CuH-Catalyzed Enantioselective 1,2-Reductions of α,β-Unsaturated Ketones

Supporting Information

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Table of Contents

I. General Information

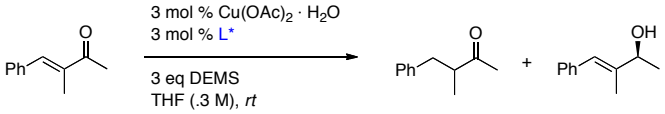
Unless otherwise noted, all reactions were performed in oven-dried glassware under an atmosphere of argon. Low temperature reactions were cooled in an acetone or isopropanol bath, hold at the indicated temperature using a cryostat. DEMS (Alfa Aesar, Stock # A10153) was used as received without further purification. THF was freshly distilled from benzophenone-sodium ketyl. Et_2O (anhydrous, Fisher, Stock # E138-20) was used as received. Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F_{254} plates (Merck, 0.25 mm thick). The developed chromatogram was analyzed by UV lamp (254 nm) or aqueous potassium permanganate ($KMnO_4$). Flash chromatography was either performed in glass columns using Silica Flash® P60 (SiliCycle, 40-63 μm), or on pre-packed SINGLE StEP™ columns (standard silica, Thomson) using a BIOTAGE SP-4® system. GCMS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column a HP-5MS cross-linked 5% phenylmethylpolysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min. Retention times (t_R) refer to the following temperature program: 50°C for 5 min; heating rate 20°C/min; 300°C for 20 min; injection temperature 250°C; detection temperature 280°C. ^1H and ^{13}C spectra were recorded at 22°C on a Varian UNITY INOVA Avance 400 MHz or a Varian UNITY INOVA 500 MHz. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. High resolution mass analyses were obtained using a VG70 double-focusing magnetic sector instrument (VG Analytical) for EI and a PE Sciex QStar Pulsar quadrupole/TOF instrument (API) for ESI.

II. Optimization conditions for regio- and stereocontrolled 1,2-reductions

Optimization procedure for the enantioselective CuH-catalyzed 1,2-reduction of α-substituted enones:

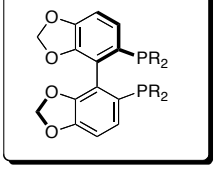
A conical 3 mL microwave vial containing a conical stir bar was charged with fine powdered $Cu(OAc)_2 \cdot H_2O$ (0.5 mg, 3 mol %, 3 μmol) and ligand (3 mol %, 3 μmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, 0.2 mL solvent was added via syringe. At rt, silane (0.3 mmol) was introduced and stirred for 10 min. The vial was then placed into a pre-cooled acetone bath at the indicated temperature and stirred for an additional 5 min. The substrate (16 mg, 0.1 mmol) was subsequently introduced *via* syringe. The side of the reaction vial was rinsed with Et_2O (2 x 50 μL). Conversion was monitored by TLC and the reaction was quenched at the indicated temperature after the indicated time by the addition of 0.5 mL sat. NH_4F/MeOH. The reaction vial was taken out of the cooling bath and warmed to rt. After filtration through SiO_2, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR and purified by column chromatography on silica gel. The purified product was analyzed by analytical HPLC on a chiral stationary phase for the determination of *ee*.

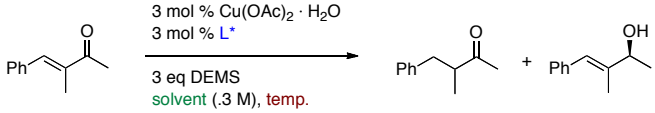
initial screening

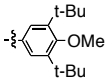


entry	Ligand	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
1	BDP	100 (*10 h*)	60	9	*n.d.*	*RM656*
2	SL-J002-1 "*JosiPhos*"	100 (*4.5 h*)	trace	90	50	*RM590*
3	SL-W001-1 "*WalPhos*"	100 (*4.5 h*)	trace	74	17	*RM586*
4	SL-T001-1 "*TaniaPhos*"	100 (*4.5 h*)	15	66	11	*RM587*
5	(*R*)-DTBM-SEGPHOS	> 90 (*4.5 h*)	trace	78	75	*RM588*
6	(*S*)-3,5-Xyl-MeO-BIPHEP	100 (*4.5 h*)	trace	85	72	*RM589*

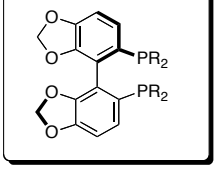
(*R*)-SEGPHOS

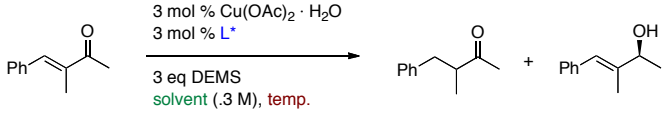


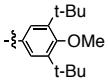


	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
R = Ph	(*R*)-SEGPHOS	THF	-25	30 (*96 h*)	trace	19	80	*RM610*
R = ^{i}Pr	(*R*)-iPr-SEGPHOS	THF	-25	5 (*96 h*)	*n.d.*	< 5	4	*RM614*
PR_2 = 	(*R*)-MP2-SEGPHOS	THF	-25	30 (*96 h*)	trace	19	59	*RM612*
PR_2 = 	(*R*)-P3-SEGPHOS	THF	-25	40 (*96 h*)	trace	21	62	*RM613*
R = 	(*R*)-DM-SEGPHOS	THF	-25	100 (*8 h*)	trace	70	81	*RM611*
R = 	(*R*)-DTBM-SEGPHOS	THF	*rt*	> 90 (*4.5 h*)	trace	78	75	*RM588*
			-25	100 (*5.5 h*)	1	87	86	*RM592*
			-50	100 (*11 h*)	trace	86	89	*RM623*
			-78	0 (*36 h*)	-	-	-	*RM599*

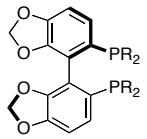
(*R*)-SEGPHOS

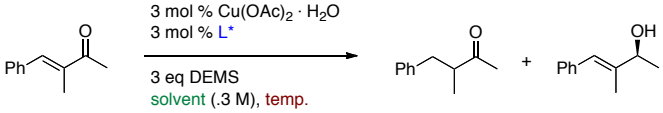


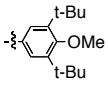


	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
R = 	(*R*)-DTBM-SEGPHOS	THF	*rt*	> 90 (*4.5 h*)	trace	78	75	*RM588*
			-25	100 (*5.5 h*)	1	87	86	*RM592*
			-50	100 (*11 h*)	trace	86	89	*RM623*
			-78	0 (*36 h*)	-	-	-	*RM599*
		toluene	-25	20 (*21 h*)	trace	5	*n.d.*	*RM604*
		DCM	-25	10 (*21 h*)	trace	1	*n.d.*	*RM605*
		hexanes	-25	40 (*21 h*)	trace	20	90	*RM606*
		DMF	-25	0 (*21 h*)	-	-	-	*RM607*
		MeOH	-25	0 (*21 h*)	-	-	-	*RM608*

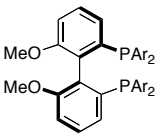
(*R*)-SEGPHOS

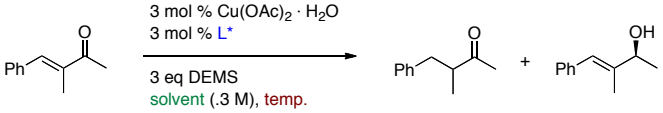




	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
R = 	(*R*)-DTBM-SEGPHOS	MTBE	-25	100 *(9 h)*	trace	86	88	*RM617*
		2-MeTHF	-25	< 10 *(21 h)*	trace	< 5	*n.d.*	*RM618*
		CPME	-25	100 *(21 h)*	2	83	85	*RM619*
		DME	-25	100 *(9 h)*	3	81	83	*RM620*
		Et_2O	-25	100 *(6 h)*	2	83	91	*RM609*
			-35	25 *(80 h)*	trace	12	87	*RM674*
			-50	< 5 *(26 h)*	*n.d.*	*n.d.*	*n.d.*	*RM669*
			-78	< 5 *(26 h)*	*n.d.*	*n.d.*	*n.d.*	*RM671*
	(*S*)-DTBM-SEGPHOS	Et_2O	-25	100 *(5 h)*	trace	87	88	*RM703*

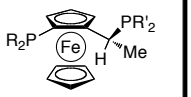
(*R*)-MeO-BIPHEP

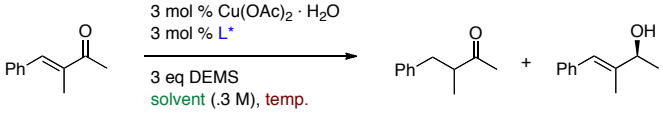




	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
R = 	(*S*)-3,5-Xyl-MeO-BIPHEP	THF	-25	100 *(21 h)*	trace	83	85	*RM593*
		Et_2O	-25	100 *(8.5 h)*	trace	96	89	*RM740*
R = 	(*S*)-3,5-iPr-MeO-BIPHEP	THF	-25 to *rt*	< 5 *(22 h)*	*n.d.*	*n.d.*	*n.d.*	*RM736*
		Et_2O	-25 to *rt*	< 5 *(20 h)*	*n.d.*	*n.d.*	*n.d.*	*RM742*
R = 	(*S*)-3,4,5-Me-MeO-BIPHEP	THF	-25	100 *(8 h)*	trace	76	84	*RM615*
		Et_2O	-25	100 *(8.5 h)*	trace	95	91	*RM741*
			-45	< 5 *(28 h)*	*n.d.*	*n.d.*	*n.d.*	*RM747*
R = 	(*R*)-3,5-tBu-4-MeO-MeO-BIPHEP	THF	-25	100 *(5 h)*	trace	98	89	*RM737*
		Et_2O	-25	100 *(9 h)*	trace	99	90	*RM743*
			-45	< 10 *(36 h)*	trace	5	86	*RM748*

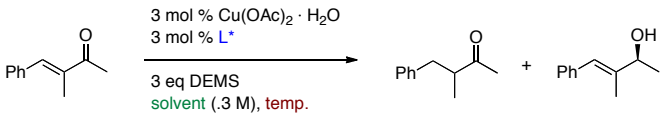
JOSIPHOS

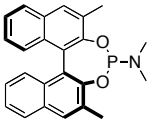
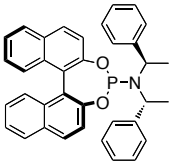




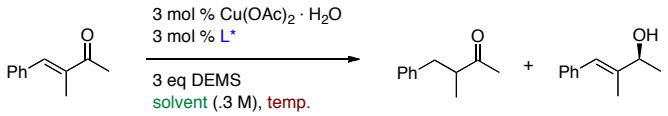
	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
R = Ph, R' = *t*-Bu	SL-J002-1	THF	*rt*	100 (*4.5 h*)	trace	90	50	*RM590*
		Et_2O	-25	70 (*32 h*)	trace	43	69	*RM594*
R = Cy, R' = Ph	SL-J004-1	Et_2O	-25	40 (*20 h*)	trace	33	42	*ZB3-208*
R = Ph, R' = 3,5-Xylyl	SL-J005-1	Et_2O	-25	100 (*20 h*)	trace	81	52	*ZB3-209*
R = 3,5-CF_3Ph, R' = 3,5-Xylyl	SL-J008-1	Et_2O	-25	100 (*20 h*)	trace	82	3	*ZB3-210*
R = 4-CF_3Ph, R' = *t*-Bu	SL-J011-1	Et_2O	-25	40 (*20 h*)	trace	31	57	*ZB3-211*
R = 3,5-Me-4-MeO, R' = *t*-Bu	SL-J013-1	Et_2O	-25	100 (*20 h*)	trace	81	54	*ZB3-212*
R = 2-Furyl, R' = 3,5-Xylyl	SL-J015-1	Et_2O	-25	100 (*40 h*)	4	85	9	*RM724*
R = 1-Naphtyl, R' = 3,5-Xylyl	SL-J404-1	Et_2O	-25	100 (*26 h*)	trace	89	25	*RM725*
R = 3,5-Me-4-MeO, R' = 2-Tolyl	SL-J425-1	Et_2O	-25 to *rt*	100 (*38 h*)	trace	86	10	*RM726*
R = *t*-Bu, R' = Ph	SL-J502-1	Et_2O	-25	100 (*40 h*)	trace	87	27	*RM727*
R = *t*-Bu, R' = 2-Tolyl	SL-J505-1	Et_2O	-25 to *rt*	15 (*38 h*)	trace	10	3	*RM728*

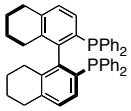
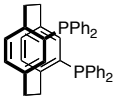
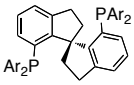
Phosphoramidates



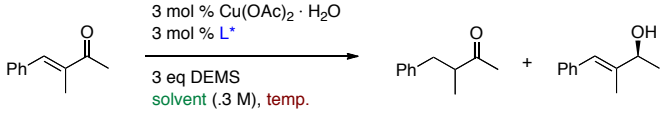
	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
	3,3'-Me-Monphos	Et_2O	-25	10 (*12 h*)	trace	7	*n.d.*	*ZB3-201*
		Et_2O	*rt*	30 (*7 h*)	trace	20	2	*ZB3-205*
	(*S,R,R*)-N(CPhHMe)$_2$	Et_2O	-25	0 (*12 h*)	-	-	-	*ZB3-202*

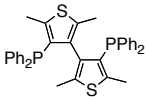
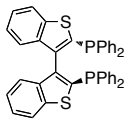
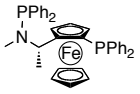
Bisphosphine ligands



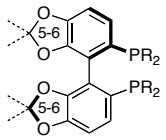
	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
	(*R*)-BINAP	THF	-25	100 (*60 h*)	trace	91	73	*RM704*
	(*S*)-H8-BINAP	THF	-25	85 (*60 h*)	trace	75	67	*RM715*
	(*R*)-[2.2]-Phanephos	THF	-25	20 (*96 h*)	*n.d.*	13	57	*RM616*
	(*S*)-(-)-DM-TUCKUP *(Ar = 3,5-Xylyl)*	THF	-25 to *rt*	10 (*72 h*)	*n.d.*	*n.d.*	*n.d.*	*RM709*

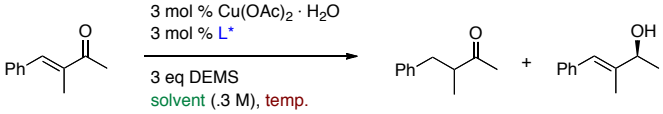
Bisphosphine ligands

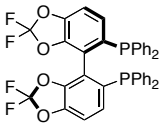
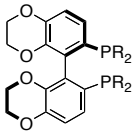


	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
	(-)-TetraMe-BITIOP	THF	-25 to *rt*	15 (*72 h*)	*n.d.*	*n.d.*	*n.d.*	*RM710*
	(*S*)-(-)-Bitianp	THF	-25	90 (*60 h*)	trace	81	62	*RM714*
	(*S,R*)-Me-BoPhoz	THF	-25 to *rt*	60 (*28 h*)	10	55	38	*RM713*
	(-)-DANP	THF	-25	50 (*60 h*)	trace	25	*n.d.*	*RM716*

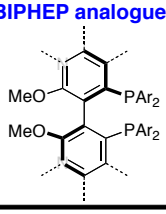
SEGPHOS analogues

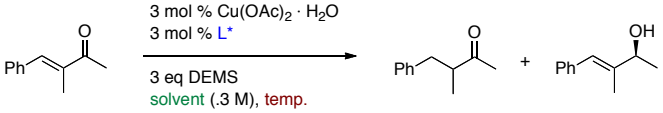


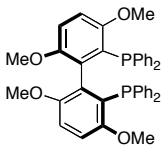
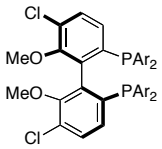
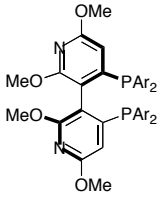


	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
	(*R*)-DifluorPhos	THF	-25 to *rt*	100 (*72 h*)	trace	91	67	*RM706*
	(*R*)-SynPhos	THF	-25	100 (*16 h*)	trace	87	77	*RM705*

BIPHEP analogues

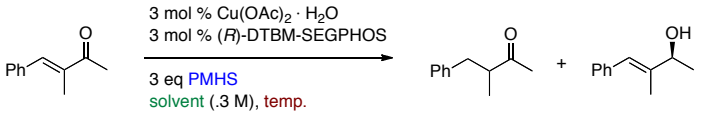




	Ligand	solvent	temp. [°C]	convn. [%] (*time*) (TLC)	1,4-reduction (isolated yield)	1,2-reduction (isolated yield)	*ee* [%] (HPLC)	exp.
		THF	-25 to *rt*	15 (*72 h*)	trace	13	14**	*RM707*
	Ar = 	THF	-25	100 (*16 h*)	trace	91	77	*RM708*
	CTH-(*R*)-Xylyl-P-Phos Ar = 	THF	-25 to *rt*	100 (*22 h*)	4	90	77	*RM738*

** = quality and source of ligand unknown

Use of PMHS as hydride source instead did not improve *ee*.

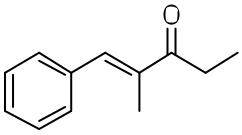


solvent	**temp. [°C]**	**convn. [%]** (*time*) (TLC)	**1,4-reduction** (isolated yield)	**1,2-reduction** (isolated yield)	***ee* [%]** (HPLC)	**exp.**
THF	-25	100 (*9 h*)	trace	82	82	*RM621*
Et_2O	-25	100 (*16 h*)	trace	72	86	*RM622*

III. Synthesis of α-substituted α,β-unsaturated ketones

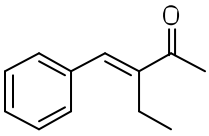
General procedure for the synthesis of α-substituted enones (unoptimized conditions). To a 50 mL round bottom flask was added 20 mL of glacial acetic acid and 2 mL of sulfuric acid. A ketone was introduced followed by the addition of an aldehyde. The vial was capped with a rubber septum and stirred overnight at rt. The mixture was then diluted with diethylether and neutralized with saturated *aq*. sodium bicarbonate and extracted three times with diethylether. The organic layer was separated and washed with water and then brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the product isolated by silica gel column chromatography using EtOAc in hexanes 3% to 8% gradient.

(*E*)-2-Methyl-1-phenylpent-1-en-3-one(3)[1]



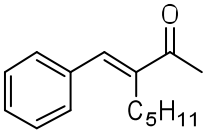
Following the general procedure for α-substituted enones, using 3-pentanone (11 mmol, 1.1 equiv) and benzaldehyde (10 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.2 Hz, 3H), 2.07 (d, *J* = 0.8 Hz, 3H), 2.85 (q, *J* = 7.2 Hz, 2H), 7.31-7.38 (m, 1H), 7.39-7.42 (m, 4H), 7.53 (s, 1H).

(*E*)-3-benzylidenepentan-2-one (4)



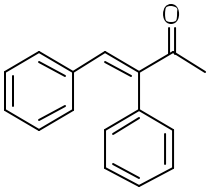
Following the general procedure for α-substituted enone, using 2-pentanone (11 mmol, 1.1 equiv) and benzaldehyde (10 mmol, 1 equiv); spectra matches previously reported data.[2]

(*E*)-3-Benzylideneoctan-2-one (5)



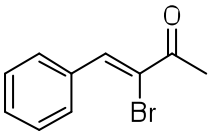
Following the general procedure for α-substituted enones, using 2-octanone (11 mmol, 1.1 equiv) and benzaldehyde (10 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.27–1.34 (m, 4H), 1.43–1.47 (m, 2H), 2.40–2.50 (m, 5H), 7.34–7.47 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 22.6, 26.4, 26.5, 29.0, 32.2, 128.7, 128.7, 129.4, 136.0, 139.6, 143.3, 200.5; HRMS(EI) calcd. for $C_{15}H_{20}O$ (M^+): 216.1514, found: 216.1520.

(*E*)-3,4-Diphenylbut-3-en-2-one (6)[5]



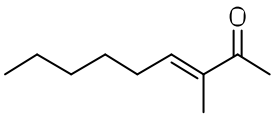
$Pd(dtbpf)Cl_2$ (7 mg, 5 mol %, 0.011 mmol) was dissolved in 1 ml (0.22 M) of THF followed by the addition of Et_3N (66 mg, 0.66 mmol, 3 equiv.), 3-bromo-4-phenyl-3-buten-2-one (0.22 mmol, 50 mg), phenylboronic acid (0.44 mmol, 2 equiv., 54 mg), and water (0.1 ml), and stirred at room temperature until the full consumption of the bromide. Product was isolated using column chromatography (6 % ethyl acetate in hexanes) yielding title compound as crystalline solid in 95% yield (190 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 7.02–7.04 (m, 2H), 7.14–7.22 (m, 5H), 7.39–7.42 (m, 3H), 7.65 (s, 1H).

(*Z*)-3-Bromo-4-phenyl-3-buten-2-one (7)[3]



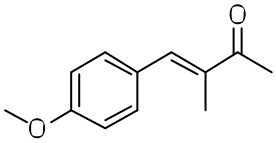
Prepared according to a previously published procedure.[4]
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.43-7.45 (m, 3H), 7.86-7.88 (m, 2H), 8.03 (s, 1H).

(*E*)-3-Methylnon-3-en-2-one (8)



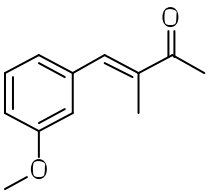
Following the general procedure for α-substituted enones, using 2-butanone (20 mmol, 10 equiv) and hexanal (2 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 1.30–1.35 (m, 4H), 1.42-1.51 (m, 2H), 1.76 (s, 3H), 2.20-2.27 (m, 2H), 2.31 (s, 3H), 6.63 (t, J = 7.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.3, 14.2, 22.7, 25.6, 28.5, 29.3, 31.8, 137.8, 144.3, 200.2; HRMS(EI) calcd. for $C_{10}H_{18}O$ (M^+): 154.1358, found: 154.1361.

(*E*)-4-(4-Methoxyphenyl)-3-methyl-3-buten-2-one (9)[5]



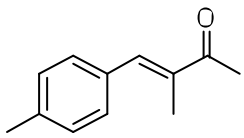
Following the general procedure for α-substituted enones, using 2-butanone (11 mmol, 1.1 equiv) and 4-methoxybenzaldehyde (10 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.45 (s, 3H), 3.85 (s, 3H), 6.94 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 7.47 (s, 1H).

(*E*)-4-(3-Methoxyphenyl)-3-methyl-3-buten-2-one (10)[1]



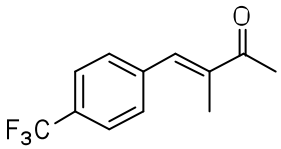
Following the general procedure for α-substituted enones, using 2-butanone (11 mmol, 1.1 equiv) and 3-methoxybenzaldehyde (10 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.46 (s, 3H), 3.83 (s, 3H), 6.89 (dd, J = 8.4 Hz, 1H), 6.94 (t, J = 1.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 8 Hz, 1H), 7.49 (s, 1H).

(*E*)-3-Methyl-4-(4-methylphenyl)-3-buten-2-one (11)[1]



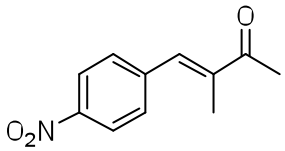
Following the general procedure for α-substituted enones, using 2-butanone (11 mmol, 1.1 equiv) and 4-tolualdehyde (10 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.38 (s, 3H), 2.46 (s, 3H), 7.22 (d, J = 8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H).

(*E*)-3-Methyl-4-(4-trifluoromethylphenyl)-3-buten-2-one (12)



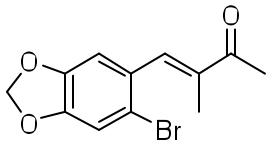
Following the general procedure for α-substituted enones, using 2-butanone (11 mmol, 1.1 equiv) and 4-(trifluoromethyl)-benzaldehyde (10 mmol, 1 equiv) used as aldehyde; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.48 (s, 3H), 7.49-7.51 (m, 3H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 26.1, 124.1 (q, $^1J_{CF}$ = 270 Hz), 125.6 (q, $^3J_{CF}$ = 4 Hz), 129.9 (q, $^2J_{CF}$ = 32 Hz), 130.0, 137.8, 139.6, 139.7, 200.1; HRMS(EI) calcd. for $C_{12}H_{11}F_3O$ (M^+): 228.0762, found: 228.0759.

(*E*)-3-Methyl-4-(4-nitrophenyl)-3-buten-2-one (13)[6]



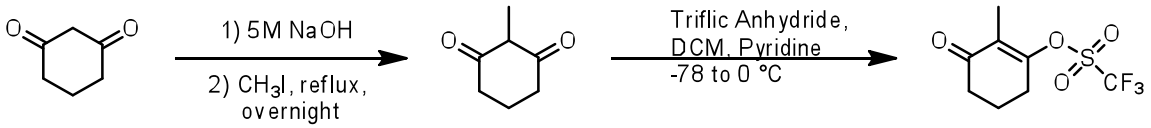
Following the general procedure for α-substituted enones, using 2-butanone (11 mmol, 1.1 equiv) and 4-nitrobenzaldehyde (10 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.49 (s, 3H), 7.51 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 8.28 (d, J = 5.2 Hz, 2H).

(*E*)-4-(6-Bromobenzo-1,3-dioxol-5-yl)-3-methyl- 3-buten-2-one (14)



Following the general procedure for α-substituted enones, using 2-butanone (11 mmol, 1.1 equiv) and 6-bromopiperonal (10 mmol, 1 equiv); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (d, J = 1.6 Hz, 3H), 2.47 (s, 3H), 6.29 (s, 2H), 6.84 (s, 1H), 7.10 (s, 1H), 7.50 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 26.1, 102.3, 110.2, 113.1, 116.1, 129.1, 138.2, 139.2, 147.3, 148.7, 200.1; HRMS(EI) calcd. for $C_{12}H_{11}BrO_3$ (M^+): 281.9892, found: 281.9899.

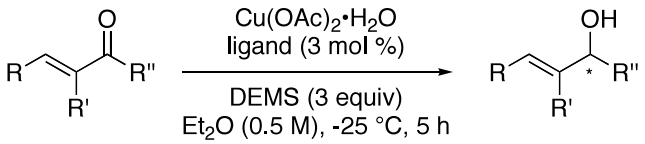
2-Methyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (17)[7]

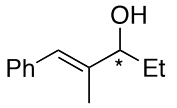


Step 1: 1,3-Cyclohexanedione (5.6 g, 50 mmol) was dissolved in 5 M NaOH (2 g in 10 mL H_2O, 50 mmol) followed by the addition of methyl iodide (16.33 g, 115 mmol, 2.3 equiv) and was refluxed overnight. Product was isolated as a crystalline solid (1.28 g, 20 % yield).[8]

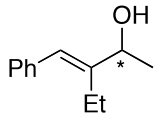
Step 2: 2-Methyl-1,3-cyclohexanedione (214 mg, 1.7 mmol) was dissolved in 10 mL of DCM (0.17 M), followed by the addition of pyridine (268 mg, 3.4 mmol, 2 equiv), and upon cooling to -78 °C, triflic anhydride (575 mg, 2.04 mmol, 1.2 equiv) was added dropwise. The mixture was warmed to 0 °C and stirred until the consumption of the starting material. Product was isolated using column chromatography (gradient 6-8 % EtOAc in hexanes).[9] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (t, J = 2 Hz, 3H), 2.05–2.12 (m, 2H), 2.47–2.51 (m, 2H), 2.72–2.76 (m, 2H).

IV. Addition to Table 2

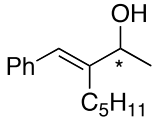




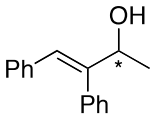
3: **L2**, (98%) 85% *ee*
L3b, (96%) 93% *ee*



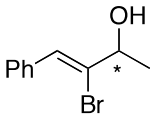
4: **L2**, (94%) 93% *ee*
L3b, (96%) 91% *ee*



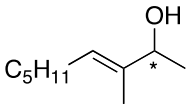
5: **L2**, (95%) 89% *ee*
L3b, (92%) 90% *ee*



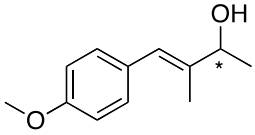
6: **L2** (*n.d.*) *n.d.*
L3b, (85%) 76% *ee*



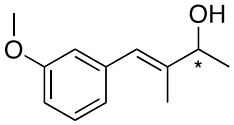
7: **L2** (*n.d.*) *n.d.*
L3b, (91%) 77% *ee*



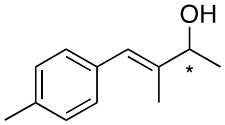
8: **L2**, (82%) 90% *ee*
L3b (89%) 88% *ee*



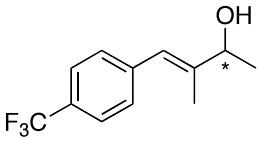
9: **L2**, (96%) 56% *ee*
L3b, (98%) 89% *ee*



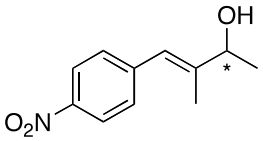
10: **L2**, (98%) 89% *ee*
L3b, (97%) 92% *ee*



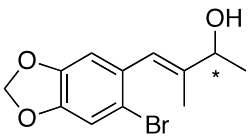
11: **L2**, (99%) 89% *ee*
L3b, (98%) 90% *ee*



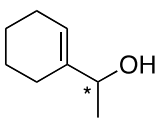
12: **L2**, (94%) 86% *ee*
L3b, (96%) 93% *ee*



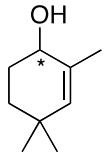
13: **L2**, (67%)[b] 84% *ee*
L3b, (88%) 95% *ee*



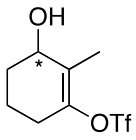
14: **L2**, (99%) 62% *ee*
L3b, (39%)[c] 71% *ee*



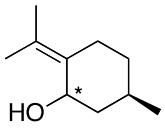
15: **L2**, (86%) 83% *ee*
L3b, (91%) 79% *ee*



16: **L2**, (90%)
95% *ee*



17: **L2**, (90%)
86% *ee*



18: **L2**, (93%) 99:1 *dr*
ent-**L2**, (88%) 4:1 *dr*

[a] Reactions were carried out on 0.25 mmol scale in 0.5 mL Et_2O. Isolated yields after column chromatography are given in parentheses. *Ee*'s were determined by chiral HPLC or chiral GC analysis. [b] 1,4-Reduction product was isolated in 24% yield. [c] Low conversion after 17 h.

