 7.24-7.39 (5H, m), 7.79 (1H, brs).

1e (R^1 = (*E*)-cinnamyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (1H, d, *J* = 15.6 Hz), 7.27-7.46 (4H, m), 7.46-7.53 (2H, m), 8.21 (1H, brs).

1f (R^1 = phenyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.46 (3H, m), 7.82-7.87 (2H, m), 8.23 (1H, brs).

1g (R^1 = 4-tolyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (3H, s), 7.21 (2H, d, *J* = 8.1 Hz), 7.72 (2H, d, *J* = 8.1 Hz), 8.17 (1H, brs).

1h (R^1 = 3-tolyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (3H, s), 7.25-7.33 (2H, m), 7.62-7.66 (2H, m), 8.13 (1H, brs).

1i (R^1 = 2-tolyl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (2.2H, s), 2.48 (0.8H, s), 7.19-7.49 (4H, m), 8.31 (1H, brs).

General procedure for enantioselective 1,3-dipolar cycloadditions of nitrile oxides. Et_3N (70 μL, 0.5 mmol) was added to a solution of hydroximoyl chloride **1** (0.2 mmol) in toluene (1 mL) at room temperature, and then the mixture was stirred vigorously at room temperature for 30 min. The mixture was filtered through a plug of Celite® (0.1 g) using pipette with toluene (0.5 x 2 mL) as an eluent to remove Et_3N•HCl. The filtrate solution was directly poured into an oven-dried test-tube, and employed without concentration. After cooling the solution to -20 °C, amine-urea **3** (17.4 mg, 0.03 mmol) and 2-hydroxy-3-methoxystyrene (**2**) (15.0 mg, 0.1 mmol) were added, and the mixture was stirred at -20 °C for 48 h. The reaction mixture was filtrated through a plug of silica gel, and then purified by column chromatography (SiO_2, Fuji Silysia PSQ60B) to obtain isoxazoline **4**.

3-Cyclohexyl-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4a): The reaction of **1a** (32.3 mg, 0.2 mmol) with **2** (13.8 mg, 0.1 mmol) gave colorless powder (23.7 mg, 86%, 90% ee) after column

chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.40 (CH_2Cl_2); mp 63-65 °C; $[\alpha]_D^{25}$ +46.2 (*c* 0.50, $CHCl_3$, 90% ee); IR (KBr) 3187, 2927, 2850, 1610, 1480, 1275, 1064, 781, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21-1.38 (5H, m), 1.67-1.89 (5H, m), 2.43 (1H, m), 2.87 (1H, ddd, *J* = 0.6, 7.8, 17.1 Hz), 3.39 (1H, ddd, *J* = 0.6, 10.8, 17.1 Hz), 3.88 (3H, s), 5.76 (1H, dd, *J* = 7.8, 10.8 Hz), 5.85 (1H, brs), 6.78-6.87 (2H, m), 6.97 (1H, ddd, *J* = 0.6, 2.1, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 ($2CH_2$), 25.9 (CH_2), 30.36 (CH_2), 30.41 (CH_2), 37.3 (CH), 42.6 (CH_2), 56.1 (CH_3), 76.5 (CH), 110.0 (CH), 118.5 (CH), 119.7 (CH), 127.3 (C), 142.3 (C), 146.4 (C), 162.8 (C); HRMS (ESI-TOF) Calcd for $C_{16}H_{22}NO_3$ $[(M+H)^+]$: 276.1594, Found: 276.1591. The enantiomeric excess of **4a** was determined by HPLC analysis (Daicel Chiralpak IC, hexane/EtOH = 80/20 (v/v), UV 225 nm, flow rate = 1.0 mL/min, 35 °C, t_{minor} = 10.4 min, t_{major} = 11.4 min).

3-Pentyl-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4b):[9] The reaction of **1b** (30.1 mg, 0.2 mmol) with **2** (15.8 mg, 0.1 mmol) gave colorless powder (22.9 mg, 78%, 73% ee) after column chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.17 (CH_2Cl_2); mp 49-50 °C; $[\alpha]_D^{26}$ +38.4 (*c* 0.10, $CHCl_3$, 73% ee); IR (KBr) 3245, 2957, 1613, 1483, 1435, 1344, 1272, 1228, 1069, 854, 829, 781, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.90 (3H, m), 1.26-1.35 (4H, m), 1.48-1.63 (2H, m), 2.36 (2H, t, *J* = 7.8 Hz), 2.87 (1H, dd, *J* = 7.8, 17.1 Hz), 3.39 (1H, dd, *J* = 10.8, 17.1 Hz), 3.88 (3H, s), 5.79 (1H, dd, *J* = 7.8, 10.8 Hz), 5.86 (1H, brs), 6.79-6.87 (2H, m), 6.99 (1H, ddd, *J* = 0.6, 2.1, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.2 (CH_2), 26.0 (CH_2), 27.6 (CH_2), 31.3 (CH_2), 44.2 (CH_2), 56.0 (CH_3), 76.7 (CH), 110.0 (CH), 118.4 (CH), 119.7 (CH), 127.3 (C), 142.3 (C), 146.4 (C), 159.1 (C); HRMS (ESI-TOF) Calcd for $C_{15}H_{21}NNaO_3$ $[(M+Na)^+]$: 286.1414, Found: 286.1418. The enantiomeric excess of **4b** was determined by HPLC analysis (Daicel Chiralpak IC, hexane/EtOH = 80/20 (v/v), UV 225 nm, flow rate = 0.5 mL/min, 35 °C, t_{minor} = 18.3 min, t_{major} = 20.6 min).

3-Isobutyl-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4c): The reaction of **1c** (27.4 mg, 0.2 mmol) with **2** (14.6 mg, 0.1 mmol) gave colorless powder (21.6 mg, 89%, 82% ee) after column

chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.13 (CH_2Cl_2); mp 68-70 °C; $[\alpha]_D^{25}$ +40.8 (*c* 0.10, $CHCl_3$, 82% ee); IR (KBr) 3242, 2956, 1614, 1480, 1440, 1350, 1277, 1229, 1068, 984, 842, 784 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 1.88 (1H, m), 2.25 (2H, d, *J* = 7.2 Hz), 2.87 (1H, dd, *J* = 7.8, 17.1 Hz), 3.37 (1H, dd, *J* = 10.8, 17.1 Hz), 3.86 (3H, s), 5.79 (1H, dd, *J* = 7.8, 10.8 Hz), 5.86 (1H, brs), 6.79-6.87 (2H, m), 6.99 (1H, ddd, *J* = 0.6, 2.1, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (CH_3), 22.6 (CH_3), 26.3 (CH), 36.6 (CH_2), 44.5 (CH_2), 56.1 (CH_3), 76.8 (CH), 110.0 (CH), 118.5 (CH), 119.7 (CH), 127.3 (C), 142.3 (C), 146.4 (C), 158.4 (C); HRMS (ESI-TOF) Calcd for $C_{14}H_{19}NNaO_3$ [$(M+Na)^+$]: 272.1257, Found: 272.1259. The enantiomeric excess of **4c** was determined by HPLC analysis (Daicel Chiralpak AD-3, hexane/EtOH = 80/20 (v/v), UV 225 nm, flow rate = 0.5 mL/min, 35 °C, t_{major} = 14.3 min, t_{minor} = 20.2 min).

3-Benzyl-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4d): The reaction of **1d** (34.0 mg, 0.2 mmol) with **2** (15.1 mg, 0.1 mmol) gave yellowish powder (13.9 mg, 49%, 87% ee) after column chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.17 (CH_2Cl_2); mp 88-89 °C; $[\alpha]_D^{22}$ +110.6 (*c* 0.10, $CHCl_3$, 87% ee); IR (KBr) 3232, 1615, 1482, 1441, 1352, 1280, 1215, 1073, 987, 848, 830, 785, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.78 (1H, dd, *J* = 8.1, 17.1 Hz), 3.27 (1H, dd, *J* = 10.8, 17.1 Hz), 3.66 (1H, d, *J* = 15.0 Hz), 3.76 (1H, d, *J* = 15.0 Hz), 3.86 (3H, s), 5.77 (1H, brs), 5.78 (1H, dd, *J* = 8.1, 10.8 Hz), 6.77-6.86 (2H, m), 6.97 (1H, ddd, *J* = 0.6, 2.1, 7.2 Hz), 7.20-7.33 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2 (CH_2), 43.5 (CH_2), 56.1 (CH_3), 77.2 (CH), 110.1 (CH), 118.5 (CH), 119.7 (CH), 127.0 (C), 127.0 (CH), 128.8 (CH), 128.8 (CH), 135.8 (C), 142.4 (C), 146.4 (C), 157.9 (C); HRMS (ESI-TOF) Calcd for $C_{17}H_{17}NNaO_3$ [$(M+Na)^+$]: 306.1101, Found: 306.1104. The enantiomeric excess of **4d** was determined by HPLC analysis (Daicel Chiralpak IC, hexane/EtOH = 80/20 (v/v), UV 225 nm, flow rate = 0.5 mL/min, 35 °C, t_{minor} = 20.6 min, t_{major} = 23.9 min).

(*E*)-Cinnamyl-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4e): The reaction of **1e** (36.3 mg, 0.2 mmol) with **2** (15.3 mg, 0.1 mmol) gave yellowish powder (24.5 mg, 81%, 51% ee) after column chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.27 (CH_2Cl_2); mp

120-122 °C; $[\alpha]_D^{26}$ +62.7 (*c* 0.10, $CHCl_3$, 51% ee); IR (KBr) 3397, 1615, 1481, 1441, 1367, 1279, 1230, 1073, 961, 909, 784, 752, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.18 (1H, dd, *J* = 7.8, 16.5 Hz), 3.66 (1H, dd, *J* = 11.1, 16.5 Hz), 3.89 (3H, s), 5.88 (1H, brs), 5.95 (1H, dd, *J* = 7.8, 11.1 Hz), 6.71 (1H, d, *J* = 16.5 Hz), 6.79-6.90 (2H, m), 7.00 (1H, ddd, *J* = 0.6, 2.1, 7.2 Hz), 7.12 (1H, d, *J* = 16.5 Hz), 7.26-7.39 (3H, m), 7.40-7.48 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.6 (CH_2), 56.1 (CH_3), 78.1 (CH), 110.2 (CH), 118.0 (CH), 118.4 (CH), 119.8 (CH), 126.8 (C), 126.9 (CH), 128.80 (CH), 128.84 (CH), 135.8 (C), 136.4 (CH), 142.4 (C), 146.4 (C), 157.7 (C); HRMS (ESI-TOF) Calcd for $C_{18}H_{17}NNaO_3$ $[(M+Na)^+]$: 318.1101, Found: 318.1098. The enantiomeric excess of **4e** was determined by HPLC analysis (Daicel Chiralpak IC, hexane/EtOH = 80/20 (v/v), UV 225 nm, flow rate = 0.5 mL/min, 35 °C, t_{minor} = 23.7 min, t_{major} = 25.0 min).

3-Phenyl-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4f):[9] The reaction of **1f** (31.2 mg, 0.2 mmol) with **2** (15.1 mg, 0.1 mmol) gave colorless powder (26.2 mg, 97%, 57% ee) after column chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.14 (CH_2Cl_2); mp 63-65 °C; $[\alpha]_D^{27}$ +24.4 (*c* 0.10, $CHCl_3$, 65% ee); IR (KBr) 3201, 2941, 2841, 1614, 1598, 1478, 1438, 1359, 1271, 1234, 1202, 1167, 1070, 981, 950, 911, 851, 828, 777, 760, 689, 532 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (1H, dd, *J* = 7.8, 16.8 Hz), 3.80 (1H, dd, *J* = 11.1, 16.8 Hz), 3.89 (3H, s), 5.86 (1H, brs), 6.00 (1H, dd, *J* = 7.8, 11.1 Hz), 6.81 (1H, dd, *J* = 2.1, 7.2 Hz), 6.85 (1H, t, *J* = 7.2 Hz), 7.04 (1H, dd, *J* = 2.1, 7.2 Hz), 7.35-7.43 (3H, m), 7.64-7.74 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.1 (CH_2), 56.1 (CH_3), 78.0 (CH), 110.2 (CH), 118.5 (CH), 119.8 (CH), 126.7 (CH), 126.9 (C), 128.6 (CH), 129.7 (C), 129.9 (CH), 142.4 (C), 146.4 (C), 156.5 (C); HRMS (ESI-TOF) Calcd for $C_{16}H_{15}NNaO_3$ $[(M+Na)^+]$: 292.0944, Found: 292.0970. The enantiomeric excess of **4f** was determined by HPLC analysis (Daicel Chiralcel OZ-3, hexane/EtOH = 90/10 (v/v), UV 225 nm, flow rate = 1.0 mL/min, 35 °C, t_{minor} = 15.9 min, t_{major} = 18.7 min).

