Electronic Supplementary Information

Dynamic Kinetic Resolution of *tert*-Alcohols
via Combination of Lipase/Brønsted Acid in Biphasic Reaction Medium

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1. General information

All reactions were monitored by thin-layer chromatography (TLC) on glass-backed silica gel 60 F_{254}, 0.2 mm plates (Merck). ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-ECA500 (^{1}H: 500 MHz, ^{13}C: 126 MHz, ^{19}F: 471 MHz) instrument. Chemical shifts were reported in δ (ppm) relative to the deuterated solvents (7.26 ppm (^{1}H) and 77.0 ppm (^{13}C) for $CDCl_3$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. Optical rotation was measured on a JASCO P-1020 polarimeter. All reagents and solvents were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), Nacalai TesqueInc. (Kyoto, Japan), Sigma-Aldrich Co., LLC (Tokyo, Japan), and FUJIFILM Wako Pure Chemical Co., Ltd. (Tokyo, Japan), Kanto Chemical Co., Inc. (Tokyo, Japan), and Kishida Chemical Co., Ltd. (Osaka, Japan), and used without further purification. Unless otherwise noted, flash chromatography was performed on silica gel 60N (particle size 40–50 μm) purchased from Kanto Chemical Co., Inc. Esters **4a**–**4f** were purified by flash chromatography using silica gel modified with aminopropyl groups (Wakogel® 50NH2, FUJIFILM Wako Pure Chemical, Tokyo, Japan). SYLGARD 184 silicone elastomer kit (Dow silicone corporation) was purchased from Amazon Japan Co., Ltd. Mesoporous silica (TMPS-4R) was purchased from Taiyo Kagaku Co., Ltd. (Tokyo, Japan).

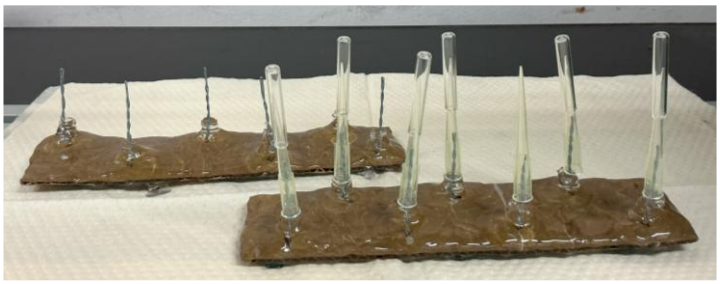
In all experiments, immobilized *Candida antarctica* lipase A (CAL-A) purchased from Sigma-Aldrich Co., LLC (Tokyo, Japan) was used as received. Product name: Lipase A *Candida antarctica* immobilized on Immobead 150, recombinant from *Aspergillus oryzae*. Product code: 41658, Lot #: BCCC9785 (activity: 1410 U/g) and BCCF4348 (activity: 1340 U/g)

2. Preparation of PDMS thimble

The PDMS thimbles were prepared using SYLGARD 184 silicone elastomer kit according to the reported method with a slight modification.[1,2]

1. **Mixing elastomer**: The elastomer base (10 mL) was mixed with curing agent (1 mL) using a spatula. The mixture was left to stand at 4 °C for 2 h to allow for degassing.
2. **Coating glass inserts**: Glass inserts (4.7 × 30 mm insert for HPLC vial) were attached on a micropipette tip and dipped in the degassed elastomer mixture.

3. **Curing**: The coated glass inserts were mounted on a hand-made wire stand and incubated at 60 °C for 1 h. This coating process was repeated once, followed by overnight incubation at 60 °C to ensure complete curing.

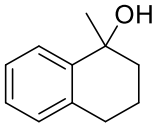


4. **Insert removal**: The coated inserts were soaked in hexane for 2 min to aid in removing the cured PDMS layer from the glass. The resulting PDMS thimbles were then air-dried under ambient conditions.

5. **Adding H_2SO_4**: A 300-μL portion of the H_2SO_4 solution was added into each PDMS thimble.
6. **Sealing**: The top edge of each thimble was coated with the elastomer mixture from Step 1. The edge was then sealed by applying heat for 30 sec at 240 °C using a curling iron.

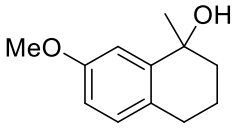
3. Synthesis of *tert*-alcohols

tert-Alcohols (±)-**1a**–**1f** were synthesized according to the reported method.[3,4] Their ^{1}H and ^{13}C NMR spectra were in good agreement with those reported.[4]



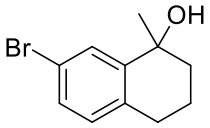
(±)-1-Methyl-1,2,3,4-tetrahydronaphthalen-1-ol (1a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.5, 1.5 Hz, 1H), 7.23-7.20 (m, 1H), 7.17 (td, J = 7.5, 1.5 Hz, 1H), 7.07 (dd, J = 7.5, 0.9 Hz, 1H), 2.85-2.73 (m, 2H), 1.99-1.89 (m, 3H), 1.87-1.78 (m, 1H), 1.57 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8, 136.2, 128.8, 127.1, 126.34, 126.27, 70.6, 39.8, 30.7, 29.9, 20.4.