V. CuH catalyzed asymmetric 1,2-reductions of α-substituted enones

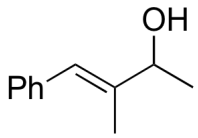
General procedure for the enantioselective CuH-catalyzed 1,2-reduction of α-substituted enones using (*R*)-DTBM-SEGPHOS (*GP1*):

A conical 3 mL microwave vial containing a conical stir bar was charged with fine powdered $Cu(OAc)_2 \cdot H_2O$ (1.3 mg, 3 mol %, 7.5 μmol) and (*R*)-DTBM-SEGPHOS (8.8 mg, 3 mol %, 7.5 μmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, 0.4 mL Et_2O was added via syringe. At rt, DEMS (120 μL, 0.75 mmol) was introduced, resulting in a brown solution after 10 min. The vial was then placed into a pre-cooled acetone bath at -25 °C and stirred for an additional 5 min. Liquid substrates (0.25 mmol) were subsequently introduced *via* syringe; solid substrates (0.25 mmol) were added all at once. The side of the reaction vial was rinsed with Et_2O (2 x 50 μL). After TLC confirmed full conversion, the reaction was quenched at -25 °C by the addition of 0.5 mL sat. NH_4F/MeOH. The reaction vial was taken out of the cooling bath and warmed to rt. After filtration through SiO_2, the solvent was evaporated *in vacuo* and the crude reaction mixture purified by column chromatography on silica gel.

General procedure for the enantioselective CuH-catalyzed 1,2-reduction of α-substituted enones using (*S*)-3,4,5-Me-MeO-BIPHEP (*GP2*):

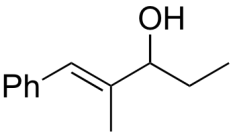
A conical 3 mL microwave vial containing a conical stir bar was charged with fine powdered $Cu(OAc)_2 \cdot H_2O$ (1.3 mg, 3 mol %, 7.5 μmol) and (*S*)-3,4,5-Me-MeO-BIPHEP (5.6 mg, 3 mol %, 7.5 μmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, Et_2O (0.4 mL) was added *via* syringe. At rt, DEMS (120 μL, 0.75 mmol) was introduced, resulting in a brown solution after 40 min. The vial was then placed into a pre-cooled acetone bath at -25 °C and stirred for an additional 5 min. Liquid substrates (0.25 mmol) were subsequently introduced *via* syringe, while solid substrates (0.25 mmol) were added all at once. The side of the reaction vial was rinsed with Et_2O (2 x 50 μL). After TLC confirmed full conversion, the reaction was quenched at -25 °C by the addition of 0.5 mL sat. NH_4F/MeOH. The reaction vial was taken out of the cooling bath and warmed to rt. After filtration through SiO_2, the solvent was evaporated *in vacuo* and the crude reaction mixture purified by column chromatography on silica gel.

(*S*)-(+)-3-Methyl-4-phenyl-but-3-en-2-ol.[10,11]



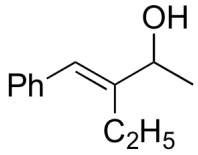
Using ***GP1***: TLC: R_f = 0.24 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25% EtOAc/hexanes; 39.8 mg (98% yield); colorless viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (d, *J* = 6.5 Hz, 3H), 1.62 (br, 1H), 1.89 (s, 3H), 4.39 (q, *J* = 6.5 Hz, 1H), 6.52 (s, 1H), 7.20-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.61, 22.00, 73.88, 124.61, 126.61, 128.32, 129.16, 137.83, 141.80; HRMS(EI) calcd. for $C_{11}H_{14}O$ (M^+) 162.1045, found: 162.1041; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 5% IPA/hexanes, 1.0 mL/min, t_R = 9.3 and 10.6 min, 91% *ee*; $[\alpha]_{589}^{20}$ = +6.2 (*c* = 0.34, $CHCl_3$) (lit. $[\alpha]_{589}^{20}$ = -7.0 (*c* = 0.27, $CHCl_3$) for (*R*)-enantiomer)[14].

(*R*)-(+)-2-Methyl-1-phenyl-pent-1-en-3-ol.[12]



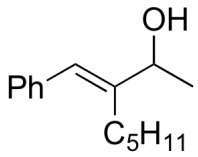
Using ***GP2***: TLC: R_f = 0.30 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25% EtOAc/hexanes; 42.3 mg (96% yield) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, *J* = 8.0 Hz, 3H), 1.64-1.70 (m, 2H), 1.73 (br, 1H), 1.85 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 1H), 6.48 (s, 1H), 7.19-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.28, 13.27, 28.10, 79.74, 126.18, 126.60, 128.30, 129.16, 137.80, 140.24; HRMS (EI) calcd. for $C_{12}H_{16}O$ (M^+): 176.1201, found 176.1201; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 2.5% IPA/hexanes, 1.0 mL/min, t_R = 15.3 and 16.9 min, 93% *ee*; $[\alpha]_{589}^{20}$ = +10.1 (*c* = 0.37, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = -10.67 (*c* = 0.003, $CHCl_3$) for (*S*)-enantiomer)[12].

(*S*)-(+)-3-Ethyl-4-phenyl-but-3-en-2-ol.



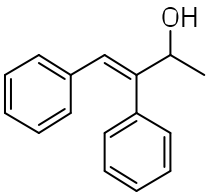
Using ***GP1***: TLC: R_f = 0.29 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25 % EtOAc/hexanes; 41.3 mg (94% yield) colorless viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7.5 Hz, 3H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.56 (br, 1H), 2.25 (dt, *J* = 21.0, 7.5 Hz, 1H), 2.43 (dt, *J* = 21.5, 7.5 Hz, 1H), 4.43-4.48 (m, 1H), 6.56 (s, 1H), 7.21-7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.16, 21.51, 22.77, 71.83, 124.18, 126.63, 128.42, 128.81, 137.89, 148.14; HRMS(EI) calcd. for $C_{12}H_{16}O$ (M^+): 176.1201, found 176.1197; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 2% IPA/hexanes, 0.5 mL/min, t_R = 40.2 and 42.3 min, 93% *ee*; $[\alpha]_{589}^{20}$ = +8.8 (*c* = 0.93, $CHCl_3$).

(*R*)-(+)-3-Pentyl-4-phenyl-but-3-en-2-ol.[13]



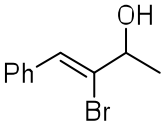
Using ***GP2***: TLC: R_f = 0.13 (10% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25 % EtOAc/hexanes; 50.1 mg (92% yield) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83-0.91 (m, 3H), 1.23-1.37 (m, 4H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.43-1.65 (m, 3H), 2.10-2.22 (m, 1H), 2.32-2.42 (m, 1H), 4.42 (q, *J* = 6.5 Hz, 1H), 6.55 (s, 1H), 7.18-7.27 (m, 3H), 7.36-7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.20, 22.55, 22.76, 28.65, 29.02, 32.40, 71.92, 124.32, 126.54, 128.35, 128.79, 137.98, 147.03; HRMS(EI) calcd. for $C_{15}H_{22}O$ (M^+): 218.1671, found 218.1667; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 2% IPA/hexanes, 1.0 mL/min, t_R = 14.2 and 15.6 min, 90% *ee*; $[\alpha]_{589}^{20}$ = +15.8 (*c* = 1.05, $CHCl_3$).

(*E*)-3,4-diphenylbut-3-en-2-ol.[11]



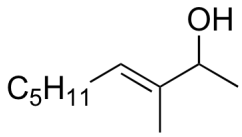
Using ***GP2***: Isolated by column chromatography using 6% EtOAc in hexanes as a clear oil; 48 mg (85% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J* = 6.4 Hz, 3H), 1.75 (broad s, 1H), 4.67 (q, *J* = 6.4 Hz, 1H), 6.69 (s, 1H), 6.91–7.37 (m, 10H); HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 4% IPA/hexanes; 0.5 mL/min, t_R= 22.9 and 24.5 min, 76 % *ee*.

(*Z*)-3-Bromo-4-phenylbut-3-en-2ol.



Using ***GP2***: Isolated by column chromatography using 6% EtOAc in hexanes as a clear oil; 51 mg (91% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 1H), 1.48 (d, *J* = 6 Hz, 3H), 4.49 (q, *J* = 6 Hz, 1H), 7.08 (s, 1H), 7.32 (t, *J* = 7 Hz, 1H), 7.37 (t, *J* = 7 Hz, 2H), 7.61 (d, *J* = 7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.7, 73.8, 127.1, 128.3, 129.3, 129.3, 131.6, 135.3; HRMS(EI) calcd. for $C_{10}H_9BrO$ (M^+): 225.9993, found: 225.9983; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 5% IPA/hexanes; 0.5 mL/min, t_R= 14.0 and 15.1 min, 77 % *ee*.

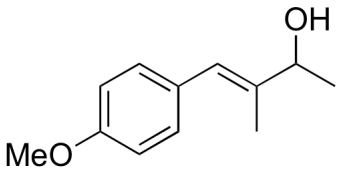
(*S*)-(+)-3-Methylnon-3-en-2-ol.



Using ***GP1***: TLC: R_f = 0.17 (10% EtOAc/hexanes, $KMnO_4$); column chromatography: Biotage, 0-10 % EtOAc/hexanes; 32.0 mg (82% yield) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.5 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.27-1.38 (m, 6H), 1.53 (br, 1H), 1.62 (s, 3H), 1.98-2.02 (m, 2H), 4.20 (q, *J* = 6.5 Hz, 1H), 5.38-5.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.58, 14.26, 21.79, 22.78, 27.66, 29.40, 31.75, 73.67, 125.59, 138.48; HRMS(EI) calcd. for $C_{10}H_{20}O$ (M^+): 156.1514, found 156.1508; HPLC separation

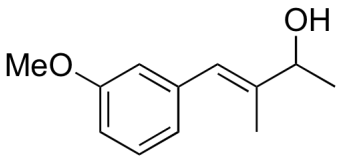
conditions: CHIRALPAK AD-H, 210 nm, 1% IPA/hexanes, 1.3 mL/min, t_R = 11.1 and 11.8 min, 90% *ee*; $[\alpha]_{589}^{20}$ = +7.5 (*c* = 0.27, $CHCl_3$).

(*R*)-(+)-4-(4-Methoxyphenyl)-3-methylbut-3-en-2-ol.[14]



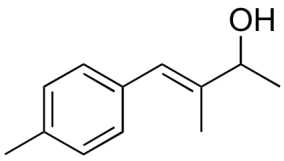
Using ***GP2***: TLC: R_f = 0.23 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25% EtOAc/hexanes; 47.0 mg (98% yield) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (d, *J* = 6.0 Hz, 3H), 1.86 (br, 1H), 1.88 (s, 3H), 3.82 (s, 3H), 4.37 (q, *J* = 5.5 Hz, 1H), 6.45 (s, 1H), 6.89 (d, *J* = 7.0 Hz, 2H), 7.23 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.48, 21.92, 55.40, 73.98, 113.72, 124.12, 130.30, 130.36, 140.10, 158.23; HRMS(EI) calcd. for $C_{12}H_{16}O_2$ (M^+): 192.1150, found 192.1143; HPLC separation conditions: CHIRALCEL OB-H, 254 nm, 10% IPA/hexanes, 1.0 mL/min, t_R = 8.5 and 12.5 min, 89% *ee*; $[\alpha]_{589}^{20}$ = +12.3 (*c* = 1.52, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = -16.7 (*c* = 1.36, $CHCl_3$) for (*S*)-enantiomer)[15].

(*R*)-(+)-4-(3-Methoxyphenyl)-3-methylbut-3-en-2-ol.[15]



Using ***GP2***: TLC: R_f = 0.19 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25 % EtOAc/hexanes; 46.6 mg (97% yield) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (d, *J* = 6.5 Hz, 3H), 1.85 (br, 1H), 1.88 (s, 3H), 3.80 (s, 3H), 4.36 (q, *J* = 6.5 Hz, 1H), 6.48 (s, 1H), 6.76-6.87 (m, 3H), 7.23-7.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.69, 21.95, 55.35, 73.75, 112.09, 114.73, 121.71, 124.40, 129.24, 139.24, 142.11, 159.51; HRMS(EI) calcd. for $C_{12}H_{16}O_2$ (M^+): 192.1150, found 192.1147; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 5% IPA/hexanes, 1.0 mL/min, t_R = 16.9 and 20.9 min, 92% *ee*; $[\alpha]_{589}^{20}$ = +9.7 (*c* = 1.33, $CHCl_3$).

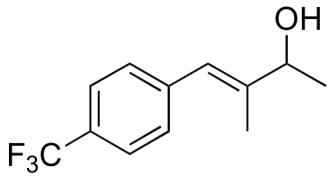
(*R*)-(+)-3-Methyl-4-(*p*-tolyl)but-3-en-2-ol.



Using ***GP2***: TLC: R_f = 0.32 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25% EtOAc/hexanes; 43.2 mg (98% yield) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (d, *J* = 6.5 Hz, 3H), 1.80 (br, 1H), 1.90 (s, 3H), 2.37 (s, 3H), 4.39 (q, *J* = 6.5 Hz, 1H), 6.50 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.54, 21.33, 21.92, 73.94, 124.50, 129.00, 129.05, 134.88, 136.23, 141.00; HRMS(EI) calcd. for $C_{12}H_{16}O$ (M^+): 176.1201, found 176.1205; HPLC

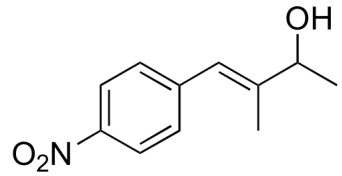
separation conditions: CHIRALPAK AD-H, 254 nm, 2% IPA/hexanes, 1.0 mL/min, t_R = 19.9 and 23.3 min, 90% *ee*; $[\alpha]_{589}^{20}$ = +15.5 (*c* = 0.54, $CHCl_3$).

(*R*)-(+)-3-Methyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-ol.



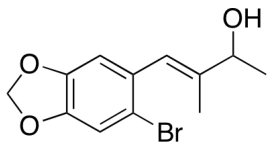
Using ***GP2***: TLC: R_f = 0.22 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25% EtOAc/hexanes; 55.3 mg (96% yield) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (d, *J* = 6.5 Hz, 3H), 1.88 (br, 1H), 1.89 (br, 3H), 4.40 (q, *J* = 6.0 Hz, 1H), 6.56 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.86, 22.07, 73.47, 122.98, 124.27 (q, $^1J_{C\text{-}F}$ = 270.1 Hz), 125.01 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 128.30 (q, $^2J_{C\text{-}F}$ = 32.1 Hz), 129.12, 141.34, 143.96; HRMS(EI) calcd. for $C_{12}H_{13}F_3O$ (M^+): 230.0918, found 230.0917; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 2% IPA/hexanes, 1.0 mL/min, t_R = 16.1 and 17.8 min, 93% *ee*; $[\alpha]_{589}^{20}$ = +5.6 (*c* = 1.24, $CHCl_3$).

(*R*)-(+)-3-Methyl-4-(4-nitrophenyl)but-3-en-2-ol.[14]



Using ***GP2***: TLC: R_f = 0.30 (50% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-50 % EtOAc/hexanes; 45.6 mg (88% yield) yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (d, *J* = 6.5 Hz, 3H), 1.72 (br, 1H), 1.92 (s, 3H), 4.41 (q, *J* = 6.5 Hz, 1H), 6.61 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.31, 22.19, 73.33, 122.55, 123.69, 129.75, 144.84, 146.15; HRMS(EI) calcd. for $C_{11}H_{13}NO_3$ (M^+): 207.0895, found 207.0902; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 5% IPA/hexanes, 1.0 mL/min, t_R = 18.3 and 20.4 min, 95% *ee*; $[\alpha]_{589}^{20}$ = +1.2 (*c* = 0.45, $CHCl_3$).

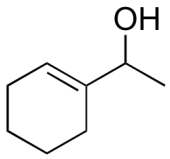
(*R*)-(+)-4-(6-Bromobenzo[d][1,3]dioxol-5-yl)-3-methylbut-3-en-2-ol.



Using ***GP1***: TLC: R_f = 0.24 (25% EtOAc/hexanes, UV + $KMnO_4$); column chromatography: Biotage, 0-25% EtOAc/hexanes; 50.9 mg (99% yield) colorless viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (d, *J* = 7.0 Hz, 3H), 1.74 (s, 3H), 1.81 (br, 1H), 4.40 (q, *J* = 7.0 Hz, 1H), 5.98 (s, 2H), 6.41 (s, 1H), 6.74 (s, 1H), 7.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.45, 21.97, 73.14, 101.86, 110.45, 112.71, 115.08, 124.10, 130.95, 142.76, 147.05, 147.24; HRMS(EI) calcd. for $C_{12}H_{13}BrO_3$ (M^+): 284.0048, found

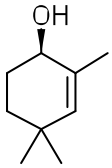
284.0037; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 5% IPA/hexanes, 1.0 mL/min, t_R = 15.1 and 19.0 min, 62% *ee*; $[\alpha]_{589}^{20}$ = +3.5 (*c* = 0.74, $CHCl_3$).

(*R*)-(+)-1-(cyclohex-1-en-1-yl)ethanol.[16,17]



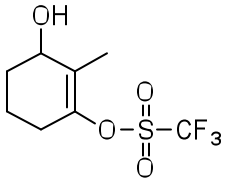
Using ***GP1***: TLC: R_f = 0.22 (30% Et_2O/pentane, $KMnO_4$); column chromatography: 0-30% Et_2O/pentane; 32.0 mg (82% yield) colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (d, *J* = 6.5 Hz, 3H), 1.41 (br, 1H), 1.53-1.70 (m, 4H), 1.94-2.08 (m, 4H), 4.17 (q, *J* = 7.0 Hz, 1H), 5.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.72, 22.81, 22.87, 23.88, 25.10, 72.40, 121.76, 141.46; GC separation conditions: Restek RT-BetaDEXcst (30 x 0.25 x 0.25 μm), carrier gas hydrogen, 1.0 mL/min, inlet T = 250 °C, FID T = 270 °C, oven T = 115 °C, t_R = 41.6 and 44.2 min, 83 % *ee*; $[\alpha]_{589}^{20}$ = +19.7 (*c* = 1.69, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = -7.4 (*c* = 2.6, $CHCl_3$) for (*S*)-enantiomer)[16].

(*R*)-2,4,4-Trimethylcyclohex-2-enol.[18]



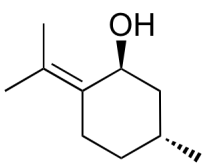
Using ***GP1***: Isolated by column chromatography using 5% EtOAc in hexanes as a clear oil; 31 mg (90% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.35–1.41 (m, 1H), 1.46–1.55 (m, 2H), 1.67–1.73 (m, 1H), 1.74 (s, 3H), 1.83–1.91 (m, 1H), 3.93 (t, *J* = 4.8 Hz, 1H), 5.24 (s, 1H). GC separation conditions: CYCLOSIL-B column (30 x 0.25 x 0.25 μm), carrier gas hydrogen, 1.0 mL/min, inlet T = 250 °C, FID T = 270 °C, oven T = 70 °C, t_R = 37.5 and 38.3 min, 95% *ee*; $[\alpha]_{589}^{21}$ = +94.3 (*c* = 0.79, CH_3OH) (lit. $[\alpha]_{589.3}^{21}$ = +80.7 (*c* = 1.05, CH_3OH).[19]

3-Hydroxy-2-methylcyclohex-1-en-1-yl trifluoromethanesulfonate.[20]



Using ***GP1***: Isolated by column chromatography using 8% EtOAc in hexanes as a clear oil; 59 mg (90% yield); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 18.7, 28.0, 31.2, 69.5, 121.1 (q, *J* = 121 Hz), 128.3, 146.7; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 1% IPA/hexanes, 1.0 mL/min, t_R= 54.1 and 57.0 min, 86% *ee*.

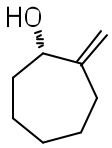
(+)-*trans*-Pulegol.[21,22]



Using ***GP1*:** ((*S*)-DTBM-SEGPHOS was used instead): *dr* (*cis*:*trans*)[23] = 21:79; TLC: R_f ((+)-*cis*-pulegol) = 0.22, R_f ((+)-*trans*-pulegol) = 0.16 (20% Et_2O/pentane, $KMnO_4$); column chromatography: 10-20% Et_2O/pentane; 26.6 mg (69% yield of *trans*, 33.9 mg – 88% overall yield) white crystals; recrystallized from pentane; mp = 75.5-76.5 °C

(crystallized from pentane; lit. mp = 76 °C)[21] ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84-0.93 (m, 1H), 0.88 (d, *J* = 6.0 Hz, 3H), 1.11 (ddd, *J* = 14.0, 12.5, 3.0 Hz, 1H), 1.26 (br, 1H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.71-1.77 (m, 1H), 1.75 (d, *J* = 2.0 Hz, 3H), 1.89-2.01 (m, 2H), 2.10-2.18 (m, 1H), 2.50 (dtd, *J* = 14.0, 3.5, 1.0 Hz, 1H), 4.85 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.95, 20.65, 22.36, 25.01, 26.40, 35.83, 42.55, 67.09, 125.68, 132.61; HRMS(EI) calcd. for $C_{10}H_{18}O$ (M^+): 154.1358, found 154.1362; $[\alpha]_{589}^{20}$ = +102.1 (*c* = 0.37, $CHCl_3$; lit. $[\alpha]_D^{20}$ = +100 (*c* = 1 in alcohol))[21].

(*S*)-2-Methylenecycloheptanol.



Using ***GP2:*** TLC: R_f = 0.33 (25% EtOAc/hexanes, $KMnO_4$ stain); column chromatography on silica gel using 5% EtOAc/hexanes; 25.8 mg (82%) yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (t, *J* = 1.2 Hz, 1H), 4.90 (t, *J* = 1.2 Hz, 1H), 4.27 (dd, J_1 = 8 Hz, J_2 = 5.2 Hz, 1H), 2.33–2.28 (m, 1H), 2.22–2.16 (m, 1H), 2.05–1.98 (m, 1H), 1.77–1.24 (m, 8H);[24] Enantiomeric excess and absolute stereochemistry were determined by Mosher ester analysis using the following procedure. 2-Methylenecycloheptanol (9.4 mg, 75 μmol) and (*R*)-Mosher acid (48 mg, 205 μmol) were dissolved in 1 mL (0.075 M) dichloromethane and stirred at rt until dissolved. Dicyclohexylcarbodiimide (50 mg, 242 μmol) and *N,N*-dimethylaminopyridine (29 mg, 237 μmol) were then added and the reaction progress was monitored by TLC until complete (3 h). The reaction mixture was diluted with Et_2O, partitioned with water, extracted 3x with Et_2O and the combined extracts dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the residue dissolved in $CDCl_3$ to determine *ee*: 78% by comparison of OMe resonances at 3.56 ppm and 3.54 ppm. Shielding of the methylene protons within the major isomer indicated that the absolute stereochemistry is *S*.[25]

VI. Tandem 1-pot asymmetric 1,2-reduction of an enone followed by 1,4-reduction of an enoate

A conical 3 mL microwave vial containing a conical stir bar was charged with fine powdered $Cu(OAc)_2 \cdot H_2O$ (1.3 mg, 3 mol %, 7.5 μmol) and (*R*)-DTBM-SEGPHOS (8.8 mg, 3 mol %, 7.5 μmol). The vial was capped with a rubber septum and the mixture placed under an atmosphere of Argon. Et_2O (0.4 mL) was added via syringe. At rt, DEMS (120 μL, 0.75 mmol) was introduced, resulting in a brown solution after 10 min. The vial was then placed into a pre-cooled acetone bath at -25 °C and stirred for additional 5 min. A pre-cooled solution of enone **1** (40.1 mg, 0.25 mmol) and enoate **21** (47.6 mg, 0.25 mmol) in Et_2O was slowly introduced *via* syringe. The side of the reaction vial was carefully rinsed with Et_2O (2 x 100 μL). After 5 h an aliquot of the reaction mixture was taken and GC/MS analysis confirmed full consumption of enone **1**. Subsequent addition of *t*-BuOH (1 M solution in Et_2O, 275 μL) and DEMS (40 μL) led to full conversion of enoate **21**, as confirmed through GC/MS analysis after additional 5 h at -25 °C. The reaction was quenched at -25 °C by the addition of 0.5 mL sat. NH_4F/MeOH. The reaction vial was removed from the cooling bath and warmed to rt. After filtration through SiO_2, the solvent was evaporated *in vacuo* and the crude reaction mixture purified by column chromatography on silica gel (Biotage, 0-10% EtOAc/hexanes).

Allylic alcohol **2** - TLC R_f = 0.09 (10% EtOAc/hexanes, UV + $KMnO_4$); 38.9 mg (96% yield) colorless viscous oil; HPLC separation conditions: CHIRALCEL OD-H, 254 nm, 5% IPA/hexanes, 1.0 mL/min, t_R = 9.4 and 10.5 min, 90% *ee*; spectral data matches previously reported data.[26]

Ester **22** - TLC R_f = 0.37 (10% EtOAc/hexanes, UV + $KMnO_4$); 45.2 mg (94% yield) colorless viscous oil; HPLC separation conditions: CHIRALCEL OB-H, 206 nm, 1% IPA/hexanes, 1.0 mL/min, t_R = 7.6 and 9.4 min, 97% *ee*; spectral data matches previously reported data.[26]

VII. Characterization data

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[22] *trans*-Stereochemistry was confirmed through X-ray analysis.
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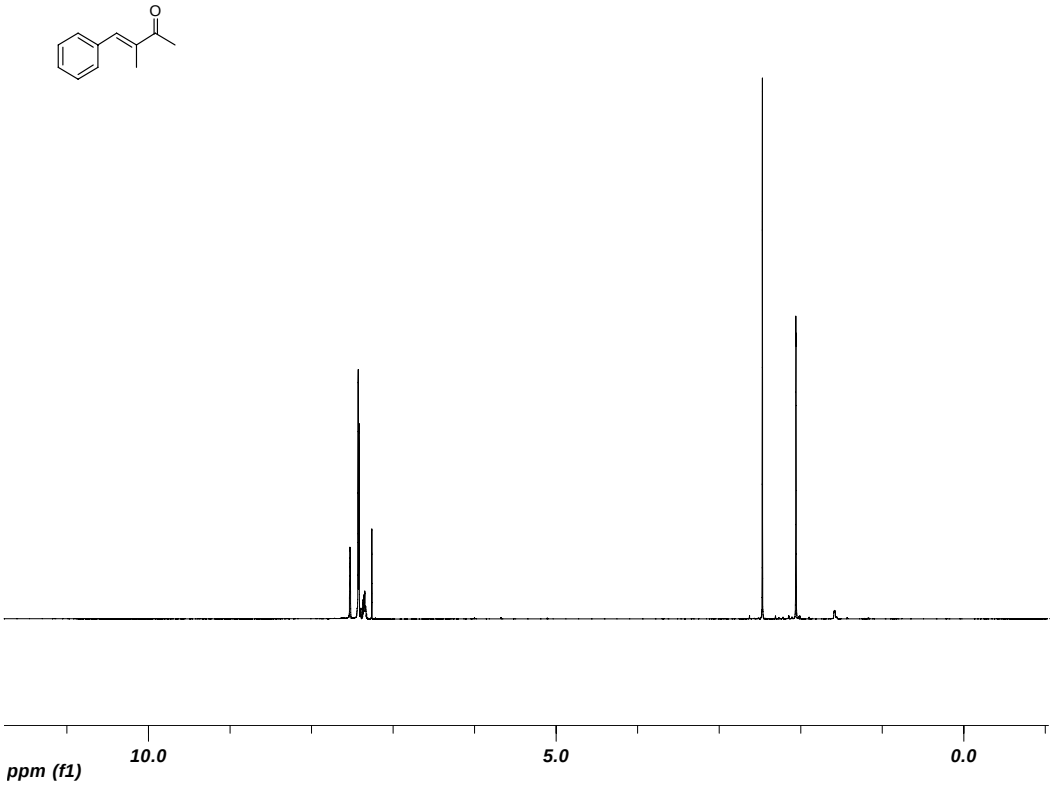
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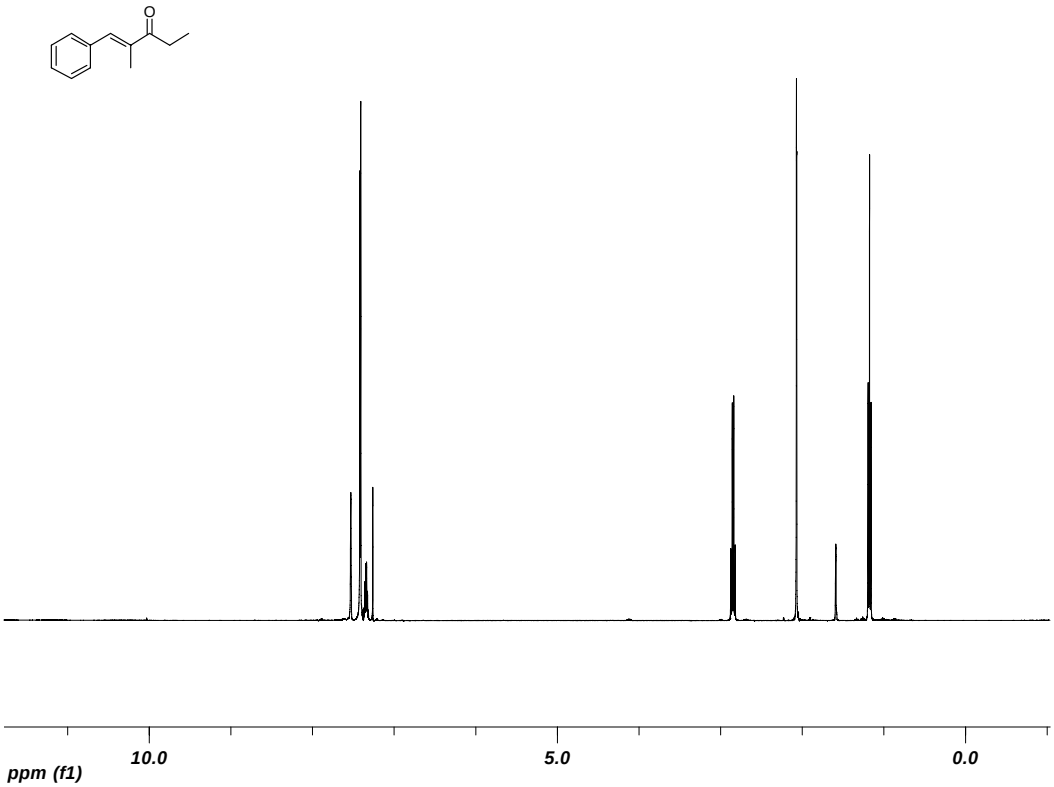
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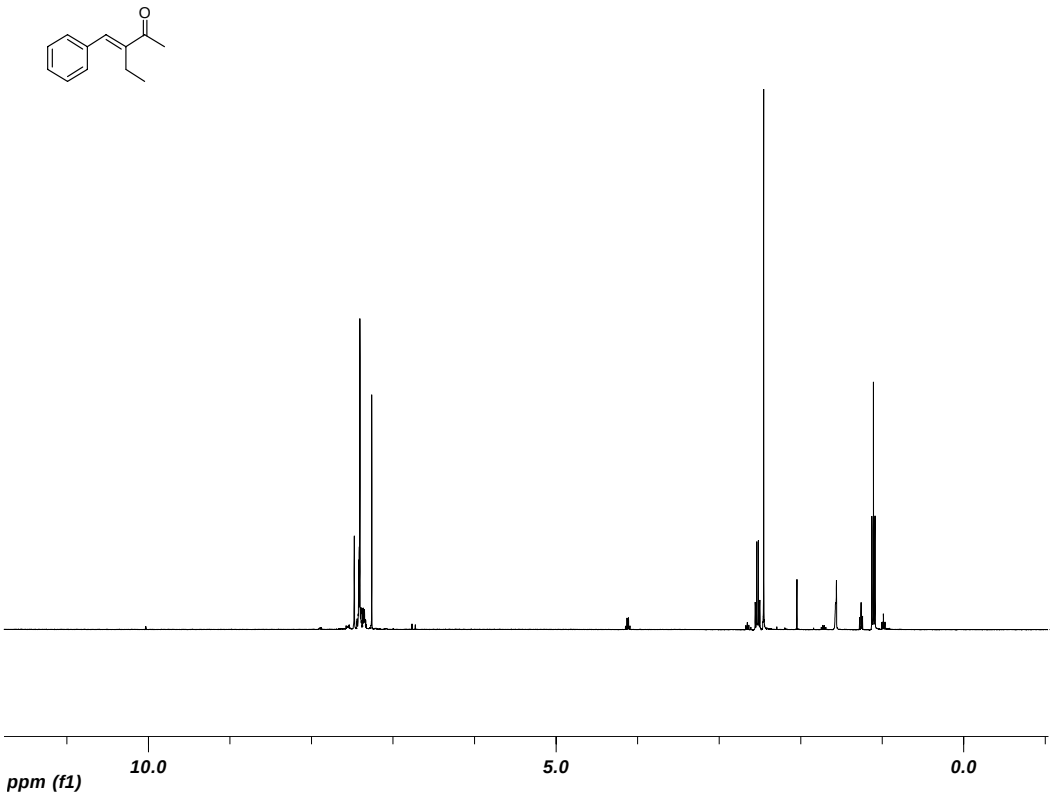
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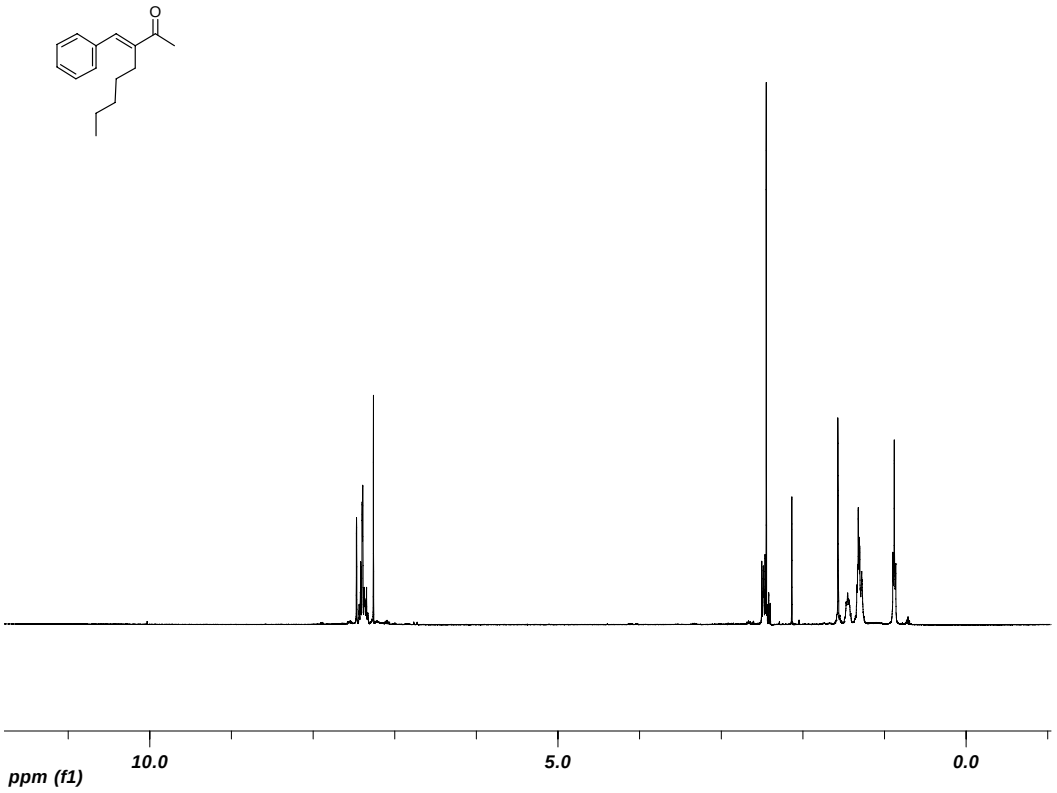
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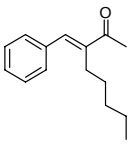

