SUPPLEMENTARY MATERIALS

Resolution of racemic aryloxy-propan-2-yl acetates via lipase-catalyzed hydrolysis: Preparation of the enantiomerically pure/enantioenriched mexiletine intermediates and analogs

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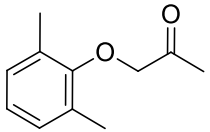
Physical and spectroscopic data of 1-(2,6-dimethylphenoxy)-propan-2-one (3a)

Oil. R_f (20% EtOAc/ Hexane): 0.54. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.25 (s, 3H); 2.36 (s, 6H); 4.35 (s, 2H); 6.96-7.03 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.41 (2 CH_3); 26.78 (CH_3); 76.81 (CH_2); 124.65 (CH); 129.25 (2 CH); 130.72 (2 C); 155.18 (C); 205.68 (C).



3a

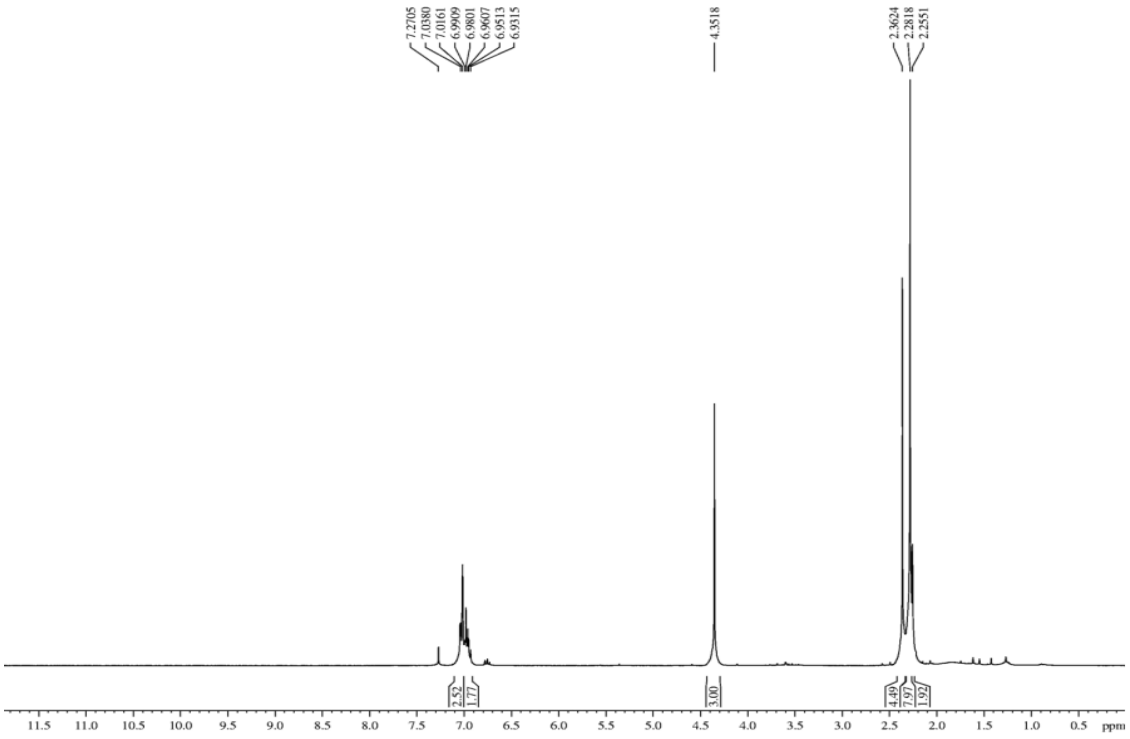
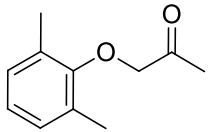


Figure S1. NMR ^{1}H of **3a** (300 MHz, $CDCl_3$).



3a

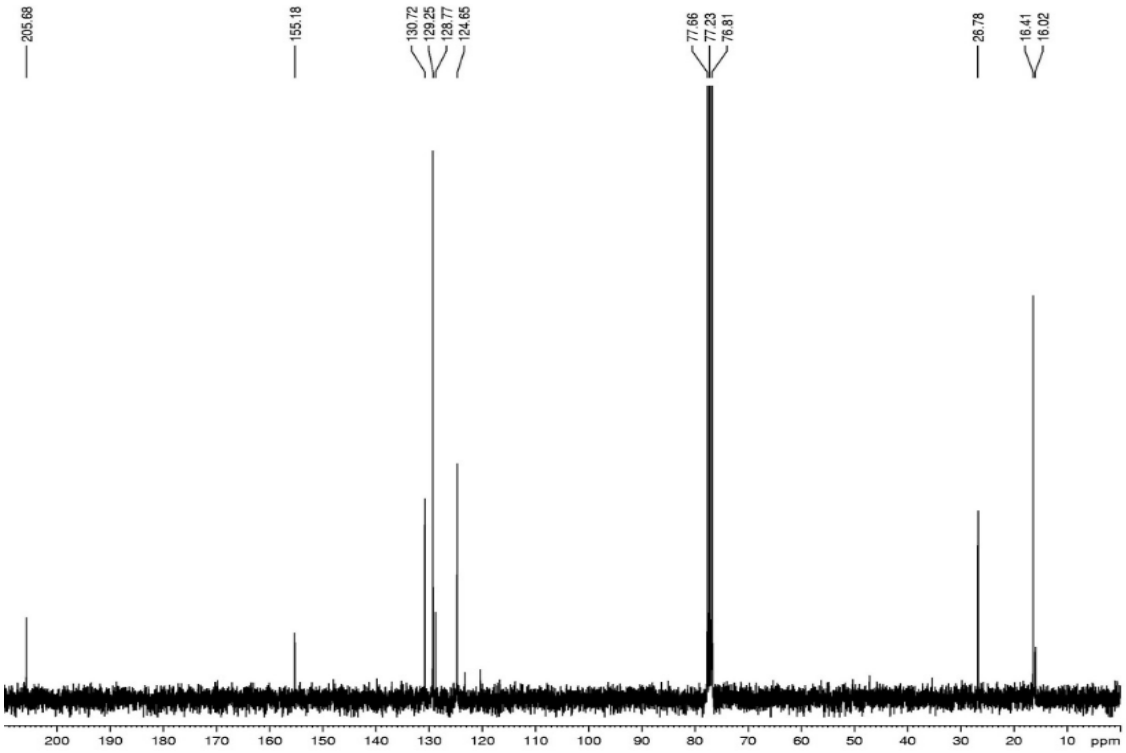
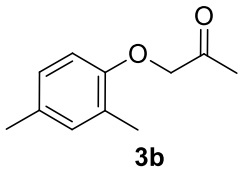


Figure S2. NMR ^{13}C of **3a** (75 MHz, $CDCl_3$).

Physical and spectroscopic data of 1-(2,4-dimethylphenoxy)propan-2-one (3b)

Yellow oil. R_f (20% EtOAc/ Hexane): 0.55. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.27 (s, 3H); 2.28 (s, 3H); 2.31 (s, 3H); 4.48 (s, 2H); 6.55 (d, *J* = 6 Hz, 1H); 6.95 (m, 2H). ^{13}C BB NMR (75 MHz, $CDCl_3$): δ (ppm) 16.37 (CH_3); 20.61 (CH_3); 26.85 (CH_3); 73.61 (CH_2); 111.02 (CH); 126.81 (C); 127.26 (CH); 130.85 (C); 132.11 (CH); 154.03 (C); 206.93 (C).



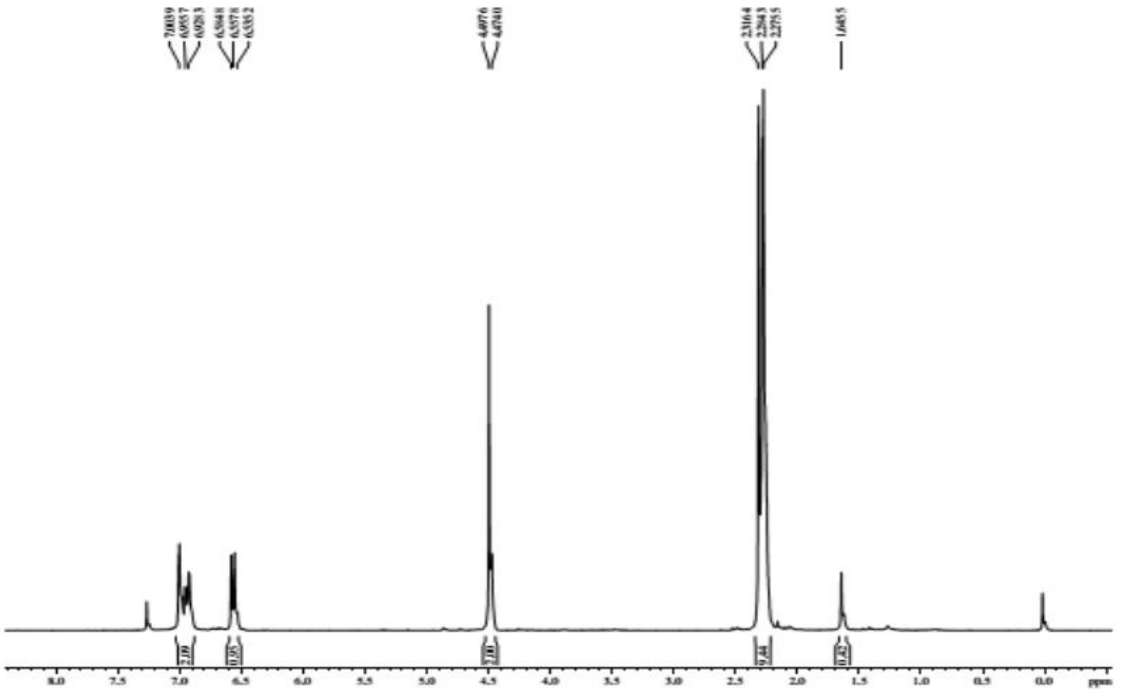
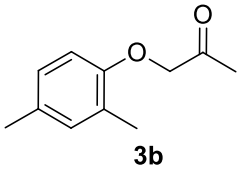


Figure S3. NMR ^{1}H of **3b** (300 MHz, $CDCl_3$).



3b

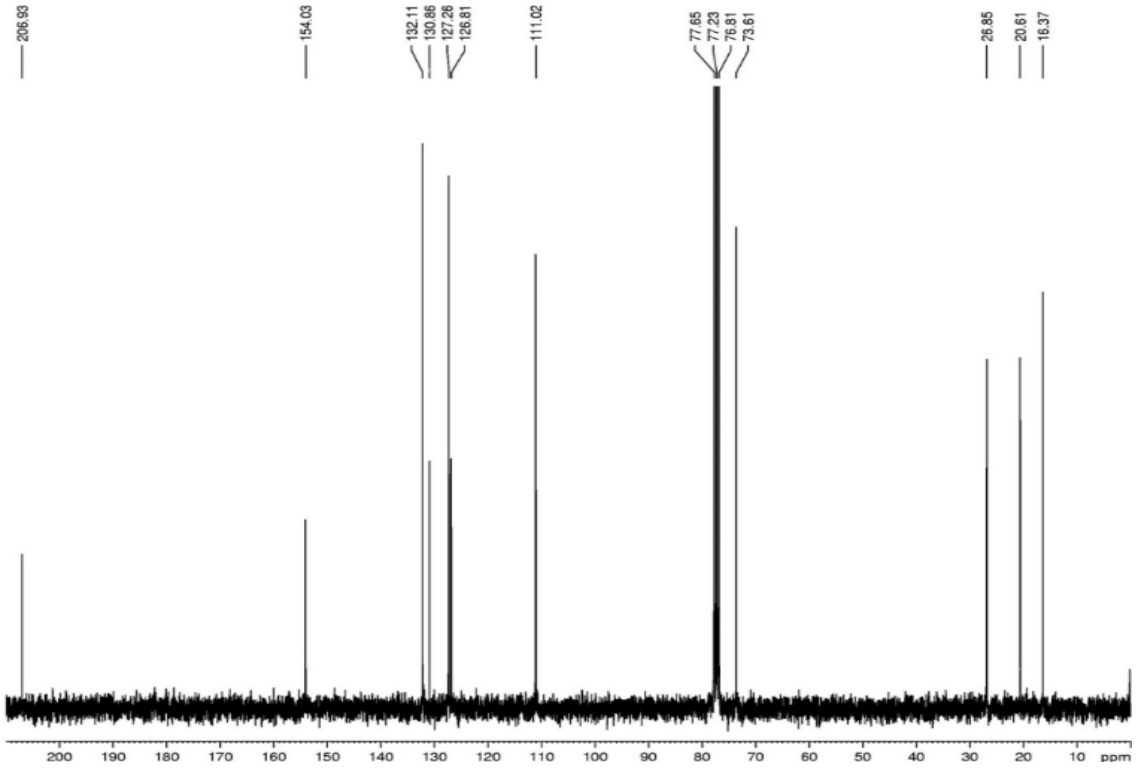
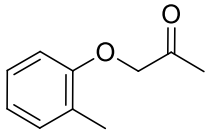


Figure S4. NMR ^{13}C of **3b** (75 MHz, $CDCl_3$).

Physical and spectroscopic data of 1-(2-methylphenoxy)-propan-2-one (3c):

Yellow oil. R_f (10%Hexane/$CHCl_3$): 0.5. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.32 (s, 3H); 2.33 (s, 3H); 4.53 (s, 2H); 6.67 (d, *J* = 8 Hz, 1H); 6.92 (t, *J* = 7.3 Hz 1H); 7.13-7.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.46 (CH_3); 26.88 (CH_3); 73.39 (CH_2); 111.03 (CH); 121.63 (CH); 127.14 (CH); 131.30 (C); 156.11 (C); 206.64 (C).