3-(4-Tolyl)-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4g): The reaction of **1g** (33.9 mg, 0.2 mmol) with **2** (14.9 mg, 0.1 mmol) gave colorless powder (27.4 mg, 98%, 48% ee) after column

chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.30 (CH_2Cl_2); mp 131-132 °C; $[\alpha]_D^{26}$ +15.9 (*c* 0.10, $CHCl_3$, 48% ee); IR (KBr) 3196, 1613, 1479, 1436, 1358, 1271, 1233, 1066, 908, 854, 817, 776, 534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (3H, s), 3.30 (1H, dd, *J* = 7.8, 16.8 Hz), 3.78 (1H, dd, *J* = 11.1, 16.8 Hz), 3.88 (3H, s), 5.88 (1H, brs), 5.98 (1H, dd, *J* = 7.8, 11.1 Hz), 6.79-6.87 (2H, m), 7.04 (1H, ddd, *J* = 0.6, 2.1, 7.2 Hz), 7.19 (2H, d, *J* = 8.1 Hz), 7.58 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_3), 42.2 (CH_2), 56.1 (CH_3), 77.8 (CH), 110.1 (CH), 118.5 (CH), 119.8 (CH), 126.7 (CH), 126.8 (C), 127.0 (C), 129.3 (CH), 140.2 (C), 142.4 (C), 146.4 (C), 156.5 (C); HRMS (ESI-TOF) Calcd for $C_{17}H_{17}NNaO_3$ [$(M+Na)^+$]: 306.1101, Found: 306.1101. The enantiomeric excess of **4g** was determined by HPLC analysis (Daicel Chiralpak AD-3, hexane/EtOH = 80/20 (v/v), UV 225 nm, flow rate = 0.5 mL/min, 35 °C, t_{major} = 40.4 min, t_{minor} = 51.9 min).

3-(3-Tolyl)-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4h): The reaction of **1h** (34.1 mg, 0.2 mmol) with **2** (14.9 mg, 0.1 mmol) gave colorless powder (27.5 mg, 98%, 53% ee) after column chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.33 (CH_2Cl_2); mp 154-155 °C; $[\alpha]_D^{24}$ +19.3 (*c* 0.10, $CHCl_3$, 53% ee); IR (KBr) 3323, 1614, 1483, 1439, 1339, 1279, 1232, 1183, 1068, 984, 950, 778, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.32 (1H, dd, *J* = 7.8, 16.8 Hz), 3.80 (1H, dd, *J* = 11.1, 16.8 Hz), 3.90 (3H, s), 5.83 (1H, brs), 5.99 (1H, dd, *J* = 7.8, 11.1 Hz), 6.80-6.88 (2H, m), 7.04 (1H, dd, *J* = 1.8, 6.9 Hz), 7.20 (1H, d, *J* = 7.5 Hz), 7.28 (1H, t, *J* = 7.5 Hz), 7.47 (1H, d, *J* = 7.5 Hz), 7.54 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (CH_3), 42.2 (CH_2), 56.1 (CH_3), 77.9 (CH), 110.1 (CH), 118.5 (CH), 119.8 (CH), 123.9 (CH), 127.0 (C), 127.3 (CH), 128.5 (CH), 129.6 (C), 130.8 (CH), 138.3 (C), 142.4 (C), 146.4 (C), 156.6 (C); HRMS (ESI-TOF) Calcd for $C_{17}H_{17}NNaO_3$ [$(M+Na)^+$]: 306.1101, Found: 306.1097. The enantiomeric excess of **4h** was determined by HPLC analysis (Daicel Chiralpak AD-3, hexane/EtOH = 80/20 (v/v), UV 225 nm, flow rate = 0.5 mL/min, 35 °C, t_{minor} = 27.7 min, t_{major} = 33.1 min).

3-(2-Tolyl)-5-(2-hydroxy-3-methoxy)phenyl-2-isoxazoline (4i): The reaction of **1i** (33.9 mg, 0.2 mmol) with **2** (14.8 mg, 0.1 mmol) gave colorless powder (26.8 mg, 96%, 54% ee) after column

chromatography purification (SiO_2 10 g, CH_2Cl_2/hexane = 50/50 – CH_2Cl_2). R_f = 0.37 (CH_2Cl_2); mp 94-96 °C; $[\alpha]_D^{25}$ +23.1 (*c* 0.10, $CHCl_3$, 54% ee); IR (KBr) 3322, 2933, 1590, 1476, 1438, 1340, 1271, 1229, 1078, 985, 849, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (3H, s), 3.36 (1H, dd, *J* = 7.5, 16.8 Hz), 3.85 (1H, dd, *J* = 11.1, 16.8 Hz), 3.88 (3H, s), 5.86 (1H, brs), 5.94 (1H, dd, *J* = 7.5, 11.1 Hz), 6.80-6.89 (2H, m), 7.06 (1H, dd, *J* = 1.8, 7.5 Hz), 7.17-7.33 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 (CH_3), 44.7 (CH_2), 56.1 (CH_3), 77.1 (CH), 110.1 (CH), 118.5 (CH), 119.8 (CH), 125.7 (CH), 127.0 (C), 128.8 (C), 128.8 (CH), 129.2 (CH), 131.4 (CH), 138.0 (C), 142.4 (C), 146.4 (C), 157.4 (C); HRMS (ESI-TOF) Calcd for $C_{17}H_{17}NNaO_3$ [$(M+Na)^+$]: 306.1101, Found: 306.1100. The enantiomeric excess of **4i** was determined by HPLC analysis (Daicel Chiralpak AD-3, hexane/EtOH = 90/10 (v/v), UV 225 nm, flow rate = 0.5 mL/min, 35 °C, t_{major} = 50.9 min, t_{minor} = 55.4 min).

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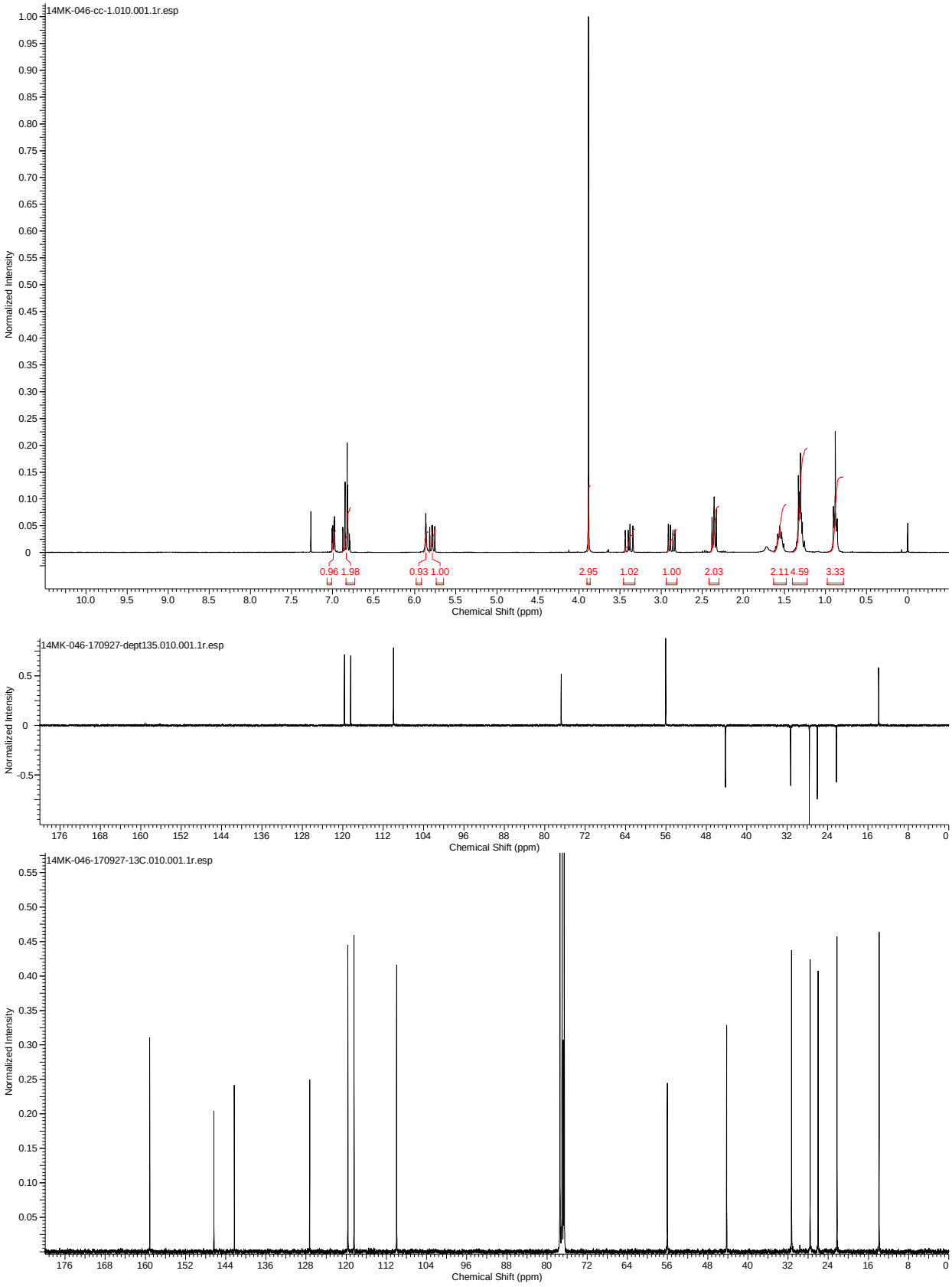
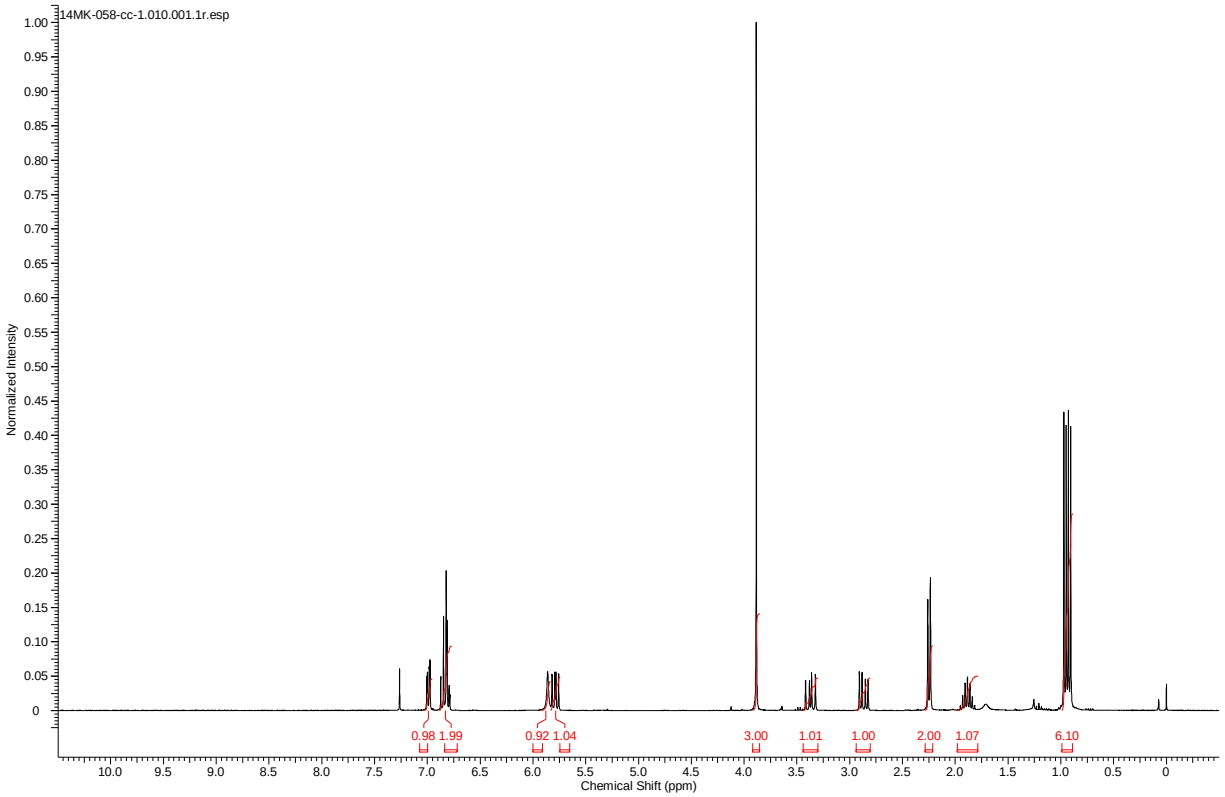
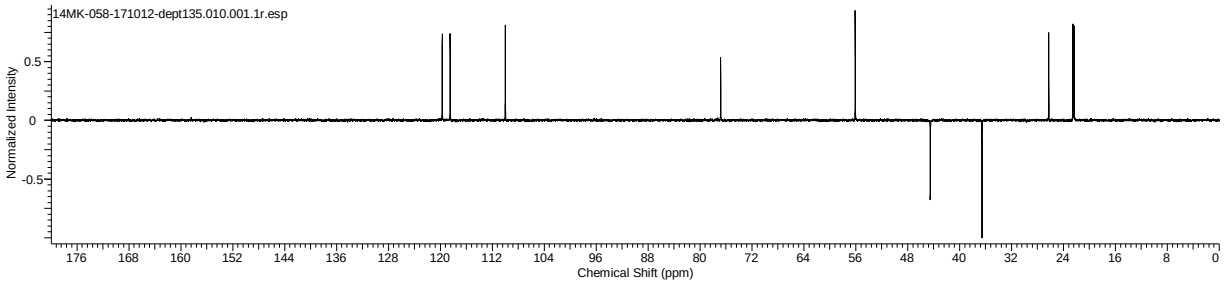
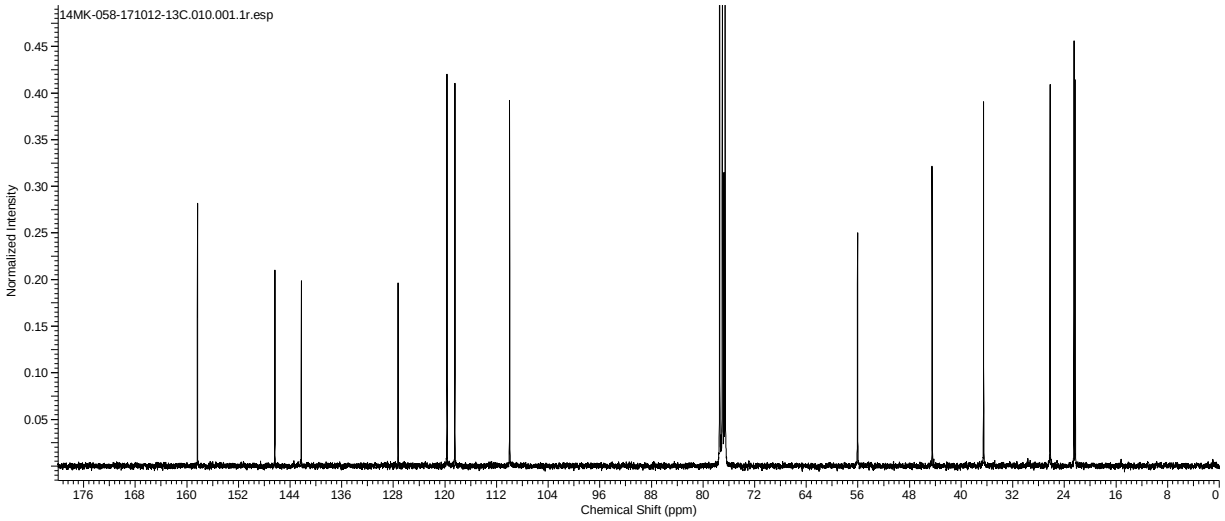
^{1}H & ^{13}C NMR Spectra of **4b**