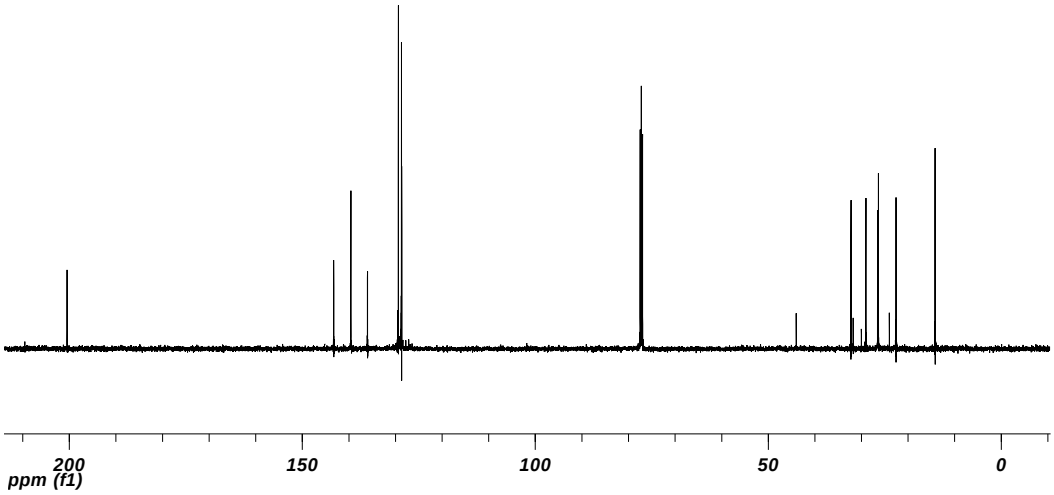
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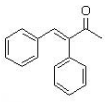

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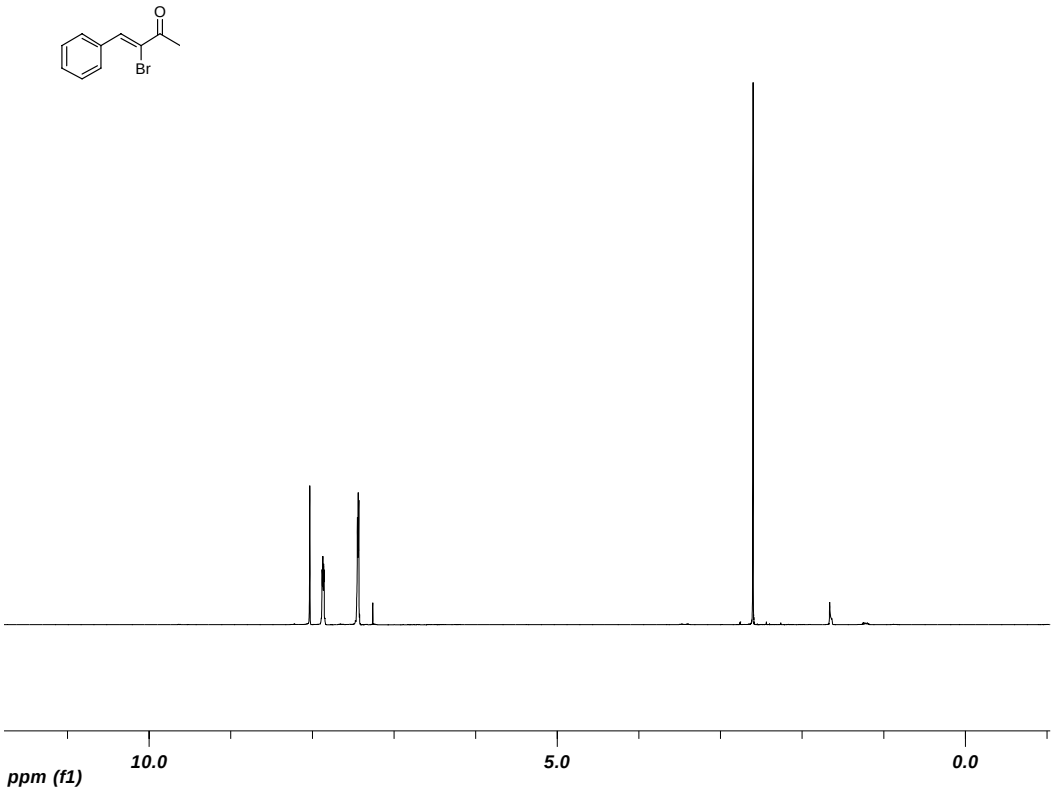
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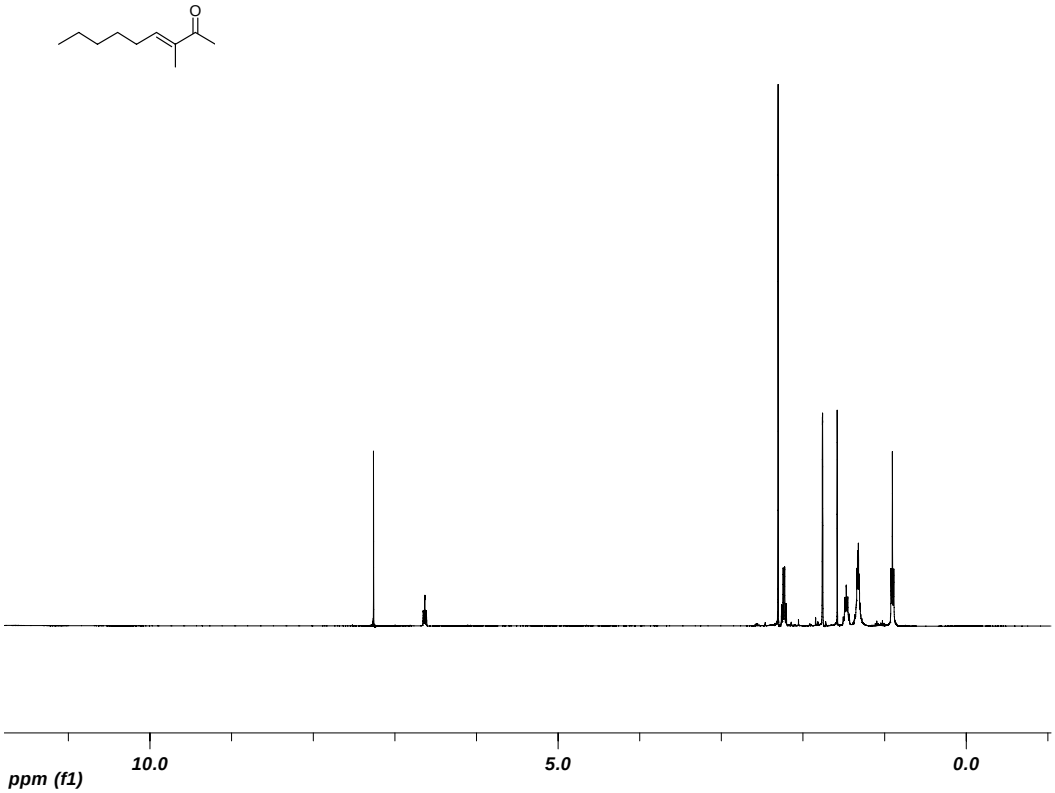
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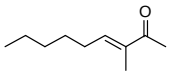
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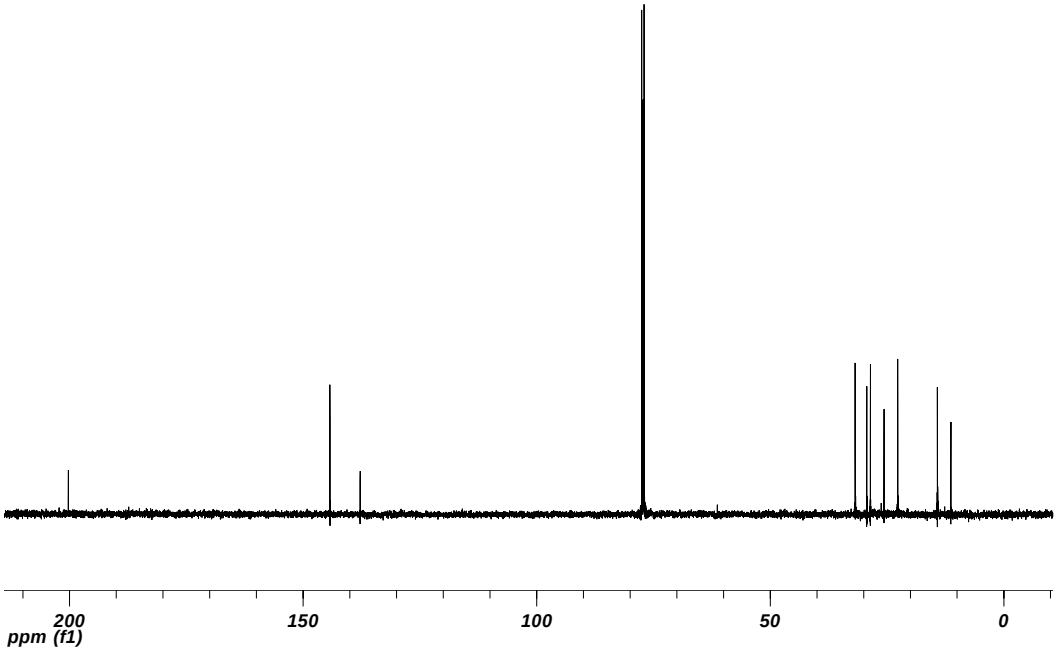
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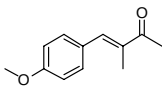
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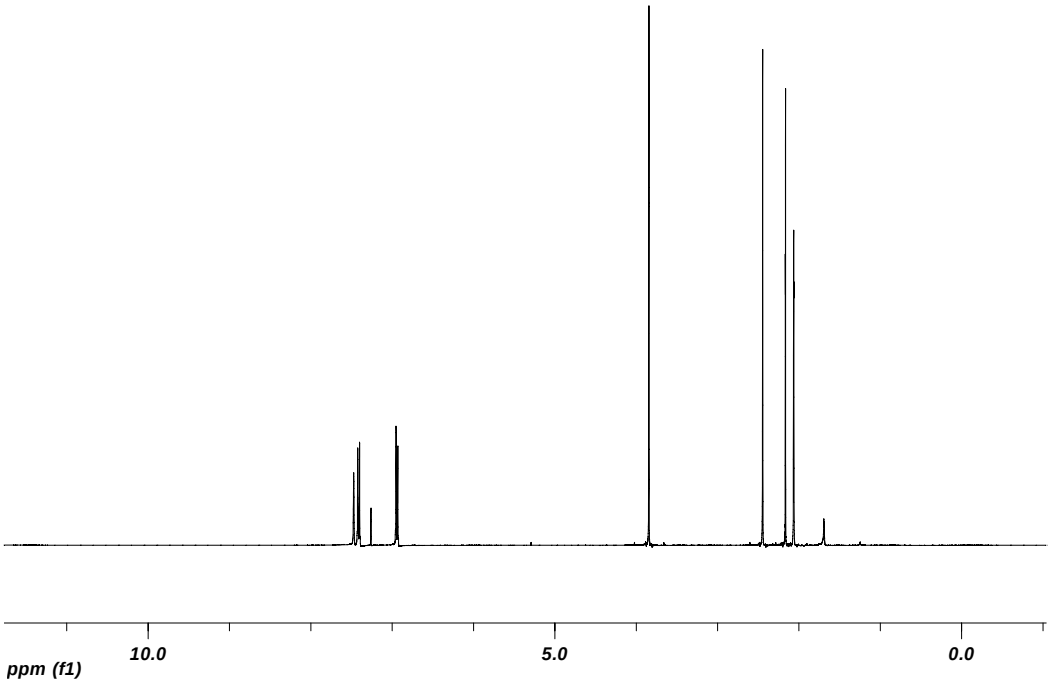
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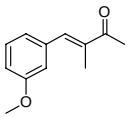
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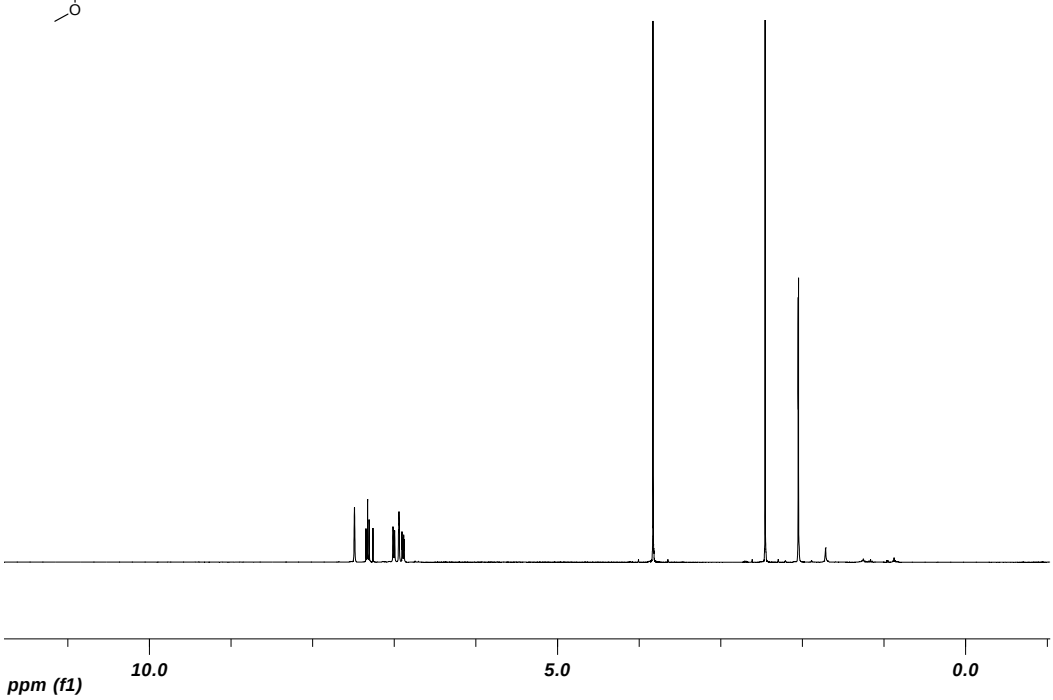
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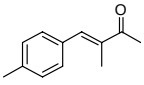
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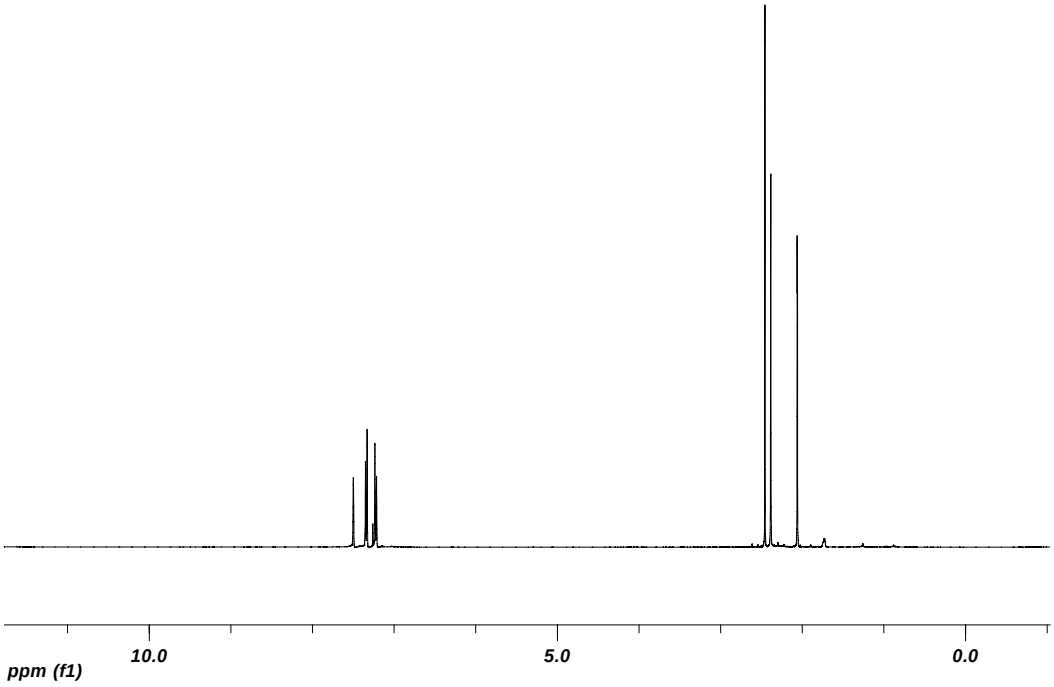
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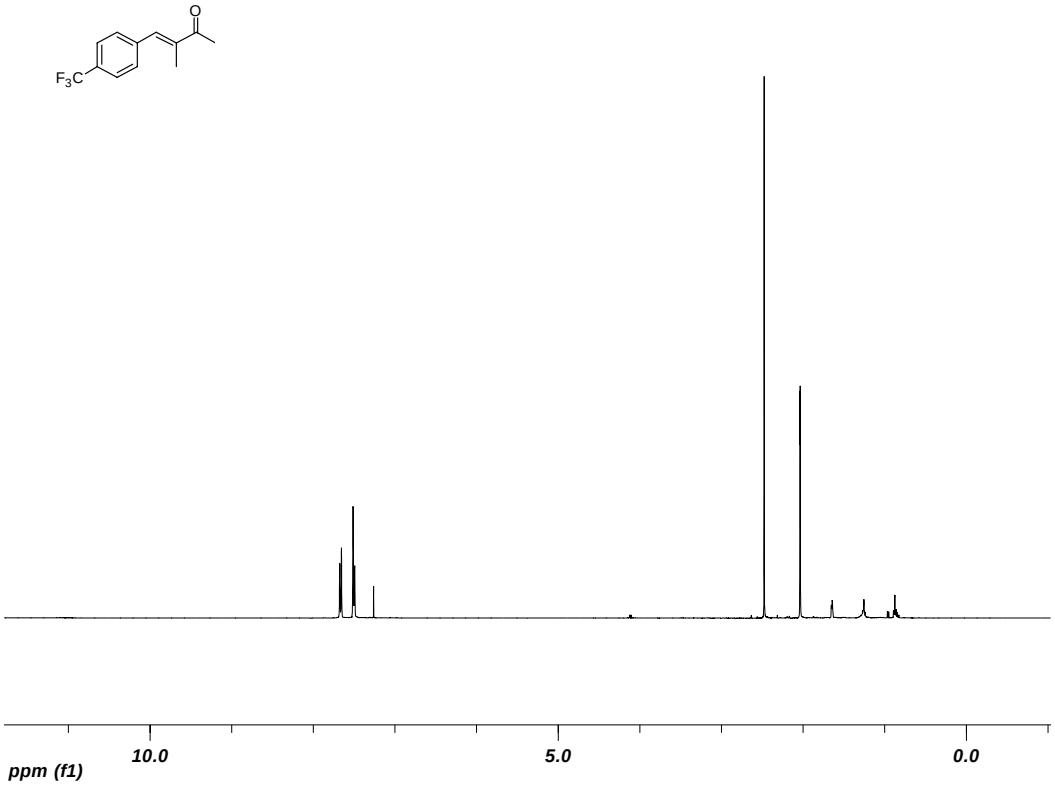
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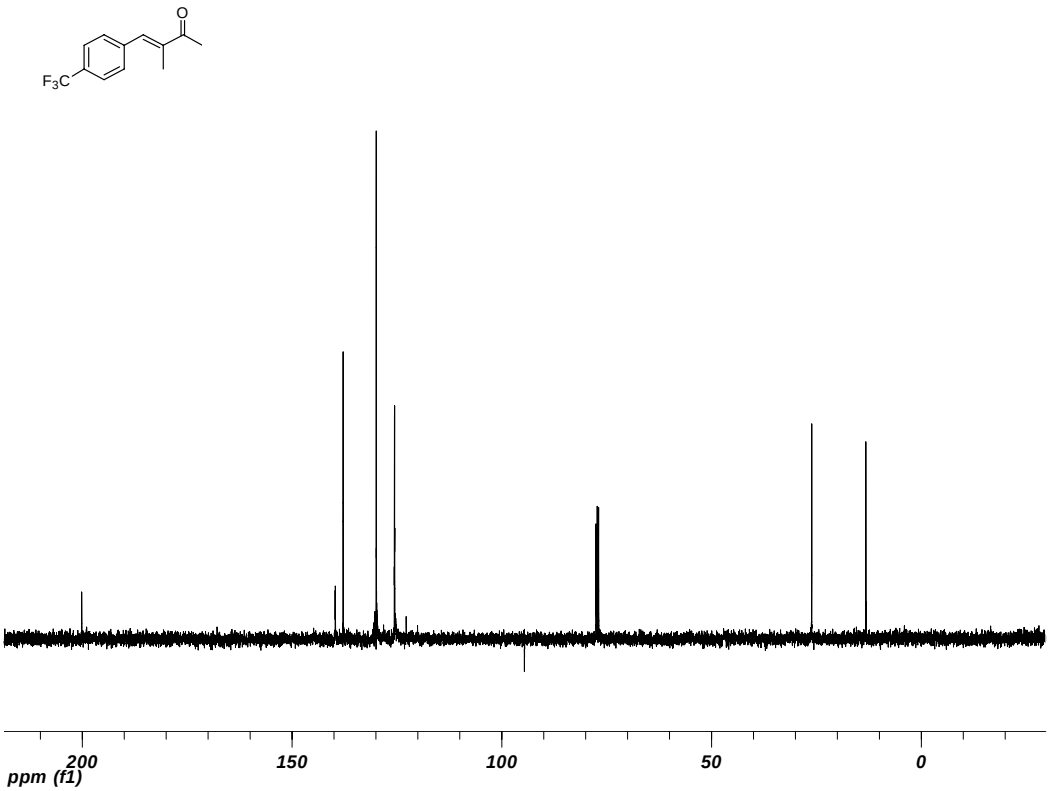
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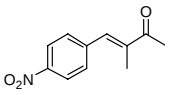
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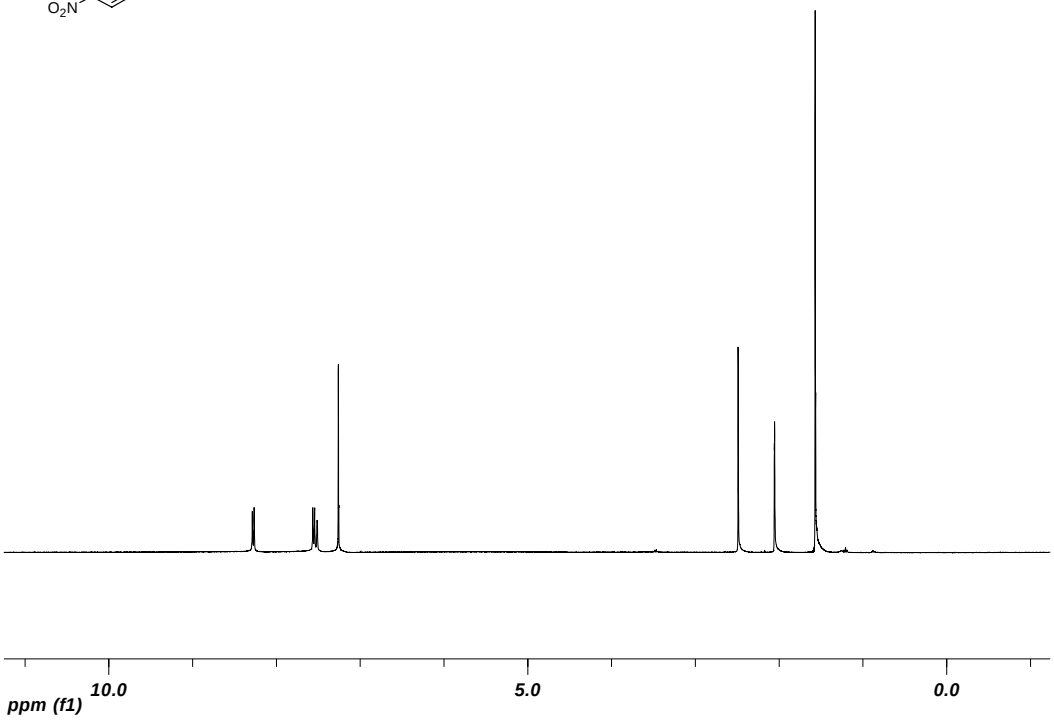
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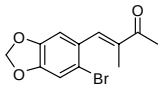
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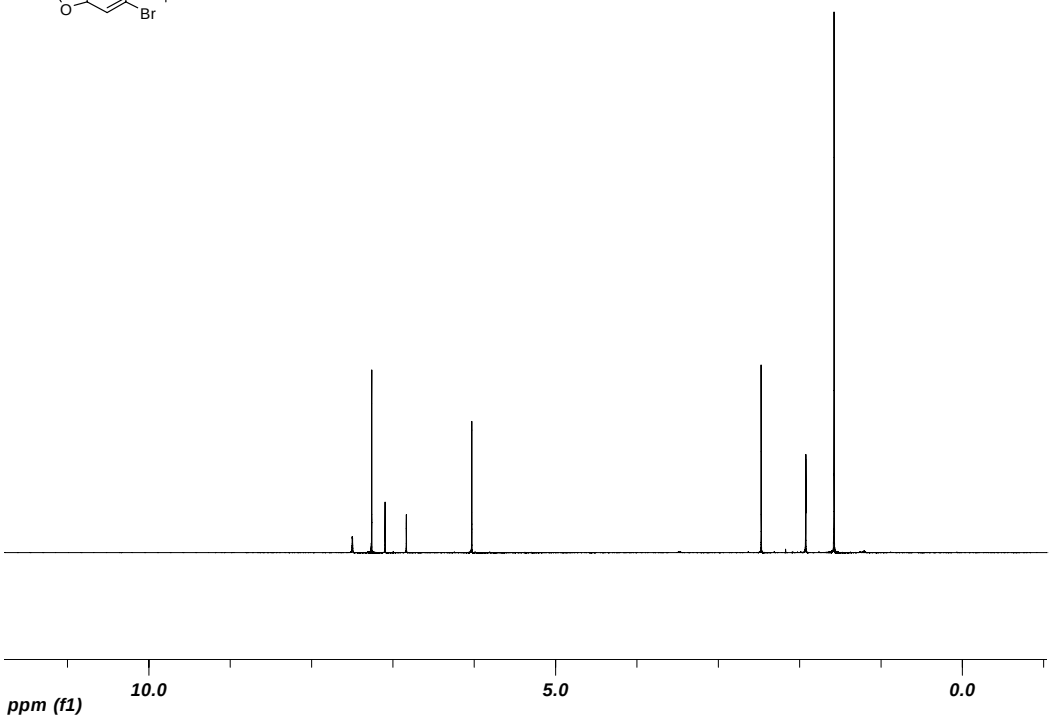
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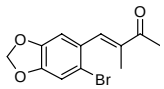
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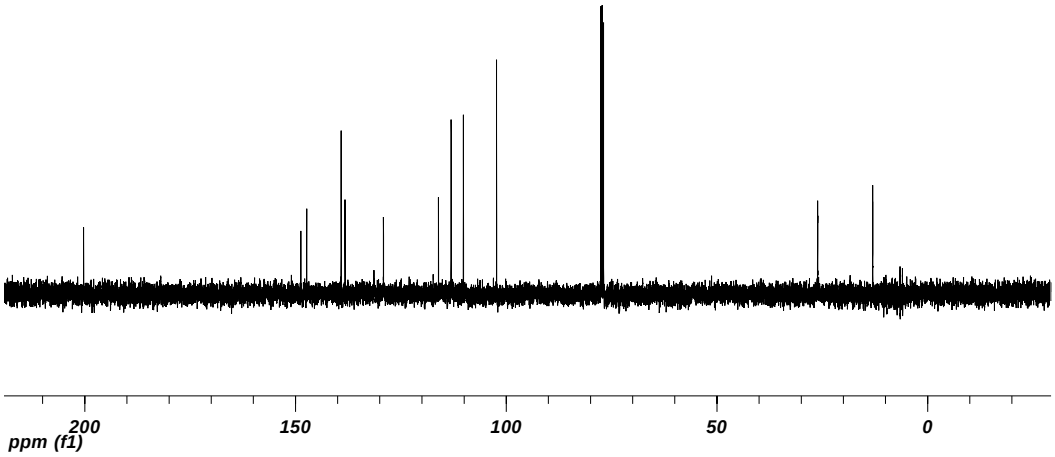
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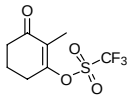
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O
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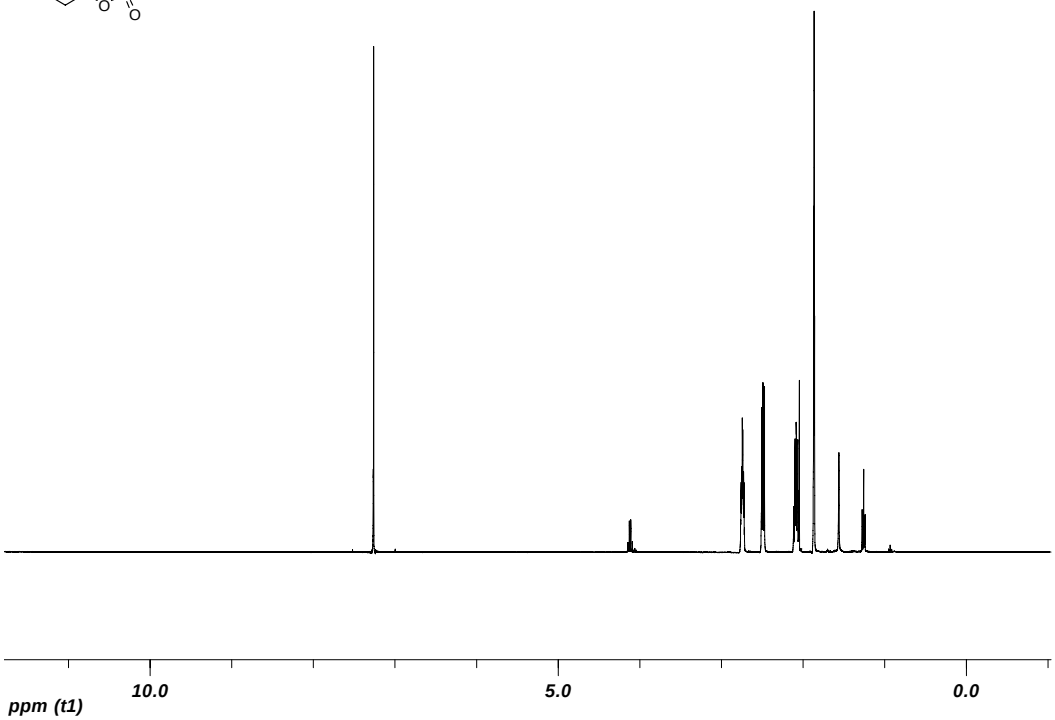
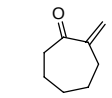
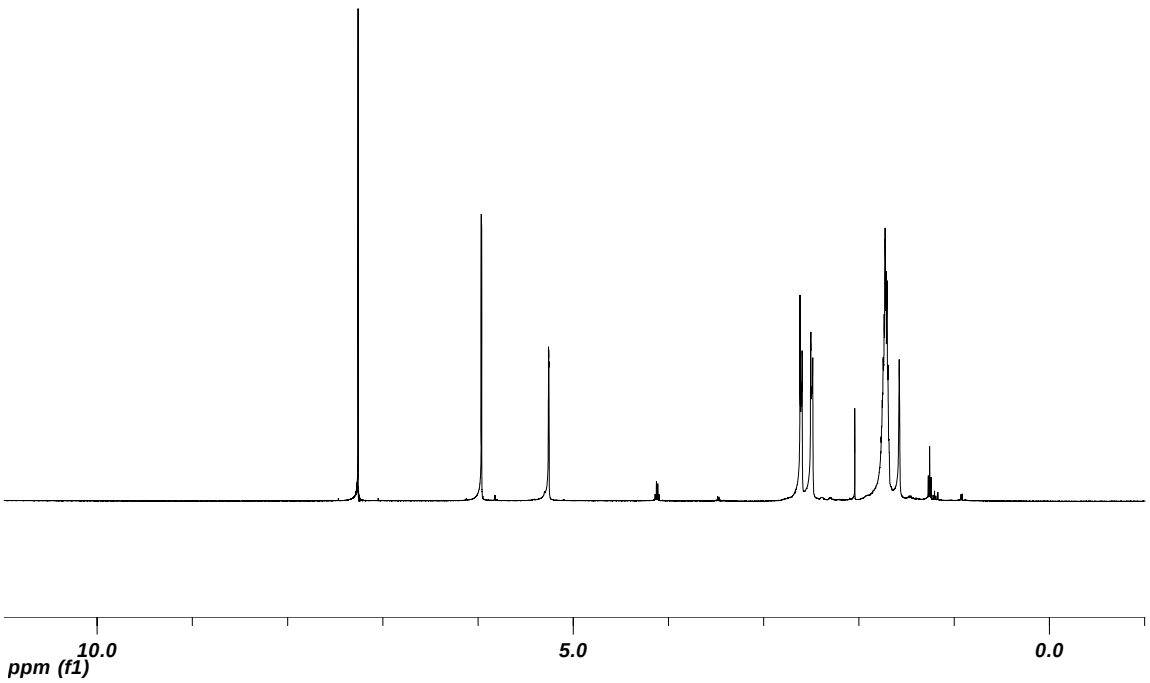
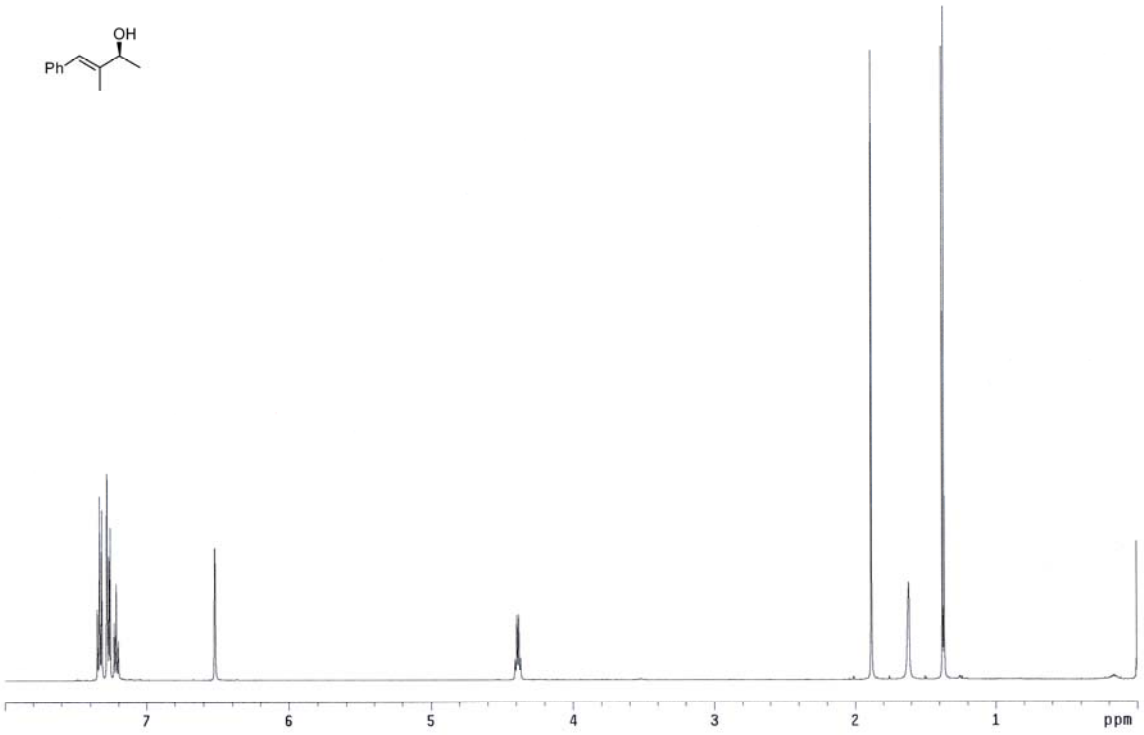
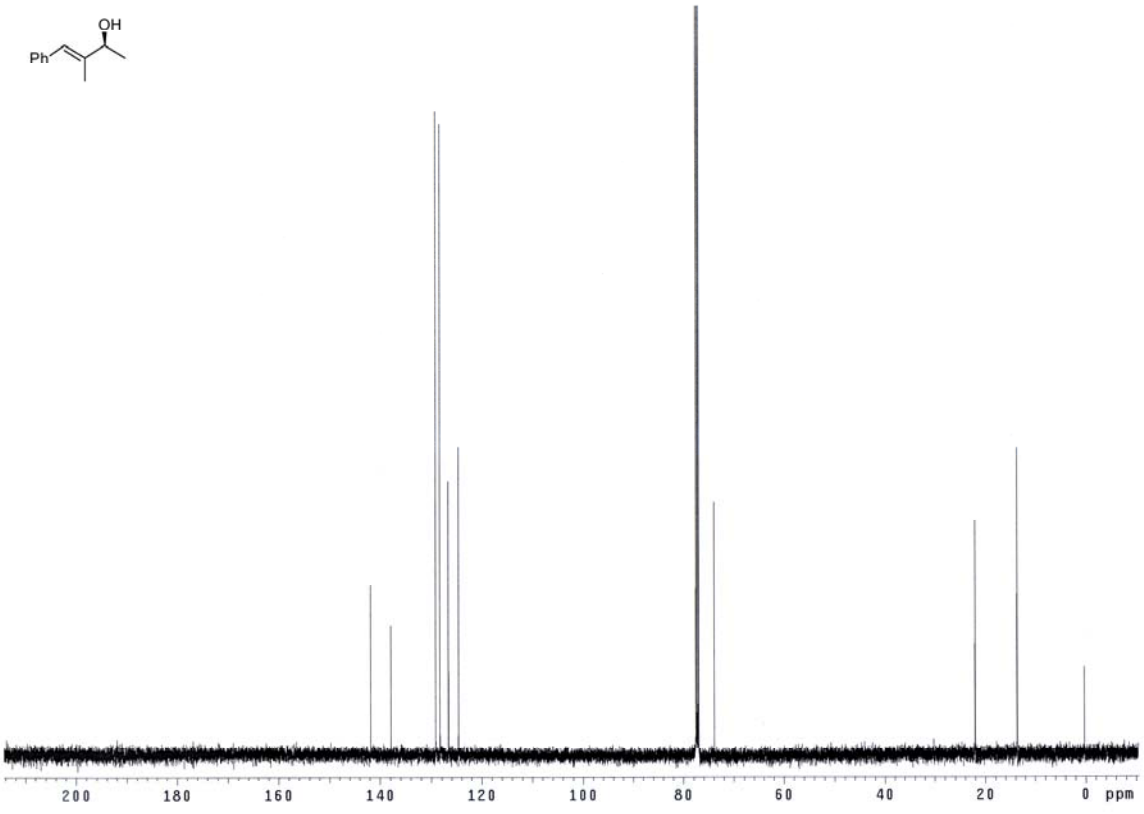