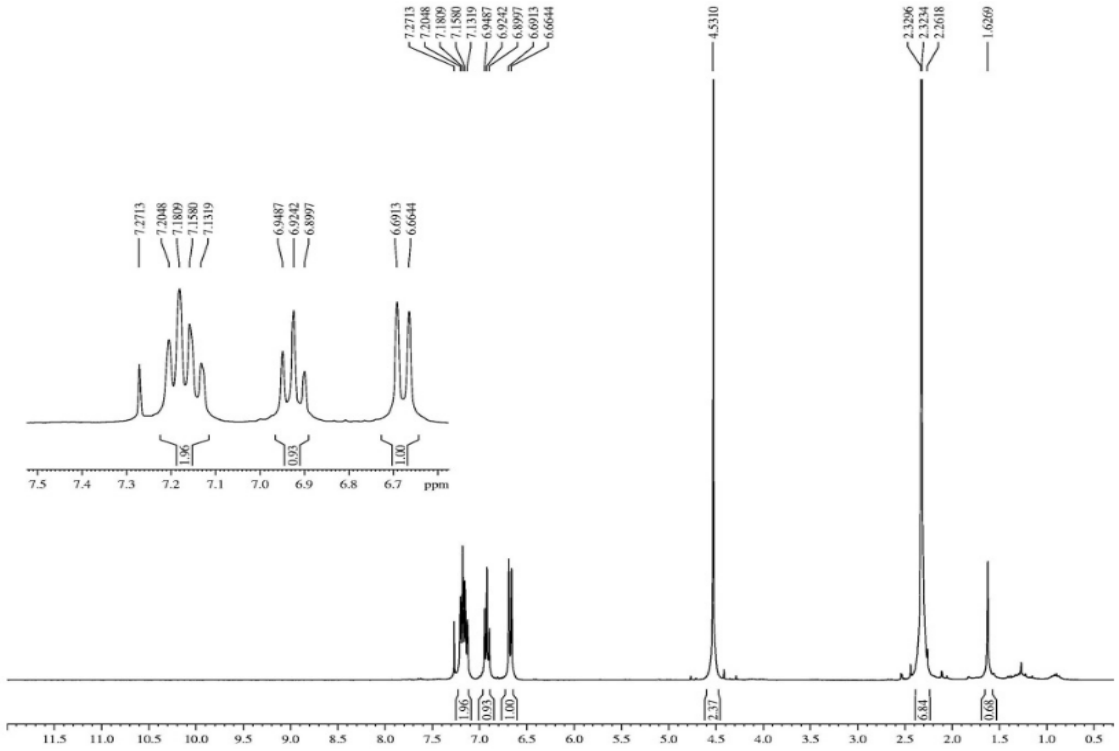
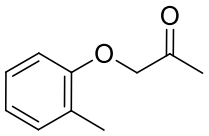


Figure S5. NMR ^{1}H of **3c** (300 MHz, $CDCl_3$)



3c

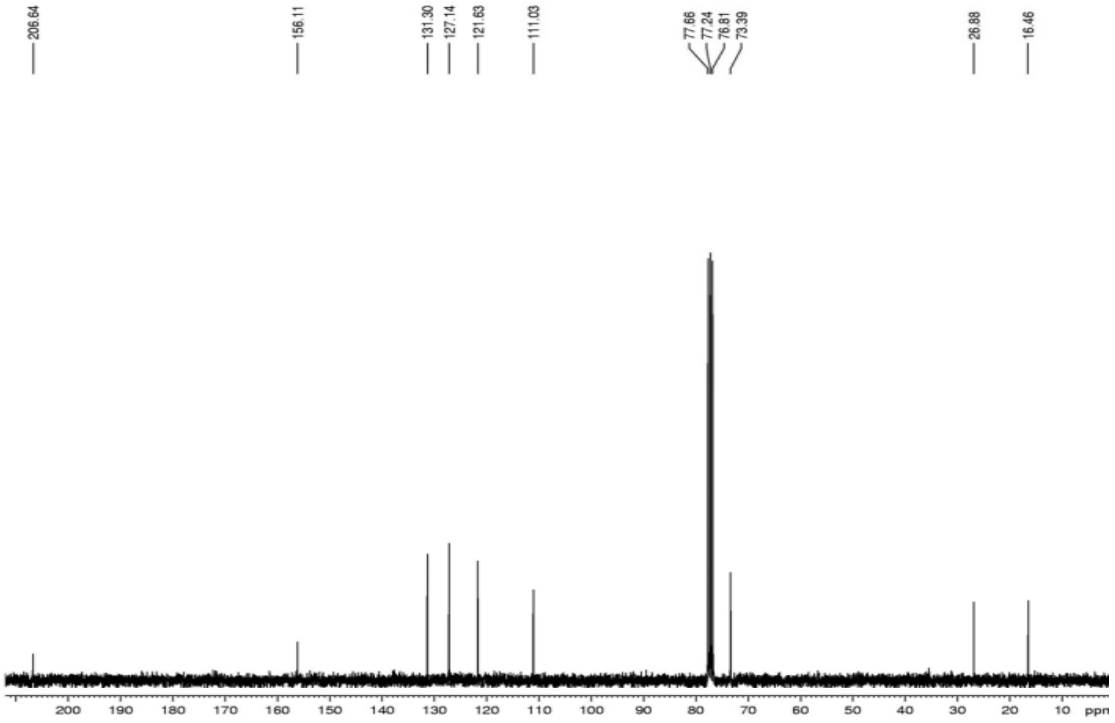
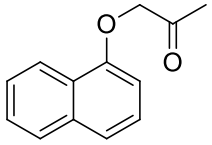


Figure S6. NMR ^{13}C of **3c** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(naphtalen-1-yloxy)propan-2-one (3d):

Brown oil. R_f (20% EtOAc/Hexane): 0.6. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.41(s, 3H); 4.71 (s, 2H); 6.69 (d, *J* = 7.6 Hz, 1H); 7.36 (t, *J* = 8.1 Hz, 1H); 7.48 (s, 1H); 7.53-8.34 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.04 (CH_3); 73.5 (CH_2); 105.08 (CH); 121.65 (CH); 122.05 (CH) 125.62 (C); 125.83 (2 CH); 126.93 (CH); 127.81 (CH); 134.87 (C); 153.0 (C); 206.32 (C).



3d

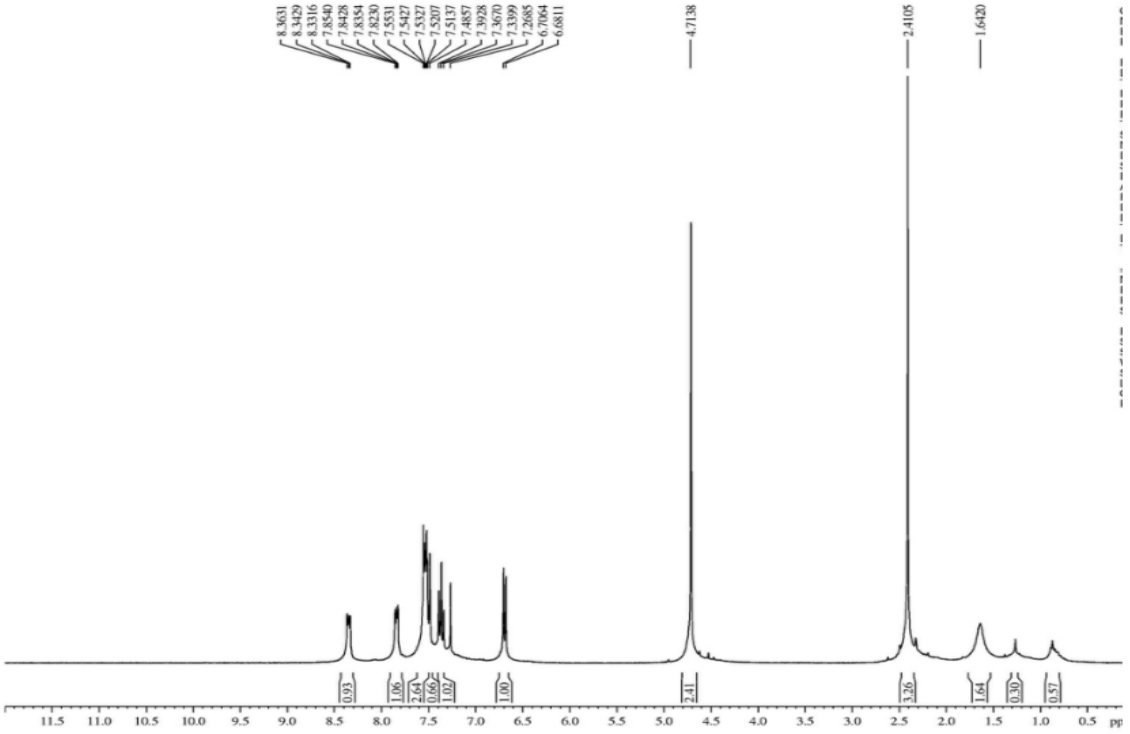
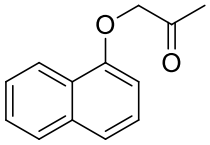


Figure S7. NMR ^{1}H of **3d** (300 MHz, $CDCl_3$)



3d

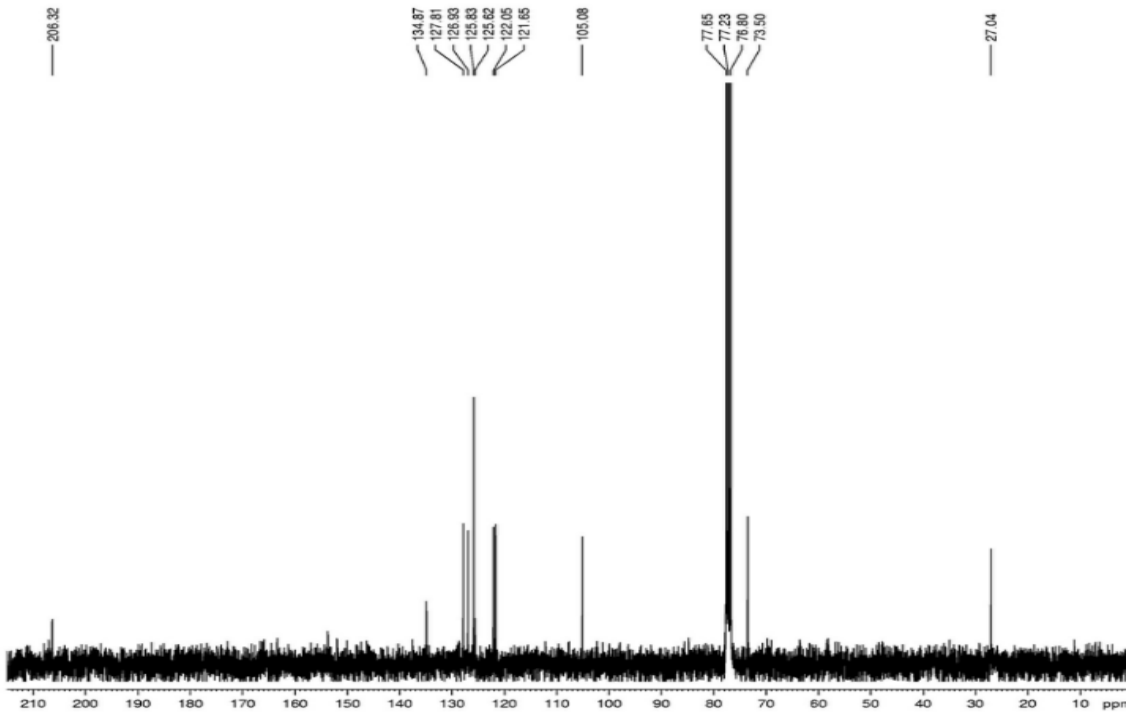
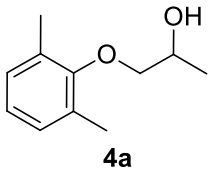


Figure S8. NMR ^{13}C of **3d** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(2,6-dimethylphenoxy)propan-2-ol (4a):

Yellow oil. R_f (20%EtOAc/Hexane): 0.36. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.26 (d, *J* = 6.4 Hz, 3H); 2.28 (s, 6H); 3.68 (ddd, *J* = 27.5, 9 and 7 Hz, 2H); 4.18-4.24 (m, 1H); 6.9-7.02 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.52 (CH_3); 18.81 (CH_3); 67.33 (CH); 77.18 (CH_2); 124.28 (CH); 129.18 (CH); 130.97 (C); 155.41 (C). For (*R*)-**4a:** $[\alpha]_D^{20}$ + 1.46 (*c* 8.0, $CHCl_3$) for >99% *ee* of the enantiomer *R*. Lit. $[\alpha]_D^{20}$ +0.9 (*c* 5.5, $CHCl_3$) for 98% *ee* of the enantiomer *R* [25].



4a

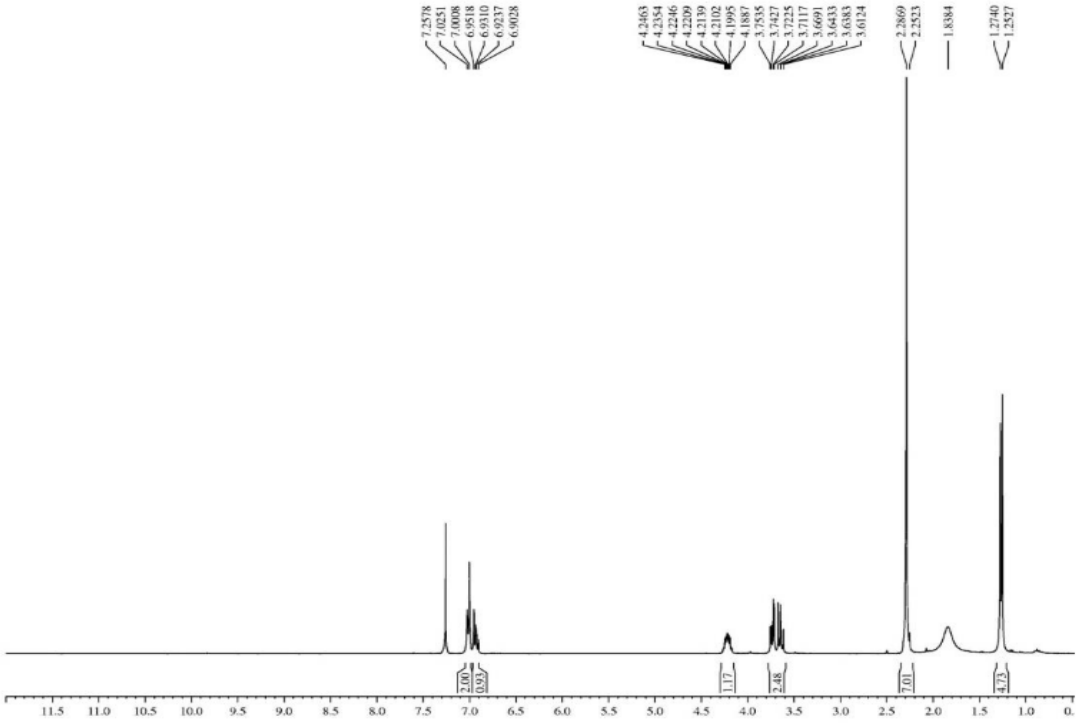
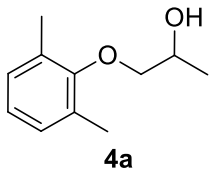


Figure S9. NMR ^{1}H of *rac*-**4a** (300 MHz, $CDCl_3$)



4a

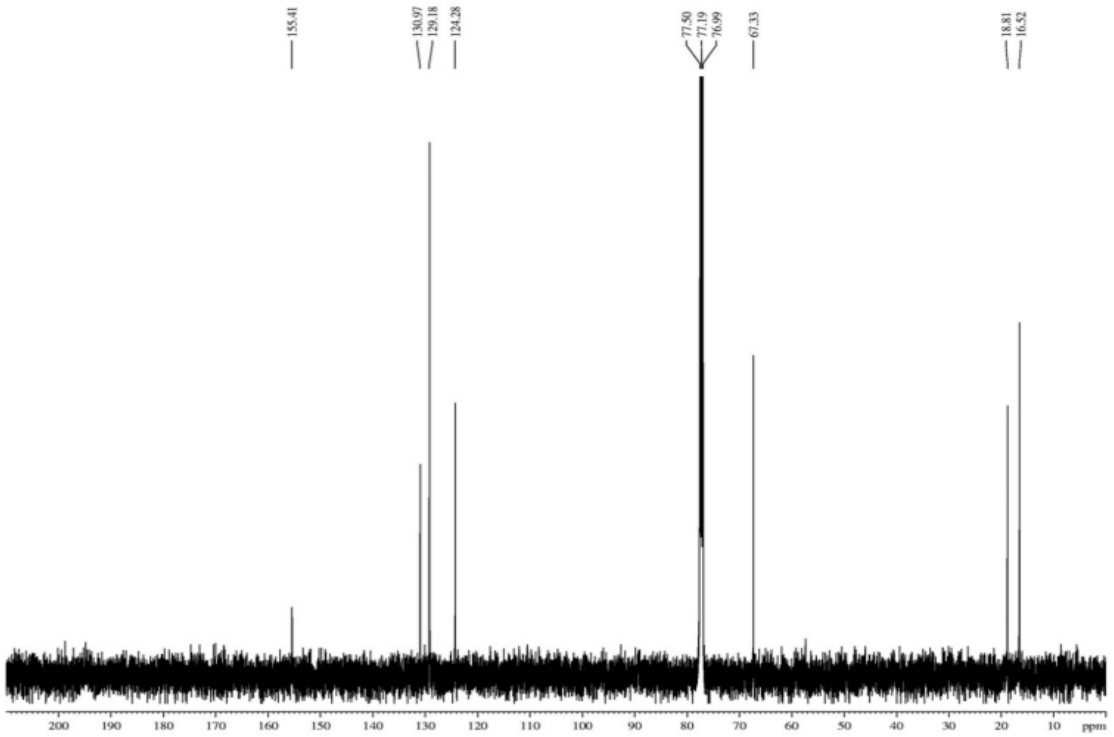
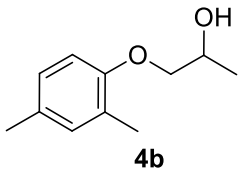


Figure S10. NMR ^{13}C of *rac*-**4a** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(2,4-dimethylphenoxy)propan-2-ol (4b):

Yellow oil. R_f (20% Hexane/ EtOAc): 0.43. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.31 (d, *J* = 3.9 Hz, 3H); 2.23 (s, 3H); 2.27 (s, 3H); 3.93 (dd, *J* = 3 and 3 Hz, 1H), 3,78 (dd, *J* = 3 and 3 Hz 1H); 4.21 (m, 1H); 6.73 (d, *J* = 6 Hz, 1H); 6.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.35 (CH_3); 20.63 (CH_3); 19.0 (CH_3); 66.7 (CH); 73.79 (CH_2); 111.63 (CH); 126.72 (C); 127.23 (CH); 130.30 (C); 131.82 (CH); 154.71 (C). For (*R*)-**4b:** $[\alpha]_D^{20}$ +30.5 (*c* 5.0, CH_2Cl_2) for >99% *ee*.