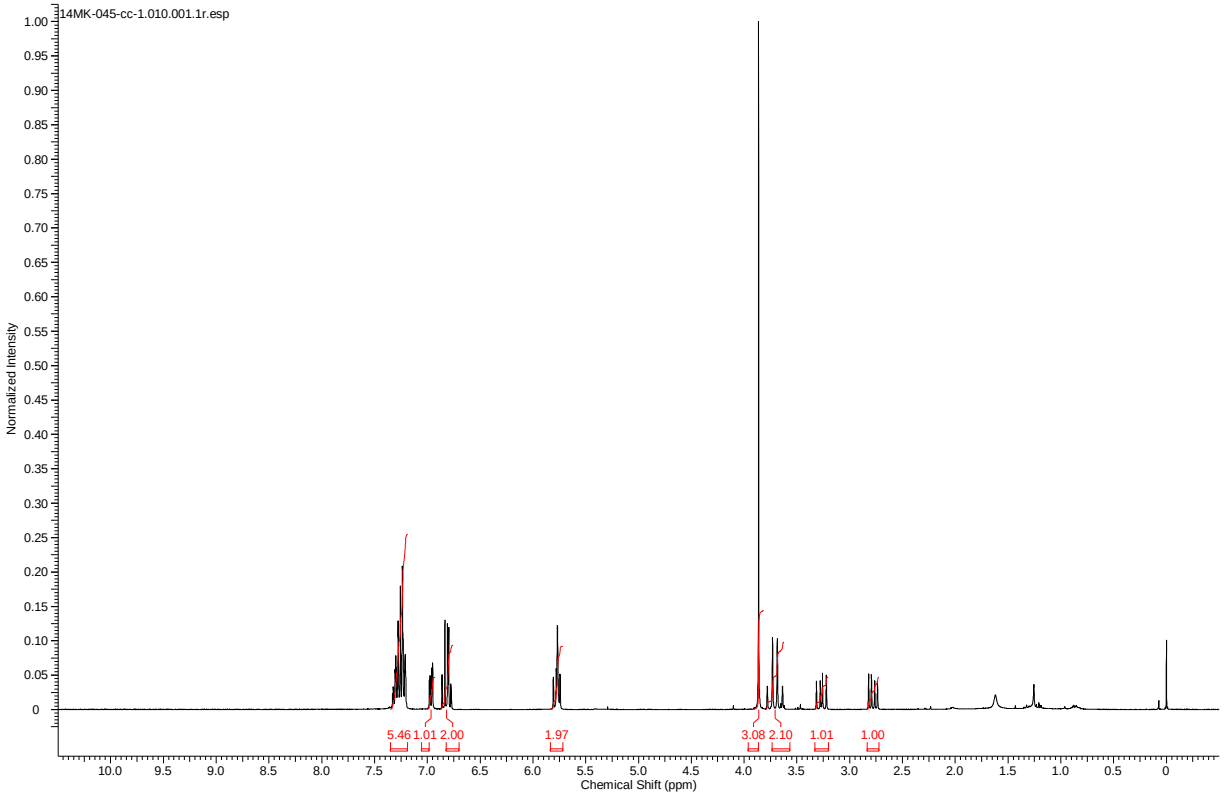
^{1}H & ^{13}C NMR Spectra of 4c

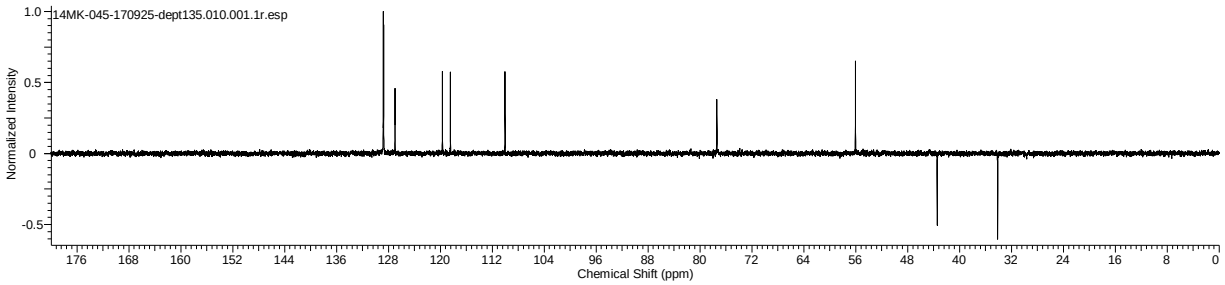


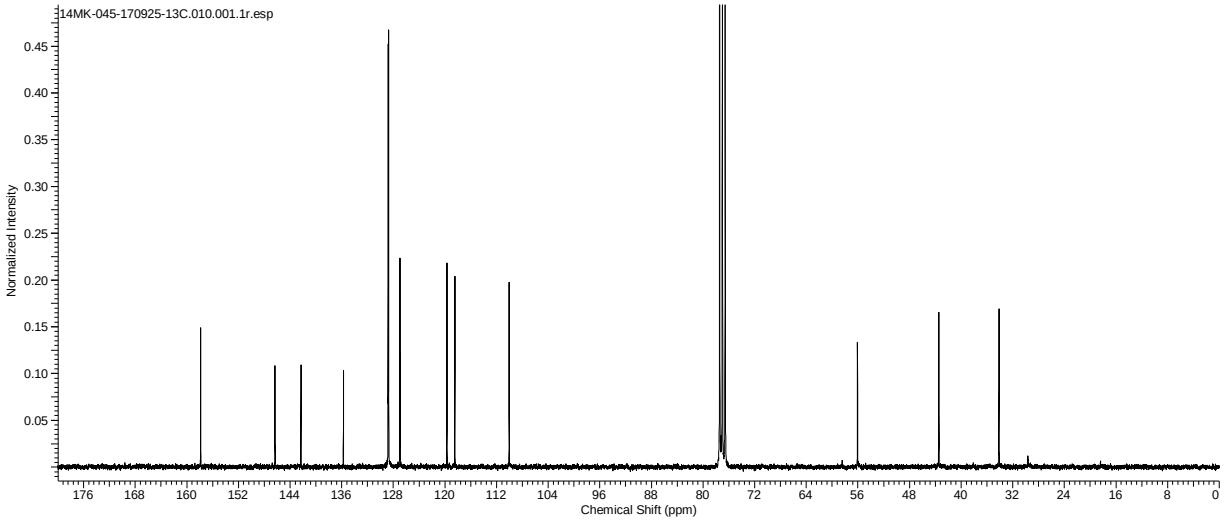




^{1}H & ^{13}C NMR Spectra of **4d**