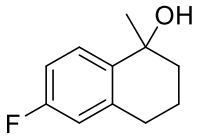
(±)-7-Methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (1b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 2.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.80 (s, 3H), 2.78-2.66 (m, 2H), 1.98-1.87 (m, 3H), 1.85-1.76 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 143.9, 129.8, 128.3, 113.7, 110.7, 70.9, 55.3, 39.8, 30.7, 29.0, 20.6.



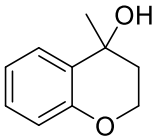
(±)-7-Bromo-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (1c)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.1 Hz, 1H), 7.28 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 2.79-2.64 (m, 2H), 1.99-1.85 (m, 3H), 1.84-1.76 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 135.0, 130.5, 130.1, 129.4, 119.8, 70.5, 39.4, 30.8, 29.3, 20.2.



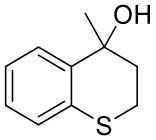
(±)-6-Fluoro-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (1d)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 9.0, 6.0 Hz, 1H), 6.90 (td, *J* = 9.0, 2.8 Hz, 1H), 6.75 (dd, *J* = 9.0, 2.8 Hz, 1H), 2.83-2.71 (m, 2H), 1.98-1.87 (m, 3H), 1.86-1.77 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6 (d, $J_{C\text{-}F}$ = 246.6 Hz), 138.63 (d, $J_{C\text{-}F}$ = 7.2 Hz), 138.60 (d, $J_{C\text{-}F}$ = 2.4 Hz), 128.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 114.7 (d, $J_{C\text{-}F}$ = 20.4 Hz), 113.4 (d, $J_{C\text{-}F}$ = 21.3 Hz), 70.3, 39.7, 30.8, 30.0, 20.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ −116.0 (td, *J* = 9.0, 6.0 Hz, 1F).



(±)-4-Methylchroman-4-ol (1e)

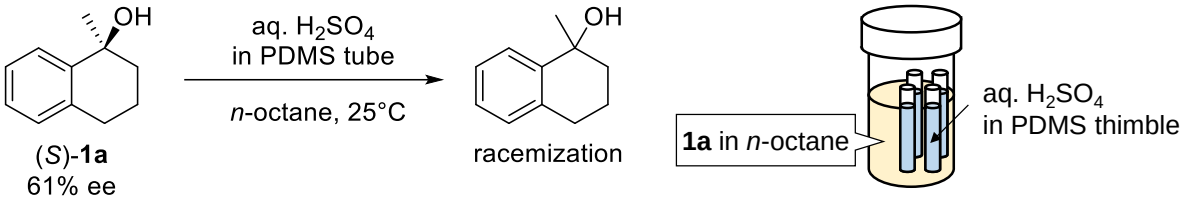
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.20-1.16 (m, 1H), 6.94 (td, *J* = 7.7, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.29 (ddd, *J* = 11.5, 7.3, 4.2 Hz, 1H), 4.23 (ddd, *J* = 11.5, 5.6, 4.2 Hz, 1H), 2.12-2.04 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 129.2, 128.4, 126.4, 120.8, 117.1, 66.4, 63.3, 38.0, 29.5.



(±)-4-Methylthiochroman-4-ol (1f)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.63 (m, 1H), 7.13-7.07 (m, 3H), 3.14-3.03 (m, 2H), 2.25-2.17 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 132.3, 127.6, 126.4, 126.2, 124.5, 69.3, 38.1, 29.6, 23.5.

4. H_2SO_4-catalysed racemization of (±)-1 in biphasic medium



Typical procedure (Scheme S1): Optically active (*S*)-**1a** was prepared by CAL-A-catalysed kinetic resolution of (±)-**1a** using vinyl hexanoate (**3**) according to our previous report.[4] A solution of (*S*)-**1a** (0.15 mmol, 61% ee) in *n*-octane (3 mL) was added to a 20-mL screw-capped vial (diameter: 27 mm). PDMS thimbles containing aq. H_2SO_4 (300 μL per thimble) were immersed in this solution. The vial was maintained at 25°C in a heating chamber (SLC-25A, Mitsubishi Electric Engineering Ltd., Tokyo, Japan) with gentle stirring of the organic phase. At specified intervals, aliquots of the organic phase were taken for chiral HPLC analysis (Table S1). The rate constant of racemization (k_{rac}) and half-life of % ee ($t_{1/2}$) were calculated from the slop of the ln(%ee) vs time plots.[5] After 24 h, the aqueous phase was neutralized with aq. $NaHCO_3$, combined with the organic phase, and extracted with EtOAc (×3). The combined organic layers were concentrated under reduced pressure, and the residue was analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as the internal standard.