10.0
5.0
0.0
ppm (t1)

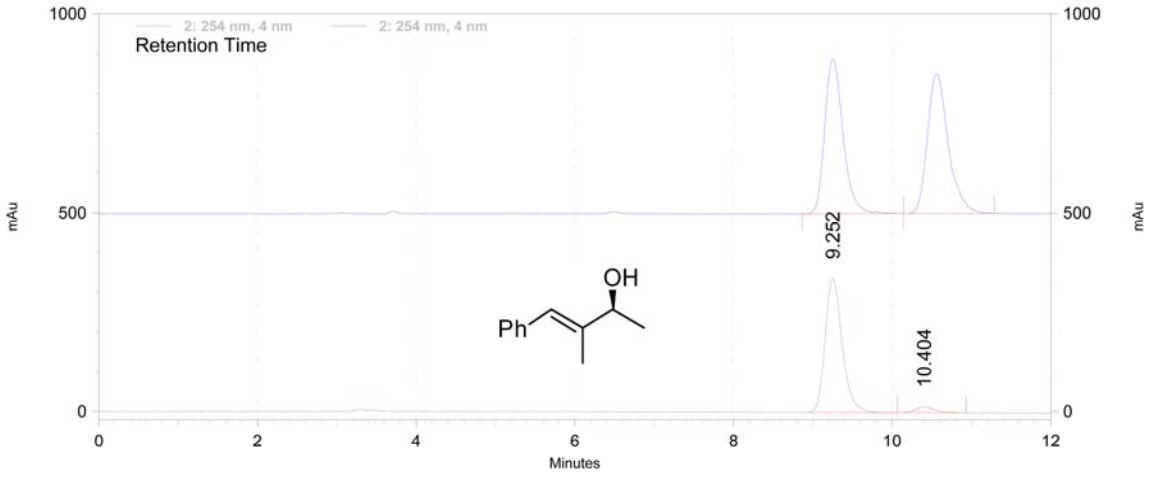

O


10.0
5.0
0.0
ppm (f1)


OH
Ph
7
6
5
4
3
2
1
ppm


OH
Ph
200
180
160
140
120
100
80
60
40
20
0
ppm

column: CHIRALCEL OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 5% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

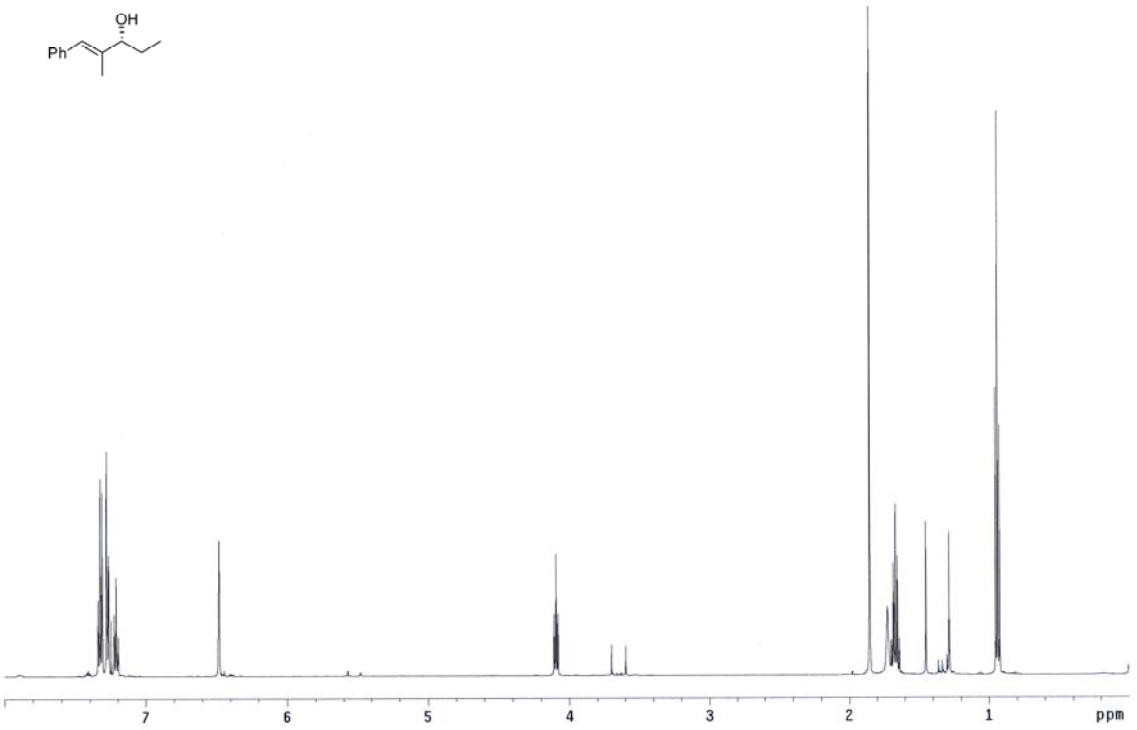
Retention Time	Area	Area %
9.452	18687789	49.35
10.760	19177710	50.65
Totals	37865499	100.00

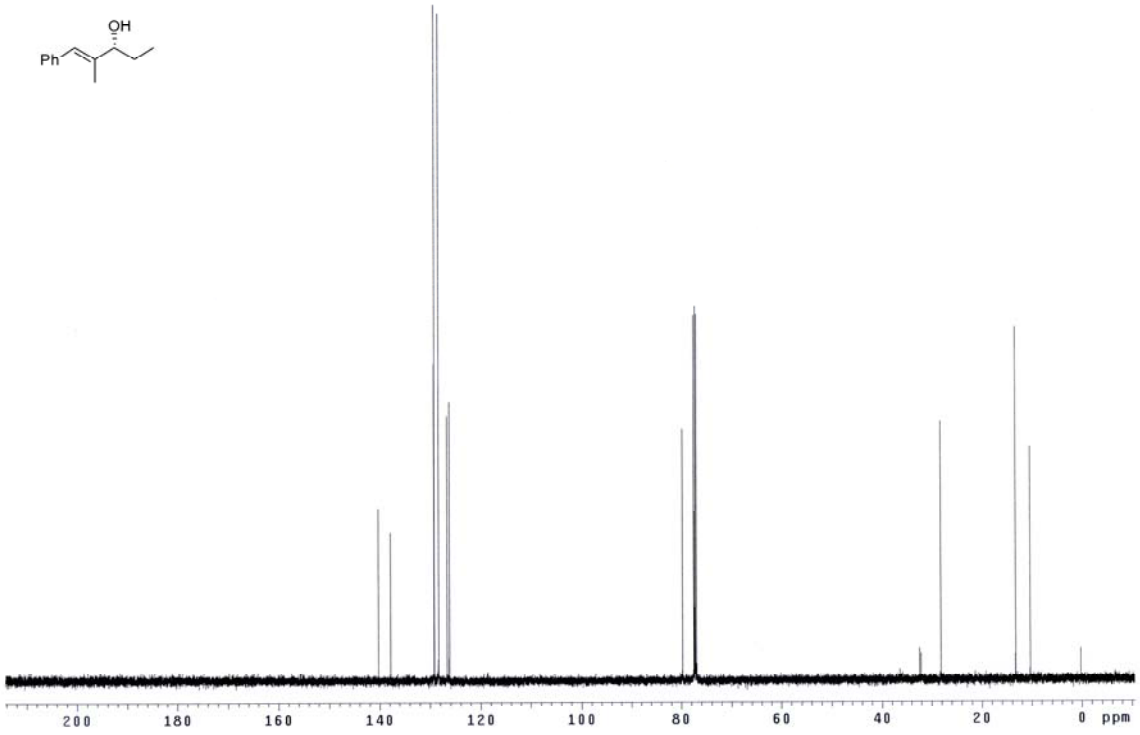
chiral experiment

2: 254 nm, 4 nm Results

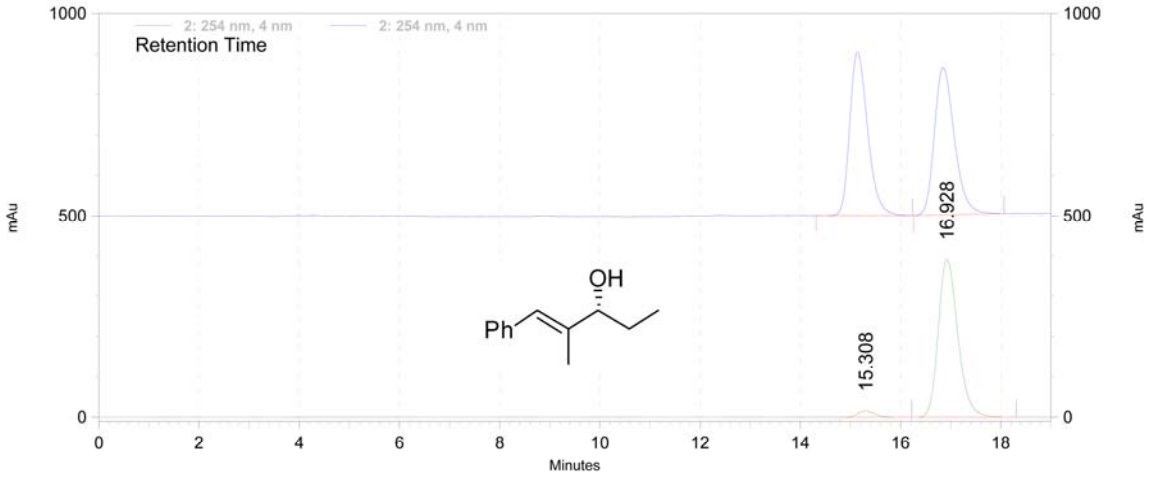
Retention Time	Area	Area %
9.252	12585252	95.51
10.404	591835	4.49
Totals	13177087	100.00

RM609_CA **91% *ee***


OH
Ph
7
6
5
4
3
2
1
ppm


OH
Ph
200
180
160
140
120
100
80
60
40
20
0
ppm

column: CHIRALCEL OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 2.5% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

Retention Time	Area	Area %
15.640	25130215	49.96
17.348	25170091	50.04

Totals	50300306	100.00

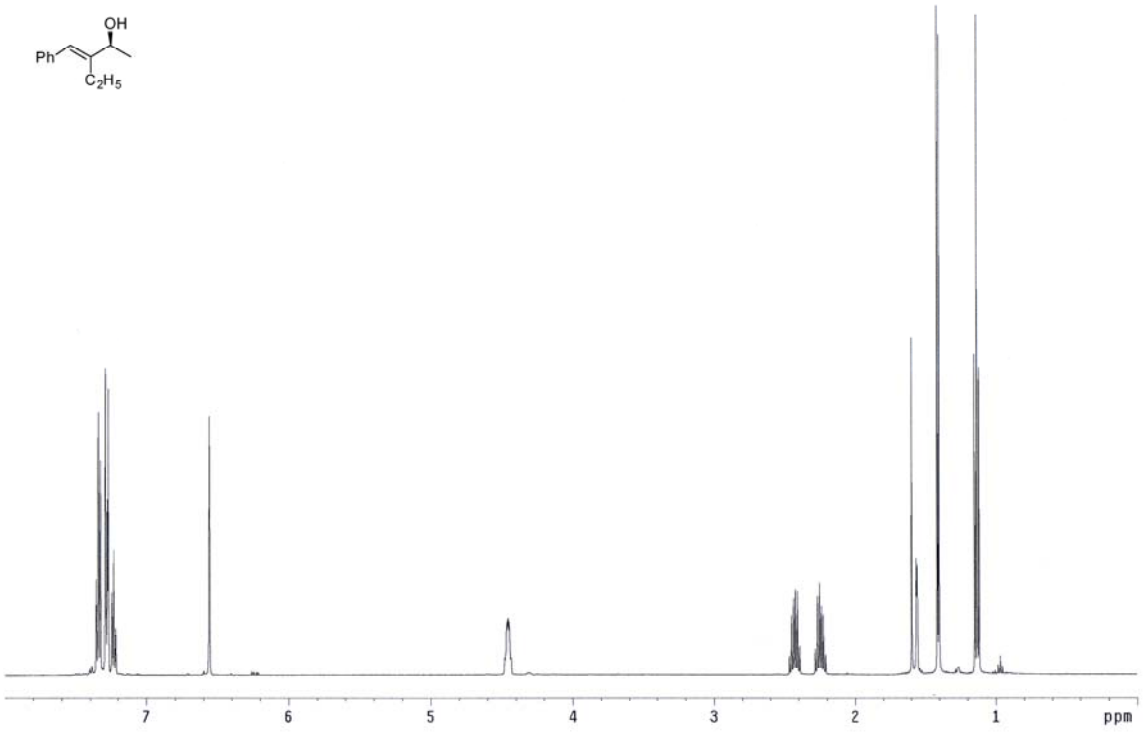
chiral experiment

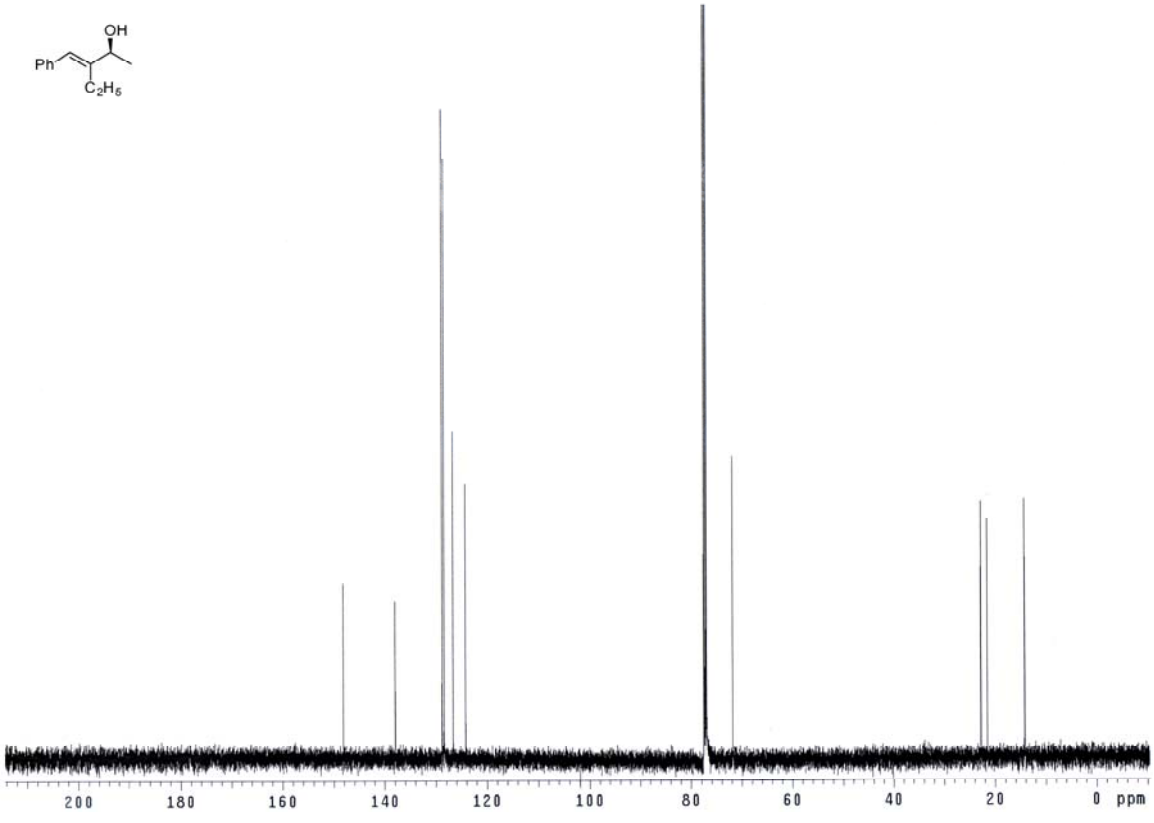
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
15.308	752500	3.44
16.928	21146504	96.56