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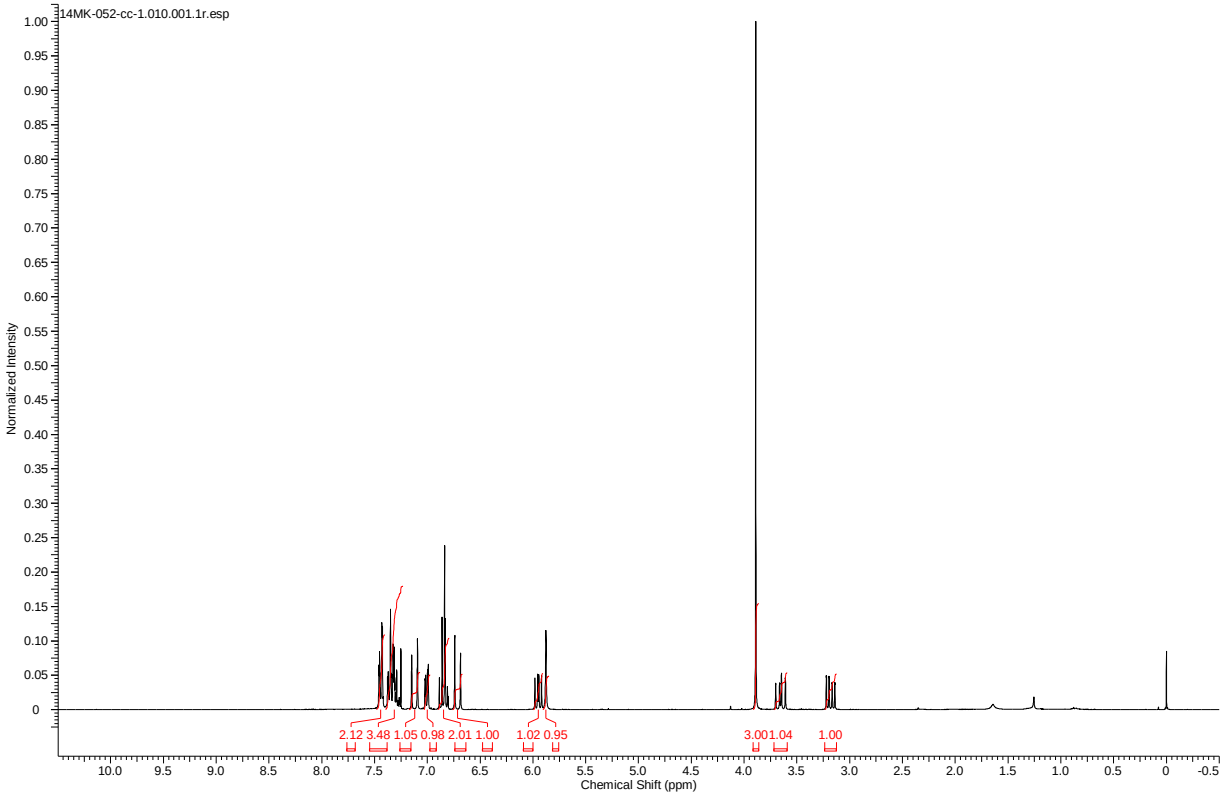
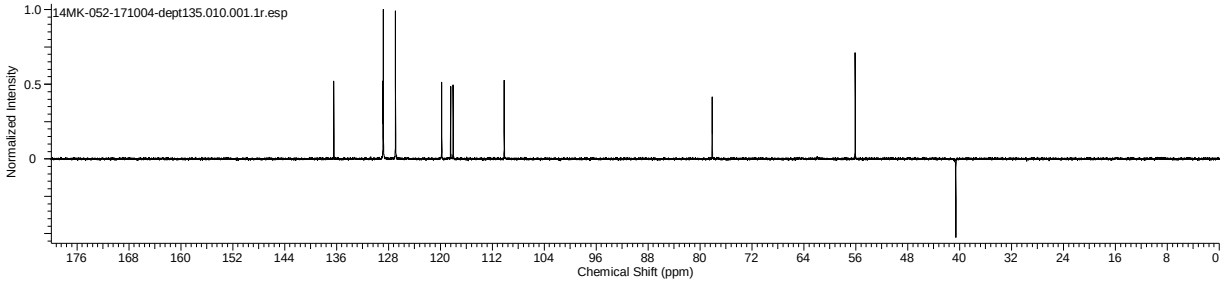
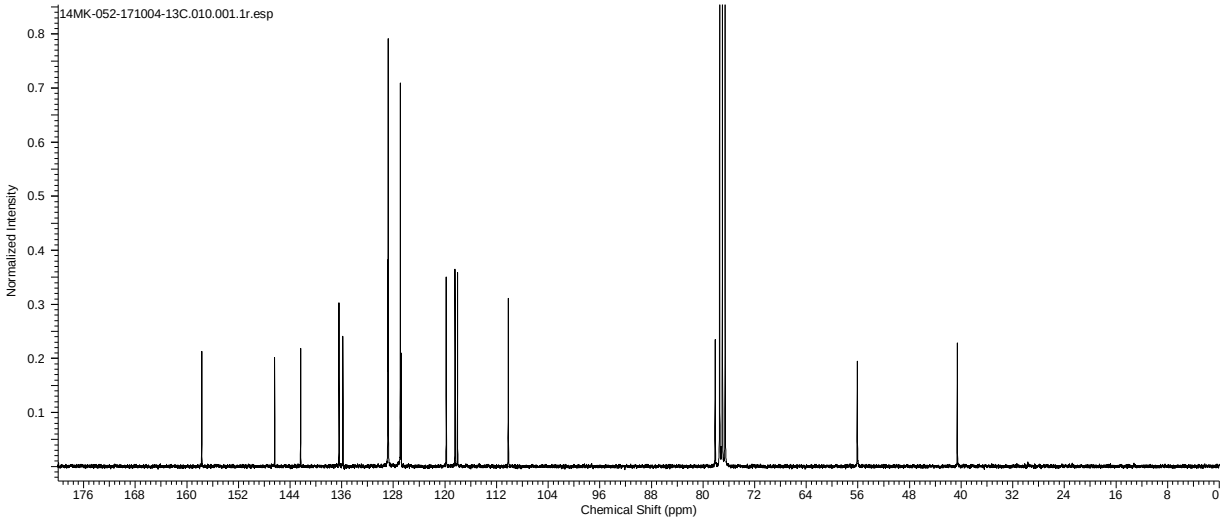
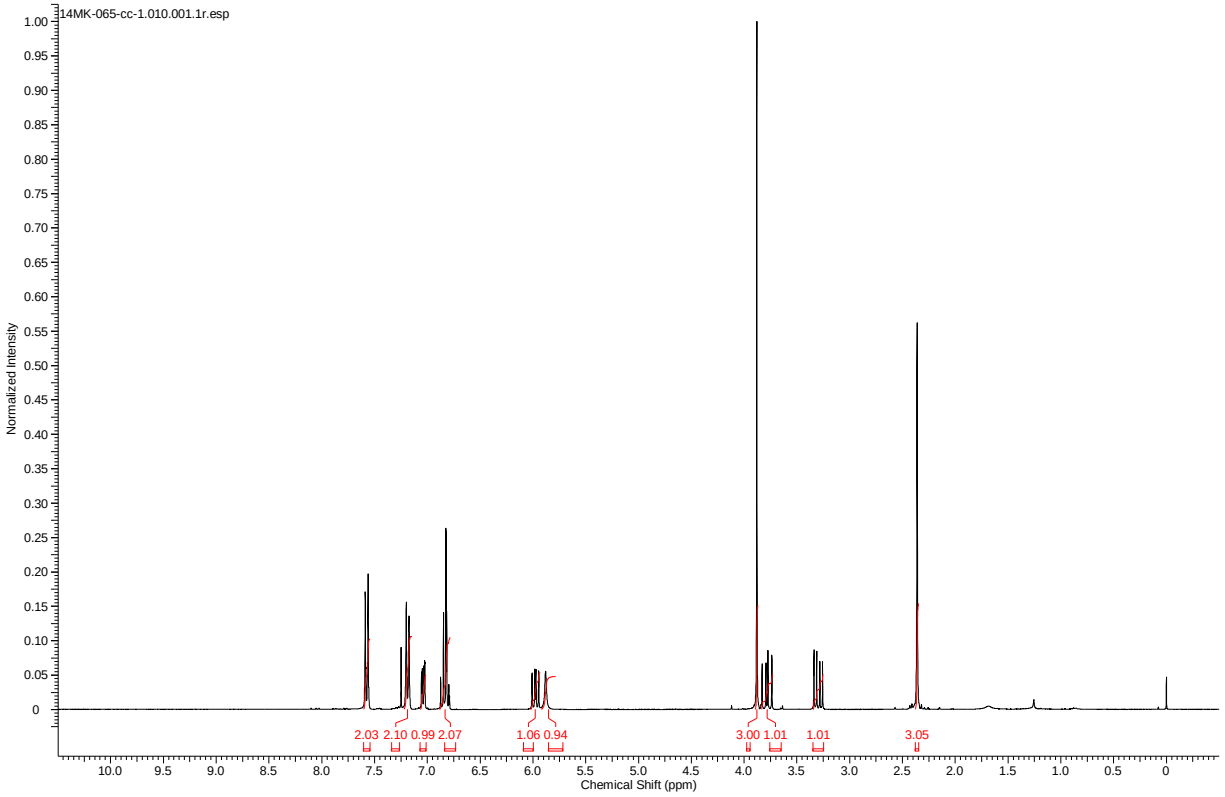
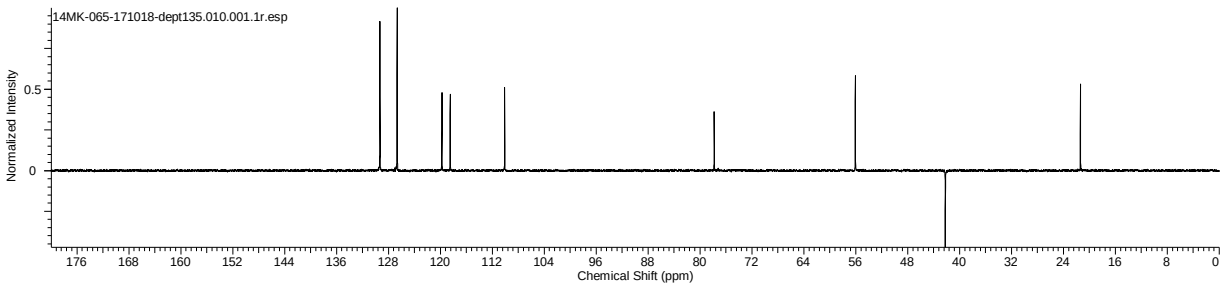