Table S1. Time course of % ee in H_2SO_4-catalysed biphasic racemization of **1a**

Entry	H_2SO_4	number of PMDS thimble		2.0 h	4.5 h	6.0 h	k_{rac} / h^{-1}	$t_{1/2}$ / h
1	5mM	2	%ee	56.9	46.4	43.7		
			ln(%ee)	4.04	3.84	3.78	0.056	12.4
2	10mM	2	%ee	53.4	43.2	40.7		
			ln(%ee)	3.98	3.77	3.70	0.071	9.8
3	20mM	2	%ee	52.2	41.5	37.0		
			ln(%ee)	3.95	3.73	3.61	0.084	8.3
4	30mM	2	%ee	44.1	32.9	26.6		
			ln(%ee)	3.79	3.49	3.28	0.14	5.0
5	20mM	3	%ee	47.1	34.4	28.9		
			ln(%ee)	3.85	3.54	3.36	0.13	5.3
6	20mM	4	%ee	40.7	28.6	19.3		
			ln(%ee)	3.71	3.35	2.96	0.19	3.6

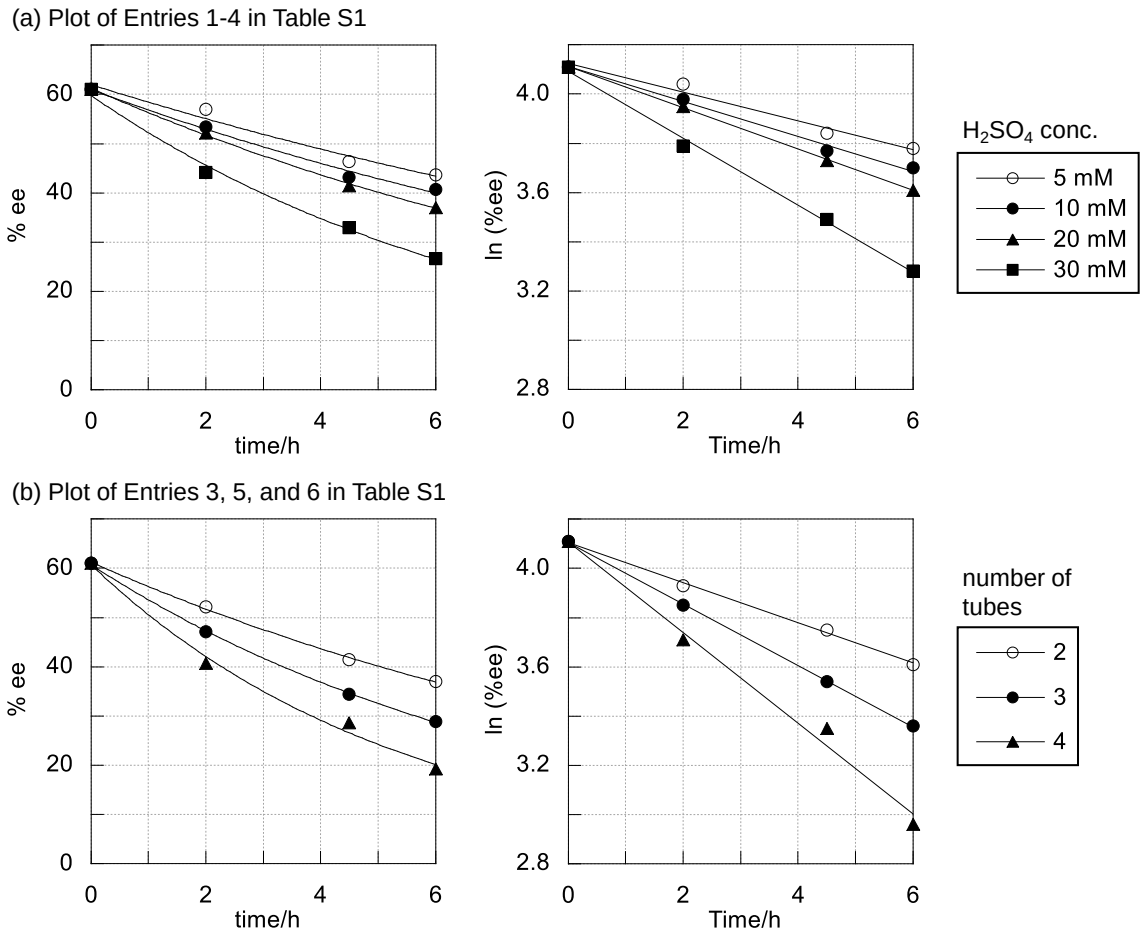


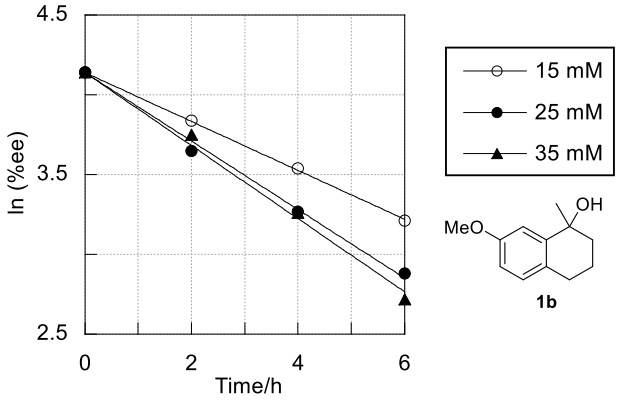
Figure S1. Time course of % ee and its ln-plot in racemization of **1a**.