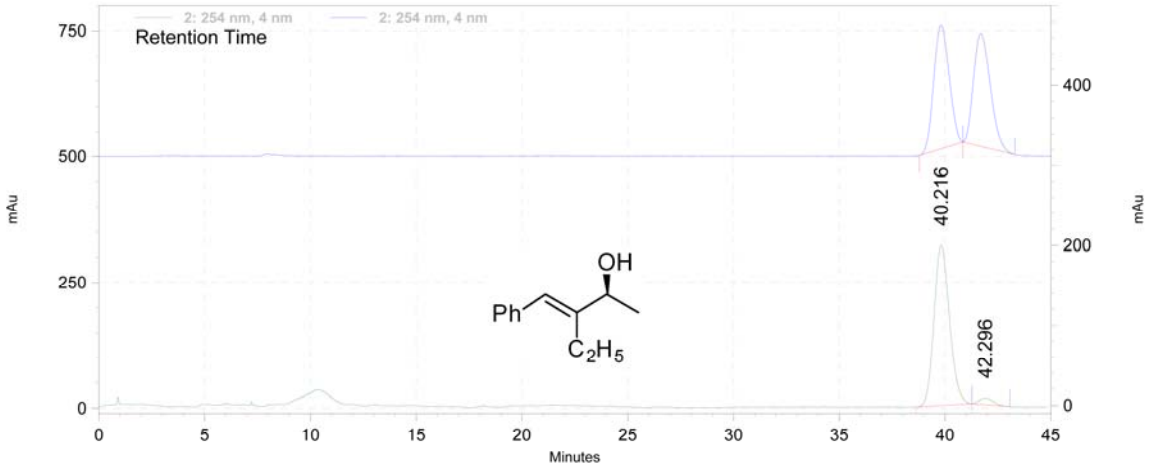
Totals	21899004	100.00

RM769_CA **93% ee**


OH
Ph
C2H5
7
6
5
4
3
2
1
ppm


OH
Ph
C2H5
200
180
160
140
120
100
80
60
40
20
0 ppm

column: CHIRALCEL OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 2% IPA/hexanes, 0.5 mL/min



racemic mixture

2: 254 nm, 4 nm Results

Retention Time	Area	Area %
39.808	24939545	50.06
41.688	24877024	49.94

Totals	49816569	100.00

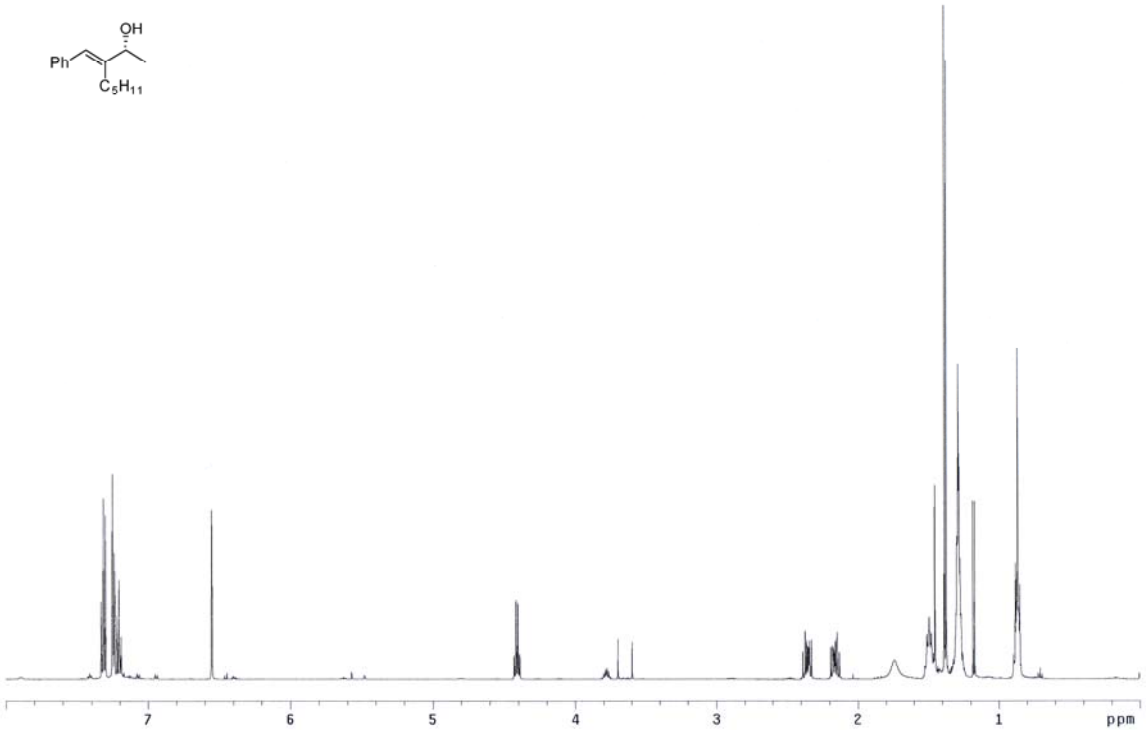
chiral experiment

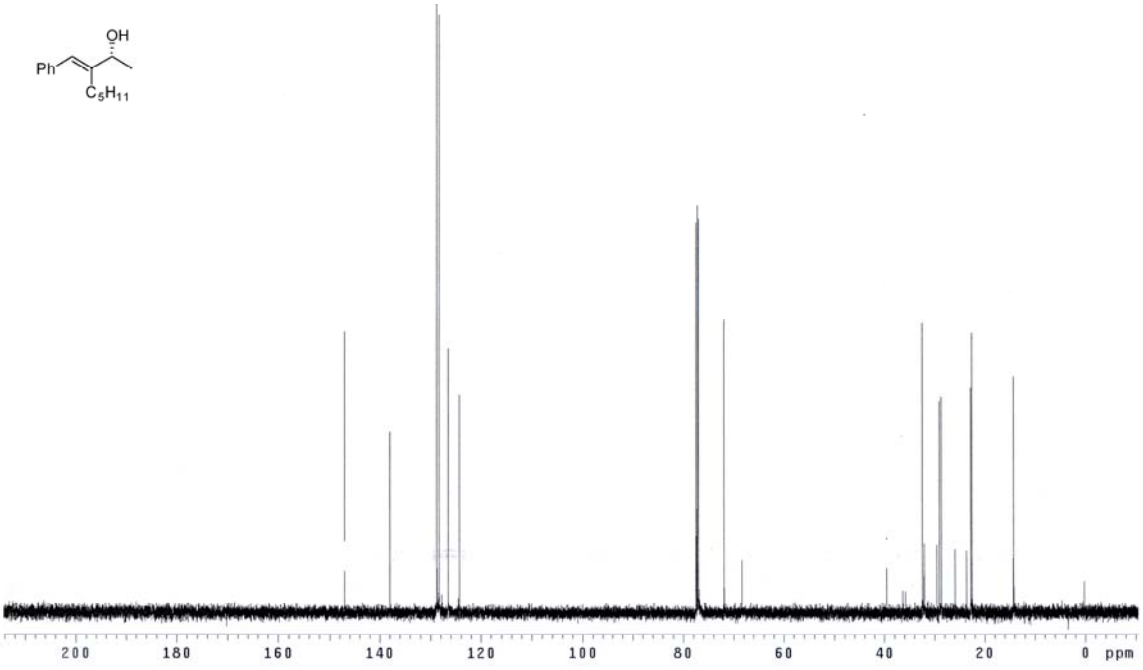
2: 254 nm, 4 nm Results

Retention Time	Area	Area %
40.216	10154345	96.51
42.296	367402	3.49

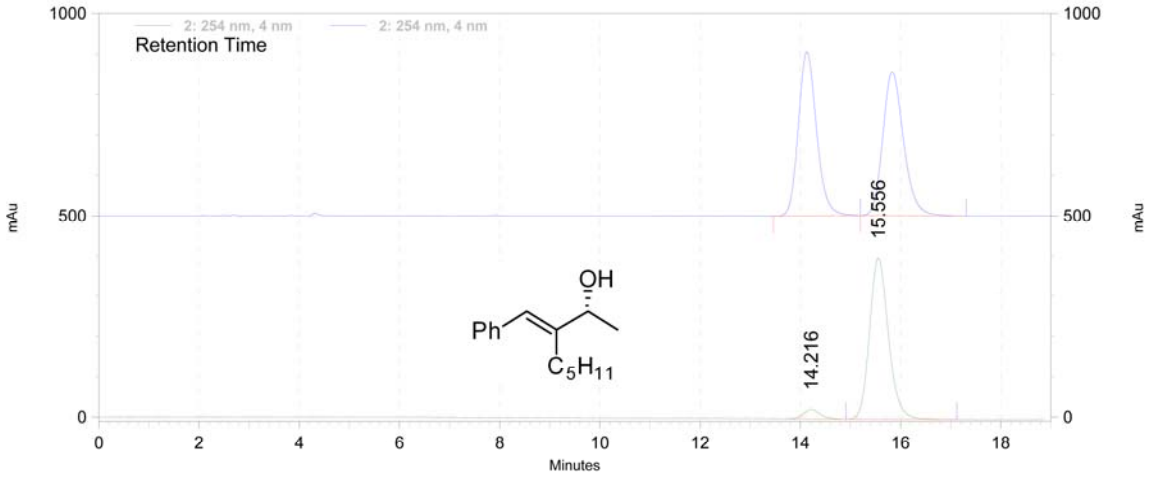
Totals	10521747	100.00

RM655_CA **93% *ee***


OH
Ph
C5H11
7
6
5
4
3
2
1
ppm


OH
Ph
C5H11
200
180
160
140
120
100
80
60
40
20
0 ppm

column: CHIRALCEL OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 2% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

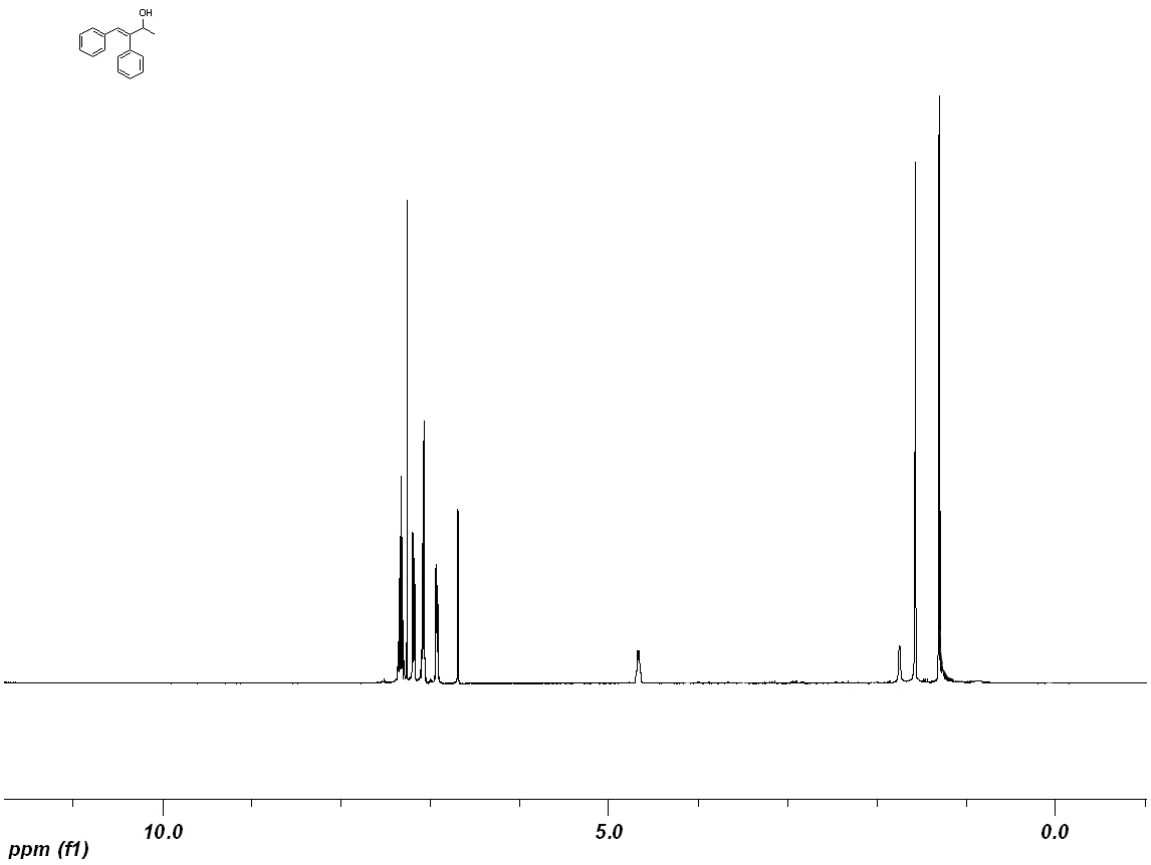
Retention Time	Area	Area %
15.132	11392421	50.02
16.836	11383052	49.98
Totals	22775473	100.00

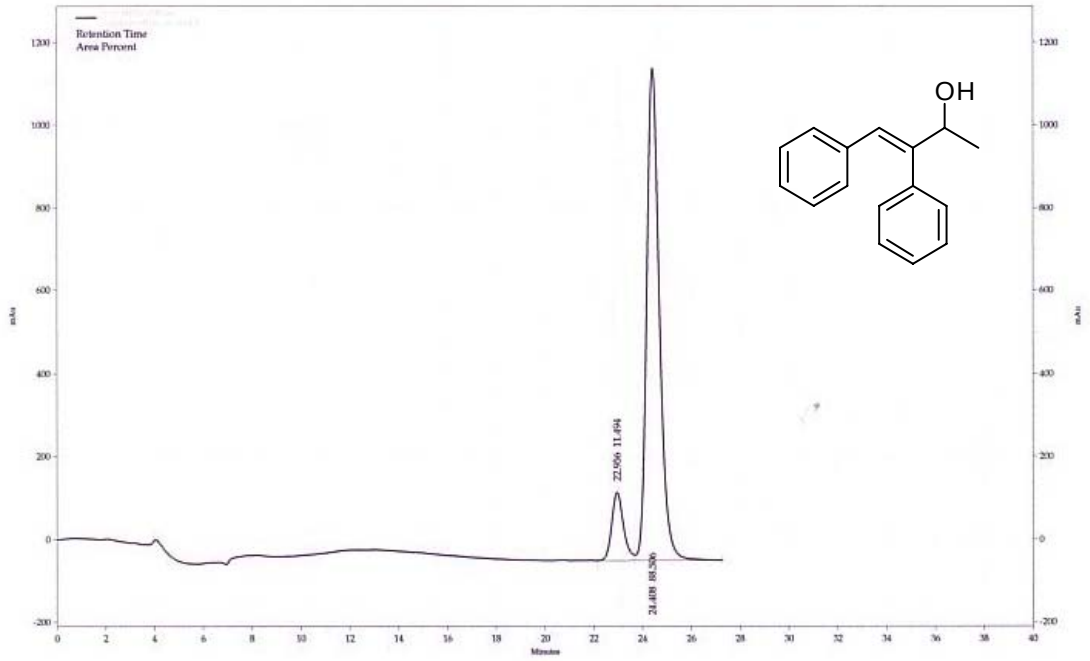
chiral experiment

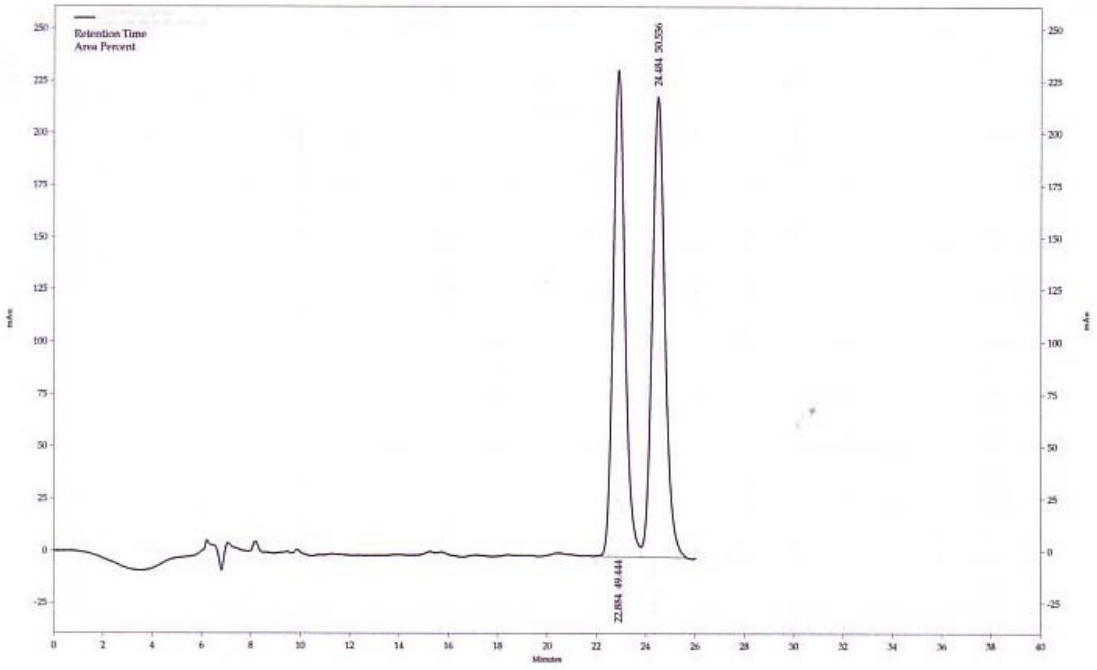
2: 254 nm, 4 nm Results

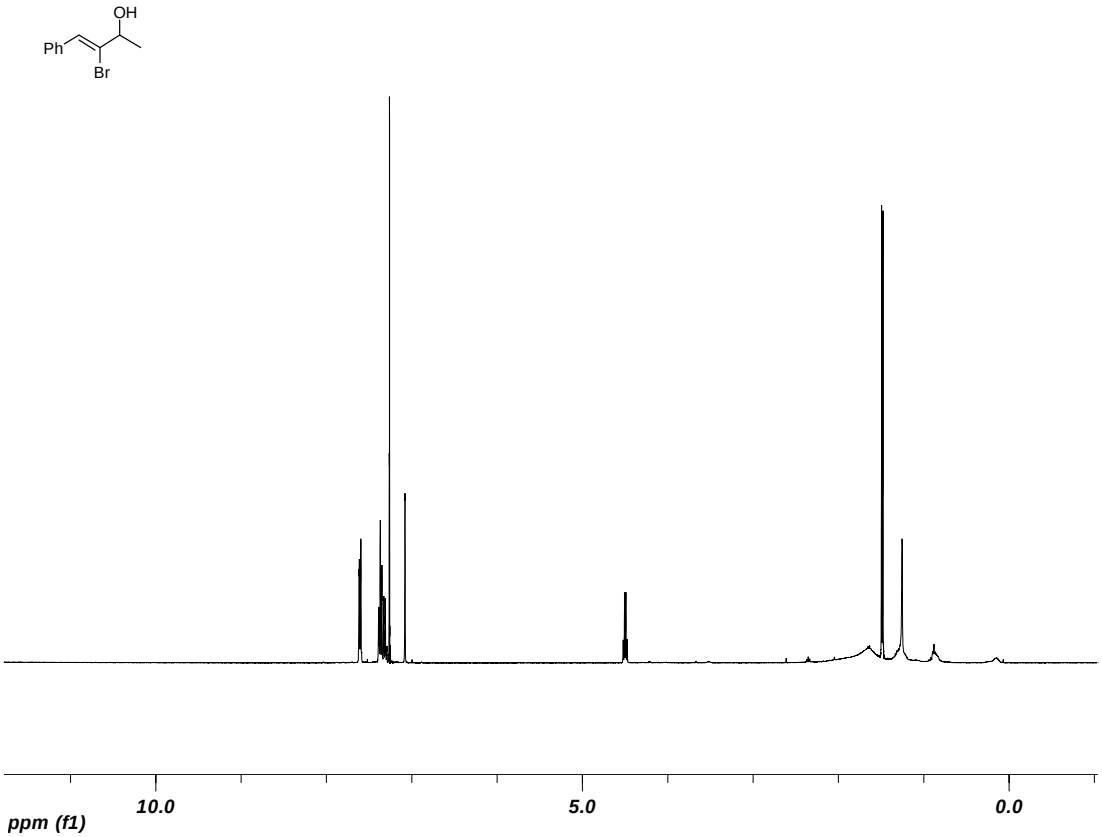
Retention Time	Area	Area %
14.216	444574	4.86
15.556	8700883	95.14
Totals	9145457	100.00

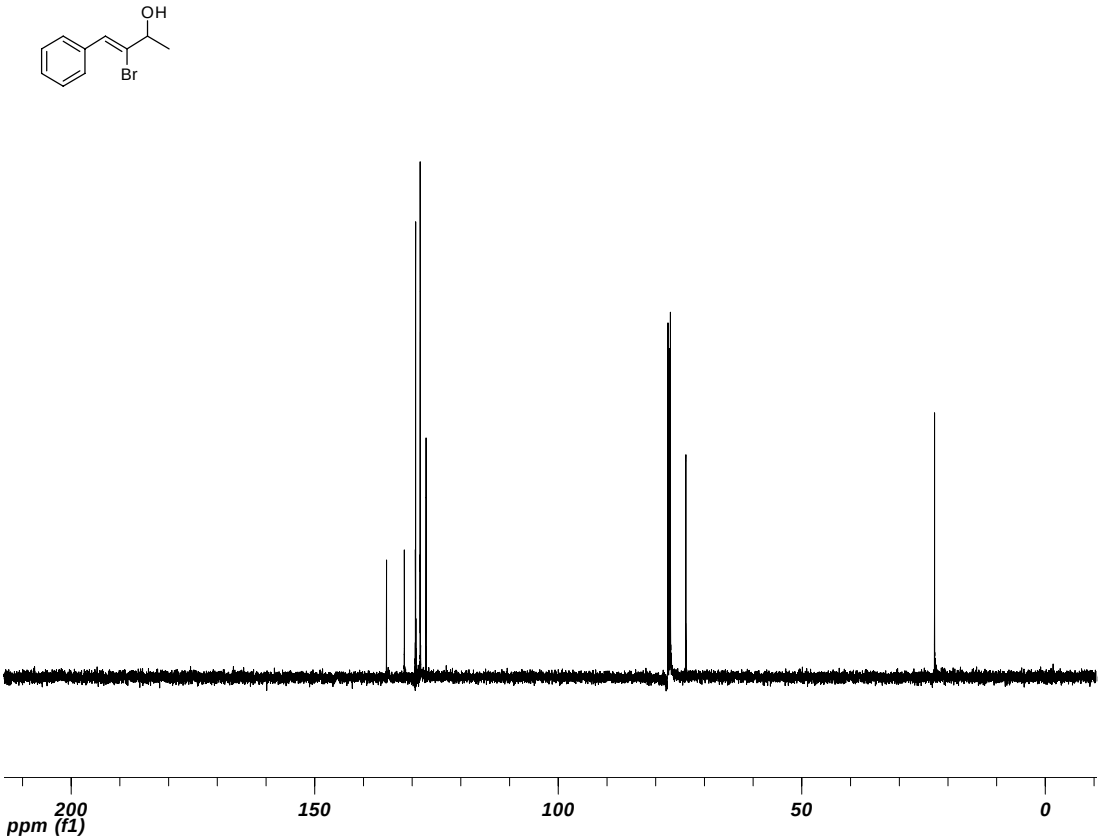
RM768_CA **90% ee**

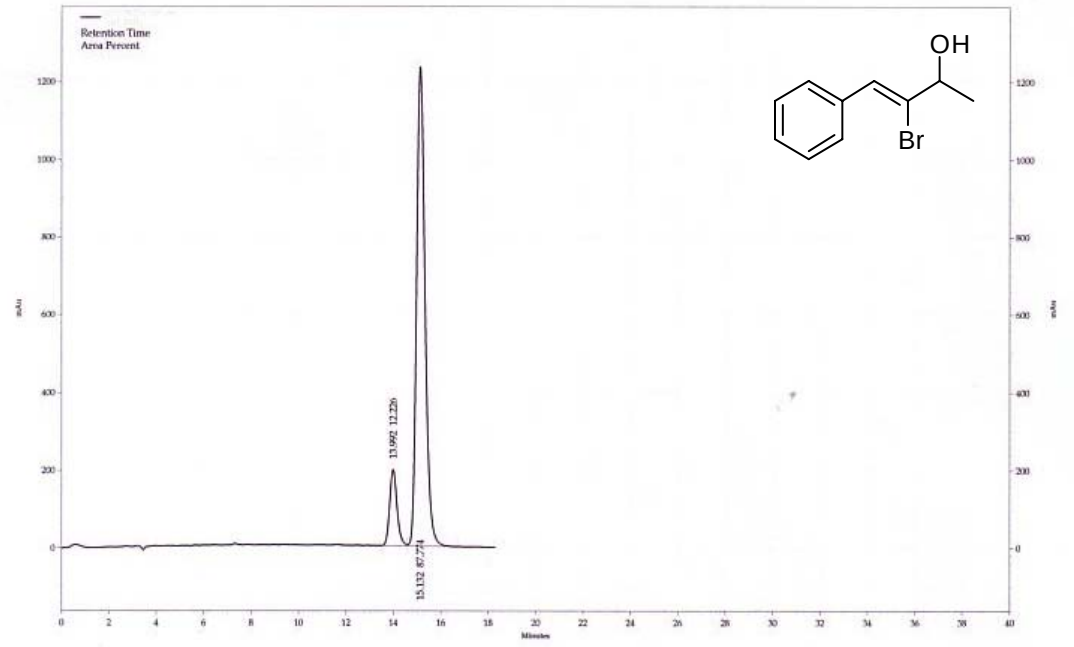

OH
10.0
5.0
0.0
ppm (f1)

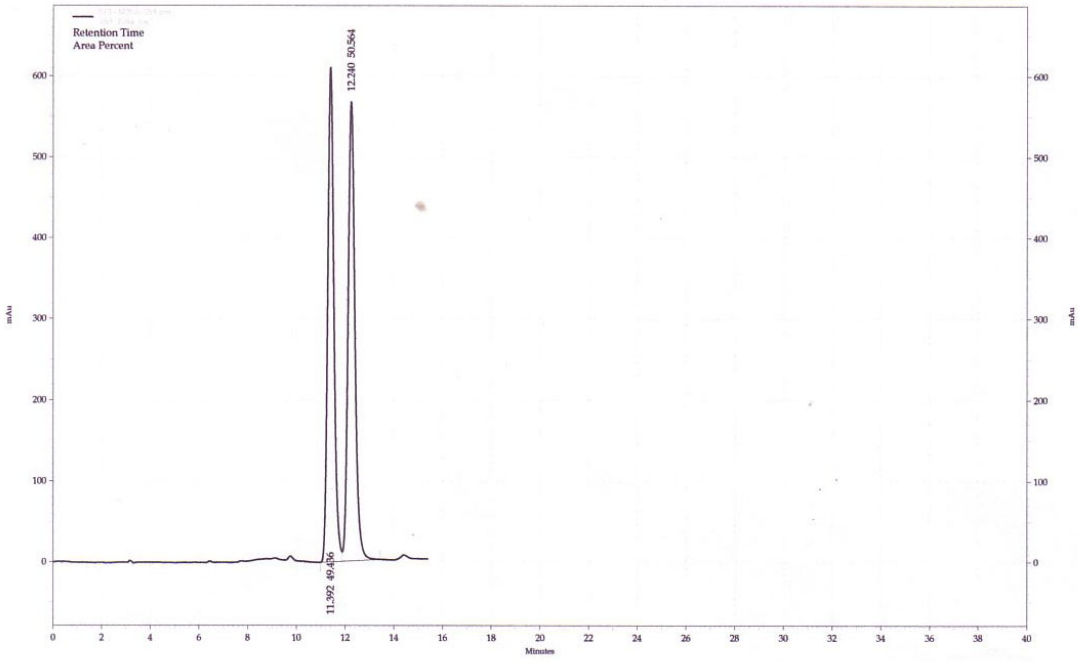

Retention Time
Area Percent
OH
22.956 11.494
24.488 88.506
mAu
Minutes

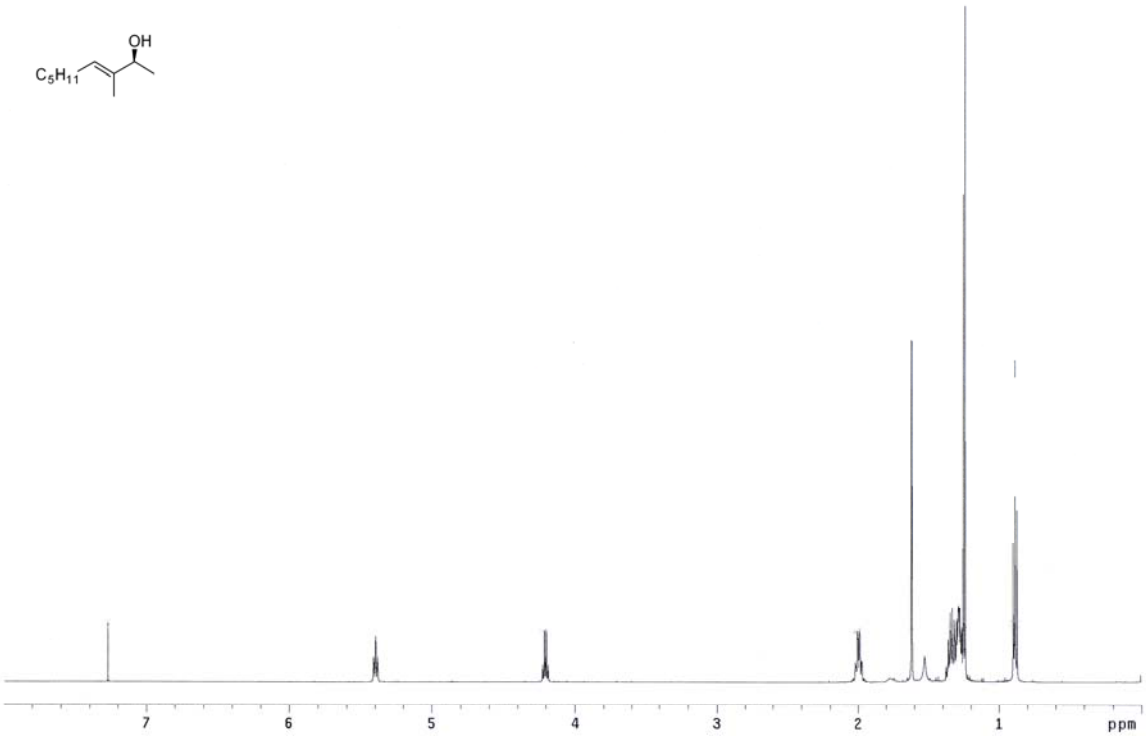

Retention Time
Area Percent
24.484 50.556
22.884 49.444
mAu
Minutes

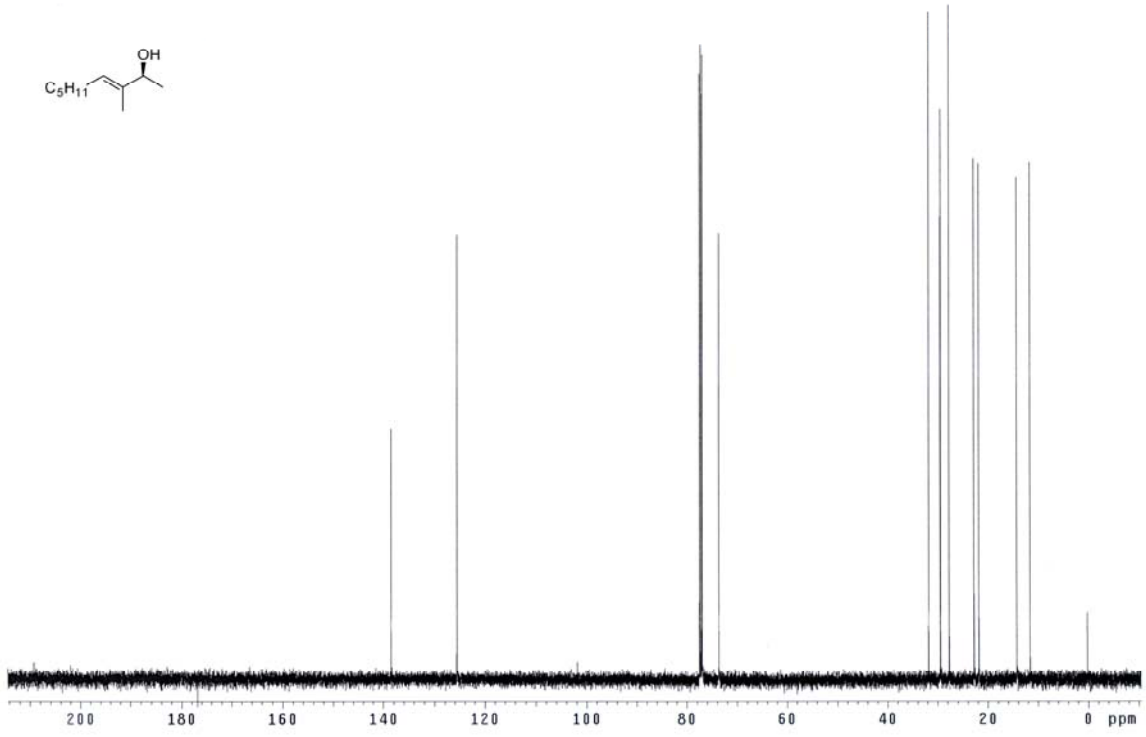

OH
Ph
Br
10.0
5.0
0.0
ppm (f1)


OH
Br
200
150
100
50
0
ppm (f1)