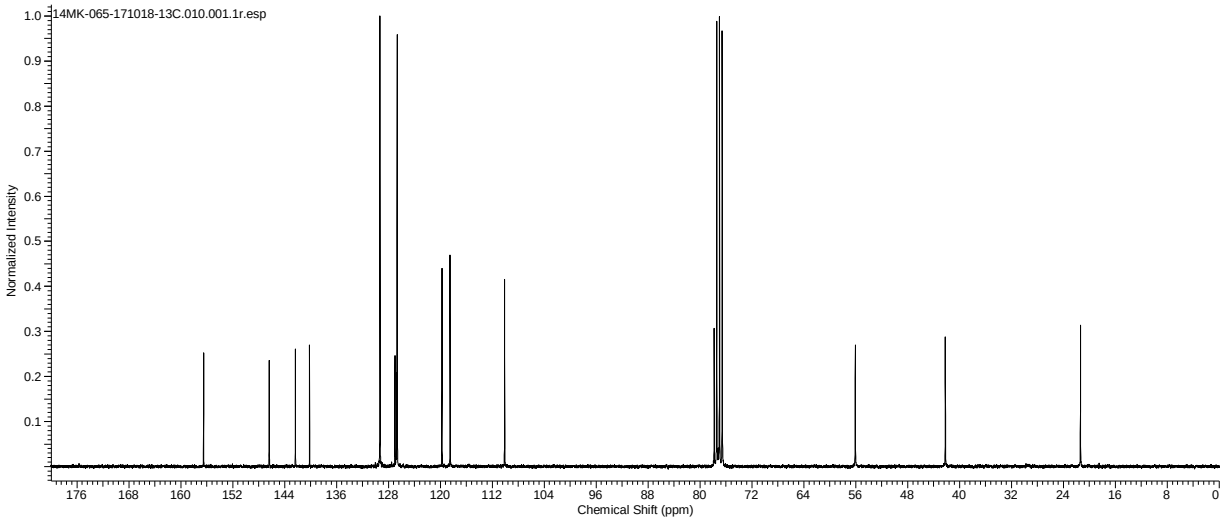




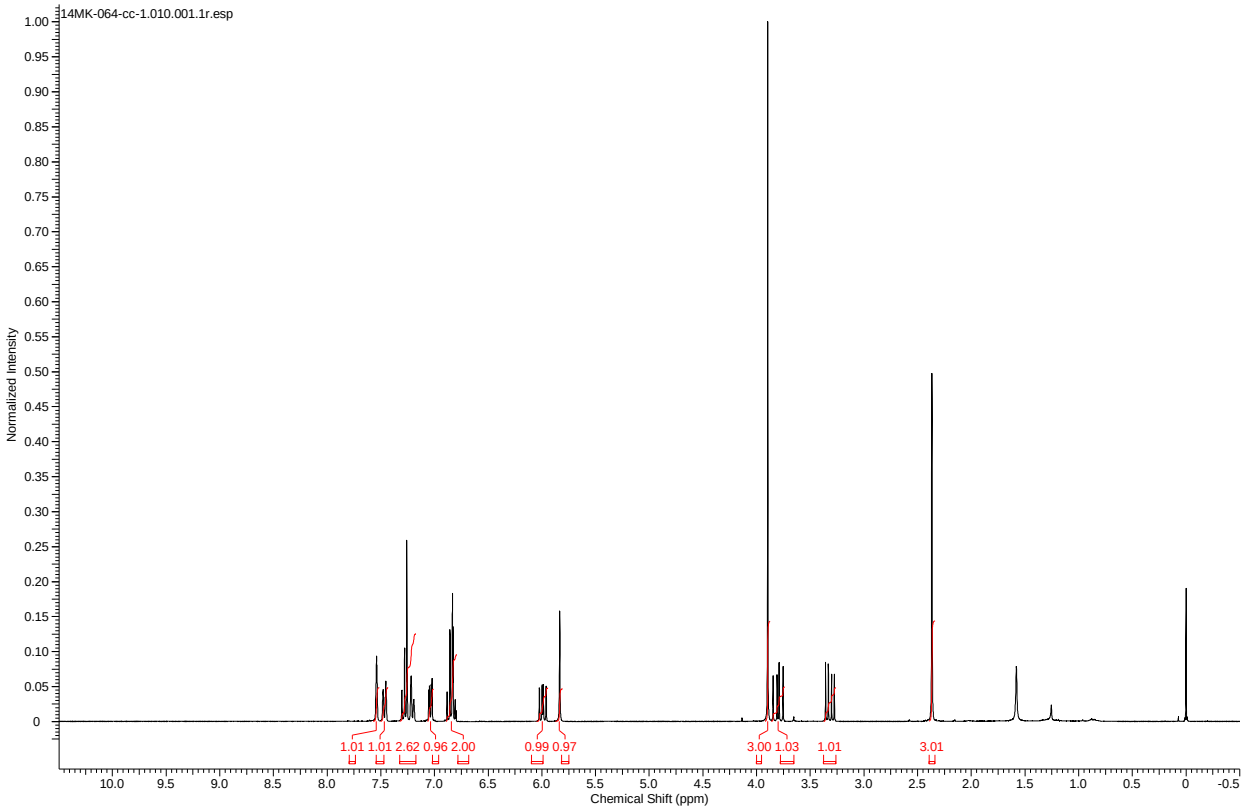
^{1}H & ^{13}C NMR Spectra of **4g**

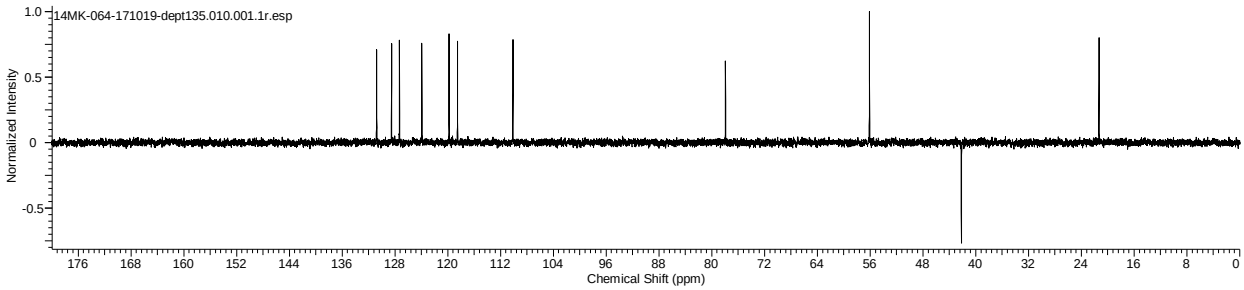


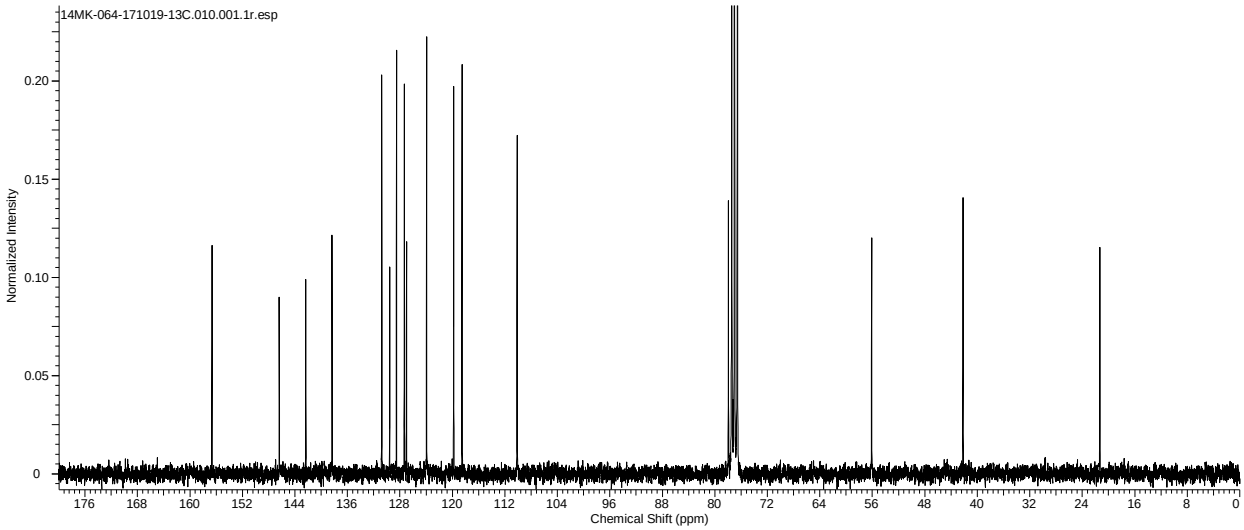




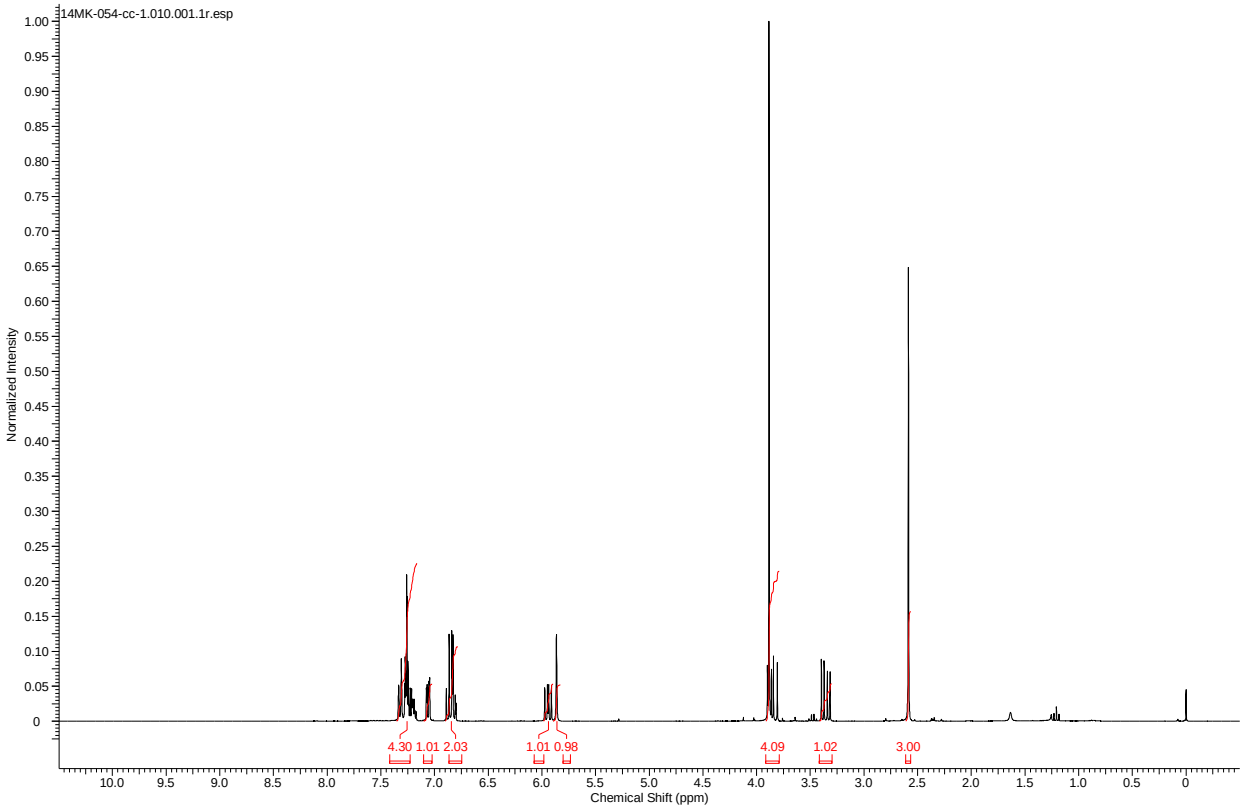
^{1}H & ^{13}C NMR Spectra of **4h**

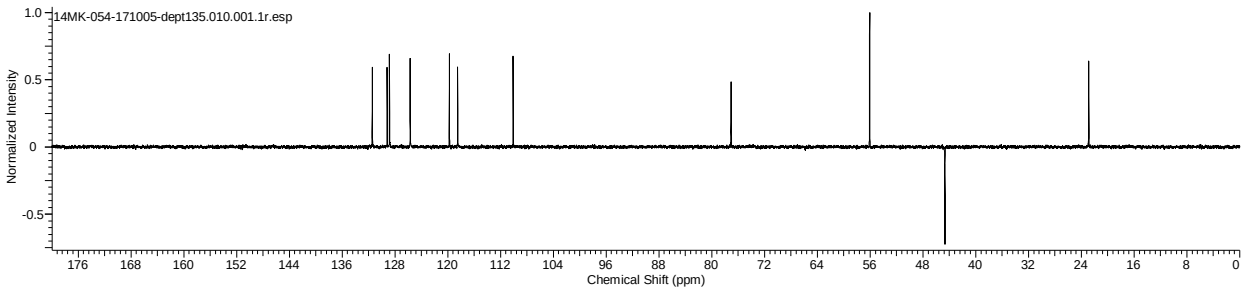


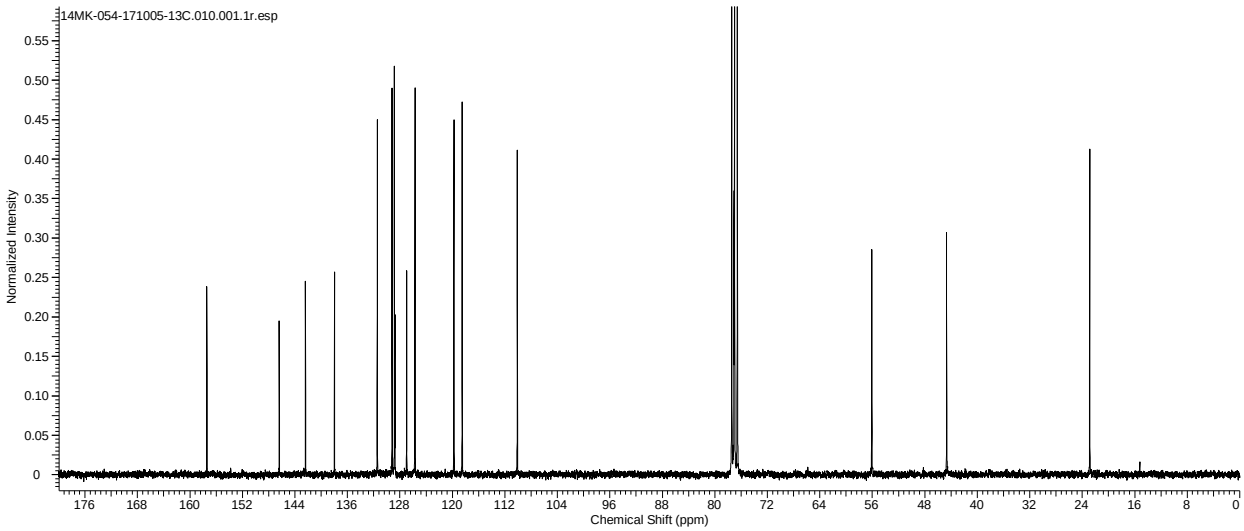




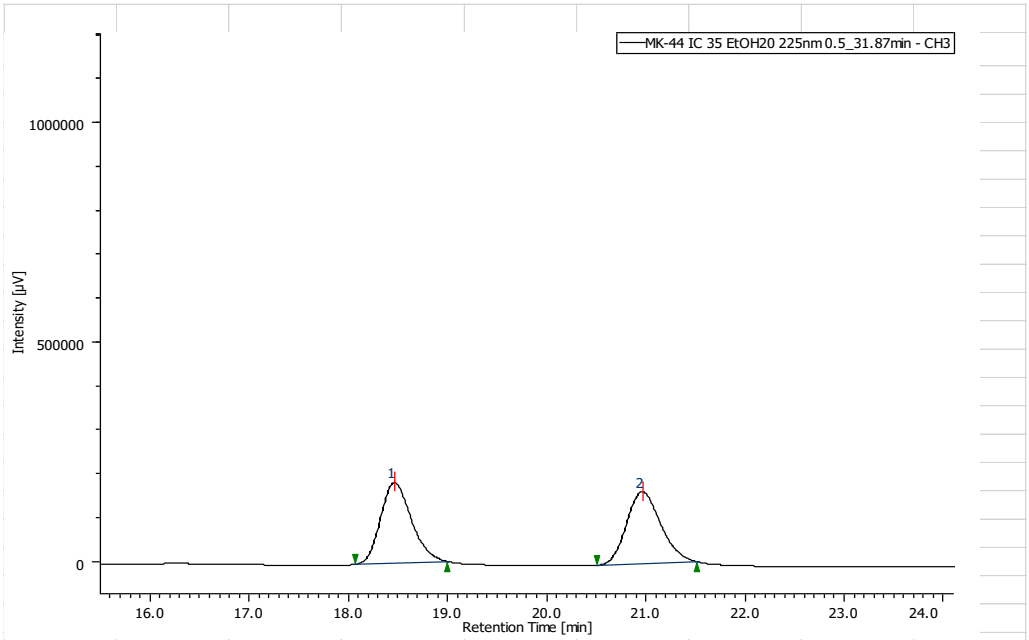
^{1}H & ^{13}C NMR Spectra of **4i**





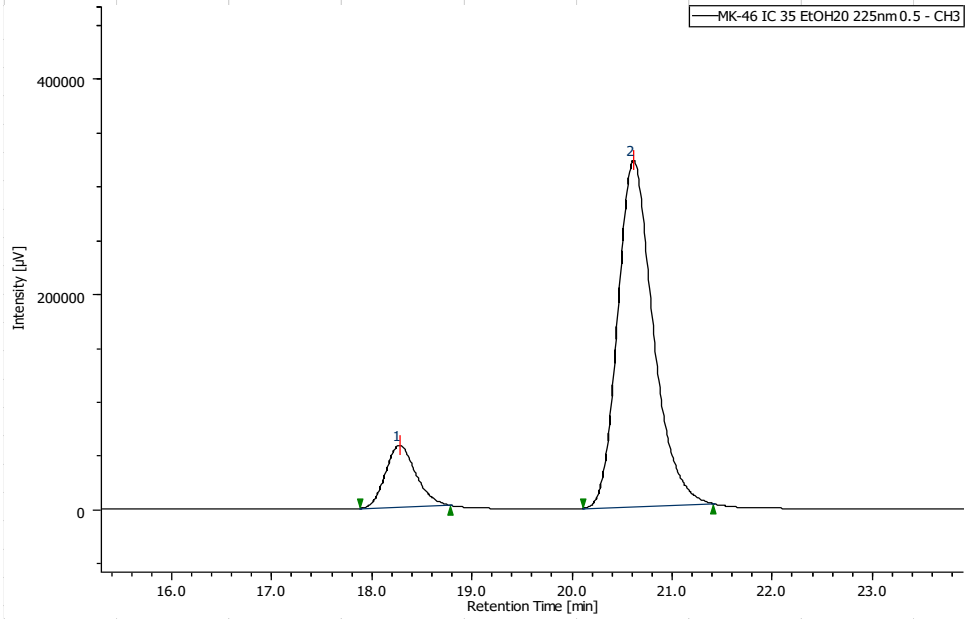