Table S2. Time course of %ee in H_2SO_4-catalysed biphasic racemization of **1b**–**1f**

(a) Racemization of **1b**

H_2SO_4 conc.	15 mM	25 mM	35 mM
Time	ln(%ee)		
0 h	4.14	4.14	4.14
2.0 h	3.84	3.65	3.75
4.0 h	3.54	3.27	3.26
6.0 h	3.21	2.88	2.72
k_{rac} / h^{-1} [a]	0.15 (n.d.)	0.22 (6)	0.23 (10)

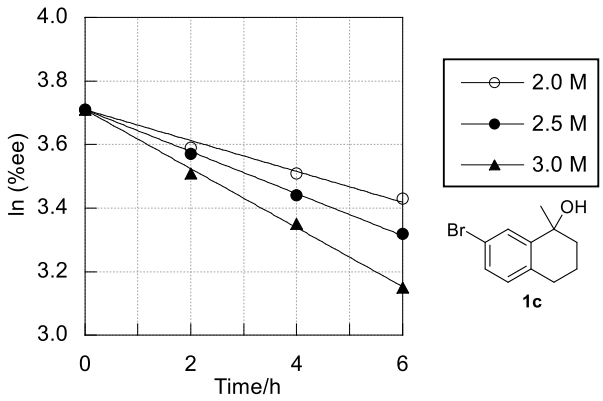
[a] Combined yield of **2b** and **2b'** at 24 h are shown in the parentheses. n.d.: not detected.



(b) Racemization of **1c**

H_2SO_4 conc.	2.0 M	2.5 M	3.0 M
Time	ln(%ee)		
0 h	3.71	3.71	3.71
2.0 h	3.59	3.57	3.51
4.0 h	3.51	3.44	3.35
6.0 h	3.43	3.32	3.15
k_{rac} / h^{-1} [a]	0.048 (n.d.)	0.066 (20)	0.093 (24)

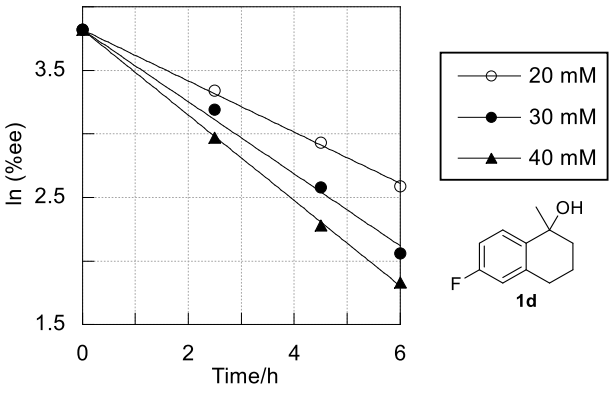
[a] Combined yield of **2b** and **2b'** at 24 h are shown in the parentheses. n.d.: not detected.



(c) Racemization of **1d**

H_2SO_4 conc.	20 mM	30 mM	40 mM
Time	ln(%ee)		
0 h	3.82	3.82	3.82
2.5 h	3.34	3.19	2.97
4.5 h	2.93	2.58	2.28
6.0 h	2.59	2.06	1.83
k_{rac} / h^{-1} [a]	0.20 (2)	0.28 (6)	0.33 (14)

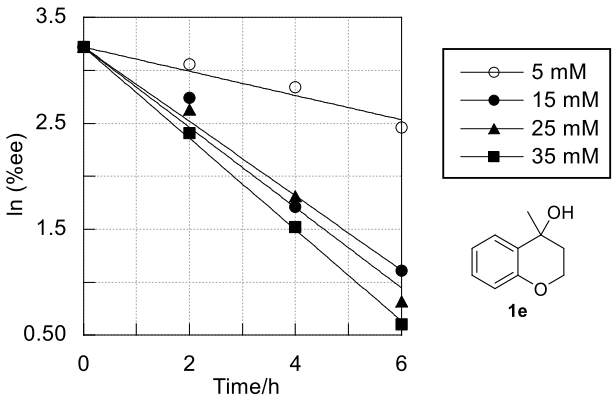
[a] Combined yield of **2b** and **2b'** at 24 h are shown in the parentheses. n.d.: not detected.