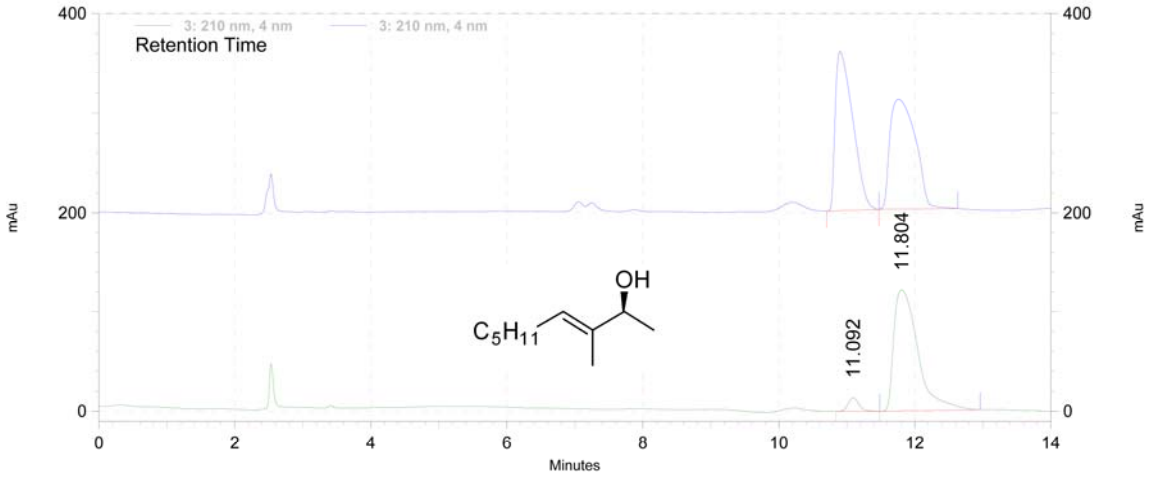

Retention Time
Area Percent
OH
Br
13.992 12.229
15.132 87.771
mAu
Minutes


Retention Time
Area Percent
12.240 50.564
11.392 49.436
mAu
Minutes


OH
C5H11
7
6
5
4
3
2
1
ppm


OH
C5H11
200
180
160
140
120
100
80
60
40
20
0 ppm

column: CHIRALPAK AD-H (serial ADH0CE-LJ049), 0.46 x 25 cm
conditions: 1% IPA/hexanes, 1.3 mL/min



racemic mixture

3: 210 nm, 4 nm Results

Retention Time	Area	Area %
10.900	2315780	49.90
11.760	2324782	50.10

Totals	4640562	100.00

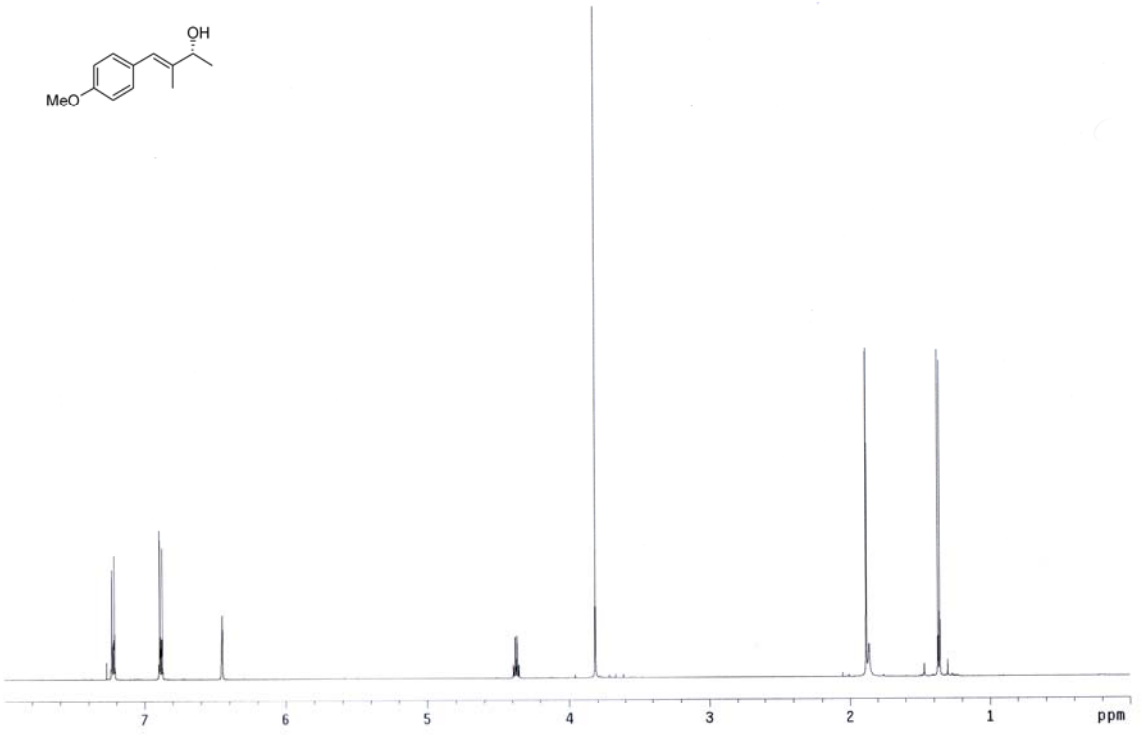
chiral experiment

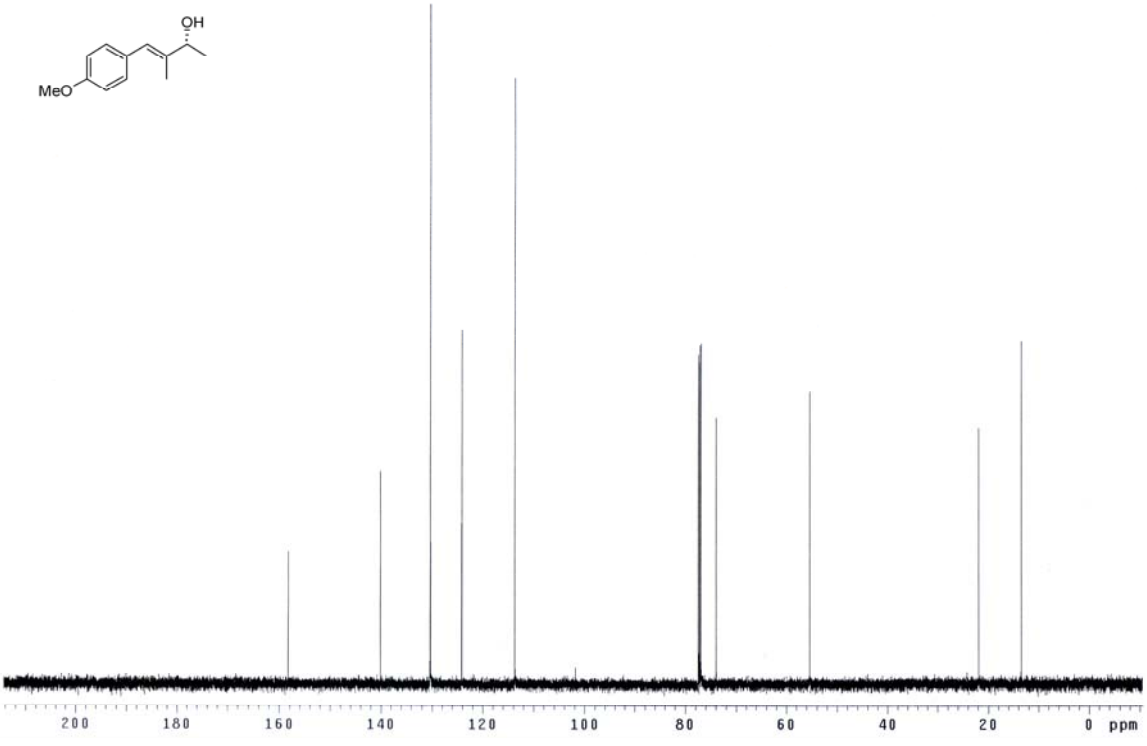
3: 210 nm, 4 nm Results

Retention Time	Area	Area %
11.092	49761	4.78
11.804	990419	95.22

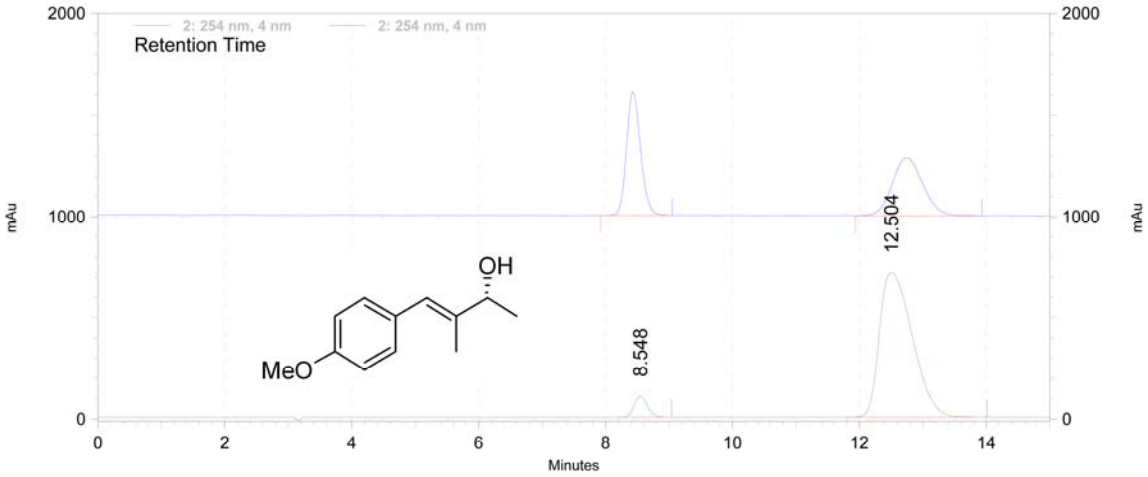
Totals	1040180	100.00

RM662_CA **90% *ee***


OH
MeO
7
6
5
4
3
2
1
ppm


OH
MeO
200
180
160
140
120
100
80
60
40
20
0 ppm

column: CHIRALCEL OB-H (serial OBH0CE-CE001), 0.46 x 25 cm
conditions: 10% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

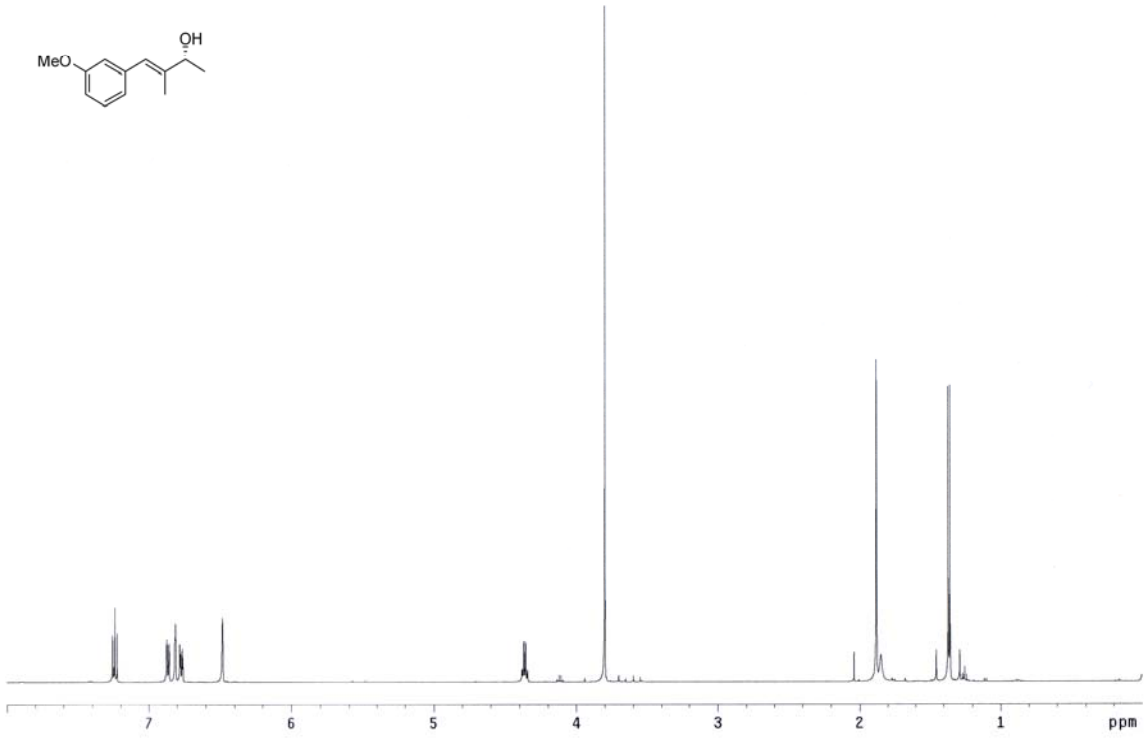
Retention Time	Area	Area %
8.532	9320462	49.67
12.844	9444695	50.33
Totals	18765157	100.00

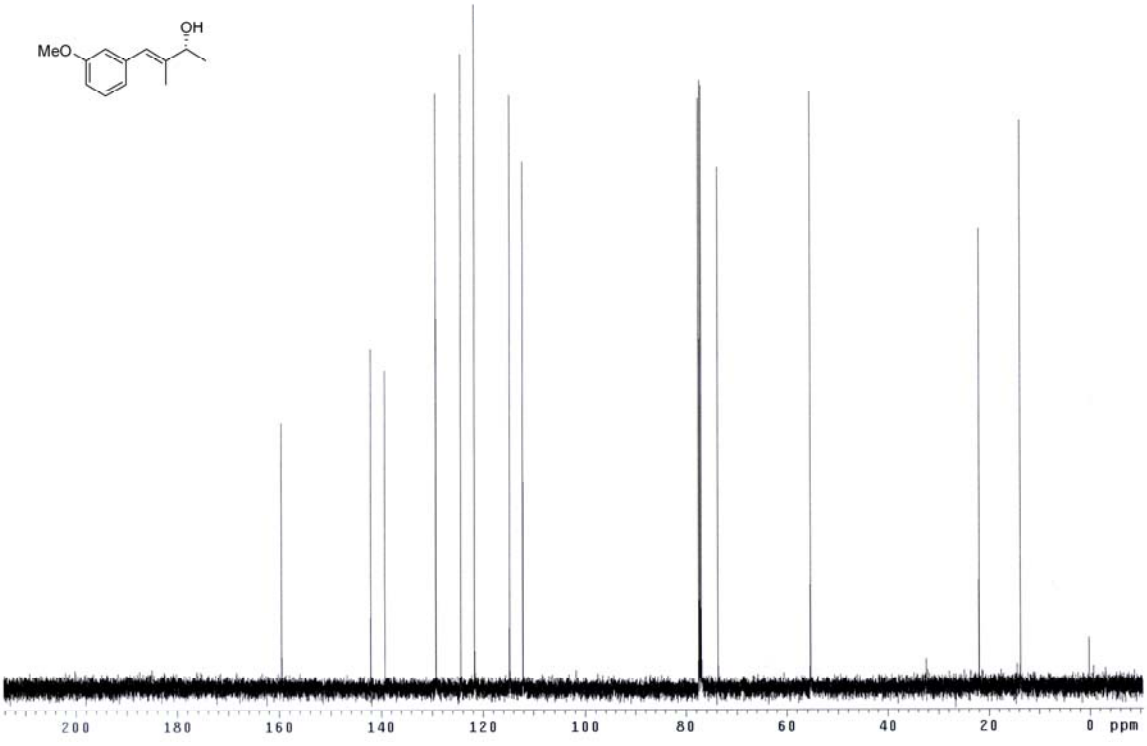
chiral experiment

2: 254 nm, 4 nm Results

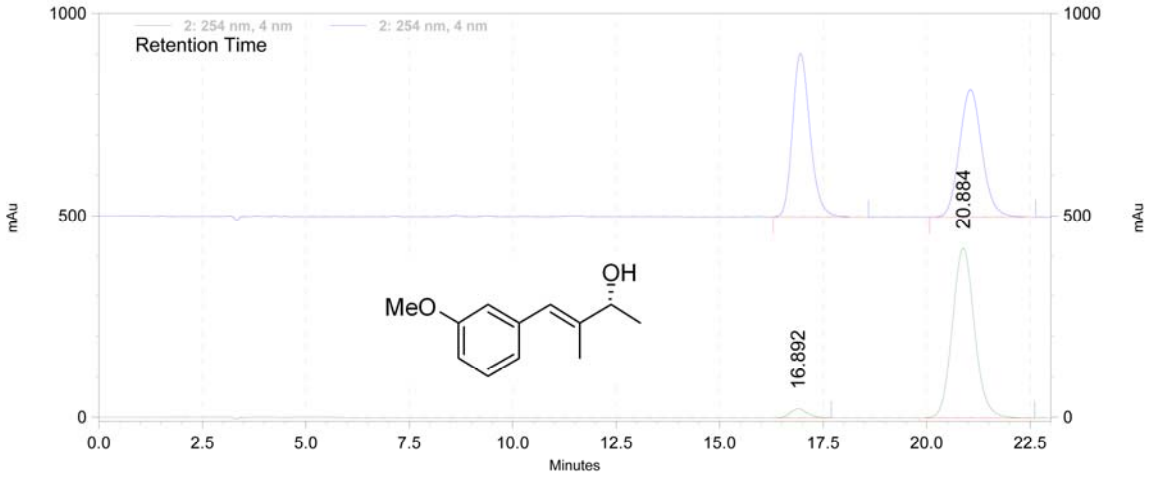
Retention Time	Area	Area %
8.548	3725778	5.51
12.504	63879102	94.49
Totals	67604880	100.00

RM733_CA **89 % *ee***


MeO
OH
7
6
5
4
3
2
1
ppm


MeO
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

column: CHIRALCEL OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 5% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

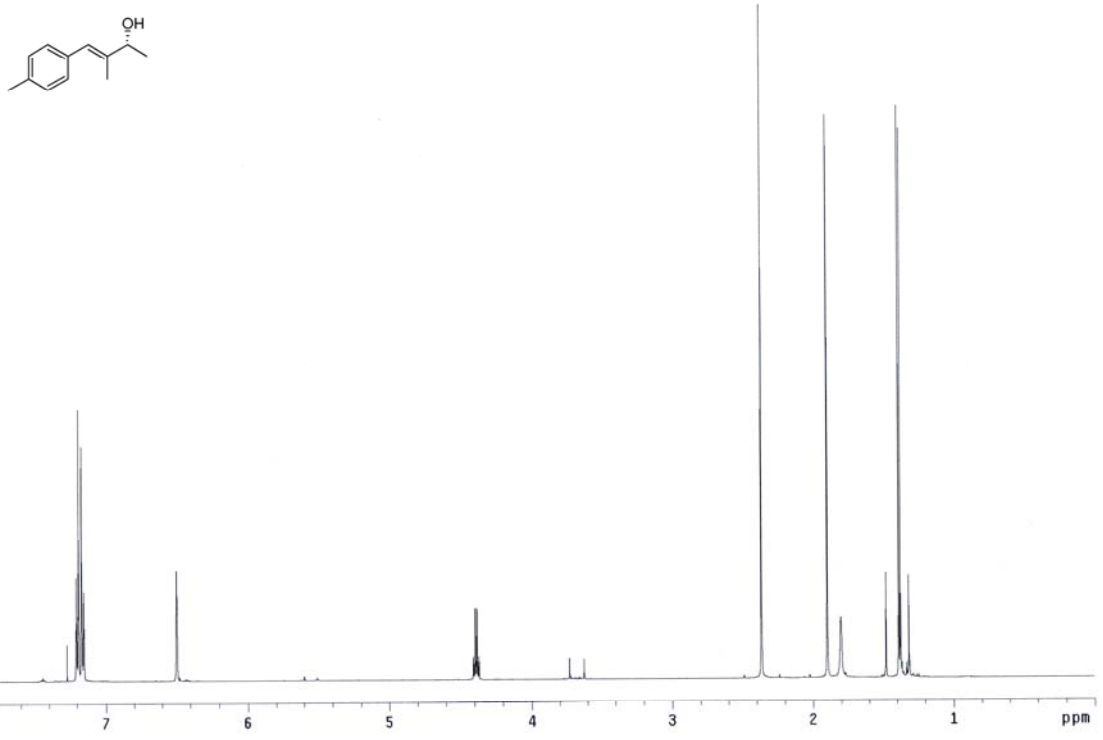
Retention Time	Area	Area %
16.948	14886737	49.96
21.056	14913513	50.04
Totals	29800250	100.00

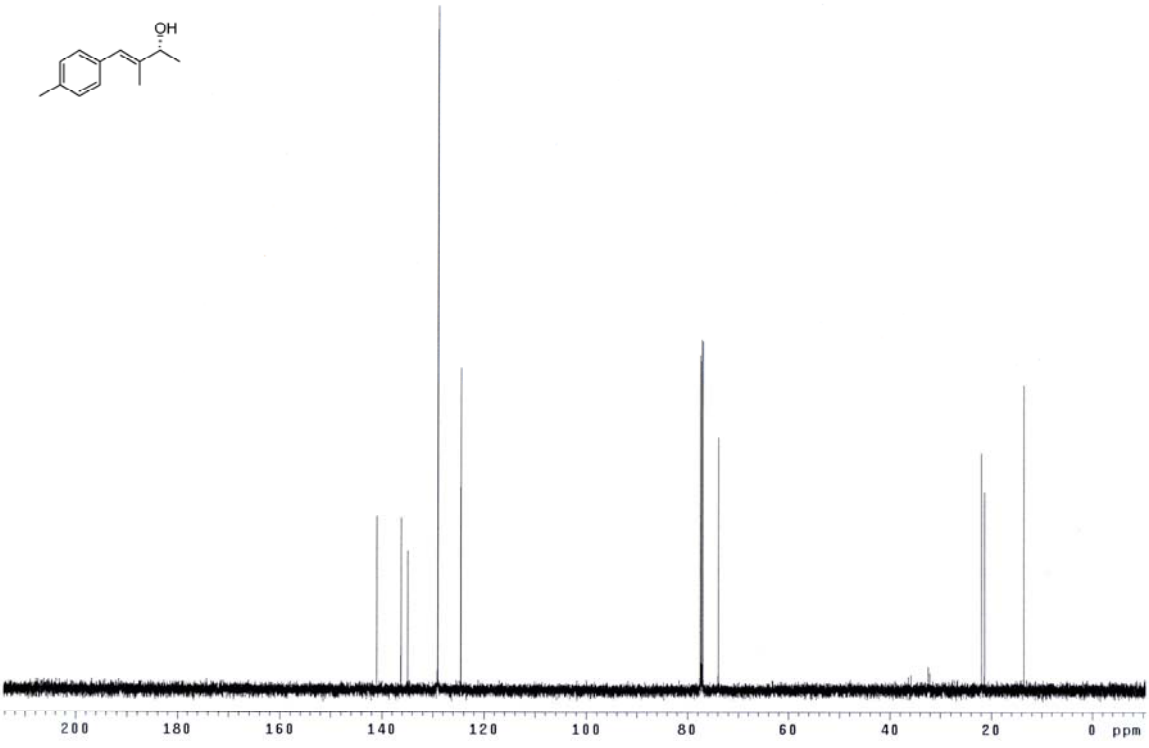
chiral experiment

2: 254 nm, 4 nm Results

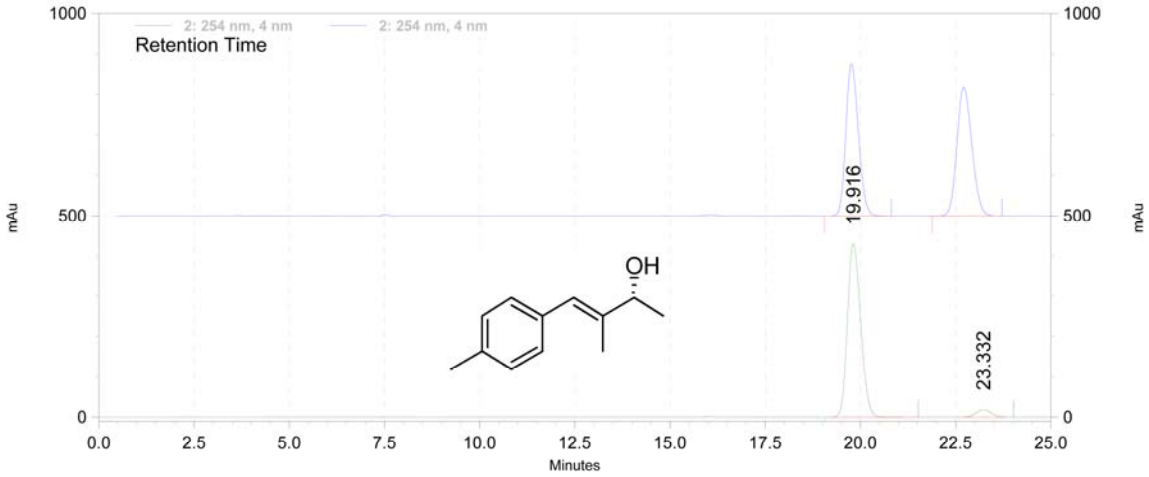
Retention Time	Area	Area %
16.892	851668	3.92
20.884	20870043	96.08
Totals	21721711	100.00

RM771_CA **92% ee**


OH
7
6
5
4
3
2
1
ppm


OH
200
180
160
140
120
100
80
60
40
20
0 ppm

column: CHIRALPAK AD-H (serial ADH0CE-LJ049), 0.46 x 25 cm
conditions: 2% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

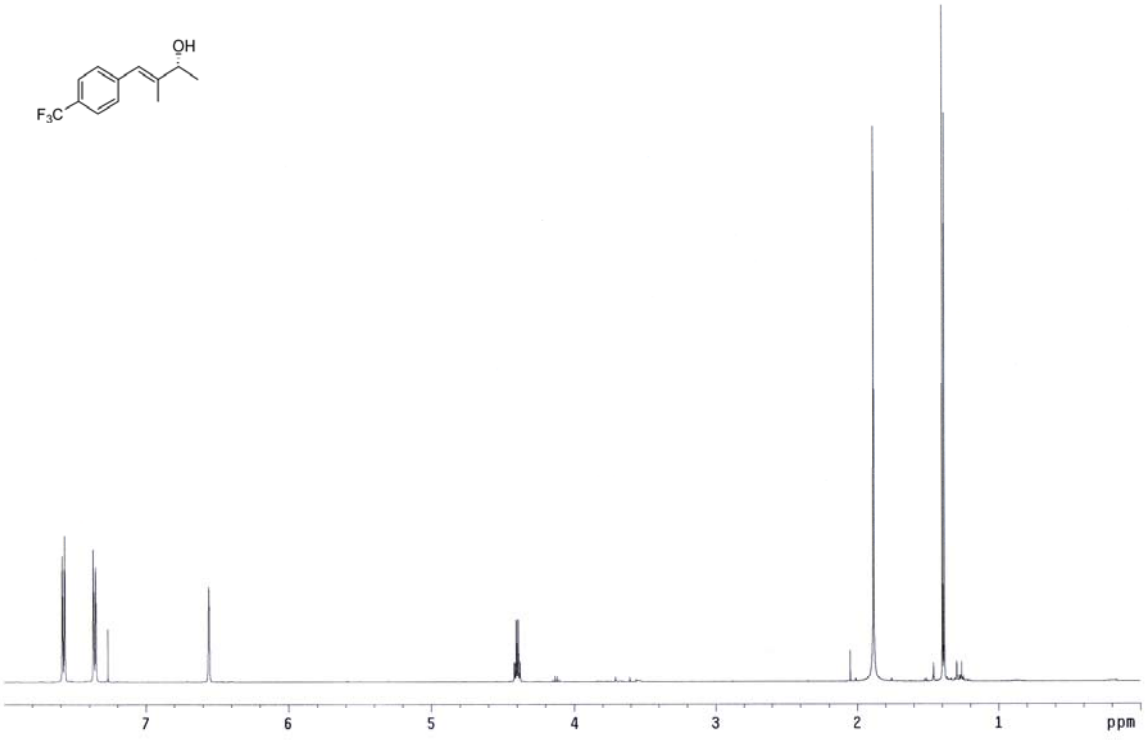
Retention Time	Area	Area %
19.264	24628867	49.87
22.212	24755737	50.13
Totals	49384604	100.00

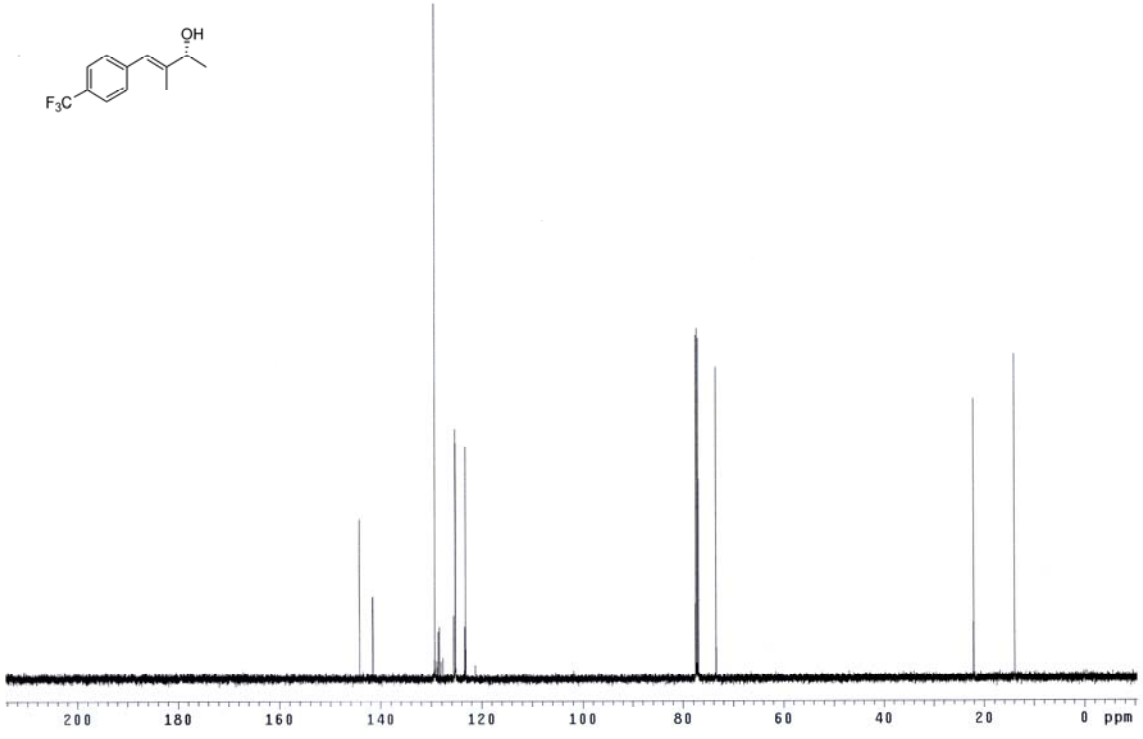
chiral experiment

2: 254 nm, 4 nm Results

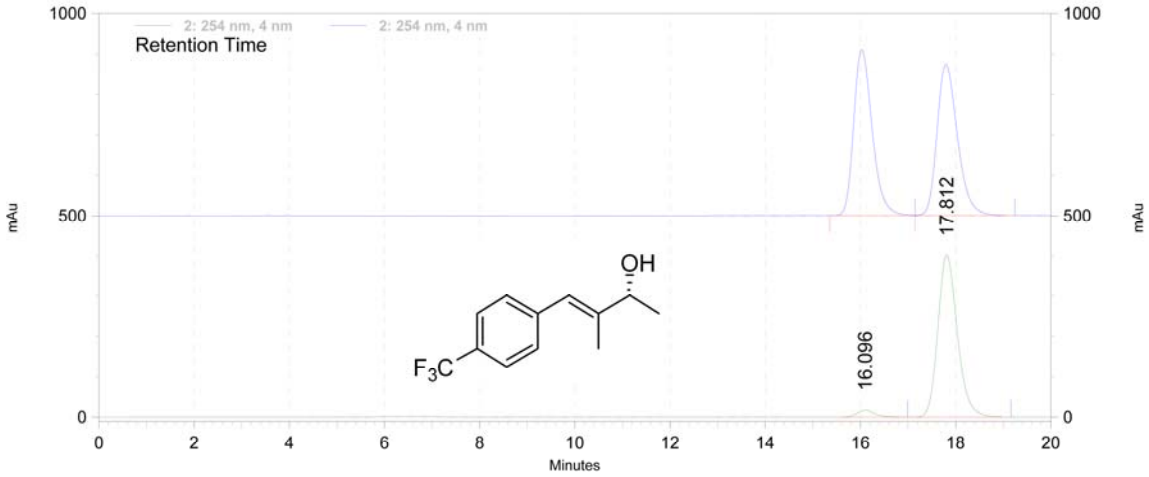
Retention Time	Area	Area %
19.916	26045810	95.10
23.332	1342390	4.90
Totals	27388200	100.00