HPLC Trace of **4b**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	18.458	3945310	183521	50.212
2	3	20.958	3926259	164177	49.879

Racemate

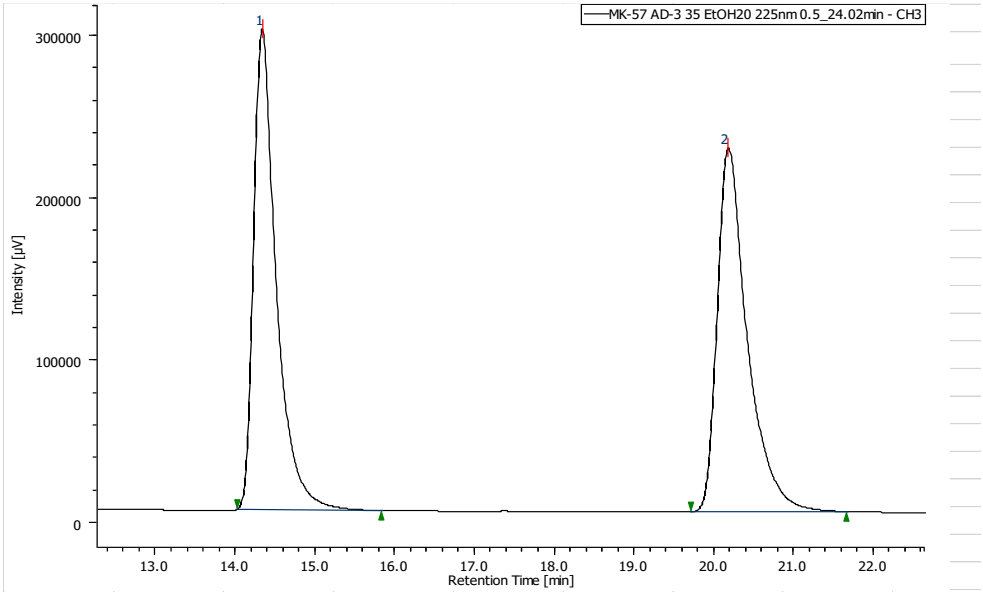


# Peak	CH	tR (min)	Area	Height	Area%
1	3	18.275	1209972	57209	13.298
2	3	20.608	7889247	320667	86.702

73% ee

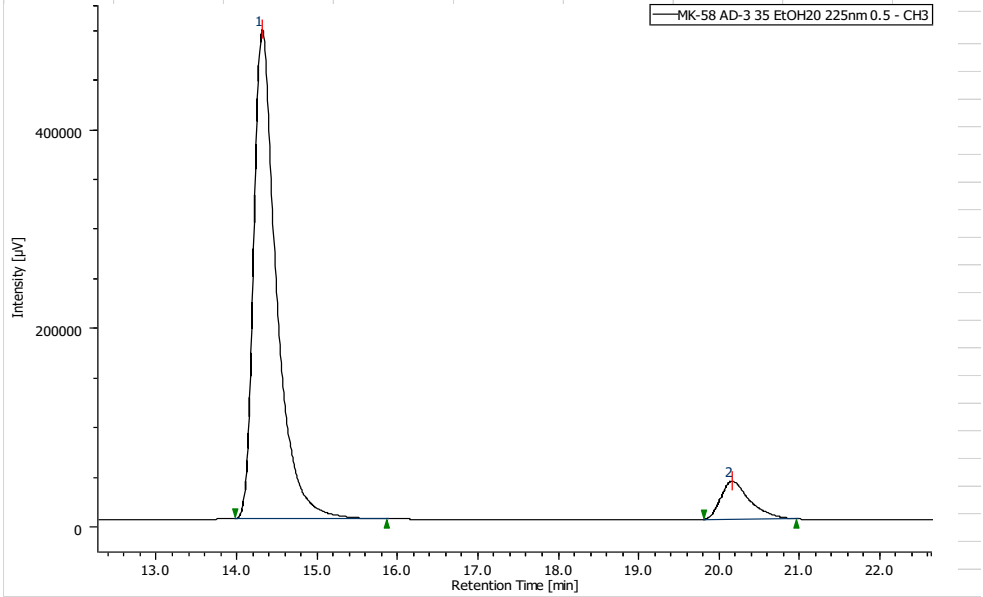
Daicel Chiralpak IC, hexane/EtOH, 80:20, v/v, detector: UV 225 nm, flow rate = 0.5 mL/min, 35 °C

HPLC Trace of **4c**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	14.342	5817508	295321	49.888
2	3	20.175	5843709	223391	50.112