(d) Racemization of **1e**

H_2SO_4 conc.	5 mM	15 mM	25 mM	35 mM
Time	ln(%ee)			
0 h	3.22	3.22	3.22	3.22
2.0 h	3.06	2.74	2.63	2.41
4.0 h	2.84	1.71	1.81	1.52
6.0 h	2.46	1.11	0.82	0.60
k_{rac} / h^{-1} [a]	0.11 (n.d.)	0.35 (n.d.)	0.38 (2)	0.43 (7)

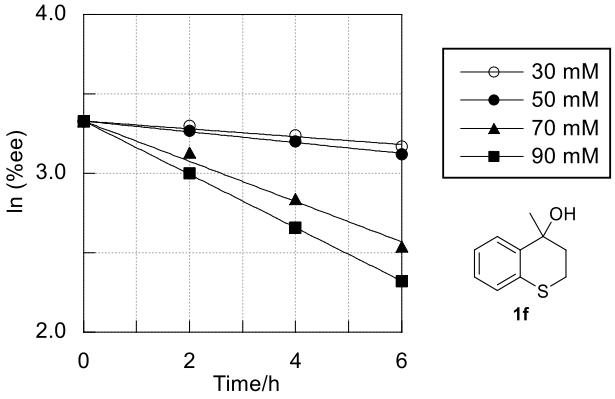
[a] Combined yield of **2b** and **2b'** at 24 h are shown in the parentheses. n.d.: not detected.



(e) Racemization of **1f**

H_2SO_4 conc.	30 mM	50 mM	70 mM	90 mM
Time	ln(%ee)			
0 h	3.33	3.33	3.33	3.33
2.0 h	3.30	3.27	3.13	3.00
4.0 h	3.24	3.20	2.84	2.66
6.0 h	3.17	3.12	2.54	2.32
k_{rac} / h^{-1} [a]	0.024 (n.d.)	0.0.35 (n.d.)	0.13 (5)	0.17 (9)

[a] Combined yield of **2b** and **2b'** at 24 h are shown in the parentheses. n.d.: not detected.



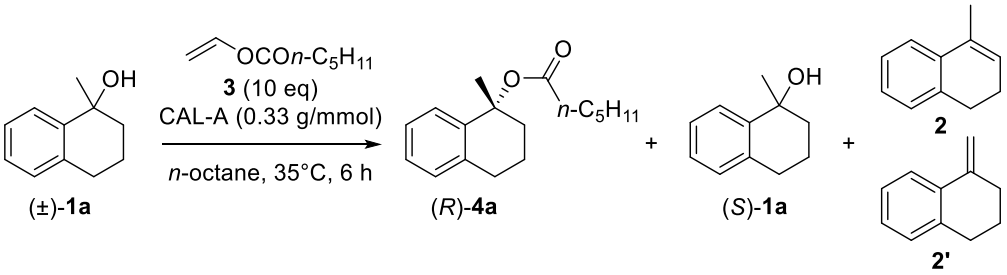
5. CAL-A-catalysed kinetic resolution of 1a in flow reactor

5.1. Investigation of filler

The kinetic resolution of (±)-**1a** with **3** was investigated under flow conditions. While the yield was 30% after 6 h when the lipase was packed alone in the column, the yield of **4a** reached 45% when Celite was mixed with the lipase as a filler to increase the residence time (Table S3).[6] In contrast, other fillers were found to be unsuitable. That is, using Florisil and mesoporous silica as the filler resulted in considerable amounts of side products **2a** and **2a'** with low yields of **4a**, probably because these fillers induced acid-mediated dehydration of **1a** and **4a**. The use of molecular sieves resulted in a low yield of **4a**, with a large amount of unreacted **1a** being recovered.

Experimental procedure: CAL-A beads (50 mg) were grinded in a mortar and mixed with the indicated filler. The mixture was then packed into an Omnifit® EZ SolventPlus™ column (6.6 mm × 100 mm) equipped with an adjustable end-piece, which was fastened to secure the packed material. The column

was fixed in a heating chamber (25°C) and connected to a 20-mL screw-capped vial (diameter: 27 mm) via 1/16" TPFE tubes. A solution of (±)-**1a** (0.15 mmol) and **3** (10 eq, 1.5 mmol) in *n*-octane (3 mL) was prepared and circulated through the column at a flow rate of 50 μL/min using a roller pump (Minato Concept, Inc., MCRP 204). After 6 h, the column was washed by flowing EtOAc (4 mL) and the combined organic solvent was concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard to determine the yield.



Entry	Filler	%Yield of **4a**
1[b]	None	30
2	Celite	45
3	Florisil	15 + **2**/**2'**
4	Mesoporous silica	4 + **2**/**2'**
5	MS4A	8 + **2**/**2'**

[a] Unless otherwise noted, the reaction was conducted using **1a** (0.15 mmol) and **3** (1.5 mmol) in *n*-octane (3.0 mL). The reactor was packed with CAL-A (50 mg) and the indicated filler (300 mg). [b] A ø2.2 mm PTFE tube was used as the column reactor.