RM772_CA **90% ee**


OH
F3C
7
6
5
4
3
2
1
ppm


OH
F3C
200
180
160
140
120
100
80
60
40
20
0 ppm

column: CHIRALCEL OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 2% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

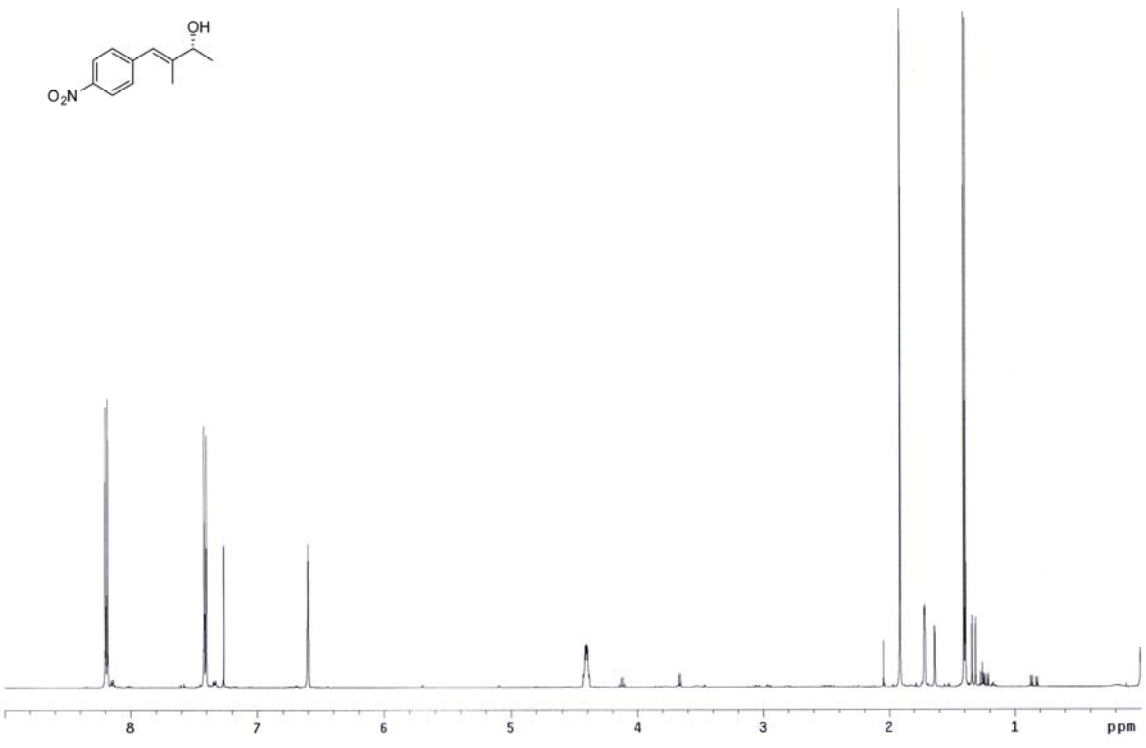
Retention Time	Area	Area %
17.224	44179122	49.83
18.996	44472226	50.17
Totals	88651348	100.00

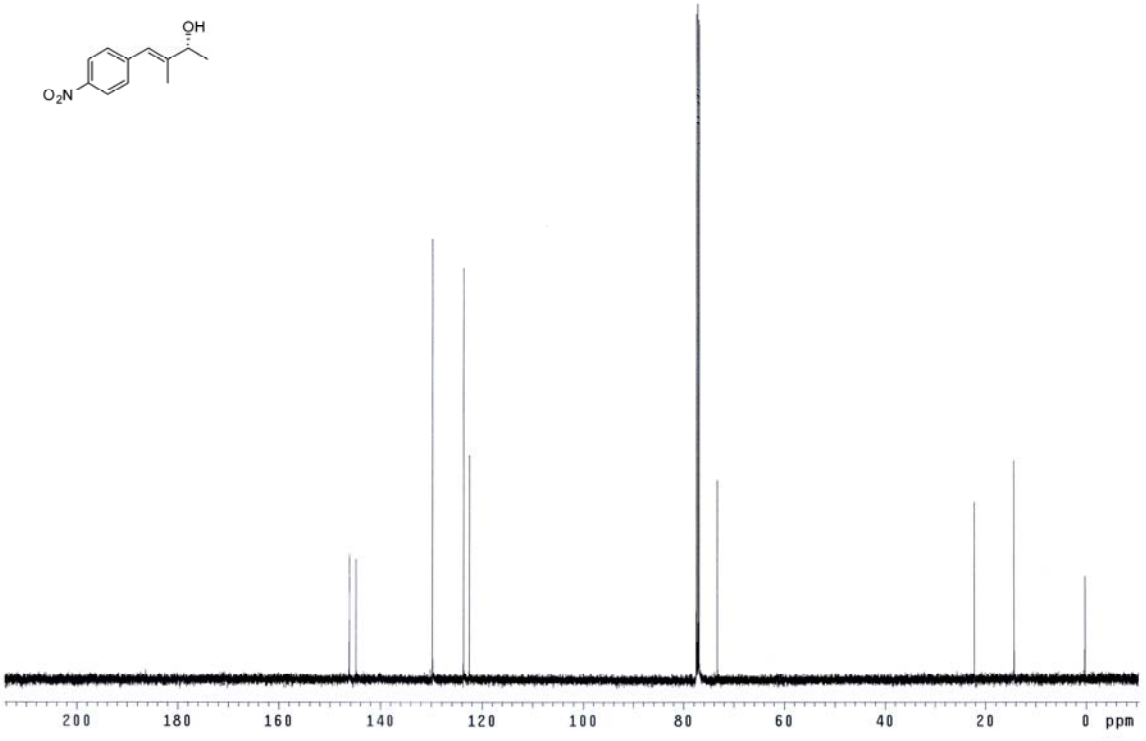
chiral experiment

2: 254 nm, 4 nm Results

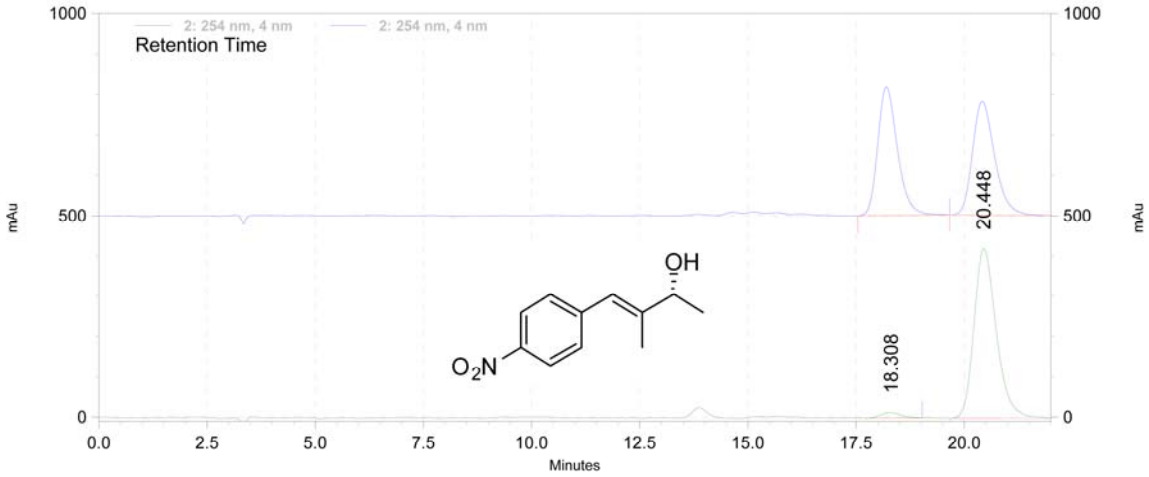
Retention Time	Area	Area %
16.096	583646	3.70
17.812	15169941	96.30
Totals	15753587	100.00

RM773_CA **93% ee**


OH
O2N
8
7
6
5
4
3
2
1
ppm


OH
O2N
200
180
160
140
120
100
80
60
40
20
0 ppm

column: OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 5% IPA/hexanes, 1.0 mL/min



racemic sample

2: 254 nm, 4 nm Results

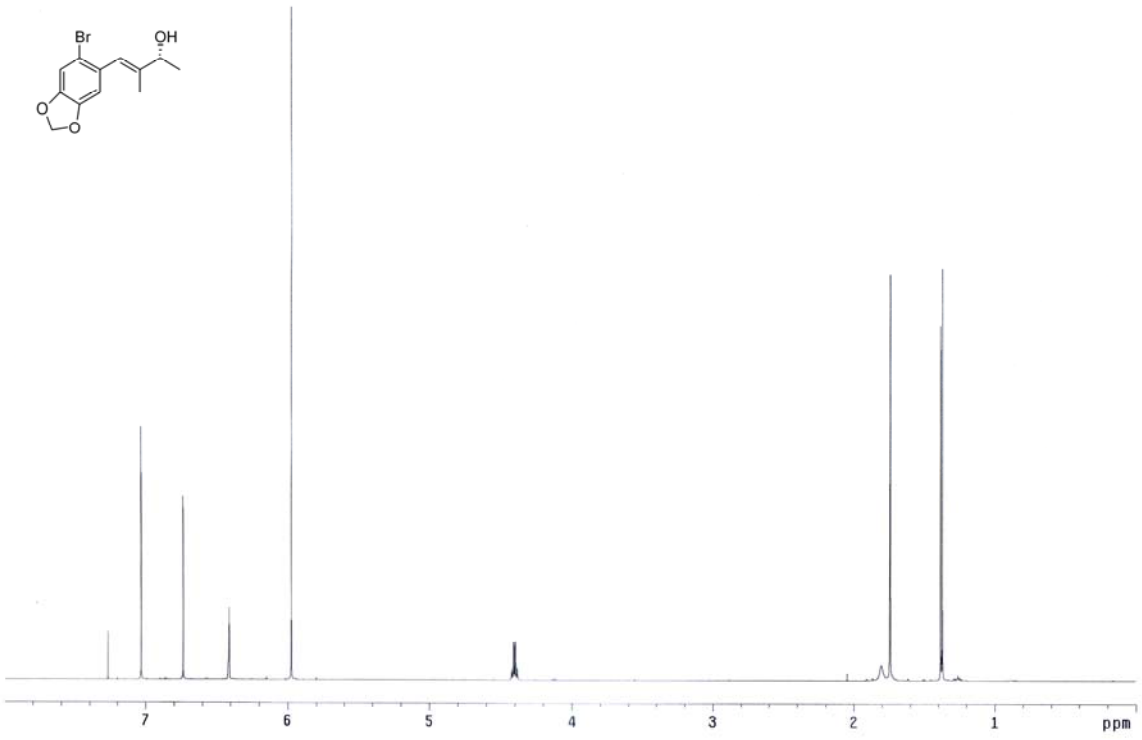
Retention Time	Area	Area %
18.200	7177014	50.15
20.412	7133983	49.85
Totals	14310997	100.00

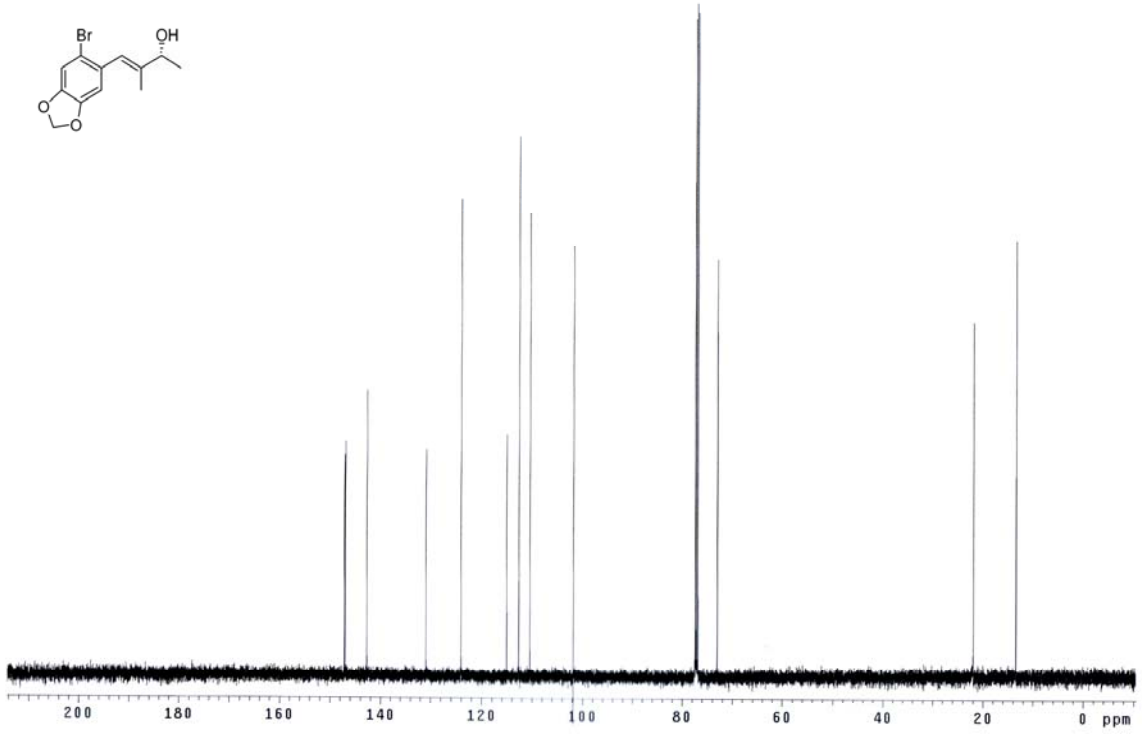
chiral experiment

2: 254 nm, 4 nm Results

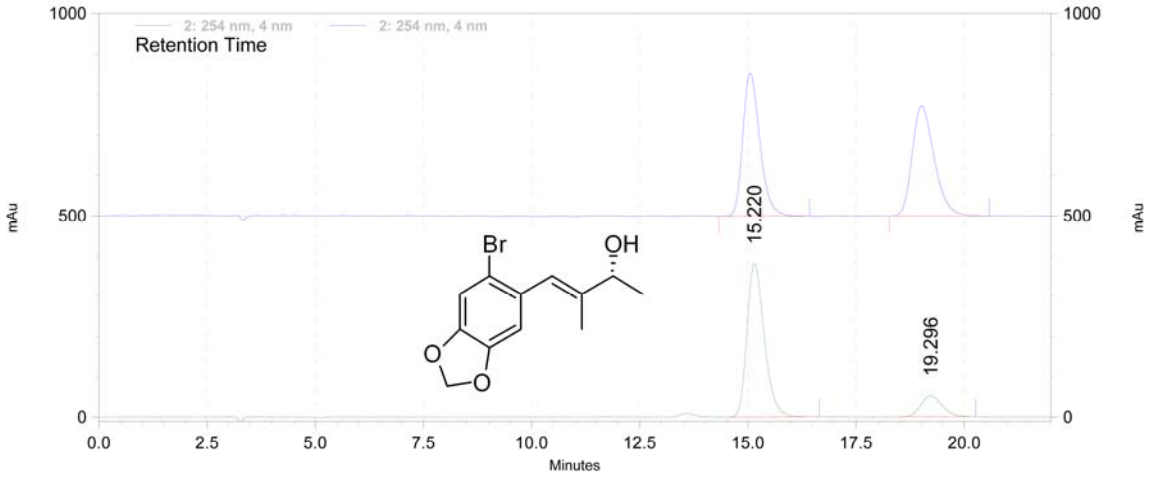
Retention Time	Area	Area %
18.308	183835	2.62
20.448	6825970	97.38
Totals	7009805	100.00

RM761_CA **95% *ee***


Br
OH
O
O
7
6
5
4
3
2
1
ppm


Br
OH
O
O
200
180
160
140
120
100
80
60
40
20
0
ppm

column: CHIRALCEL OD-H (serial ODH0CE-L1108), 0.46 x 25 cm
conditions: 5% IPA/hexanes, 1.0 mL/min



racemic mixture

2: 254 nm, 4 nm Results

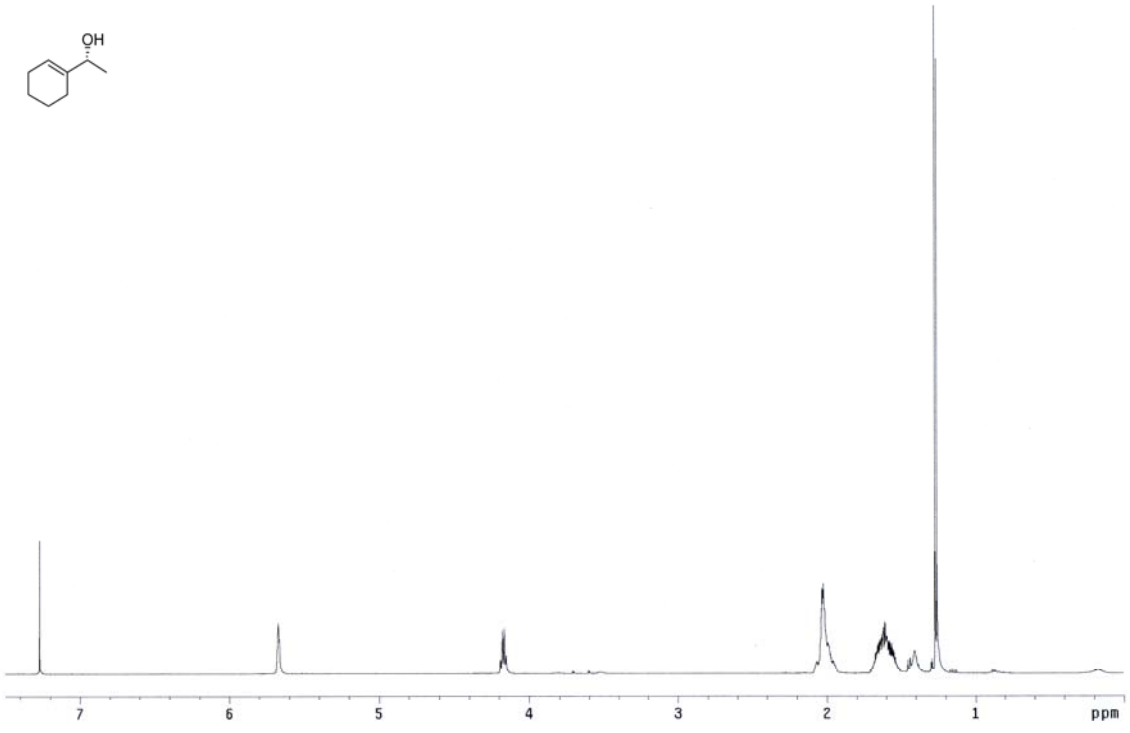
Retention Time	Area	Area %
15.052	9731569	50.32
19.016	9606169	49.68
Totals	19337738	100.00

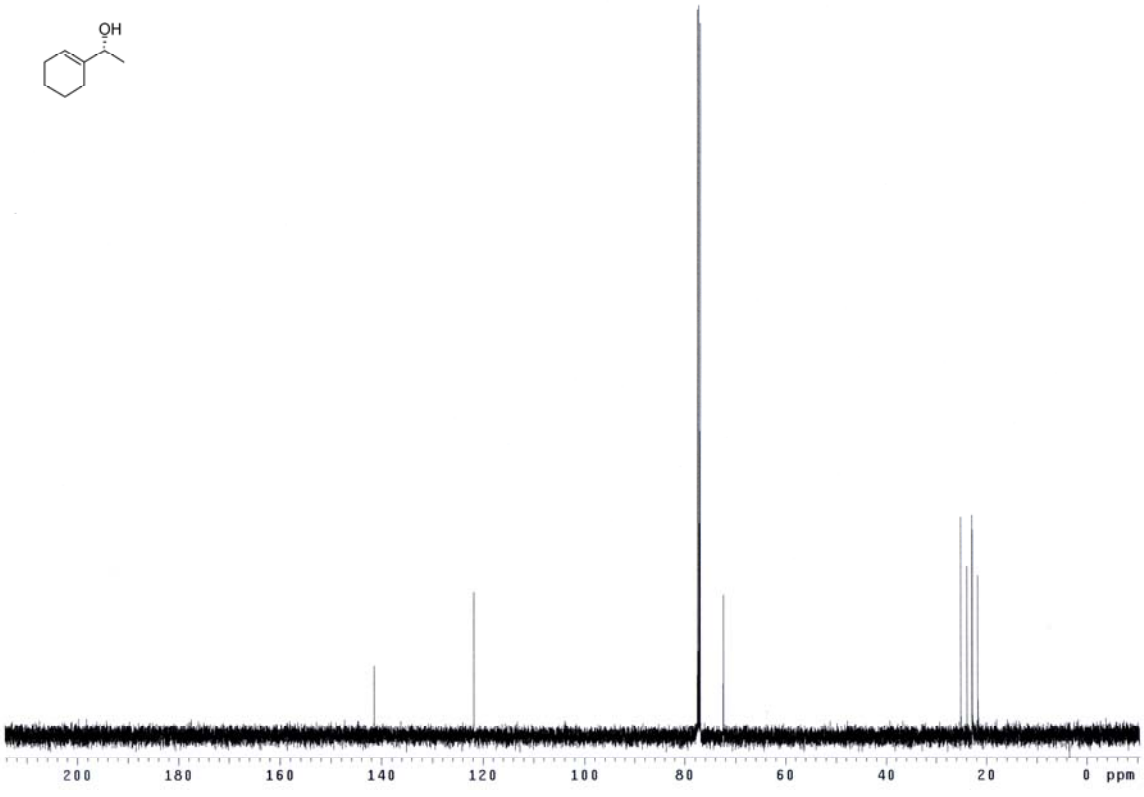
chiral experiment

2: 254 nm, 4 nm Results

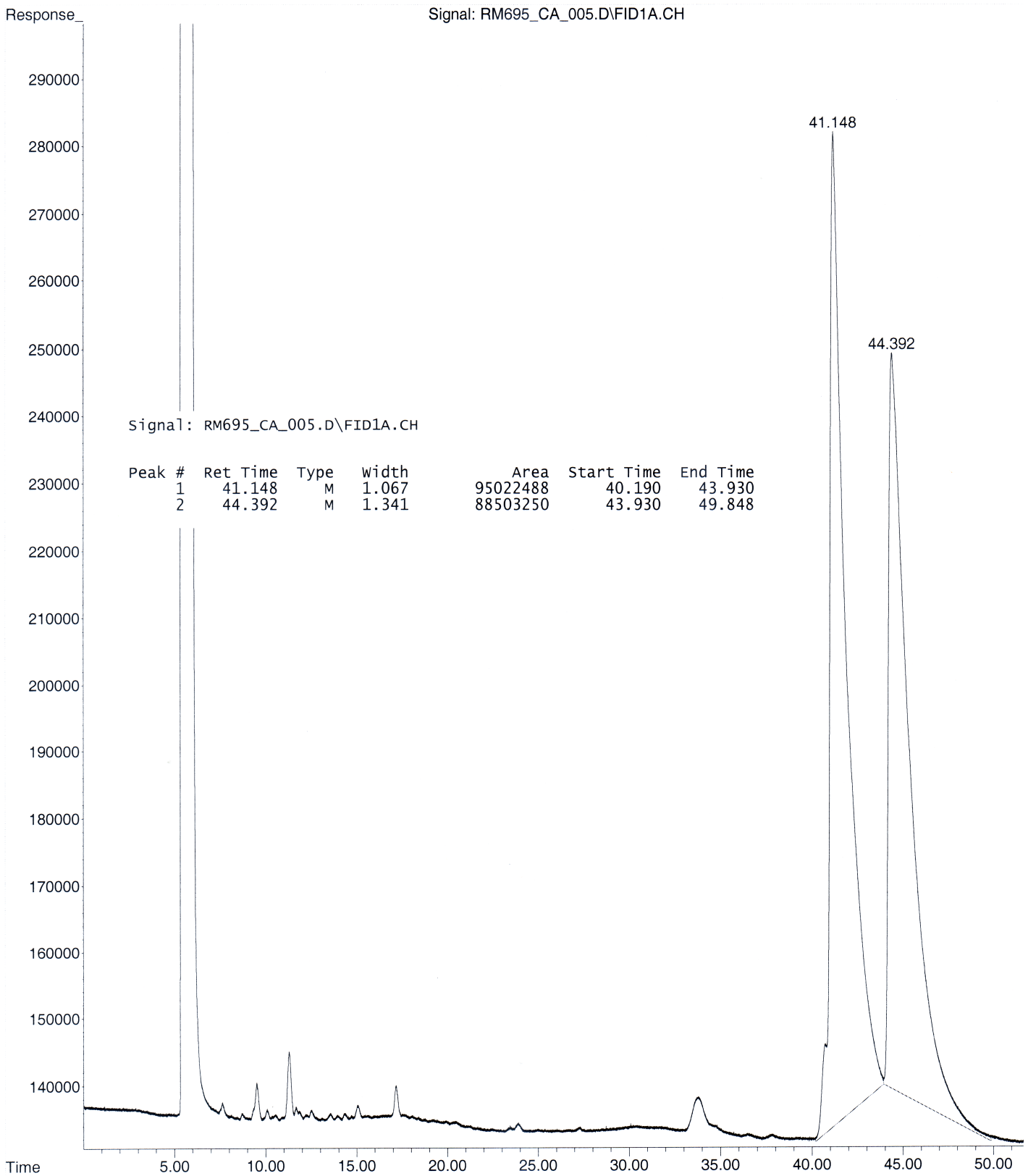
Retention Time	Area	Area %
15.220	10538988	85.64
19.296	1767373	14.36
Totals	12306361	100.00

RM763_CA **71% *ee***


OH
7
6
5
4
3
2
1
ppm


OH
200
180
160
140
120
100
80
60
40
20
0 ppm

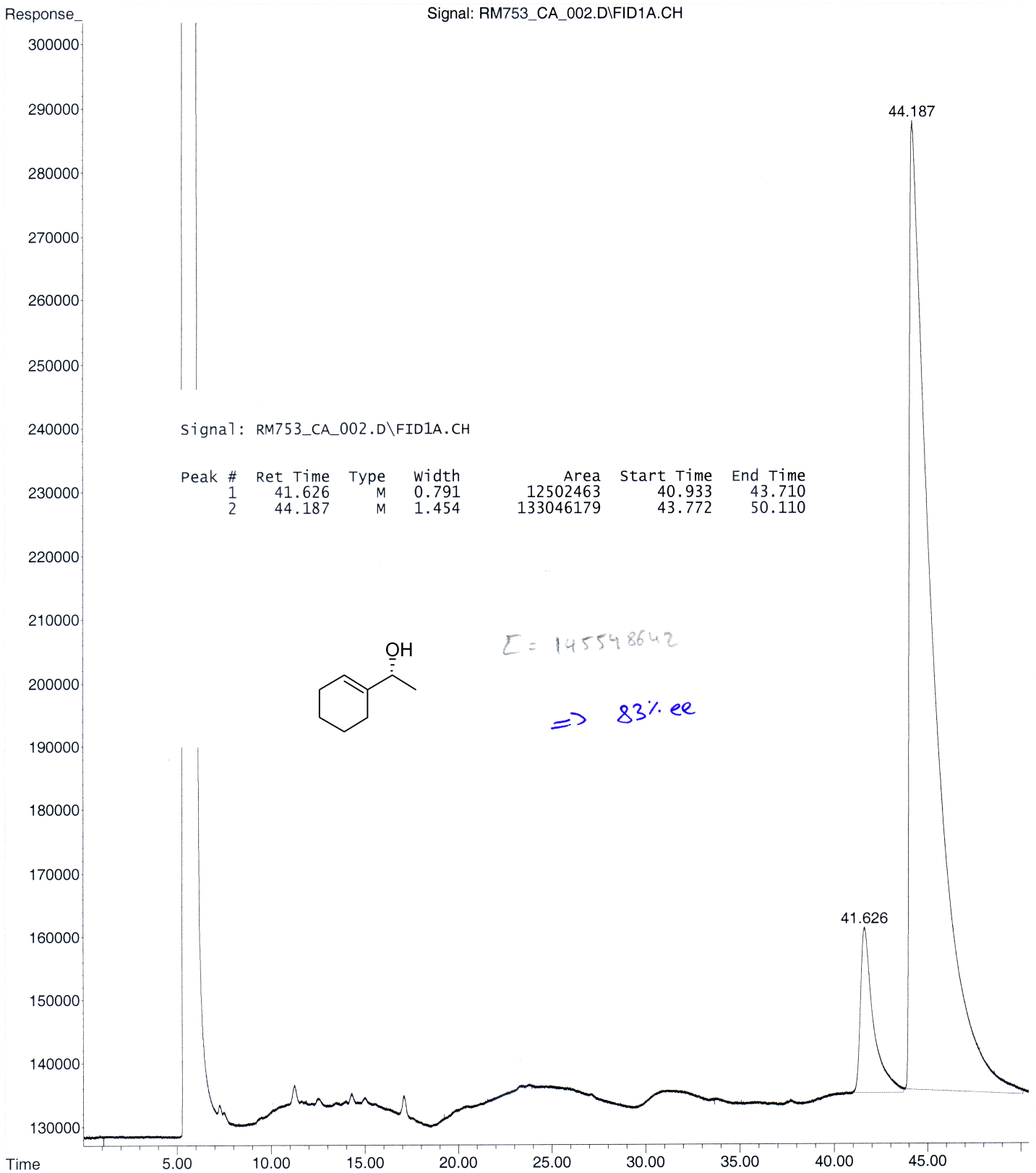
File :C:\msdchem\1\DATA\RM\RM695_CA_005.D
Operator : RM
Acquired : 28 Oct 2009 17:48 using AcqMethod chiral test.M
Instrument : HP G1530A
Sample Name: RM695_CA_005
Misc Info :
Vial Number: 1