Racemate

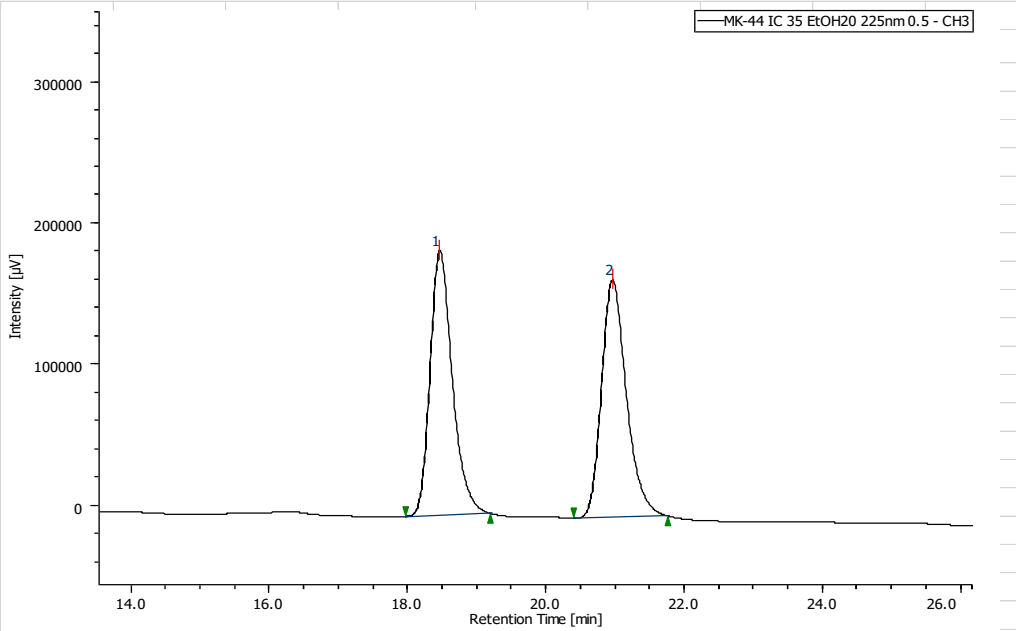


# Peak	CH	tR (min)	Area	Height	Area%
1	3	14.317	9682898	491959	91.059
2	3	20.150	950759	38108	8.941

82% ee

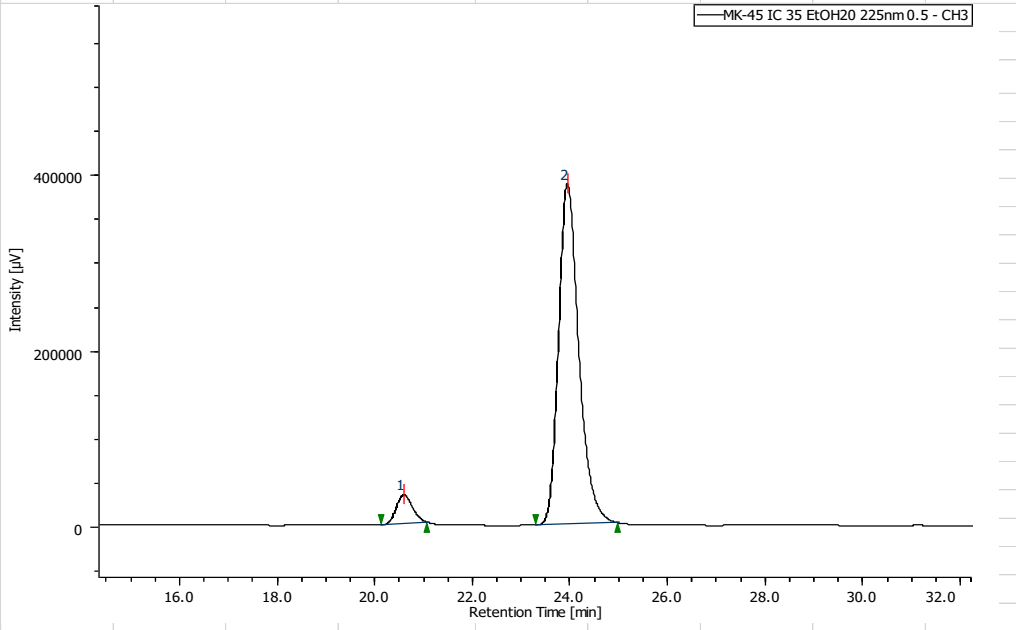
Daicel Chiralpak AD-3, hexane/EtOH, 80:20, v/v, detector: UV 225 nm, flow rate = 0.5 mL/min, 35 °C

HPLC Trace of **4d**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	18.458	4171374	186640	49.749
2	3	20.958	4205923	167782	50.206

Racemate

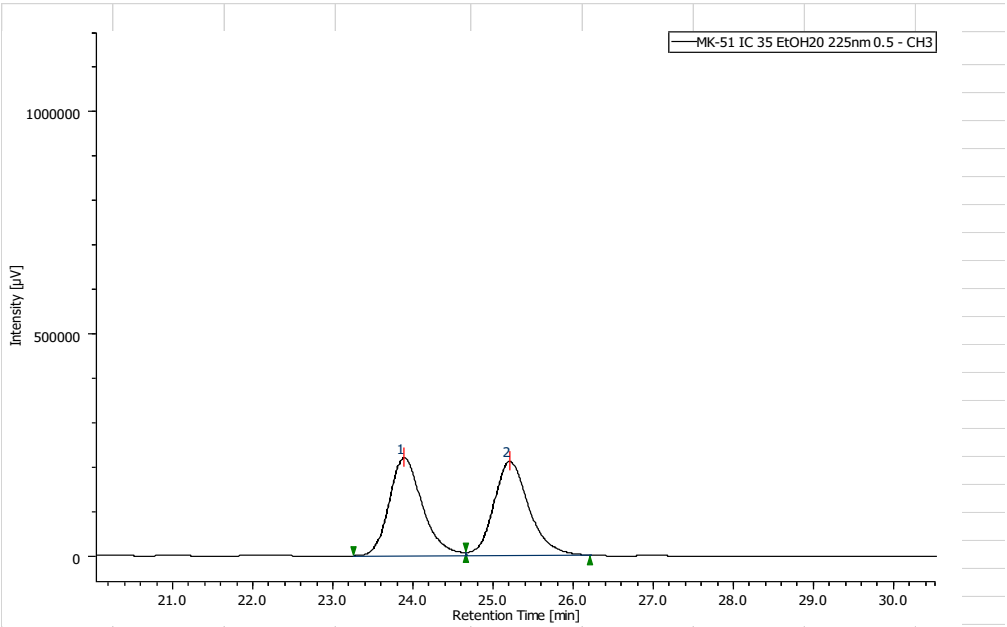


# Peak	CH	tR (min)	Area	Height	Area%
1	3	20.592	761360	32888	6.383
2	3	23.933	11165901	387123	93.617

87% ee

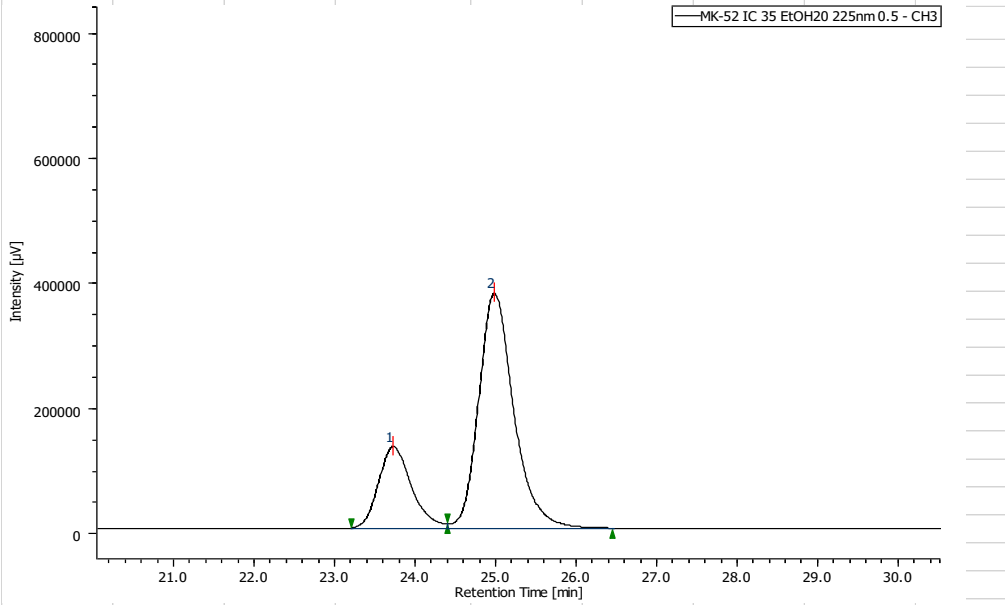
Daicel Chiralpak IC, hexane/EtOH, 80:20, v/v, detector: UV 225 nm, flow rate = 0.5 mL/min, 35 °C

HPLC Trace of **4e**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	23.883	6326547	219644	49.631
2	3	25.200	6420535	210529	50.369

Racemate

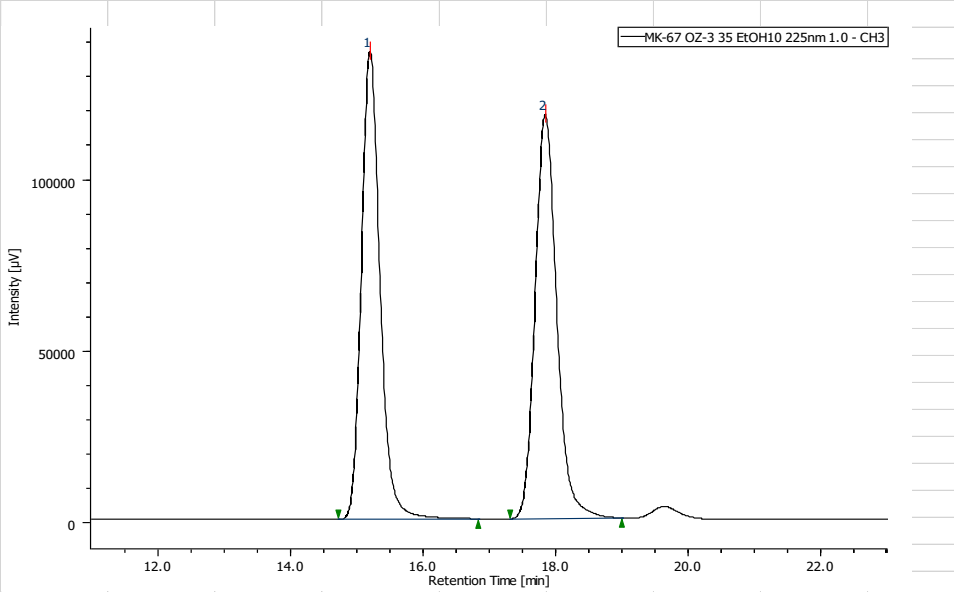


# Peak	CH	tR (min)	Area	Height	Area%
1	3	23.725	3684269	130187	24.538
2	3	24.975	11330238	374533	75.462

51% ee

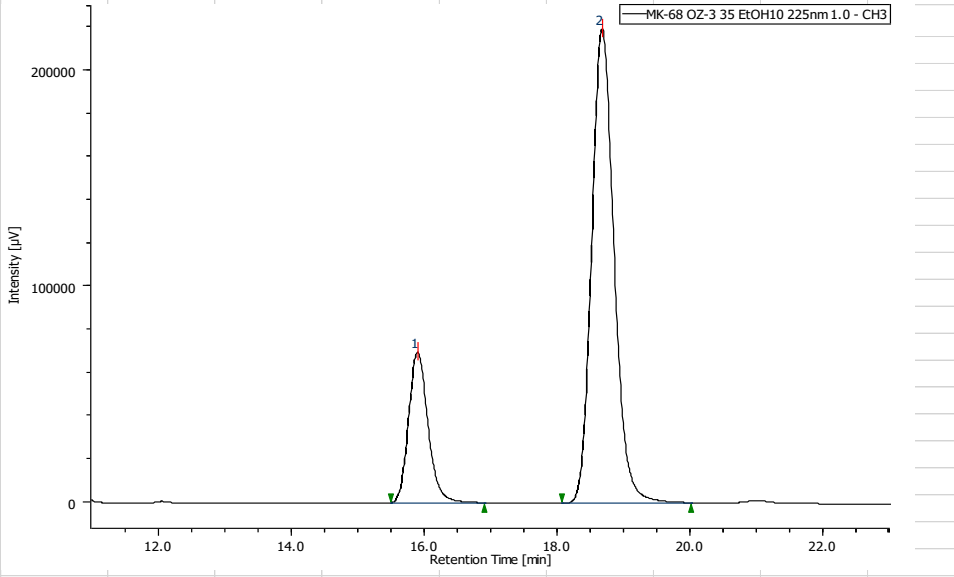
Daicel Chiralpak IC, hexane/EtOH, 80:20, v/v, detector: UV 225 nm, flow rate = 0.5 mL/min, 35 °C

HPLC Trace of **4f**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	15.200	2663586	136089	49.921
2	3	17.842	2671983	117507	50.079