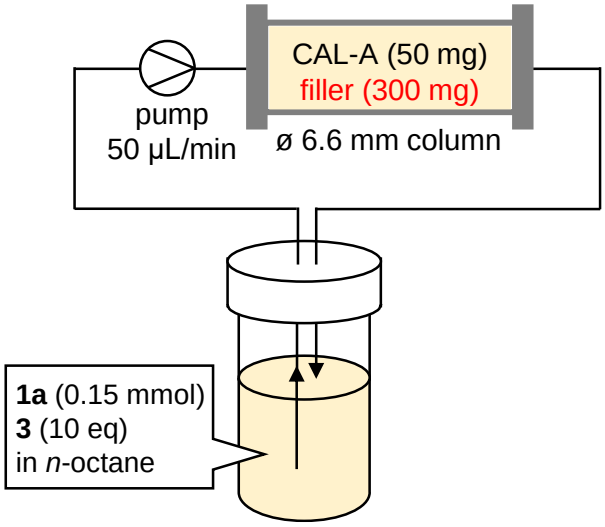


Figure S2. Effects of filler on the CAL-A-catalysed flow esterification reaction[a]

5.2 Investigation of additives in flow experiment

The effects of additives on the yield of **4a** in the CAL-A-catalysed kinetic resolution of (±)-**1a** under continuous flow conditions were investigated (Fig. S3). The addition of the inorganic base Na_2CO_3 significantly improved the yield, and CAL-A retained high catalytic activity over a 6-h period (● vs ○). In contrast, the use of bile salts such as sodium taurocholate (■) and sodium deoxycholate (▲) in place of Na_2CO_3 was ineffective, despite their known effectiveness as surfactants in lipase-catalysed reactions in aqueous media.[7] Given that the kinetic resolution in Fig. S3 occurs in the organic phase using immobilized CAL-A, the beneficial effect of Na_2CO_3 can be attributed to its basicity. Specifically, Na_2CO_3 may enhance catalytic activity by neutralizing hexanoic acid, a side product of the hydrolytic reaction of vinyl ester **3**, which could otherwise deactivate the acid-labile lipase.[4]

The total amount of (*R*)-**4a** produced during the first 6 h of operation was 0.20 mmol in the presence of Na_2CO_3 and 0.14 mmol in its absence, using 50 mg of CAL-A (1340 U/g). Accordingly, the enzyme unit requirement per mmol of (*R*)-**4a** produced was calculated to be 3.4×10^2 U/mmol with Na_2CO_3 and 4.9×10^2 U/mmol without Na_2CO_3.

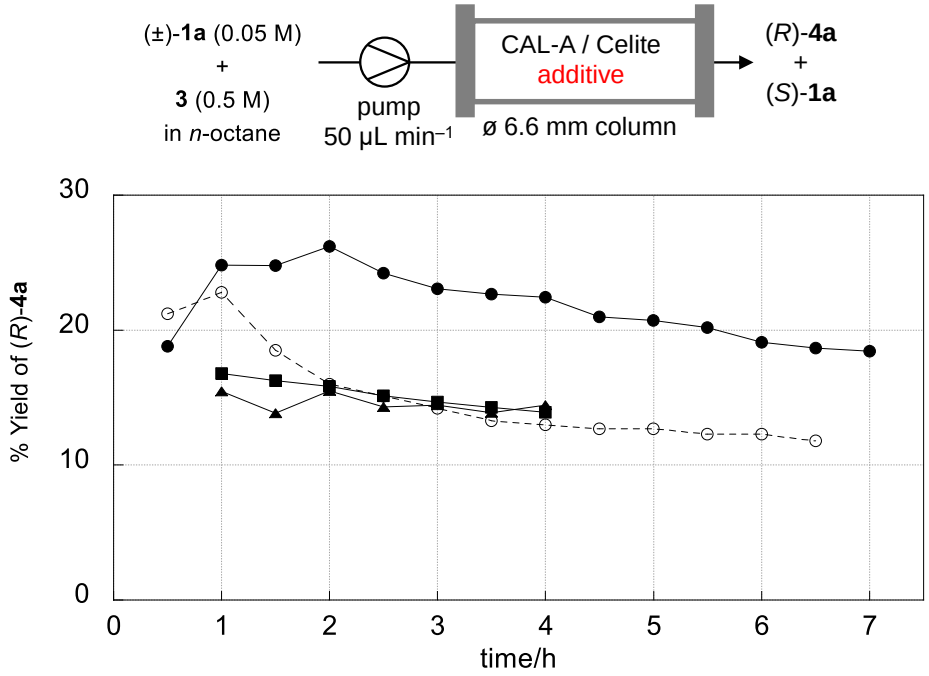


Figure S3. CAL-A-catalysed kinetic resolution of (±)-**1a** under flow conditions. The reaction was conducted using an *n*-octane solution containing (±)-**1a** (0.05 M) and **3** (0.5 M, 10 eq.) at a flow rate of 50 µL min^{-1} (residence time 20 min). The column reactor was packed with CAL-A (50 mg), Celite (330 mg), and the indicated additive (300 mg): (●) Na_2CO_3; (○) none; (■) sodium taurocholate; (▲) sodium deoxycholate.