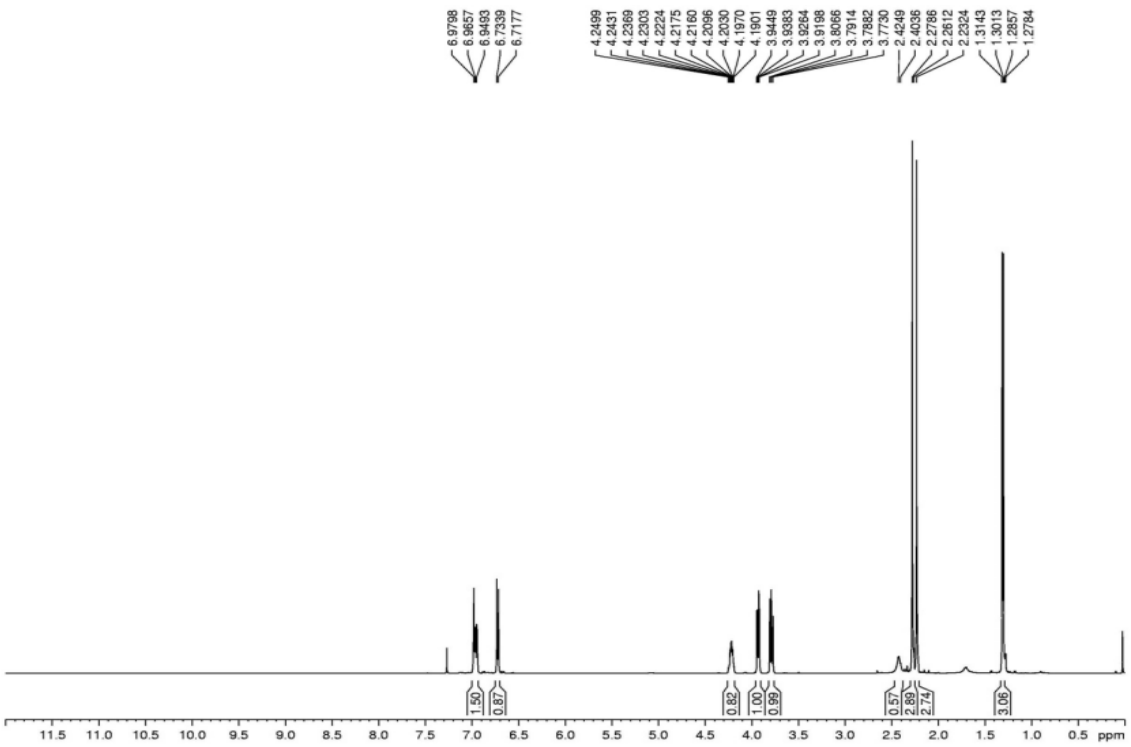
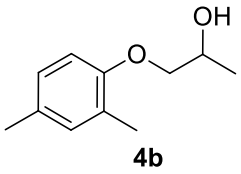


Figure S11. NMR ^{1}H of *rac*-**4b** (300 MHz, $CDCl_3$)



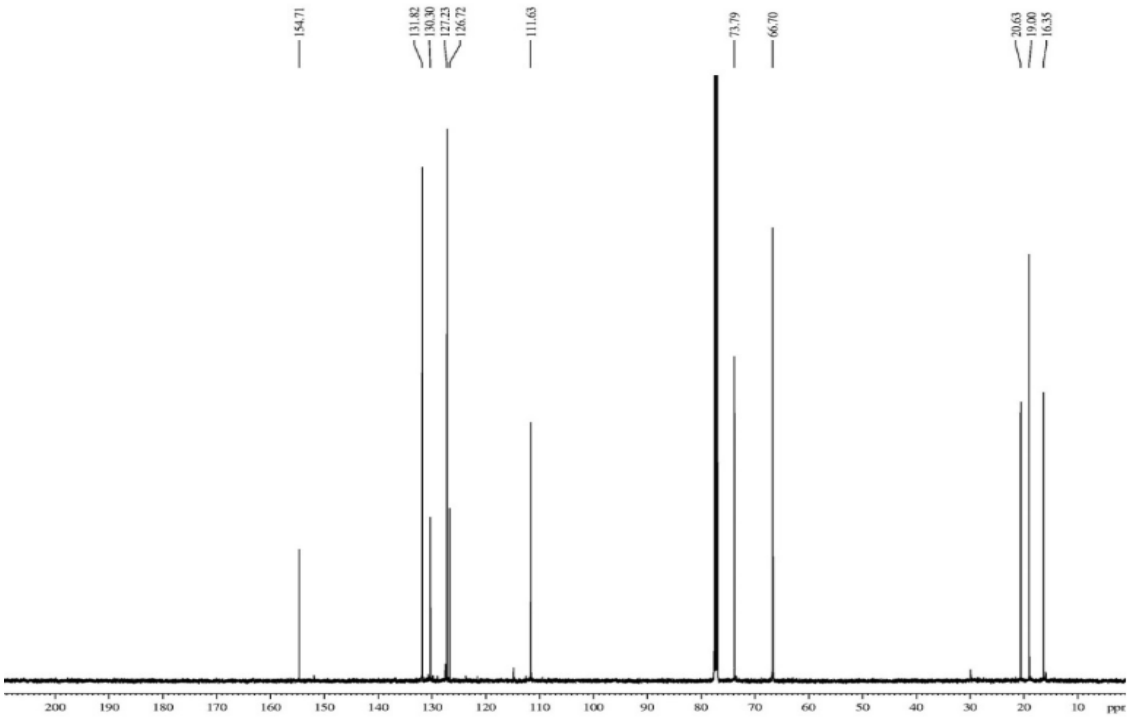
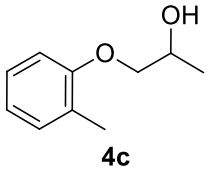


Figure S12. NMR ^{13}C of *rac*-**4b** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(2-methylphenoxy)propan-2-ol (4c):

Yellow oil. R_f (10%Hexane:$CHCl_3$): 0.4. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.31(d, *J* = 6 Hz, 3H); 2.26 (s, 3H); 3.81 (dd, *J* = 6 and 3 Hz, 1H); 3.96 (dd, *J* = 6 and 3 Hz, 1H); 4.22 (m, 1H); 6.82 (t, *J* = 9 and 3 Hz, 1H); 6.89 (t, *J* = 15 and 9 Hz, 1H); 7.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.40 (CH_3); 19.06 (CH_3); 66.69 (CH); 73.56 (CH_2); 111.53 (CH); 121.08 (CH); 126,98 (C); 127.07 (CH); 131.01 (CH); 156.82 (C). For (*R*)-**4c:** $[\alpha]_D^{20}$ -9.8 (*c* 5.0, CH_2Cl_2) for 98% *ee*.



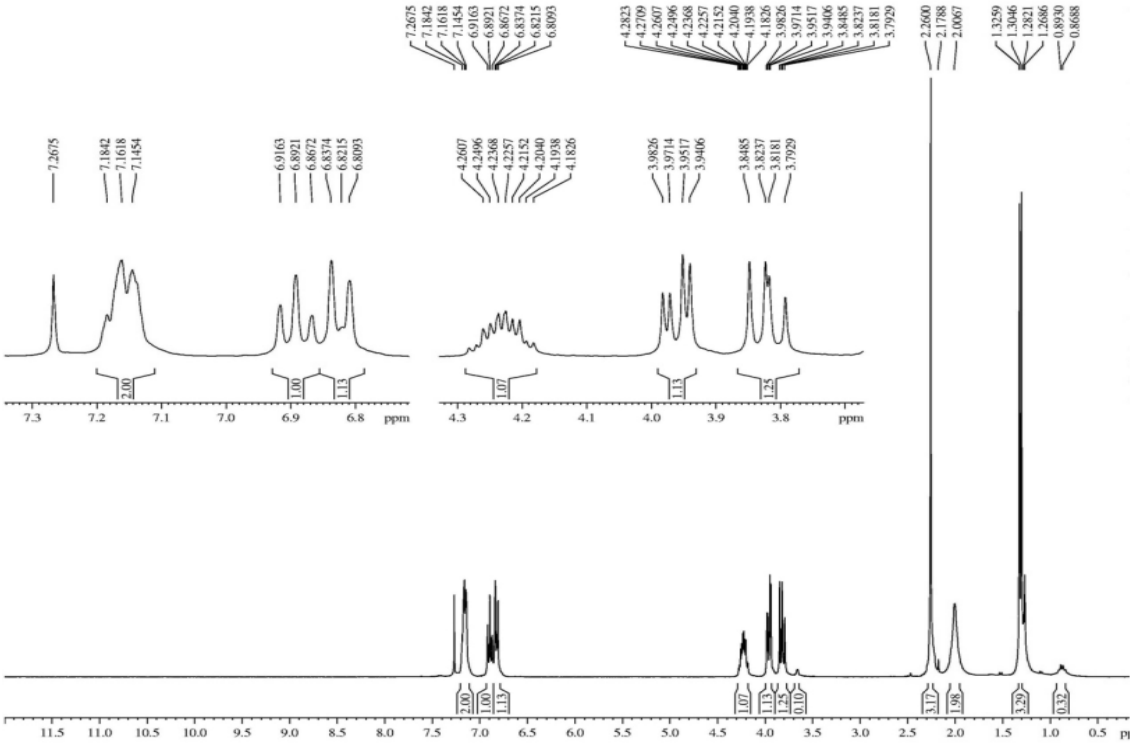
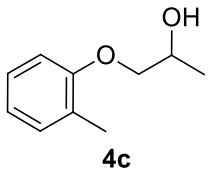


Figure S13. NMR ^{1}H of *rac*-**4c** (300 MHz, $CDCl_3$).



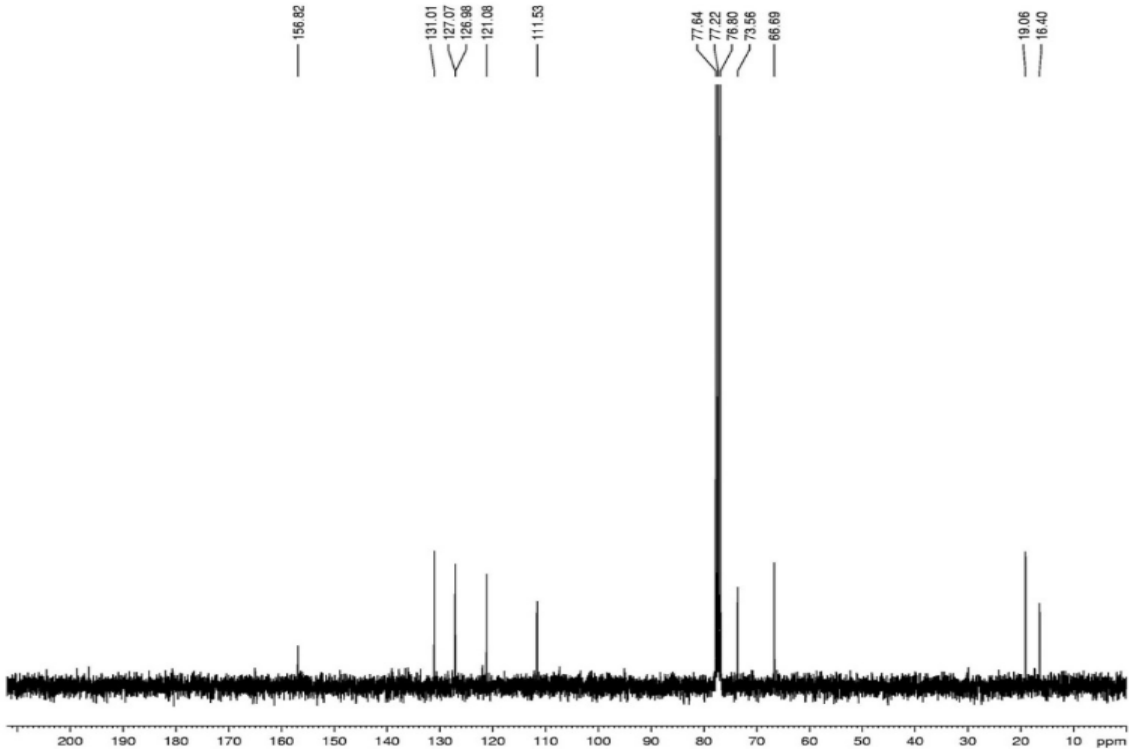
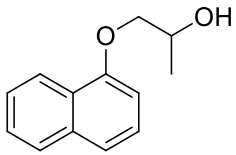


Figure S14. NMR ^{13}C of *rac*-**4c** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(naphtalen-1-yloxy)propan-2-ol (4d):

White solid. R_f (20% EtOAc/ Hexane): 0.4. m.p.: 62.8–64.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.41 (d, *J* = 6Hz, 3H); 4.06 (m, 2H); 4.36 (m, 1H); 6.82 (d, *J* = 9 Hz, 2H); 7.40 (t, *J* = 18 and 9 Hz, 1H); 7.53 (m, 2H); 7.86 (m, 1H); 8.32 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 19.24 (CH_3); 66.56 (CH); 73.60 (CH_2); 105.19 (CH); 120.82 (CH); 121.88 (CH) 125.43 (CH); 125.69 (C); 125.95 (CH); 126.58 (C); 127.70 (CH); 134.87 (C); 154.37 (C). For (*R*)-**4d:** $[\alpha]_D^{20}$ +16.0 (*c* 5.0, CH_2Cl_2) for >99% *ee*.