Signal: RM695_CA_005.D\FID1A.CH

Peak #	Ret Time	Type	Width	Area	Start Time	End Time
1	41.148	M	1.067	95022488	40.190	43.930
2	44.392	M	1.341	88503250	43.930	49.848

File :C:\msdchem\1\DATA\RM\RM753_CA_002.D
Operator : RM
Acquired : 28 Oct 2009 21:07 using AcqMethod chiral test.M
Instrument : HP G1530A
Sample Name: RM695_CA_002
Misc Info :
Vial Number: 1

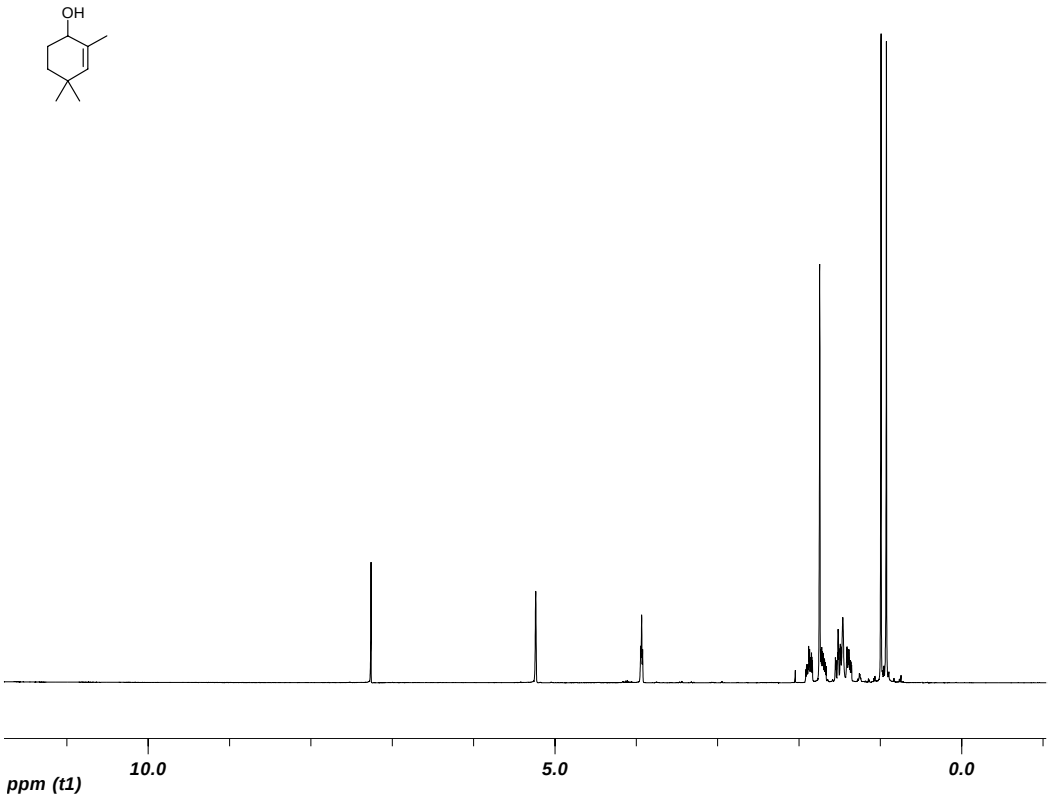


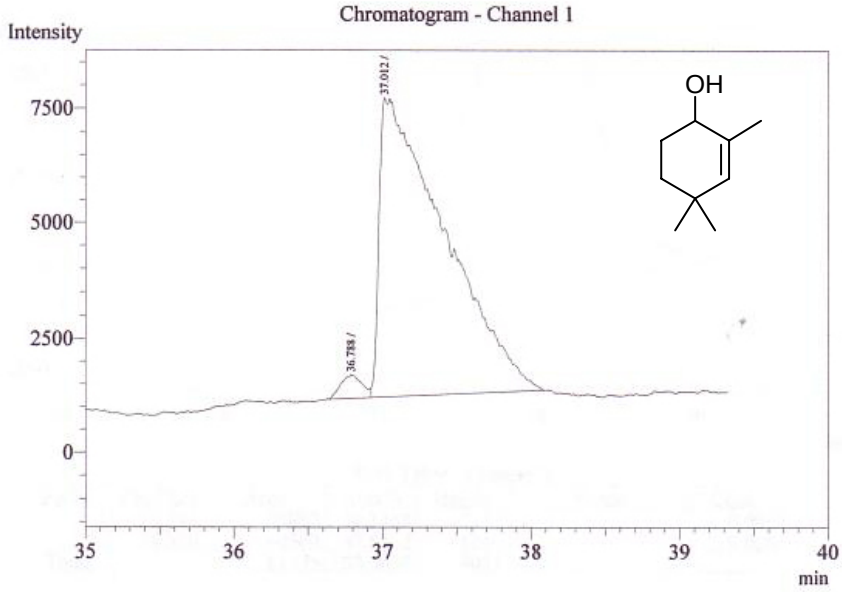
Signal: RM753_CA_002.D\FID1A.CH

Peak #	Ret Time	Type	Width	Area	Start Time	End Time
1	41.626	M	0.791	12502463	40.933	43.710
2	44.187	M	1.454	133046179	43.772	50.110

Σ = 145548642

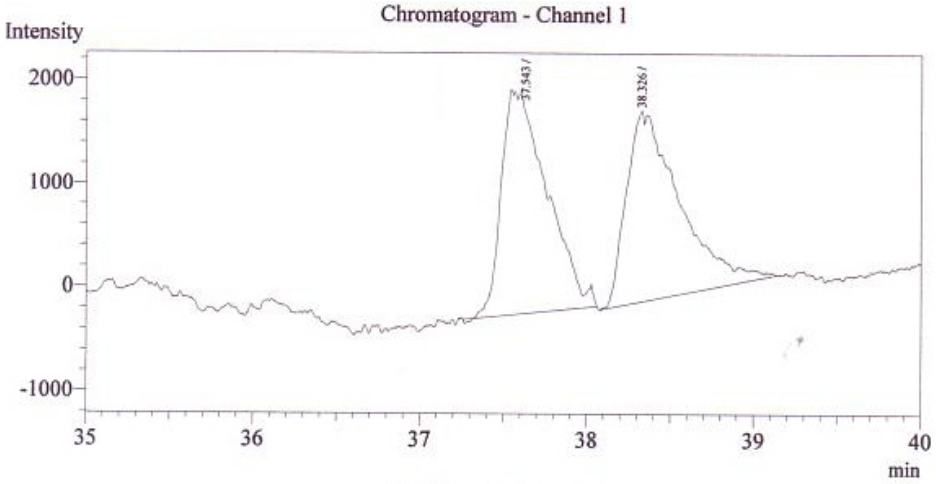
=> 83% ee


OH
10.0
5.0
0.0
ppm (t1)



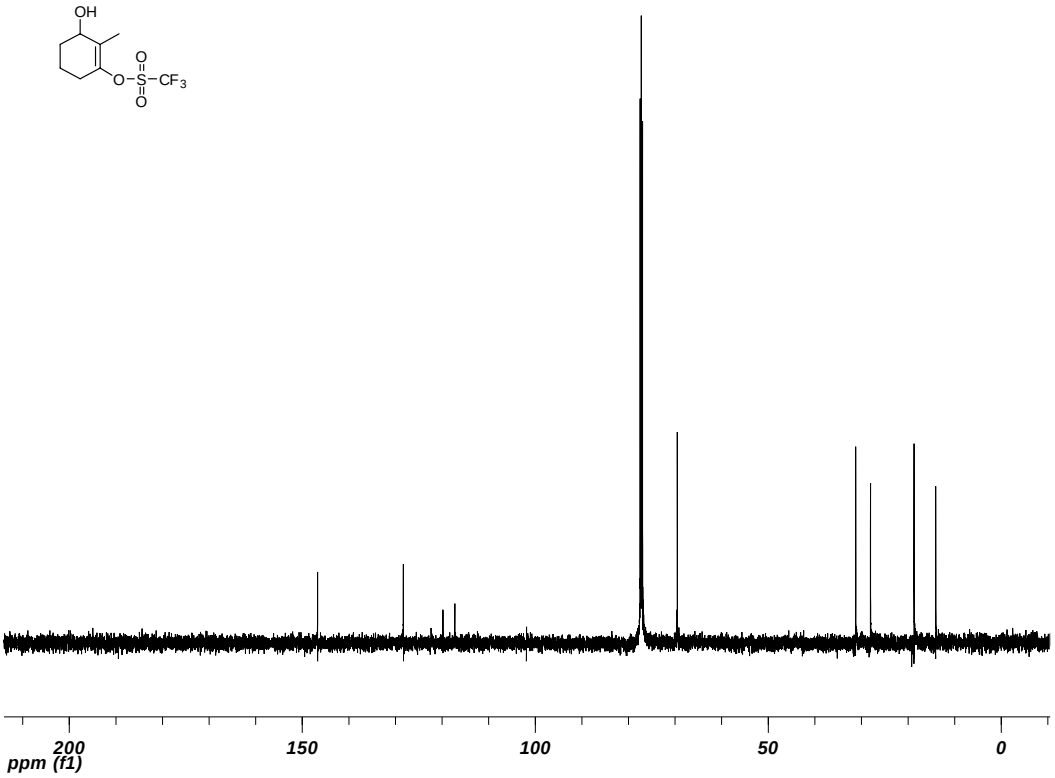
Peak Table - Channel 1

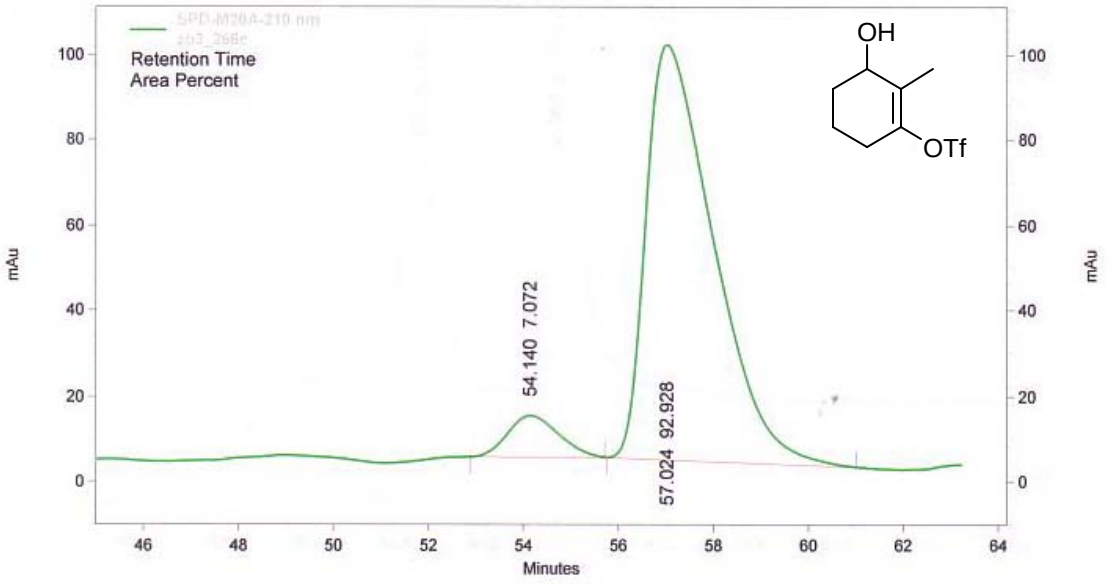
Peak#	Ret.Time	Area	Area%	Height	Name	Conc.
1	36.788	5262	2.5793	520		0.000
2	37.012	198730	97.4207	6505		0.000
Total		203992	100.0000	7025		

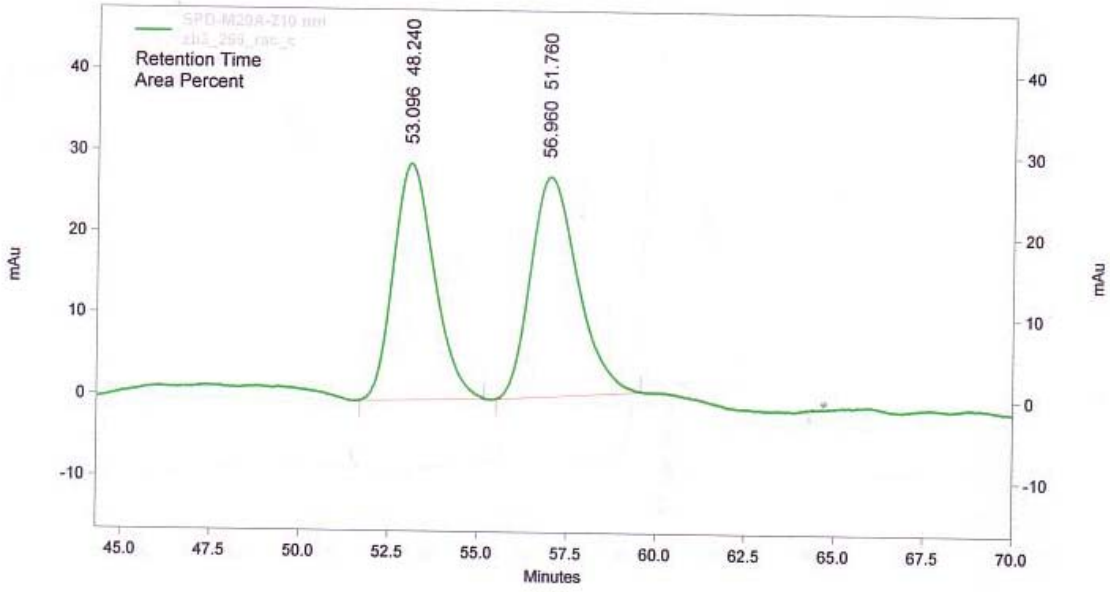


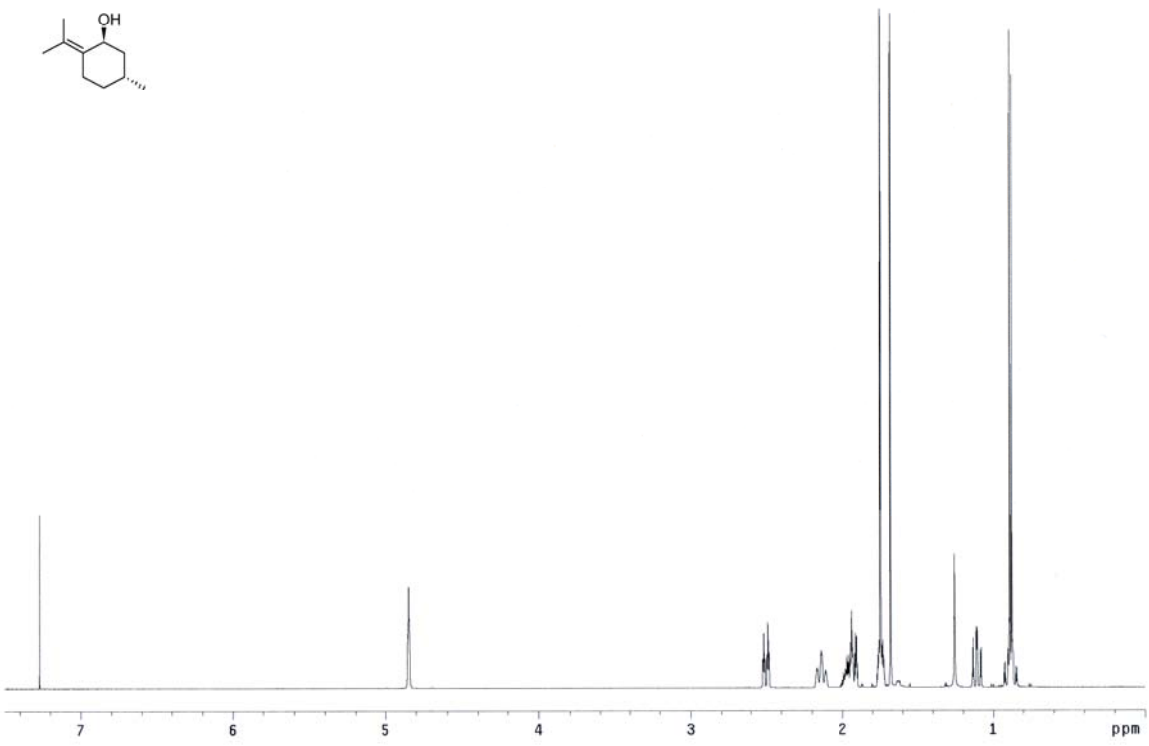
Peak Table - Channel 1

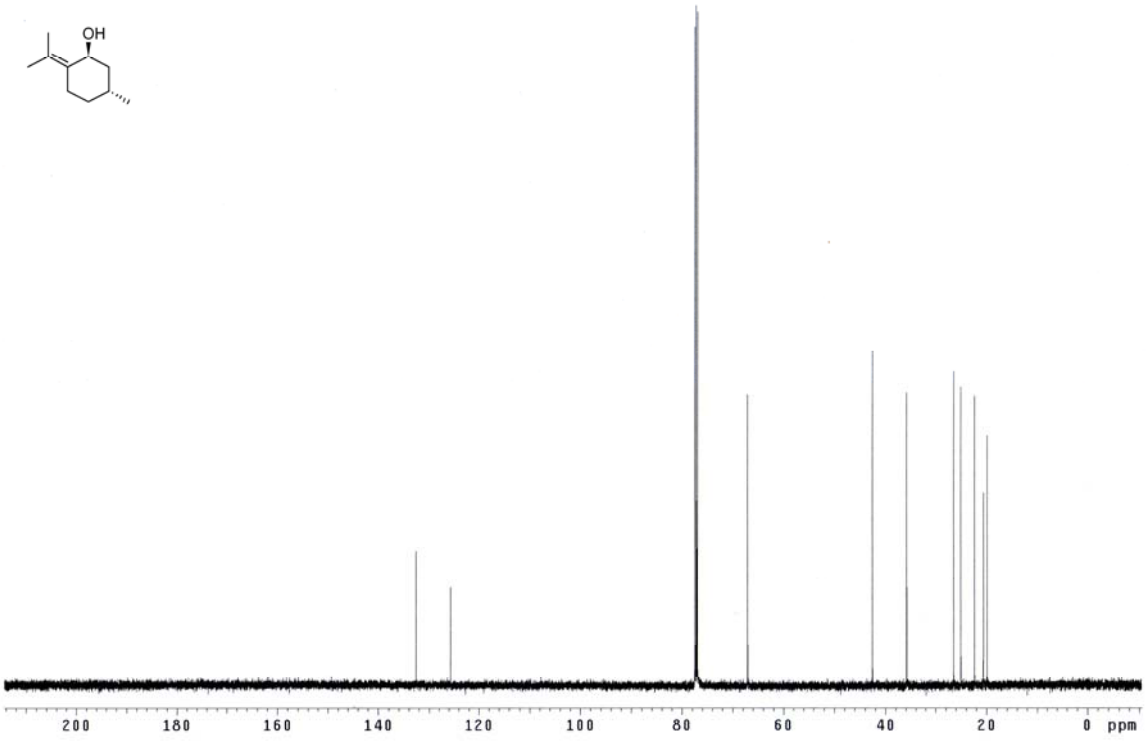
Peak#	Ret.Time	Area	Area%	Height	Name	Conc.
1	37.543	40807	50.1468	2171		0.000
2	38.326	40568	49.8532	1840		0.000
Total		81375	100.0000	4011		

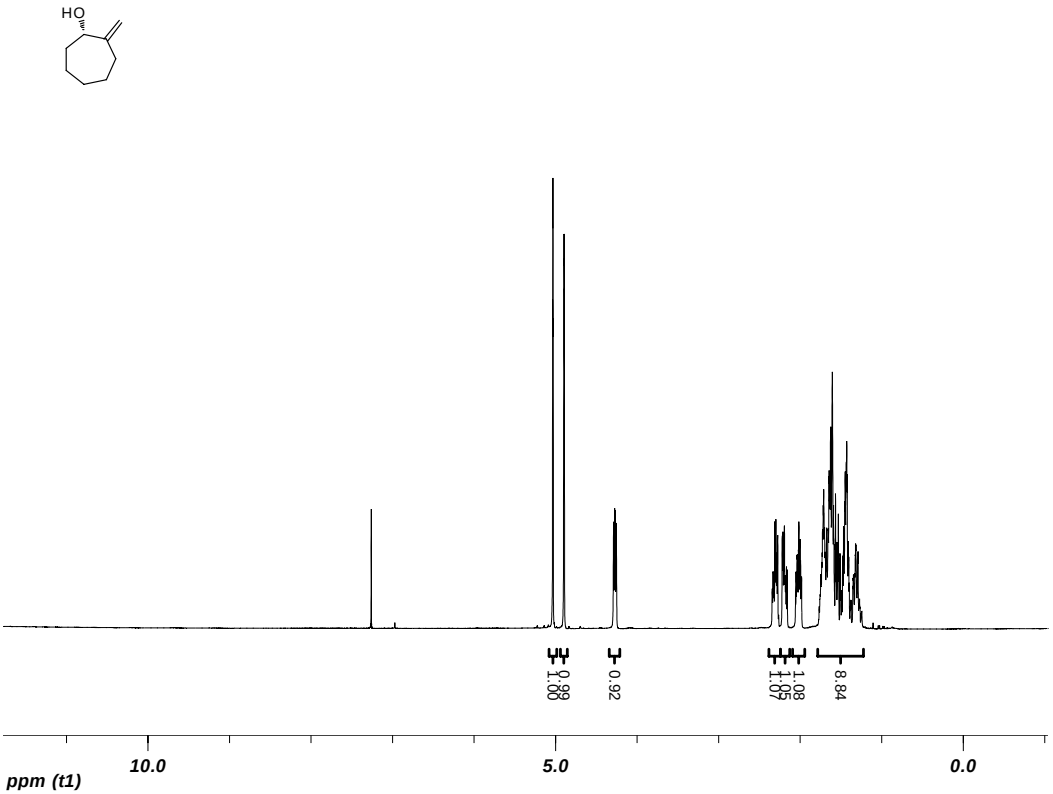

OH
O
O
S
O
CF3
200
150
100
50
0
ppm (f1)

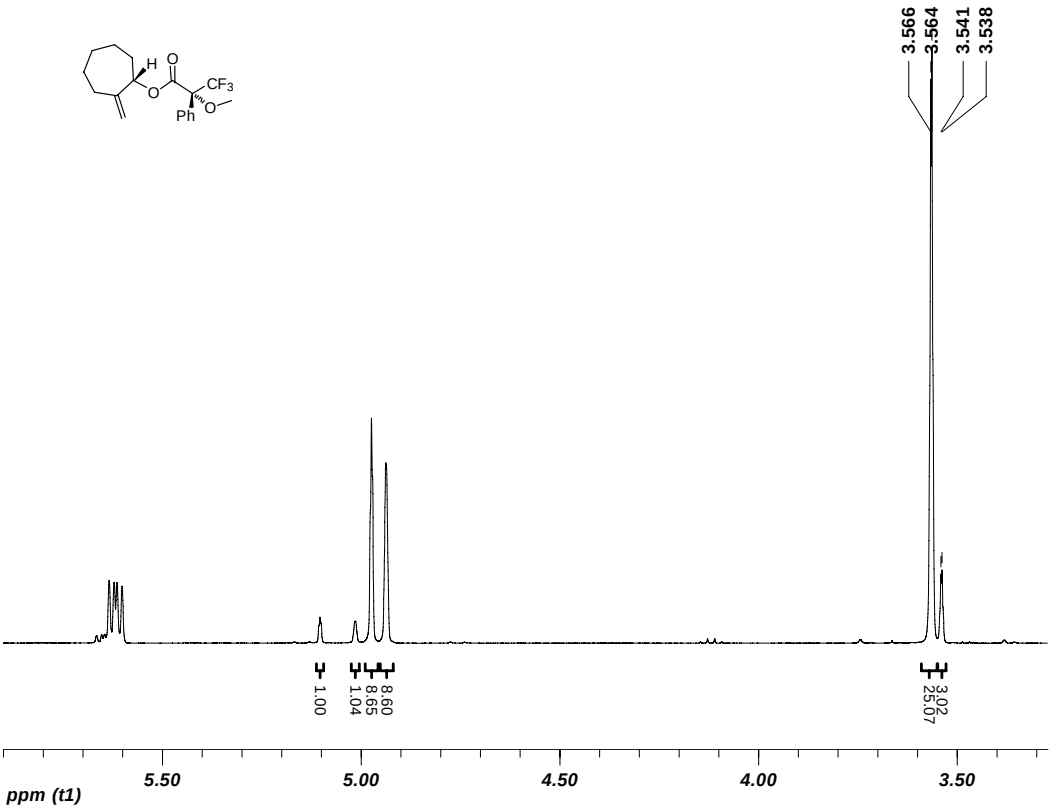

SPD-M20A-210 nm
Retention Time
Area Percent
OH
OTf
54.140 7.072
57.024 92.928
mAu
Minutes

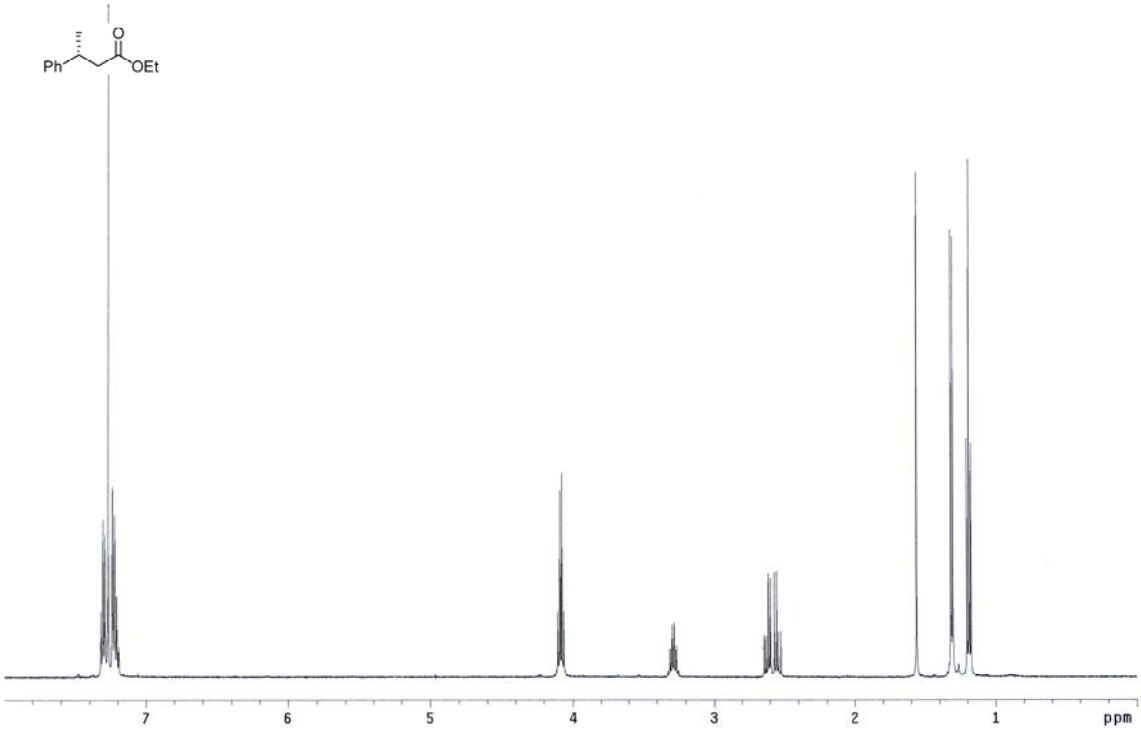

SPD-M20A-210 nm
Retention Time
Area Percent
53.096 48.240
56.960 51.760
mAu
Minutes


OH
7
6
5
4
3
2
1
ppm

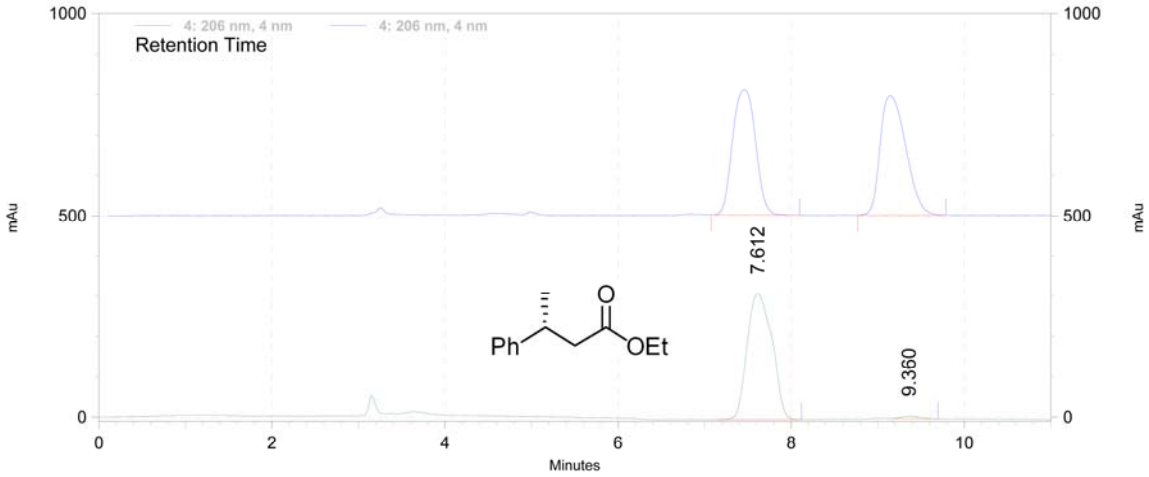

OH
200
180
160
140
120
100
80
60
40
20
0 ppm


HO
1.00
0.89
0.92
1.07
1.05
1.08
8.84
10.0
5.0
0.0
ppm (t1)


H
O
O
CF3
Ph
O
3.566
3.564
3.541
3.538
1.00
1.04
8.65
8.60
25.07
3.02
5.50
5.00
4.50
4.00
3.50
ppm (t1)


Ph
O
OEt
7
6
5
4
3
2
1
ppm

column: CHIRALCEL OB-H (serial OBH0CE-CE001), 0.46 x 25 cm
conditions: 1% IPA/hexanes, 1.0 mL/min



racemic mixture

4: 206 nm, 4 nm Results

Retention Time	Area	Area %
7.356	18945590	48.45
9.044	20159350	51.55
Totals	39104940	100.00

chiral experiment

4: 206 nm, 4 nm Results

Retention Time	Area	Area %
7.612	5189630	98.64
9.360	71398	1.36
Totals	5261028	100.00

RM921_CA1 **97% *ee***