Experimental procedure (Figures 2 and S3): CAL-A beads (50 mg) were grinded in a mortar and mixed with Celite (450 mg), and Na_2CO_3 or the indicated additive (300 mg). The mixture was packed into an Omnifit® EZ SolventPlus™ column (6.6 mm × 100 mm) equipped with an adjustable end-piece, which was fastened to secure the packed material. The column was fixed in a heating chamber (25°C), and connected to a fraction collector (ADVANTEC CHF122SC) and a 25-mL syringe on a syringe pump (YMC YSP-301) using 1/16" TPFE tubes. A solution of (±)-**1a** (0.05 M) and **3** (0.5 M) in *n*-octane was prepared and continuously pumped through the column reactor. The outlet solution was collected in fractions every 30 min using a fraction collector. Each collected fraction was subjected to chiral HPLC analysis. Since no side products and decomposition were observed in ^{1}H NMR analysis of each crude mixture, the yield of (*R*)-**4a** was calculated based on the ee values of **1a** and **4a** using the following equation:[8,9]

Yield (%) = ee(**1a**) / [ee(**1a**) + ee(**4a**)] × 100

Reusability of CAL-A

The reusability of CAL-A in the kinetic resolution was investigated under the recycle flow conditions (Figure S4). When a column reactor packed with fresh CAL-A was used, the yield of **4a** reached 40% at 8 h (●). In contrast, a significantly slower reaction rate was observed when the column reactor reused from the previous experiment was employed (○).

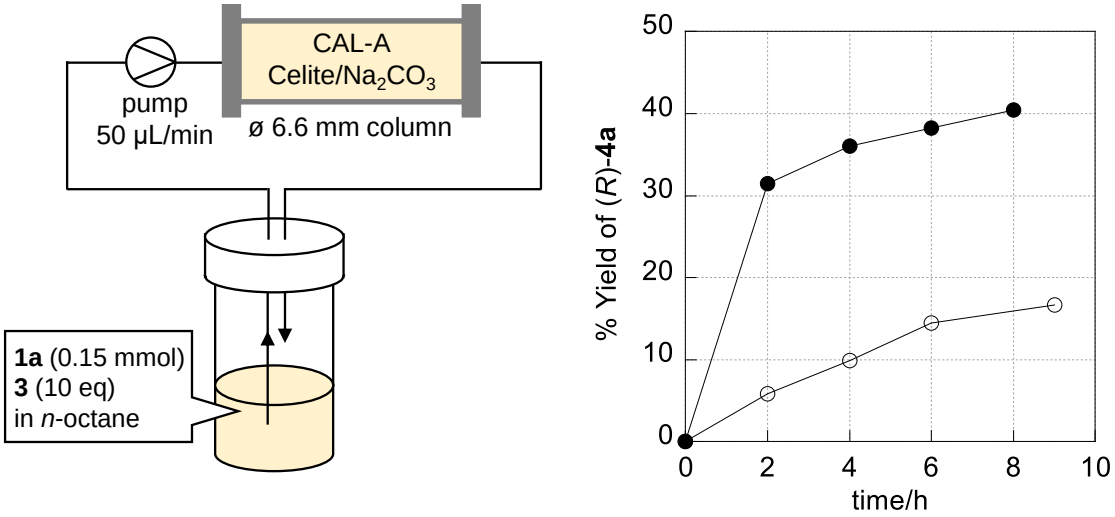


Figure S4. Reuse of CAL-A-packed column in kinetic resolution of **(±)-1a**. The reaction was conducted using an *n*-octane solution (3.3 mL) containing (±)-**1a** (0.15 mmol) and **3** (1.5 mmol) at a flow rate of 50 μL min^{-1} (residence time 20 min). The column reactor was packed with CAL-A (50 mg), Celite (330 mg), and Na_2CO_3 (200 mg): (●) freshly prepared column; (○) reused column.

6. Lipase/H_2SO_4-cocatalysed biphasic DKR of (±)-1

Experimental procedure using H_2SO_4 solution sealed in PDMS thimbles: An Omnifit® EZ SolventPlus™ column (6.6 mm × 100 mm) was charged with $MgSO_4$ (140 mg), and then a mixture of grinded CAL-A (50 mg), Celite (330 mg) and Na_2CO_3 (200 mg). The adjustable end-piece was fastened to secure the packed material. The column was connected to a 20-mL screw-capped vial (27-mm diameter) by 1/16" TPFE tubes. A solution of (±)-**1a** (0.15 mmol) and **3** (10 eq, 1.5 mmol) in *n*-octane (3.3 mL) was added to the vial, and PDMS thimble containing aq. H_2SO_4 (300 μL × 4) were immersed into the solution. The column and the vial were fixed in a heating chamber (25 °C), and the solution was circulated at a flow rate of 50μL/min using a roller pump with gentle stirring (Figure S3). After 26 h, the column was washed by flowing EtOAc (4 mL). H_2SO_4 solution in PDMS thimbles were collected and neutralized by aq. $NaHCO_3$. The organic solvent and the aqueous phase were combined and extracted with EtOAc (× 3). The combined organic layers were concentrated under reduced pressure. The residue was further concentrated using a Smart Evaporator C1 (BioChromato, Inc., Kanagawa,

Japan) to remove remaining vinyl hexanoate. The residue was purified by flash column chromatography using silica gel modified with aminopropyl groups (Wakogel® 50NH2, FUJIFILM Wako Pure Chemical, Tokyo, Japan) to give (*R*)-**4a** (91% isolated yield, >99% ee).