4d

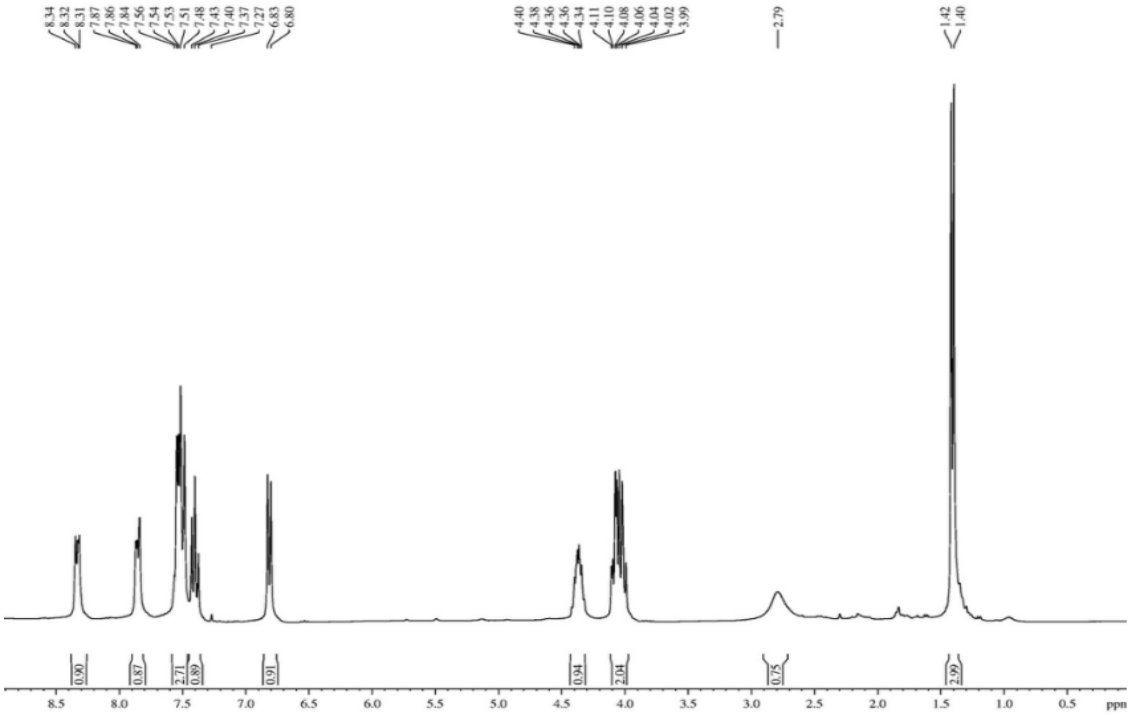
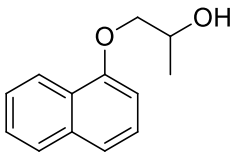


Figure S15. NMR ^{1}H of *rac*-**4d** (300 MHz, $CDCl_3$)



4d

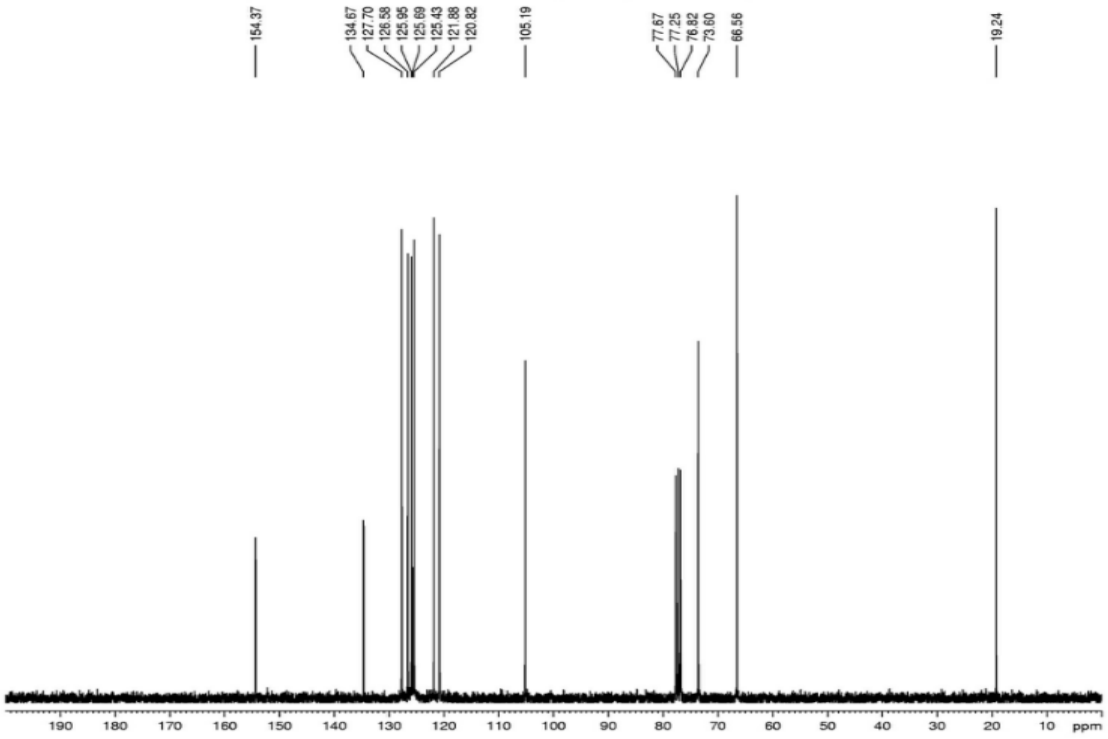
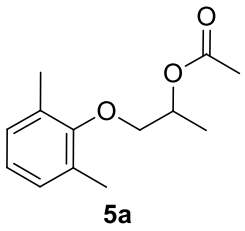


Figure S16. NMR ^{13}C of *rac*-**4d** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(2,6-dimethylphenoxy)propan-2-yl acetate (5a):

Yellow oil. R_f (20% Hexane:$CHCl_3$): 0.6. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.41 (d, *J* = 6.5 Hz, 3H); 2.11 (s, 3H); 2.33 (s, 6H); 3.82 (d, *J* = 4.8 Hz, 2H); 5.22-5.3 (m, 1H); 6.93 (dd, *J* = 8.4 and 6.2 Hz, 1H); 7.01 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm); 16.24 (CH_3); 16.73 (2 CH_3); 21.36 (CH_3); 69.85 (CH); 73.85 (CH_2); 124.14 (CH); 129.03 (2 CH); 130.9 (2 C); 155.42 (C); 170.7 (C). For (*S*)-**5a:** $[\alpha]_D^{20}$ -10.8 (*c* 8, $CHCl_3$) for >99% *ee*.



5a

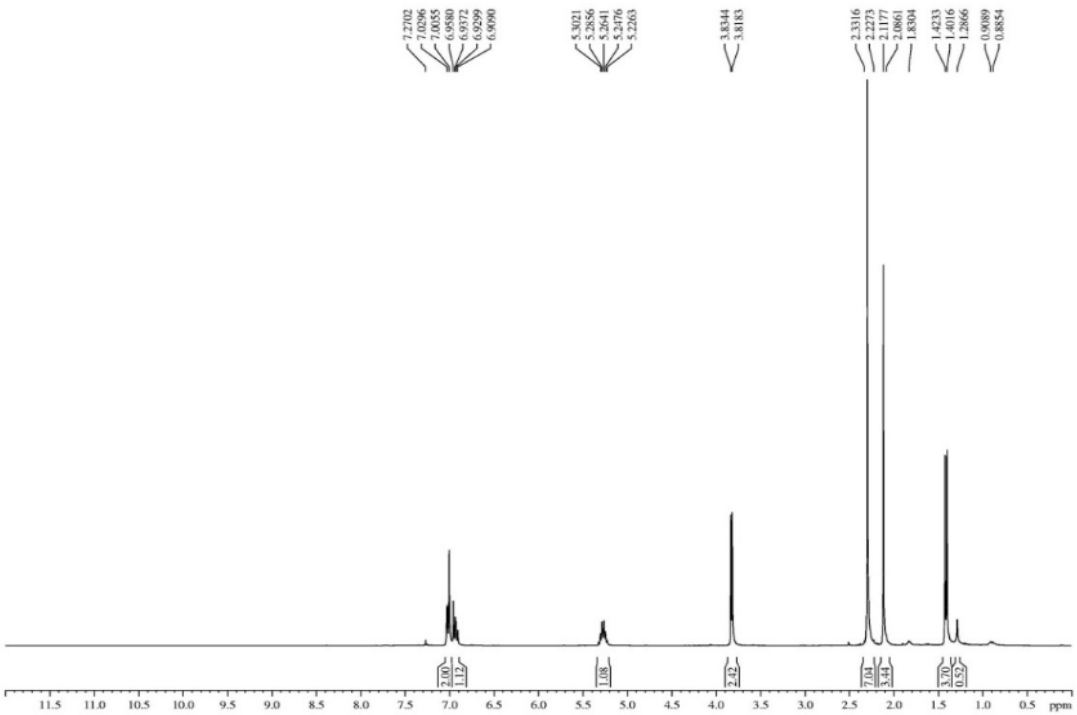
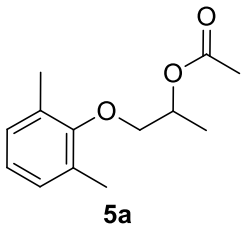


Figure S17. NMR ^{1}H of *rac*-**5a** (300 MHz, $CDCl_3$)



5a

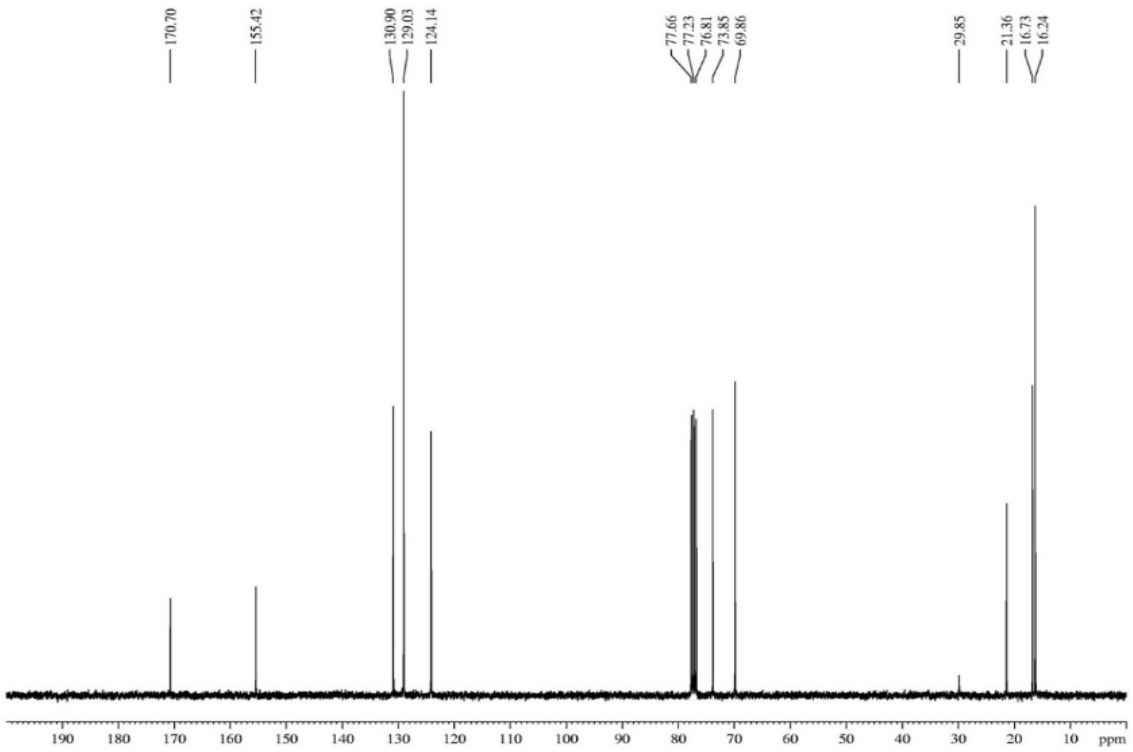
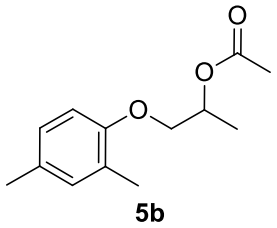


Figure S18. NMR ^{13}C of *rac*-**5a** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(2,4-dimethylphenoxy)propan-2-yl acetate (5b):

White solid. R_f (20%Hexane/ EtOAc): 0.65. m.p.: 40–41.7 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.36 (d, *J* = 3.8 Hz, 3H); 2.08 (s, 3H); 2.20 (s, 3H); 2.27 (s, 3H); 3.94-4.00 (m, 2H); 5.28-5.32 (m, 1H); 6.70 (d, *J* = 4.7 Hz, 1H); 6.94-6.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.20 (CH_3); 16.93 (CH_3); 20.62 (CH_3); 21.40 (CH_3); 69.16 (CH); 70.60 (CH_2); 111.46 (CH); 126.98 (C); 127.11 (CH); 130.17 (C); 131.75 (CH); 154.80 (C); 170.76 (C). For (*S*)-**5b:** $[\alpha]_D^{20}$ -38.8 (*c* 8, CH_2Cl_2) for >99% *ee*.



5b

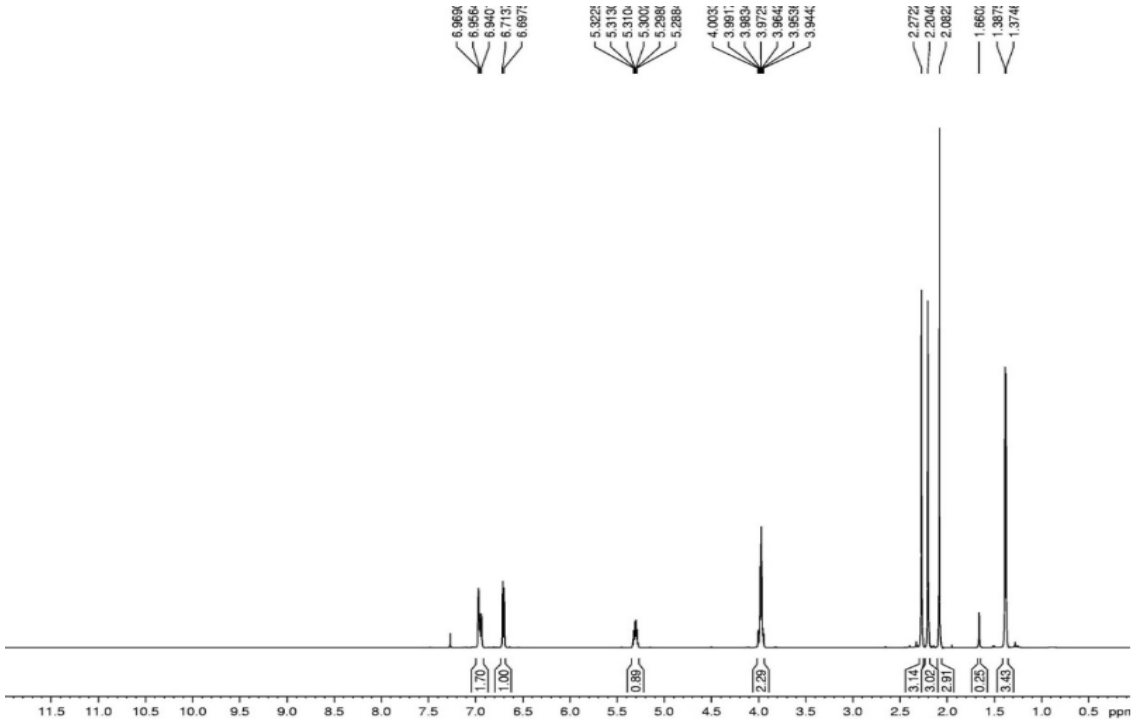
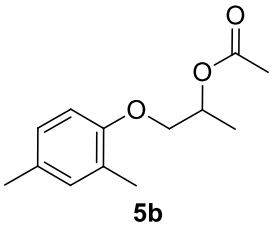