Racemate

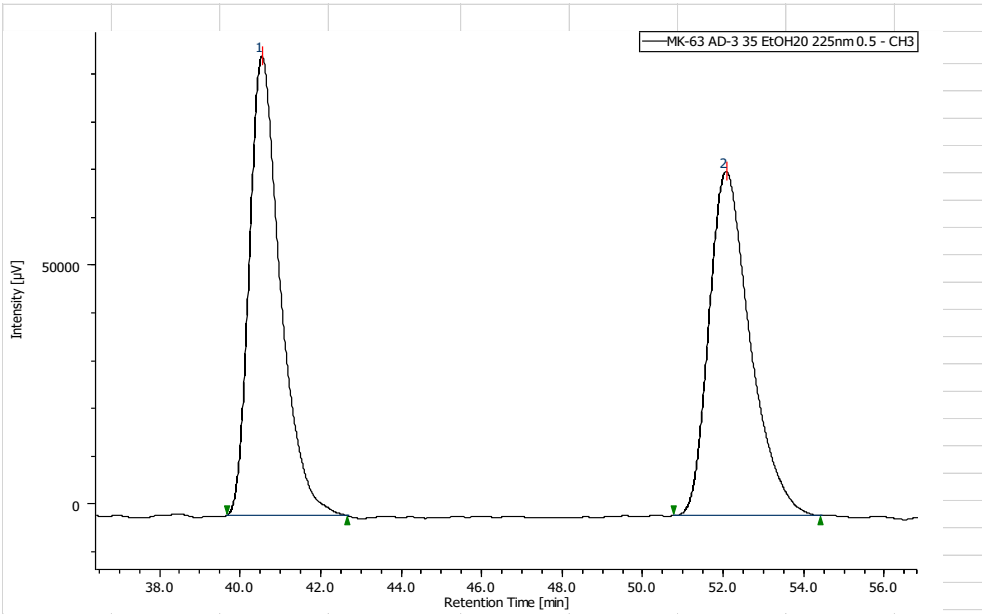


# Peak	CH	tR (min)	Area	Height	Area%
1	3	15.900	1425404	69821	21.686
2	3	18.675	5147573	219635	78.314

57% ee

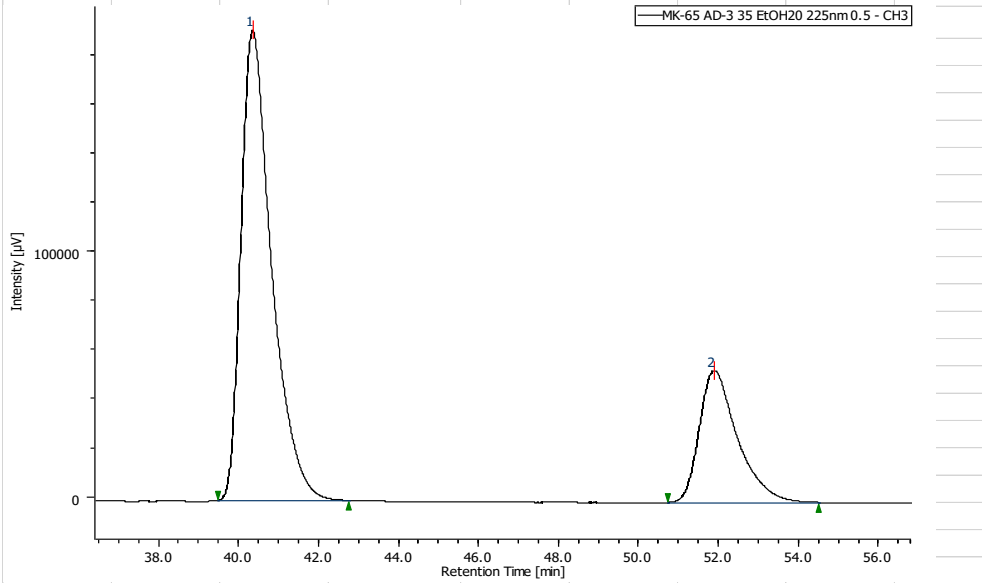
Daicel Chiralcel OZ-3, hexane/EtOH, 90:10, v/v, detector: UV 225 nm, flow rate = 1.0 mL/min, 35 °C

HPLC Trace of **4g**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	40.542	5160805	96066	50.241
2	3	52.050	5111216	71933	49.759

Racemate

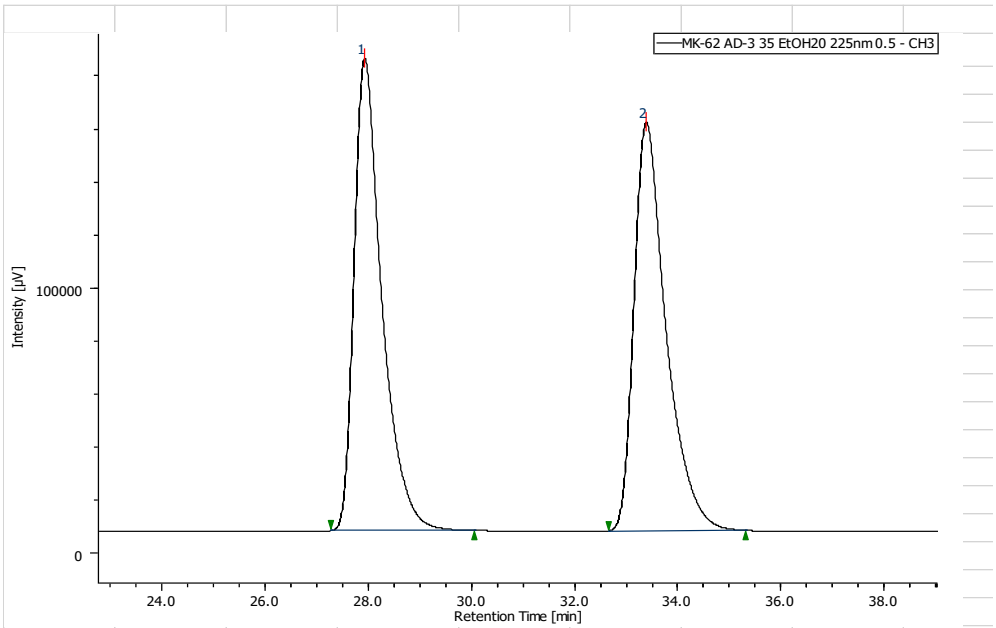


# Peak	CH	tR (min)	Area	Height	Area%
1	3	40.350	10154260	191168	74.126
2	3	51.875	3544360	53597	25.874

48% ee

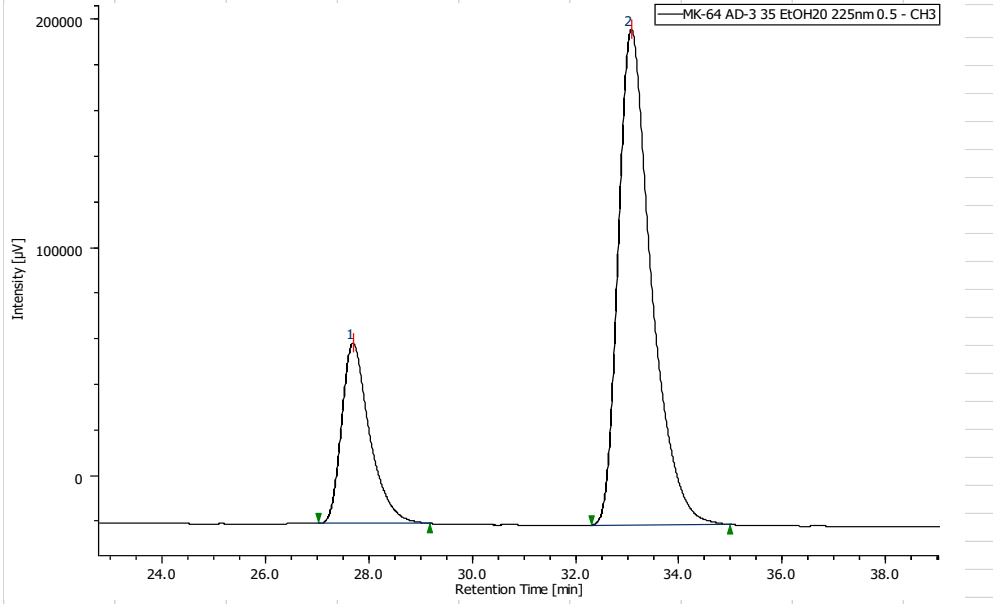
Daicel Chiralpak AD-3, hexane/EtOH, 80:20, v/v, detector: UV 225 nm, flow rate = 0.5 mL/min, 35 °C

HPLC Trace of **4h**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	27.933	6629908	177623	50.008
2	3	33.375	6627902	153525	49.992

Racemate

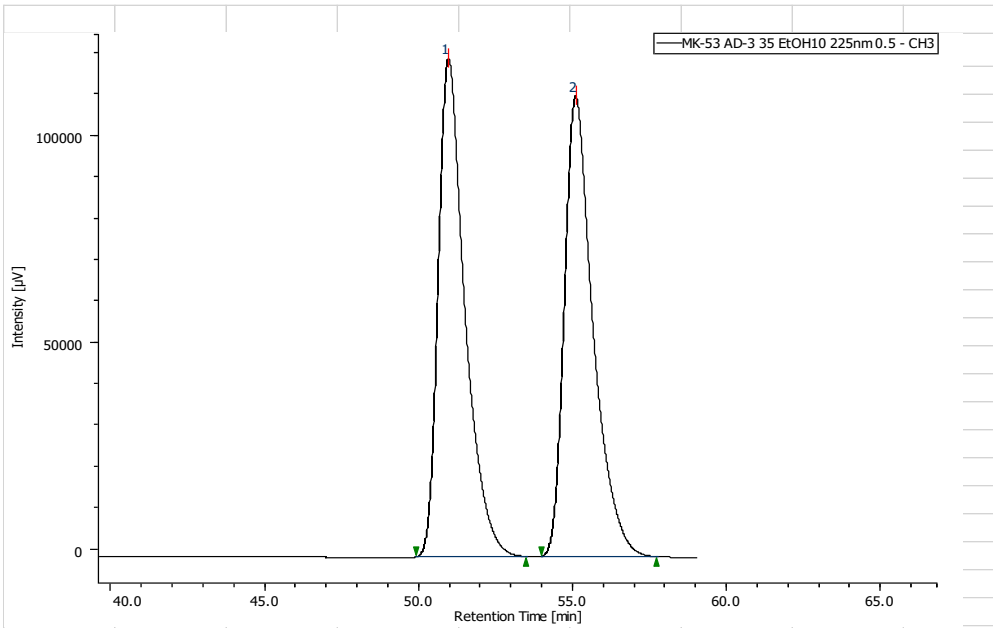


# Peak	CH	tR (min)	Area	Height	Area%
1	3	27.692	2974307	79004	23.669
2	3	33.058	9591876	216699	76.331

53% ee

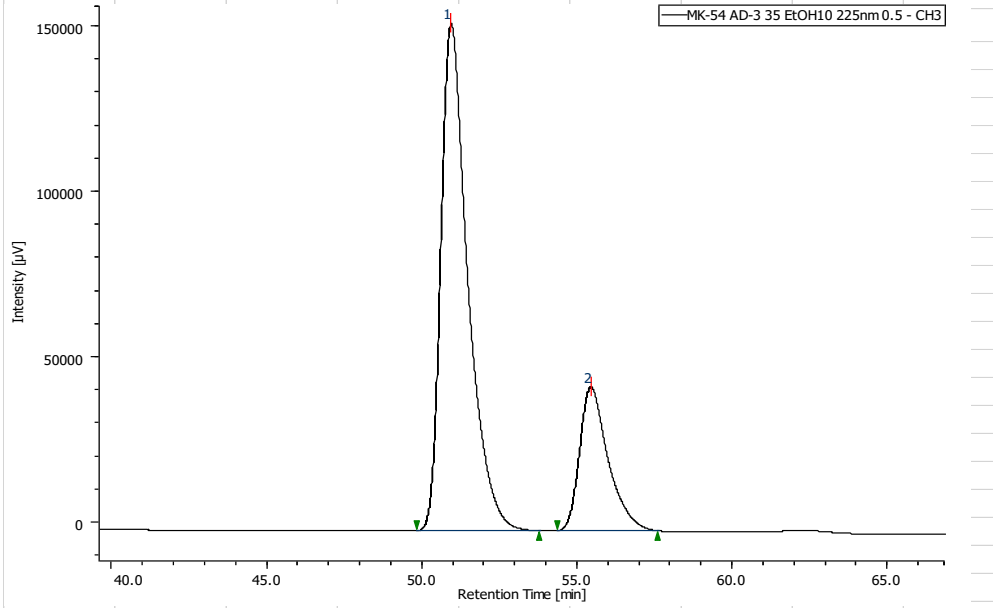
Daicel Chiralpak AD-3, hexane/EtOH, 80:20, v/v, detector: UV 225 nm, flow rate = 0.5 mL/min, 35 °C

HPLC Trace of **4i**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	50.958	7221220	120257	50.052
2	3	55.083	7206276	111241	49.948

Racemate



# Peak	CH	tR (min)	Area	Height	Area%
1	3	50.933	9228364	153016	76.859
2	3	55.433	2778439	43420	23.141

54% ee

Daicel Chiralpak AD-3, hexane/EtOH, 90:10, v/v, detector: UV 225 nm, flow rate = 0.5 mL/min, 35 °C