Figure S19. NMR ^{13}H of *rac*-**5b** (300 MHz, $CDCl_3$)



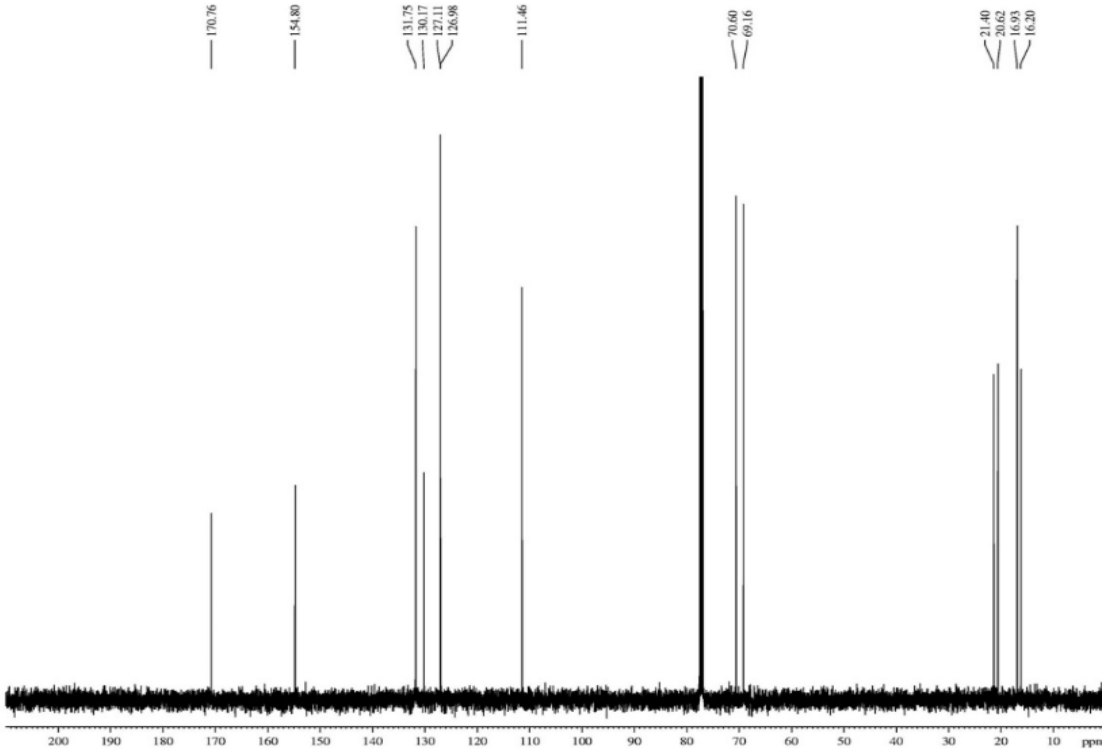
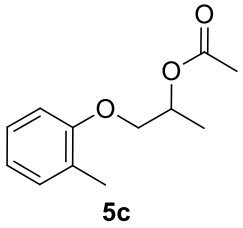


Figure S20. NMR ^{13}C of *rac*-**5b** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(*o*-toliloxy)propan-2-yl acetate (5c):

Yellow oil. R_f (10% Hexane/ EtOAc): 0.5. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.40 (d, *J* = 6 Hz, 3H); 2.09 (s, 3H); 2.24 (s, 3H); 4.01 (t, *J* = 3 Hz, 2H); 5.32 (m, 1H); 6.81 (d, *J* = 6 Hz, 1H); 6.89 (t, *J* = 21 and 6 Hz, 1H); 7,16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.23 (CH_3); 16.88 (CH_3); 21.33 (CH_3); 69.14 (CH); 70.29 (CH_2); 111.32 (CH); 120.94 (CH); 126.93 (CH); 127.18 (C); 130.90 (CH); 156.84 (C); 170.83 (C). For (*S*)-**5c:** $[\alpha]_D^{20}$ -19.42 (*c* 5, $CHCl_3$) for >99% *ee*.



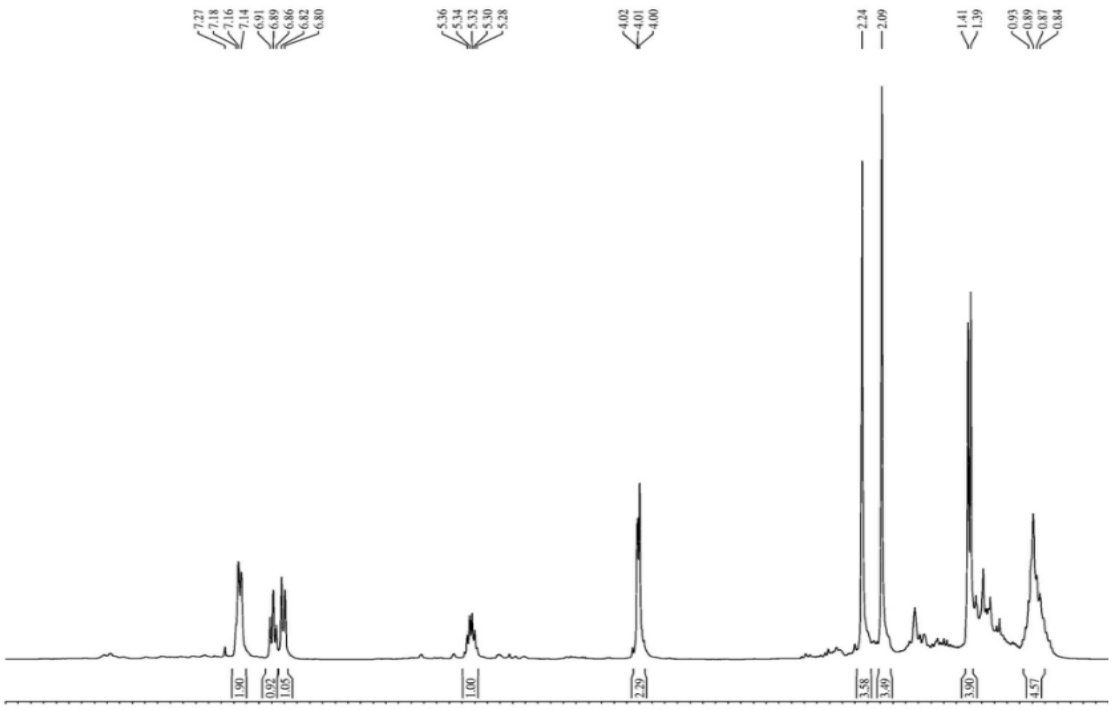
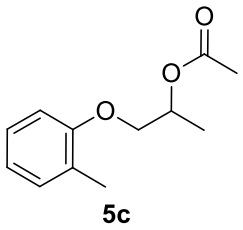


Figure S21. NMR ^{1}H of *rac*-**5c** (300 MHz, $CDCl_3$)



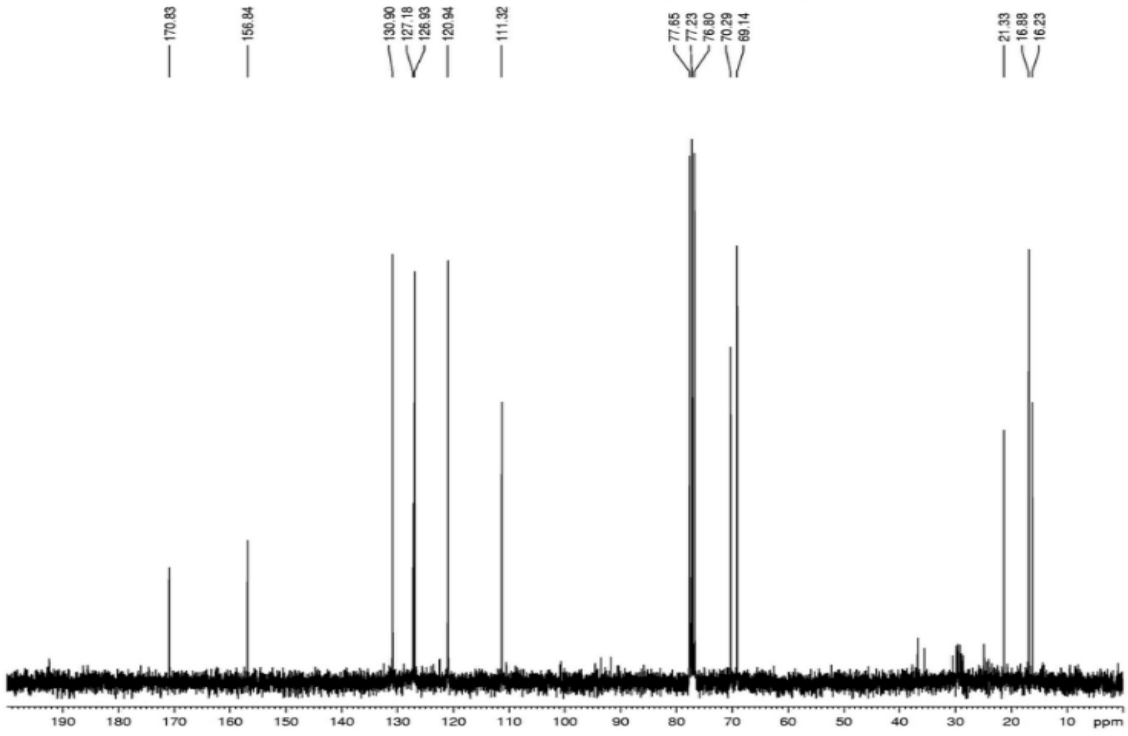
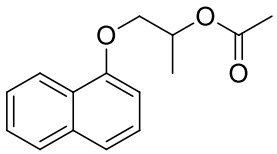


Figure S22. NMR ^{13}C of *rac*-**5c** (75 MHz, $CDCl_3$)

Physical and spectroscopic data of 1-(naphtalen-1-yloxy)propan-2-yl acetate (5d):

White solid. R_f (20%Hexane/EtOAc): 0.5. m.p.: 55.8–56.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.48 (d, *J* = 6Hz, 3H); 2.11 (s, 3H); 4.19 (m, 2H); 5.47 (m, H); 6.76 (d, *J* = 9 Hz, 1H); 7.40-8.27 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 17.11 (CH_3); 21.50 (CH_3); 69.07 (CH); 70.66 (CH_2); 105.09 (CH); 120.95 (CH); 122.25 (CH); 125.58 (CH); 125.95 (C); 125.99 (CH); 126.73 (CH); 127.70 (CH); 134.81 (C); 154.62 (C); 170.90 (C). For (*S*)-**5d:** $[\alpha]_D^{20}$ -26.73 (*c* 9, $CHCl_3$) for 95% *ee*.



5d

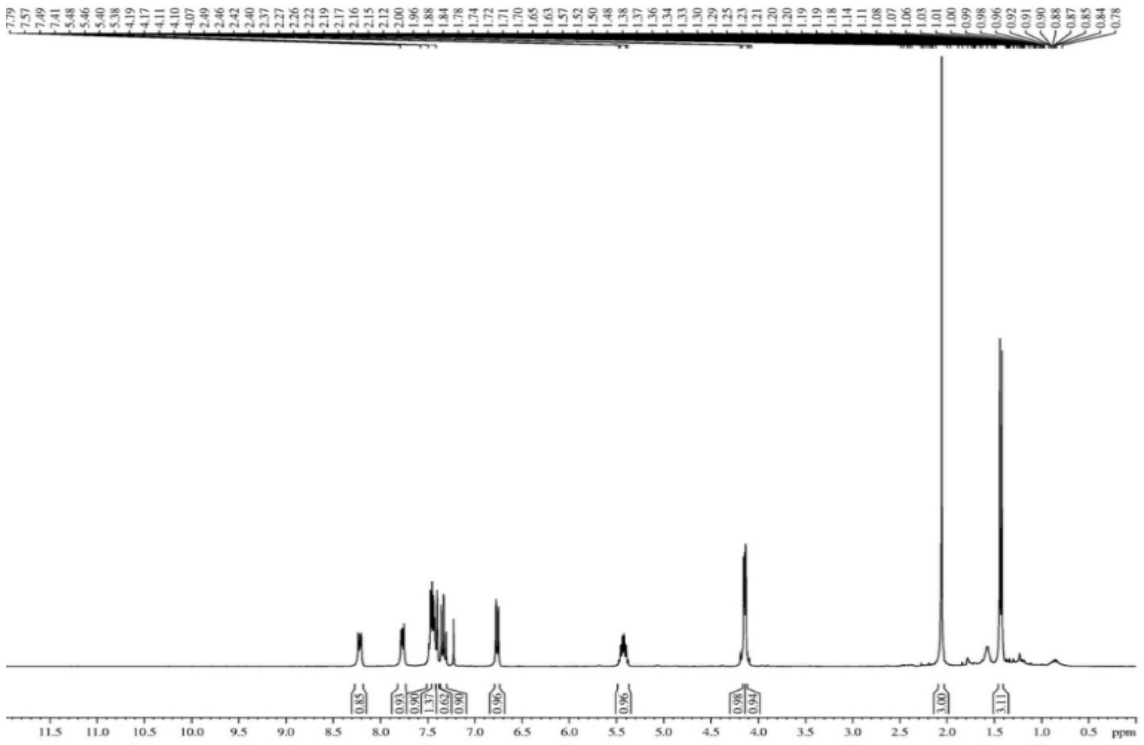
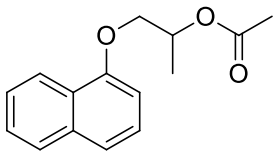


Figure S23. NMR ^{1}H of *rac*-**5d** (300 MHz, $CDCl_3$)



5d

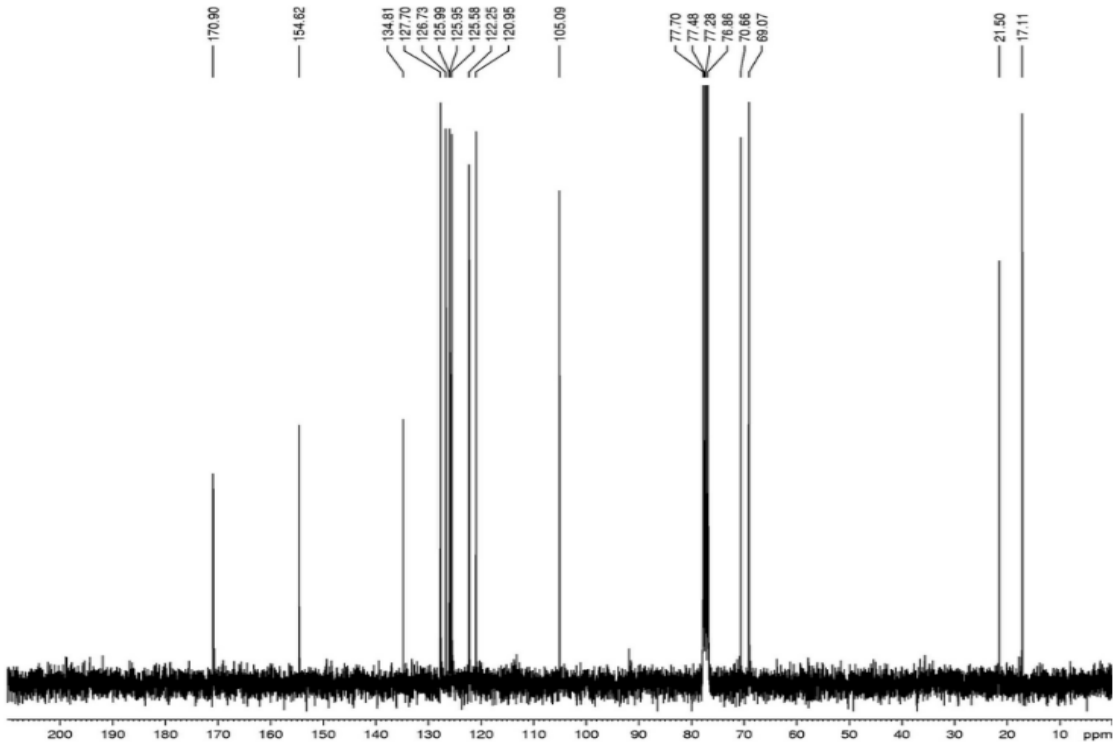
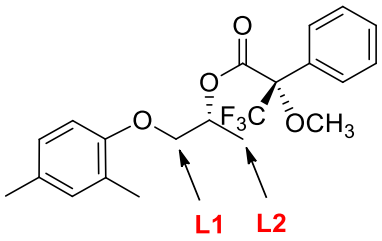


Figure S24. NMR ^{13}C of *rac*-**5d** (75 MHz, $CDCl_3$)

Spectroscopic data of (*R*)-ED-4b

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.49 (d, *J* = 6 Hz, 3H); 2.09 (s, 3H); 2.25 (s, 3H); 3.56 (s, 3H); 3.98 (m, 2H); 5.56 (m, 1H); 6.62 (d, *J* = 6 Hz, 1H); 6.93 (d, *J* = 12 Hz, 2H); 7.34 (m, 3H); 7.55 (d, *J* = 6 Hz, 2H).



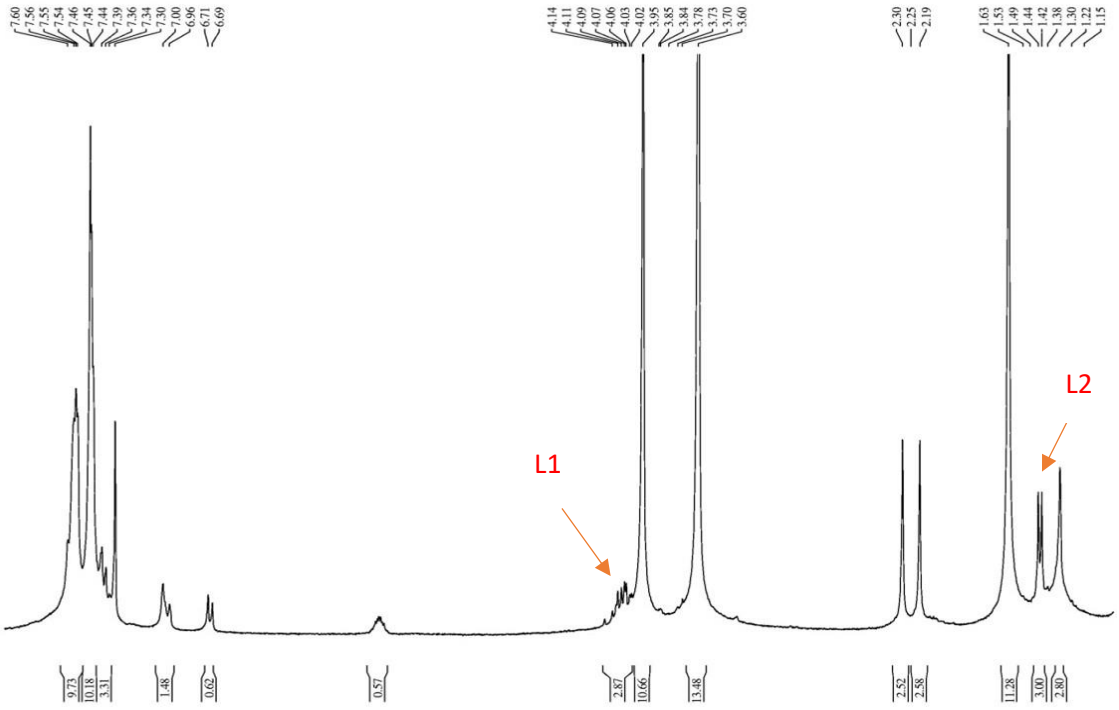


Figure S25. NMR ^{1}H of (***R*)-ED-4b** (300 MHz, $CDCl_3$).

Spectroscopic data of (*S*)-ED-4b

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.43 (d, *J* = 6Hz, 3H); 2.30 (s, 3H); 2.19 (s, 3H); 3.60 (s, 3H); 4.02 (m, 2H); 5.23 (m, 1H); 6.70 (d, *J* = 6 Hz, 1H); 6.97 (d, *J* = 12 Hz, 2H); 7.45 (m, 3H); 7.55 (d, *J* = 6 Hz, 2H).

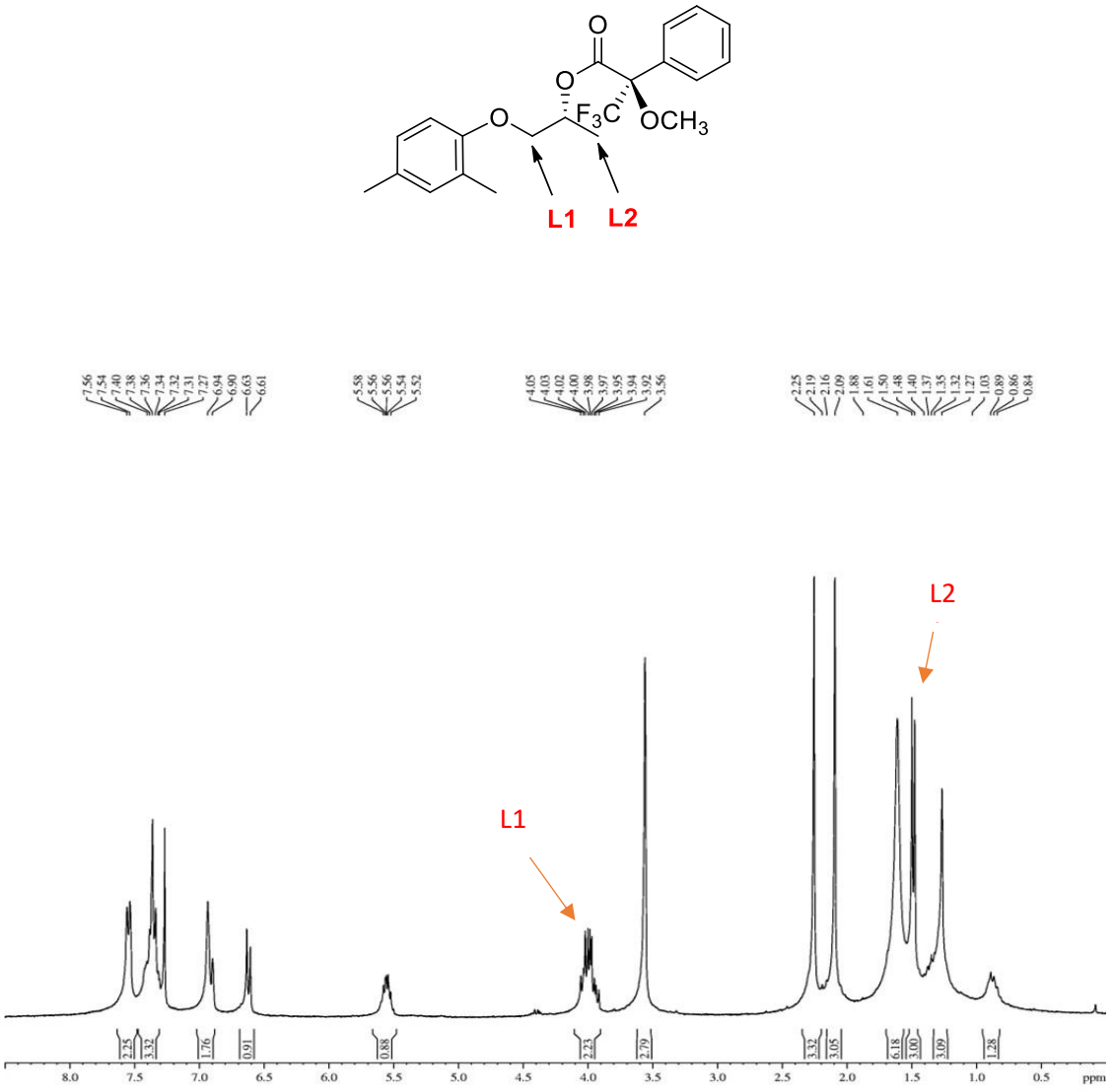
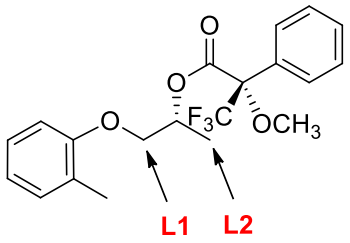


Figure S26. NMR ^{1}H of (***S*)-ED-4b** (300 MHz, $CDCl_3$).

Spectroscopic data of (*R*)-ED-4c

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.44 (d, *J* = 6Hz, 3H); 2.13 (s, 3H); 3.57 (s, 3H); 4.04 (m, 2H); 5.57 (m, 1H); 6.74 (d, *J* = 9 Hz, 1H); 6.88 (t, *J* = 15 and 9 Hz, 2H); 7.32 (m, 5H); 7.57 (d, *J* = 9 Hz, 2H).



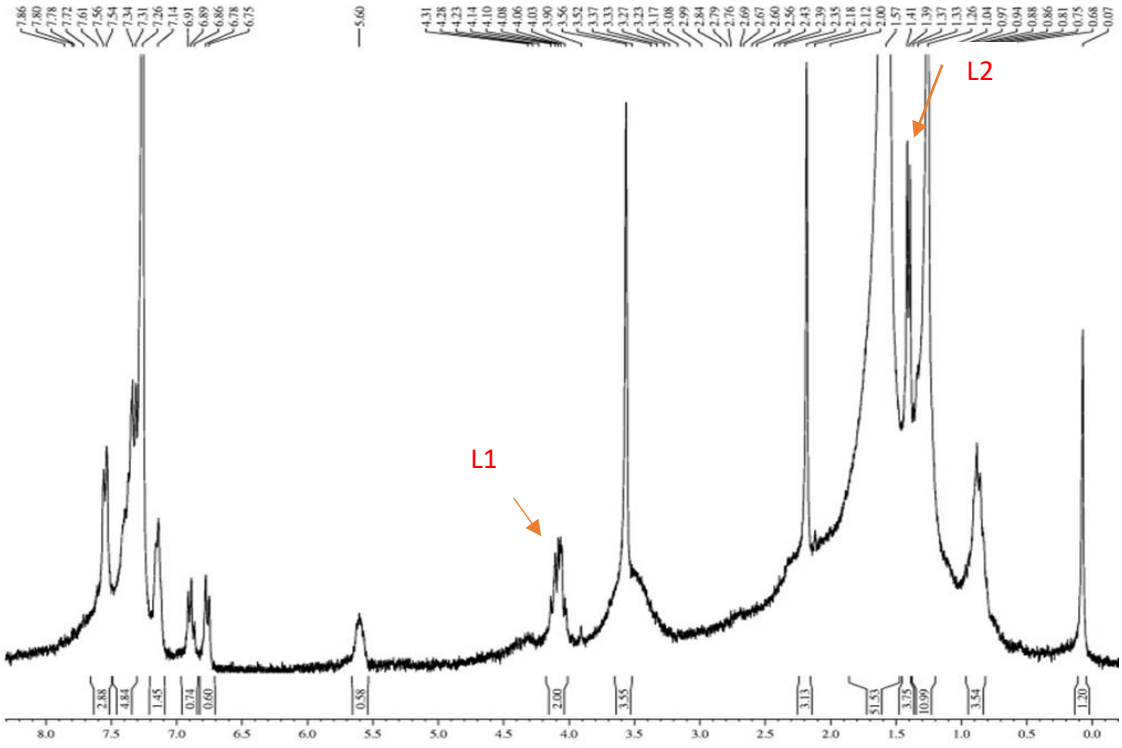
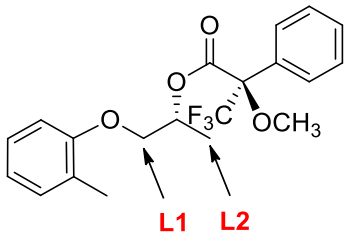


Figure S27. NMR ^{1}H of (***R*)-ED-4c** (300 MHz, $CDCl_3$).

Spectroscopic data of (*S*)-ED-4c

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.38 (d, *J* = 6Hz, 3H); 2.18 (s, 3H); 3.56 (s, 3H); 4.02 (m, 2H); 5.60 (m, 1H); 6.76 (d, *J* = 9 Hz, 1H); 6.89 (t, *J* = 15 and 9 Hz, 1H); 7.14 (s, 1H); 7.31(m, 4H); 7.56 (d, *J* = 6 Hz, 2H).



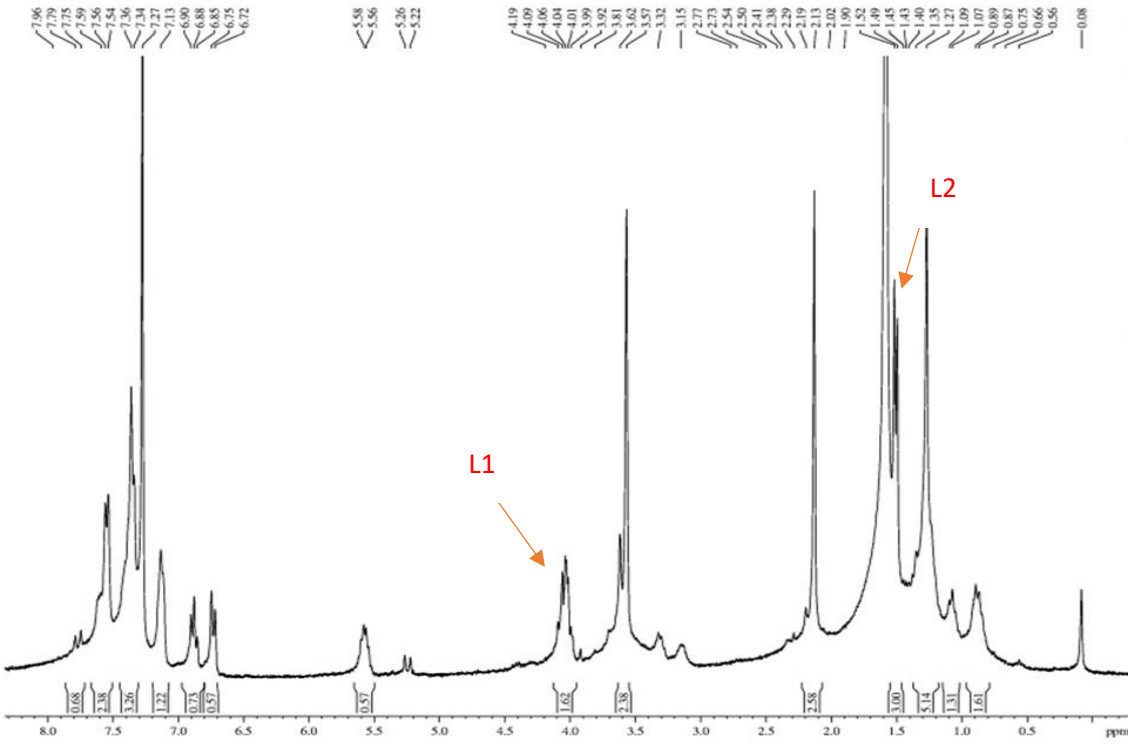


Figure S28. NMR ^{1}H of (***S*)-ED-4c** (300 MHz, $CDCl_3$).

Spectroscopic data of (*R*)-ED-4d

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.56 (d, *J* = 6Hz, 3H); 3.56 (s, 3H); 4.20 (m, 2H); 5.75 (m, 1H); 6.73 (d, *J* = 6 Hz, 1H); 7.22 (m, 2H); 7.36 (d, *J* = 6 Hz, 2H); 7.46 (m, 3H), 7.54 (d, *J* = 9 Hz, 2H); 7.79 (d, *J* = 9 Hz, 1H); 8.14 (d, *J* = 9 Hz, 1 H).

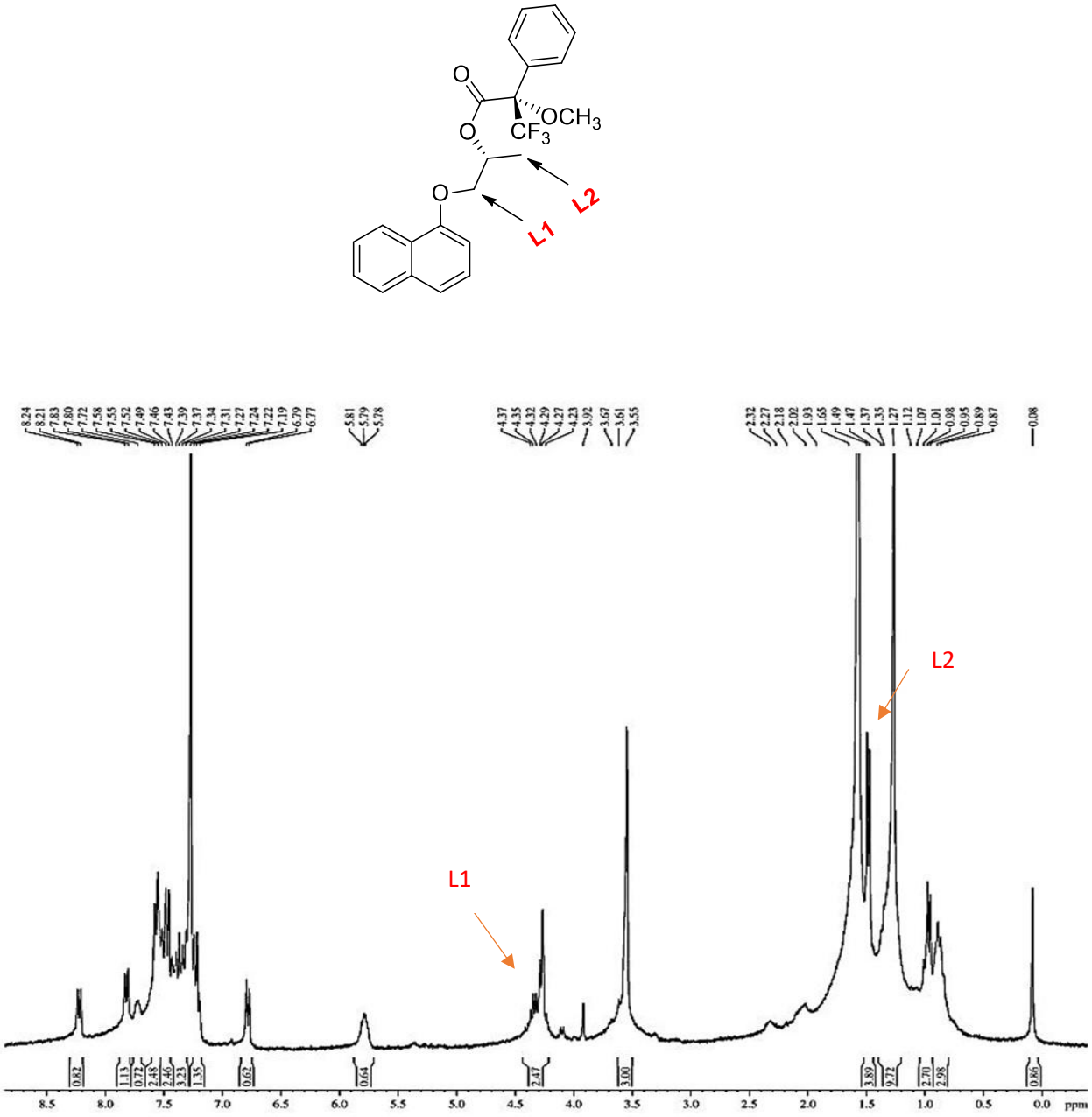
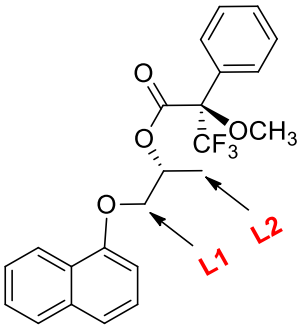


Figure S29. NMR ^{1}H of (***R*)-ED-4d** (300 MHz, $CDCl_3$).

Spectroscopic data of (*S*)-ED-4d

^{1}H RMN ($CDCl_3$, 300 MHz): δ (ppm) 1.36 (d, *J* = 6 Hz, 3H); 3.60 (s, 3H); 4.32 (m, 2H); 5.79 (m, 1H); 6.78 (d, *J* = 6 Hz, 1H); 7.22 (m, 2H); 7.34 (m, 3H); 7.43 (m, 2H), 7.57 (d, *J* = 9 Hz 2H); 7.82 (d, *J* = 9 Hz 1H), 8.23 (d, *J* = 9 Hz, 1 H).



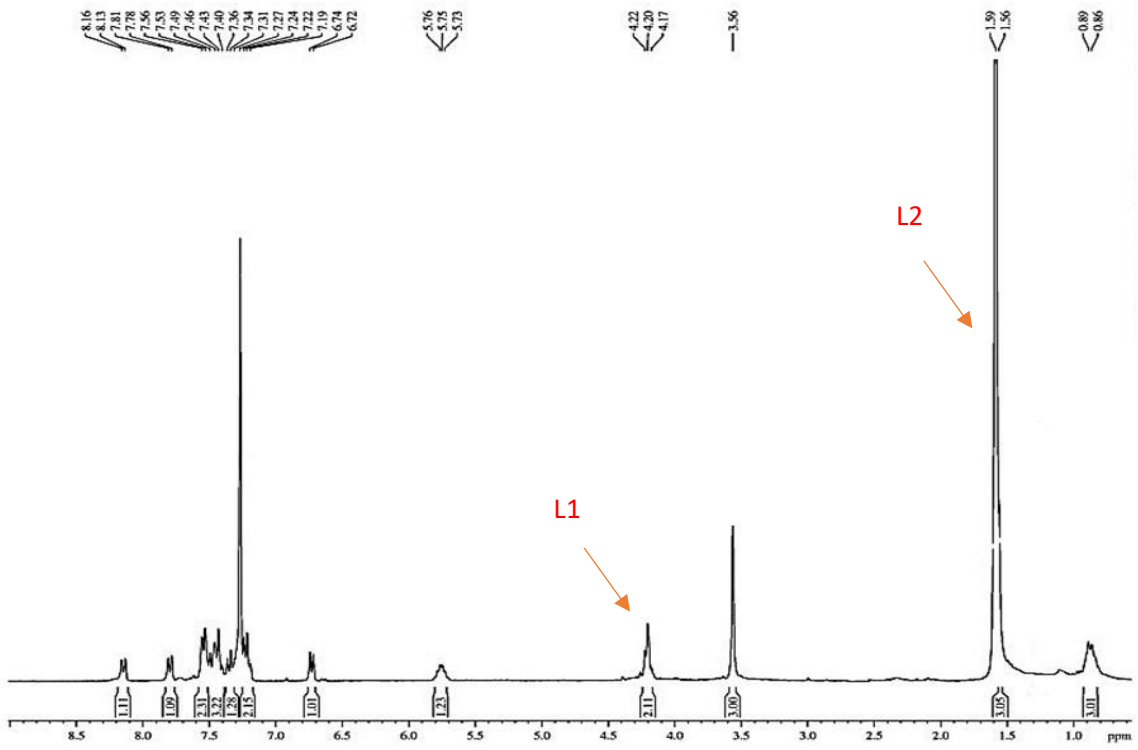


Figure S30. NMR ^{1}H of (***S*)-ED-4d** (300 MHz, $CDCl_3$).

Chromatograms obtained by GC/HPLC of alcohols 4a-d and acetates 5a-d

Resolution value (Rs) for *rac*-**4a**: 2.0

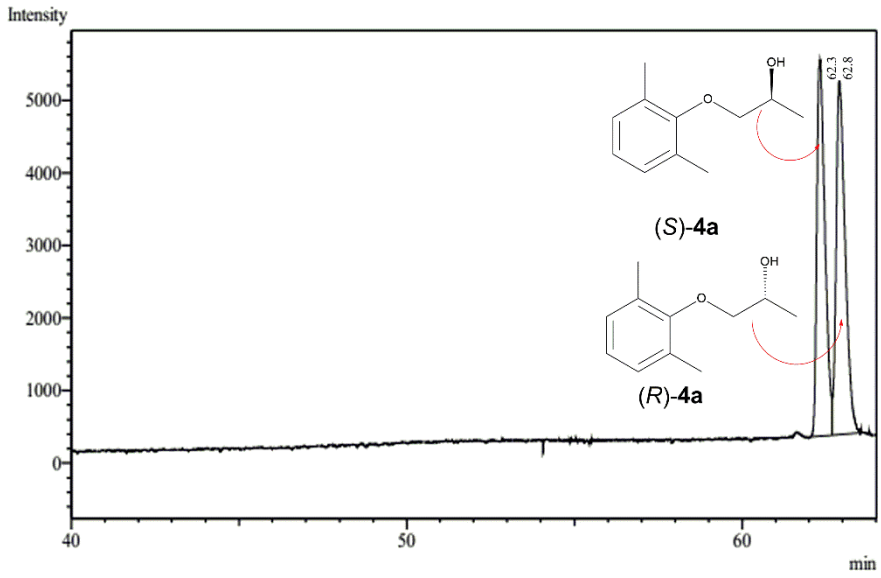
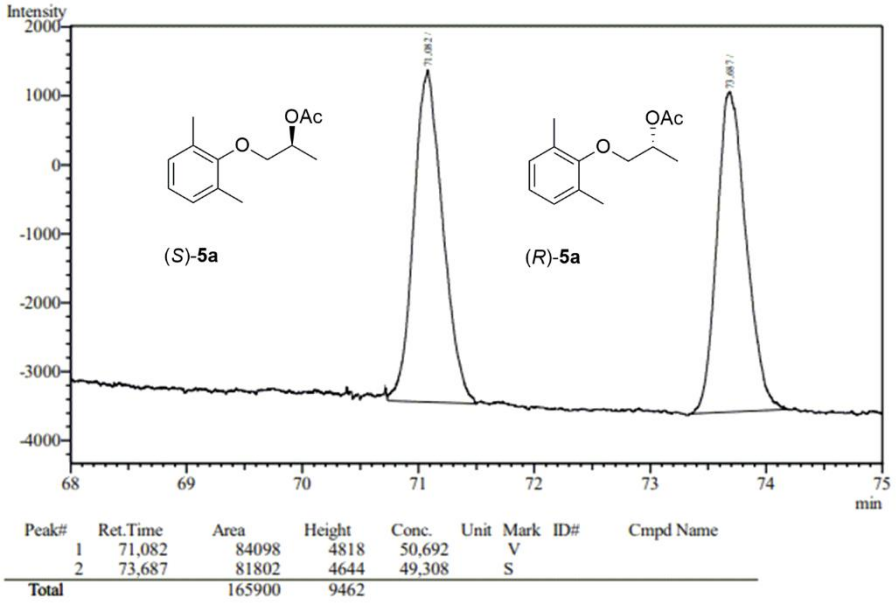


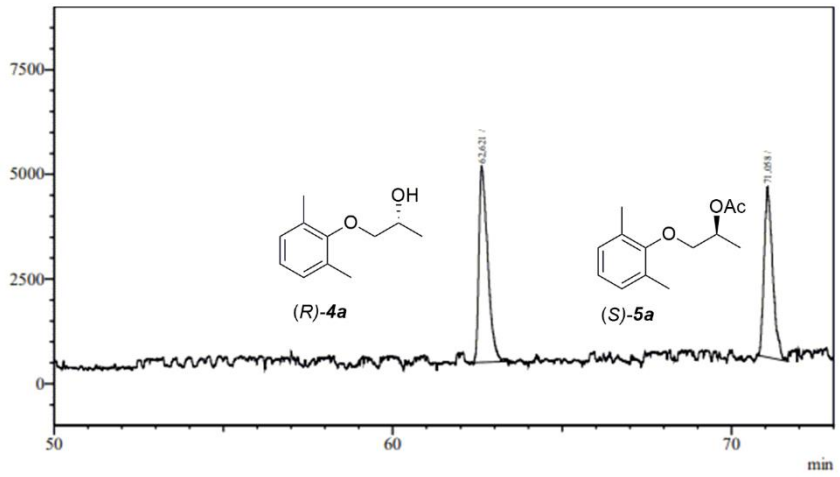
Figure S31. Chromatogram obtained by GC from *rac-4***a**

Resolution value (Rs) for *rac*-**5a**: 3.3



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	71,082	84098	4818	50,692		V		
2	73,687	81802	4644	49,308		S		
Total		165900	9462					

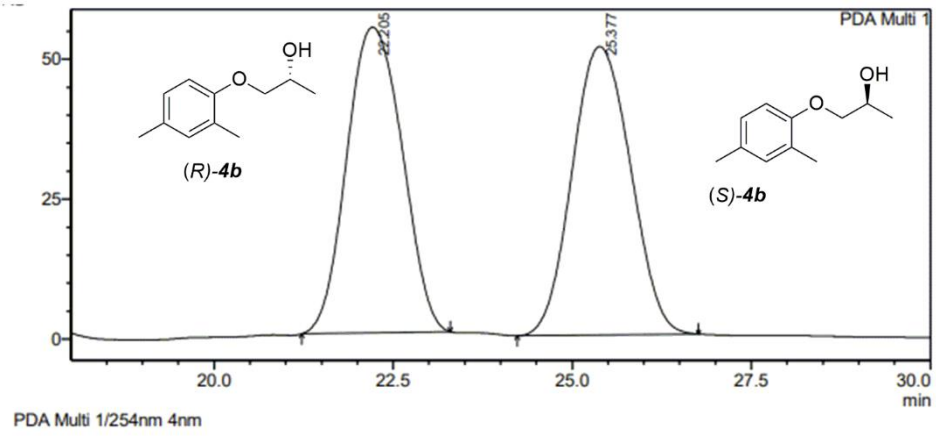
Figure S32. Chromatogram obtained by GC from *rac*-**5a**



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	62,621	84419	4687	53,522				
2	71,058	71302	4074	45,206		S		
3	73,775	2005	297	1,271				
Total		157726	9058					

Figure S33. Chromatogram obtained by GC from (*R*)-**4a** and (*S*)-***5a*** after enzymatic hydrolysis of acetate r*ac*-**5a** in the presence of TLL immobilized on Immobead 150, using acetonitrile as co-solvent

Resolution value (Rs) for *rac*-**4b**: 1.5



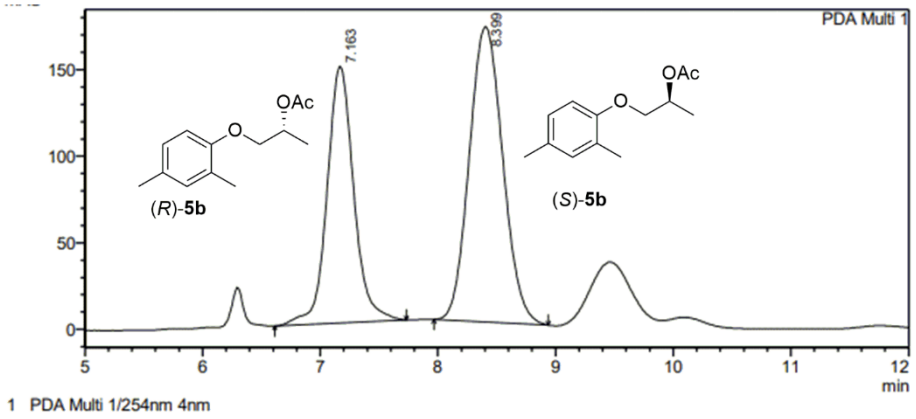
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.205	2941400	54576	50.135	51.433
2	25.377	2925513	51534	49.865	48.567
Total		5866912	106110	100.000	100.000

Figure S34. Chromatogram obtained by HPLC from *rac*-**4b**

Resolution value (Rs) for *rac*-**5b**: 2.3

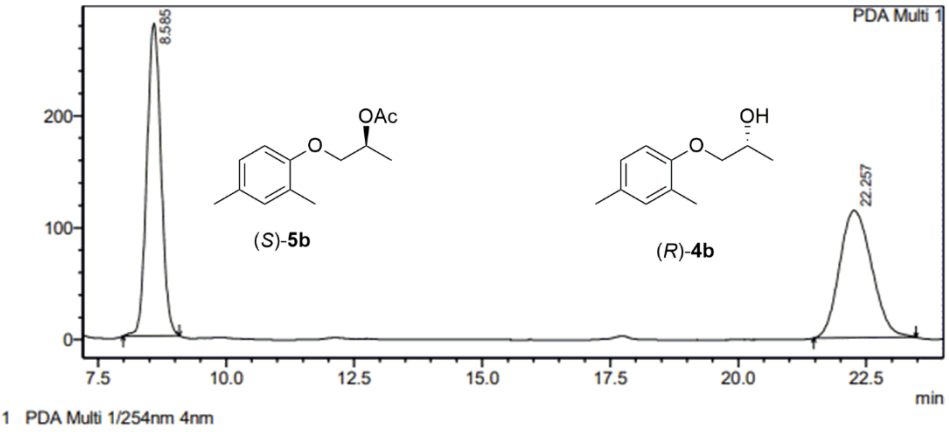


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.163	2347108	148355	40.986	46.527
2	8.399	3379488	170502	59.014	53.473
Total		5726596	318857	100.000	100.000

Figure S35. Chromatogram obtained by HPLC from *rac*-**5b**



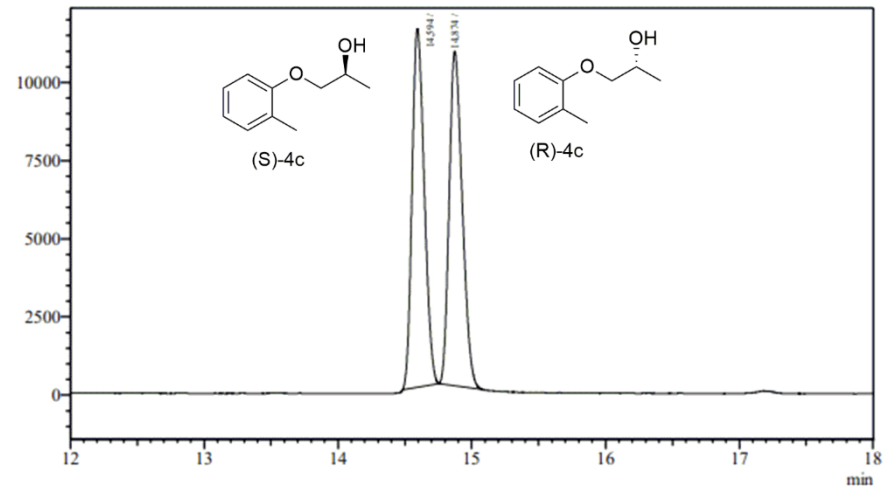
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.585	5374356	278584	51.866	71.028
2	22.257	4987702	113636	48.134	28.972
Total		10362059	392220	100.000	100.000

Figure S36. Chromatogram obtained by HPLC from (*S*)-**5b** and (*R*)-**4b** after enzymatic hydrolysis of acetate r*ac*-**5b** in the presence of TLL immobilized on Immobead 150, using acetonitrile as co-solvent

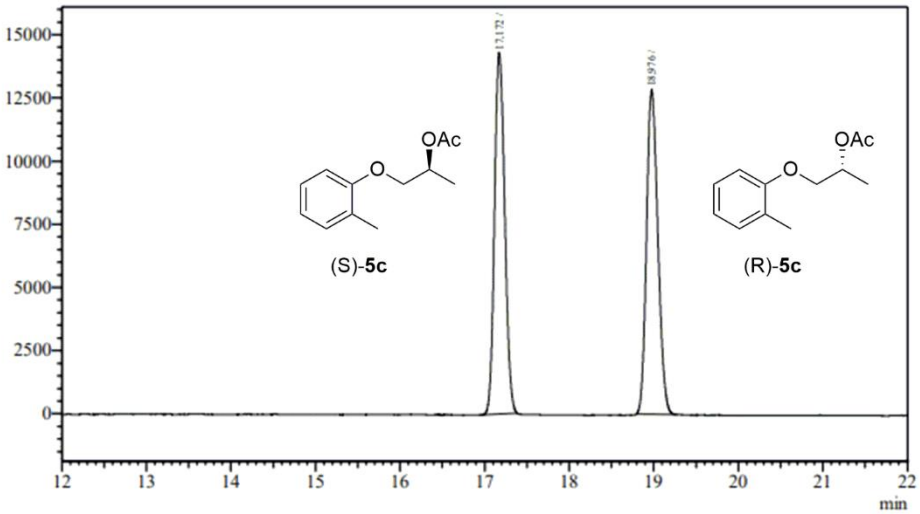
Resolution value (Rs) for *rac*-**4c**: 2.7



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	14,594	72772	11464	49,999				
2	14,874	72775	10692	50,001				
Total		145547	22156					

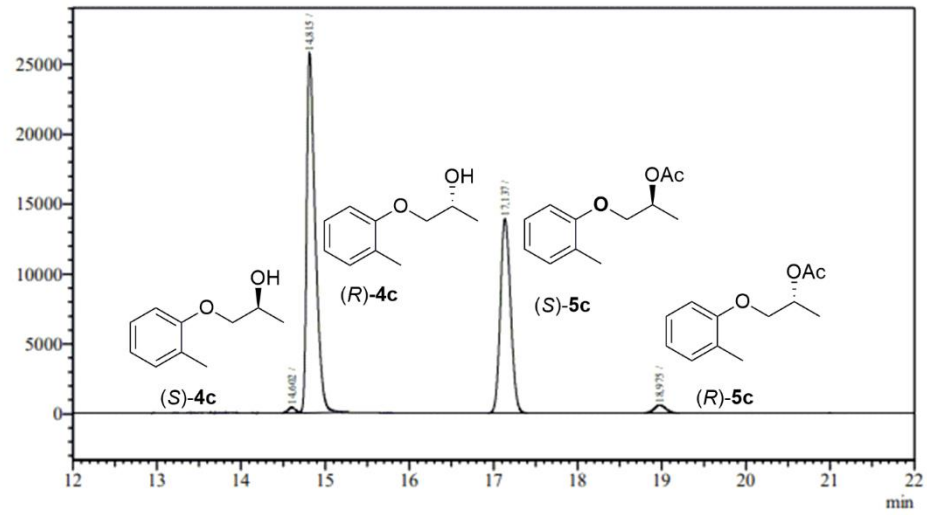
Figure S37. Chromatogram obtained by GC from *rac*-**4c**

Resolution value (Rs) for *rac*-**5c**: 4.5



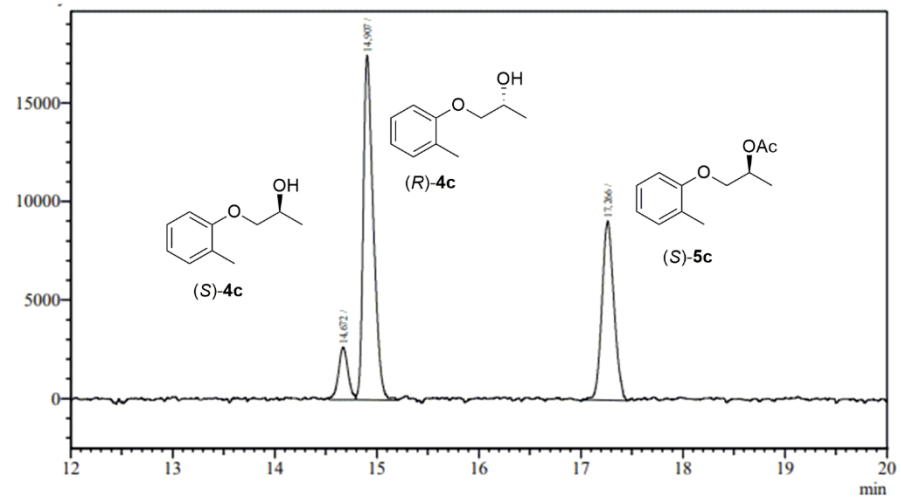
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	17,172	120197	14300	50,126				
2	18,976	119592	12844	49,874				
Total		239789	27144					

Figure S38. Chromatogram obtained by GC from *rac*-**5c**



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	14,602	2421	402	0,785				
2	14,815	182935	25687	59,354		V		
3	17,137	117530	13878	38,133				
4	18,975	5322	558	1,727				
Total		308208	40525					

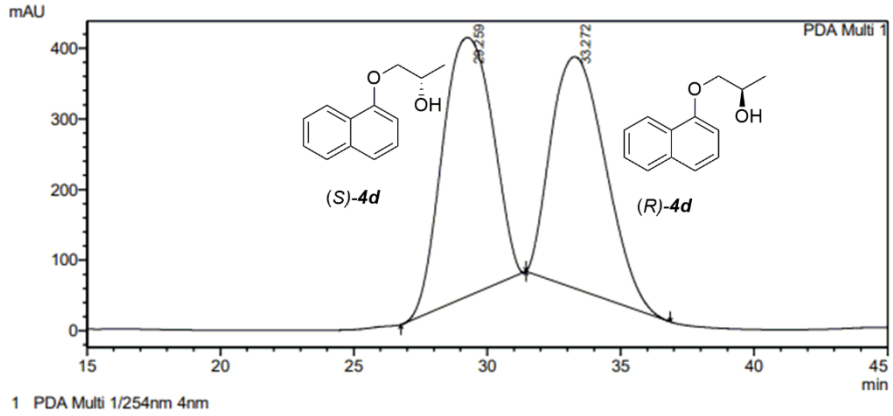
Figure S39. Chromatogram obtained by GC from (*S*)-**4c,** (*R*)-**4c,** (*S*)-**5c** and (*R*)-**5c** after enzymatic hydrolysis of acetate r*ac*-**5c** in the presence of TLL immobilized on Immobead 150, using acetonitrile as co-solvent



Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	14,672	17325	2672	8,215		V		
2	14,907	119287	17470	56,565		SV		
3	17,266	74271	9070	35,219				
Total		210883	29212					

Figure S40. Chromatogram obtained by GC from (*S*)-**4c,** (*R*)-**4c** and (*S*)-**5c** after enzymatic hydrolysis of acetate r*ac*-**5c** in the presence of lipase from *P. fluorescens* in the absence of co-solvent

Resolution value (Rs) for *rac*-**4d**: 1.6



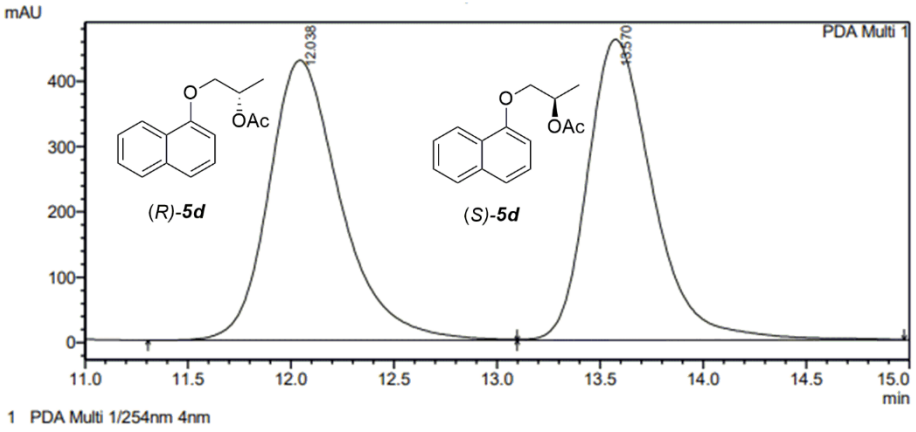
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	29.259	48120266	366312	50.679	52.759
2	33.272	46831194	328004	49.321	47.241
Total		94951459	694317	100.000	100.000

Figure S41. Chromatogram obtained by HPLC from *rac*-**4d**

Resolution value (Rs) for *rac*-**5d**: 4.7

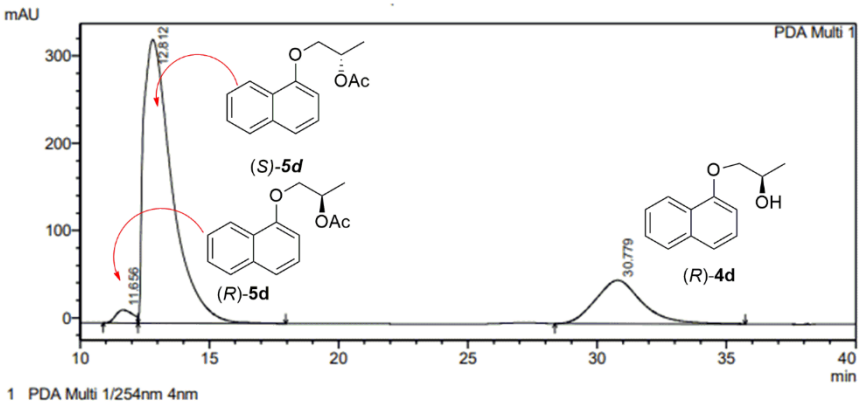


PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.038	10408428	428273	50.690	48.223
2	13.570	10125210	459827	49.310	51.777
Total		20533638	888100	100.000	100.000

Figure S42. Chromatogram obtained by HPLC from *rac*-***5d***



PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.656	676050	14890	2.139	3.824
2	12.812	24682916	324711	78.112	83.399
3	30.779	6240459	49744	19.749	12.776
Total		31599425	389346	100.000	100.000

Figure S43. Chromatogram obtained by HPLC from (*R*)-**5d,** (*S*)-**5d** and (*R*)-**4d** after enzymatic hydrolysis of acetate r*ac*-**5d** in the presence of TLL immobilized on Immobead 150, using acetonitrile as co-solvent