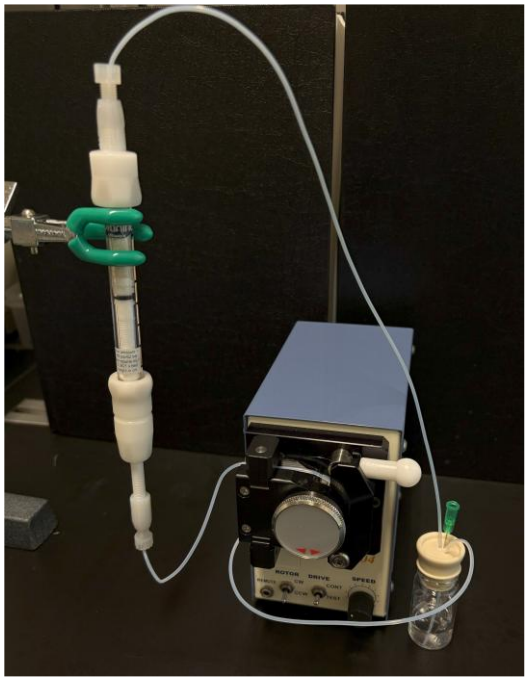
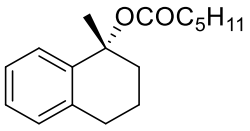


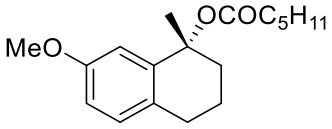
Figure S5. Setup for recycling flow reaction (heating chamber is not shown).

Experimental procedure of DKR in a Pickering emulsion: A water-in-oil Pickering emulsion was prepared according to a previously reported procedure.[10] Briefly, a mixture of silica nanoparticles (90 mg), *n*-octane (3.0 mL), and aqueous H_2SO_4 (7 mM, 0.90 mL) was homogenized in a 20 mm-diameter vial for 90 seconds at 20,000 rpm using a T10 basic ULTRA-TURRAX homogenizer (IKA) equipped with a S10N-5G dispersing tool (ø = 5 mm). After the emulsion droplets precipitated, the supernatant was removed, and a solution of (±)-**1a** (0.15 mmol) and **3** (10 equiv., 1.5 mmol) in *n*-octane (3.0 mL) was gently added to the vial. Anhydrous $MgSO_4$ (400 mg) was then placed on top of the emulsion layer. The reaction was initiated by adding CAL-A (50 mg) on top of the $MgSO_4$, and the vial was left standing in a heating chamber at 35 °C without stirring. After 26 h, solid $NaHCO_3$ was added to neutralize the acid. The mixture was diluted with EtOAc and filtered through a pad of $MgSO_4$. The combined organic layer was concentrated under reduced pressure, and the residue was analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard to determine the yield of (*R*)-**4a** (57% yield, >99% ee).

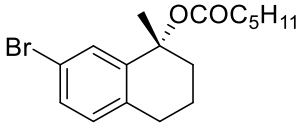


(*R*)-1-Methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4a)[4]: Purified by column chromatography using Wakogel 50NH2 (hexane/EtOAc = 10:1); 91% yield; a colorless oil; $[\alpha]^{27}{}_D = -28$

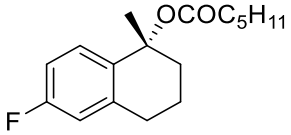
(*c* 1.00, CH_3OH) (lit.[4] $[\alpha]^{23}_D = -25$ (*c* 0.95, CH_3OH), 99% ee, *R*); HPLC analysis CHIRALPAK IJ-3 (hexane/*i*-PrOH = 98:2 1 mL/min, 220 nm, 25°C) 4.6 (*S*), 5.5 (*R*) min (>99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.19-7.13 (m, 2H), 7.08-7.06 (m, 1H), 2.91-2.85 (m, 1H), 2.74 (dt, *J* = 16.5, 4.8 Hz, 1H), 2.54 (td, *J* = 12.4, 3.2 Hz, 1H), 2.29-2.19 (m, 2H), 2.14-2.09 (m, 1H), 1.99-1.93 (m, 1H), 1.82-1.75 (m, 1H), 1.73 (s, 3H), 1.60-1.53 (m, 2H), 1.34-1.23 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 140.4, 136.5, 128.7, 127.0, 126.0, 125.8, 81.1, 35.5, 34.5, 31.2, 29.5 (2C), 24.7, 22.3, 20.9, 13.9.



(*R*)-7-Methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4b)[4]: Purified by column chromatography using Wakogel 50NH2 (hexane/EtOAc = 10:1); 87% yield; a colorless oil; $[\alpha]^{28}_D = -64$ (*c* 1.03, CH_3OH) (lit.[4] $[\alpha]^{23}_D = -53$ (*c* 0.72, CH_3OH), 99% ee, *R*); HPLC analysis CHIRALPAK IC-3 (hexane/*i*-PrOH = 98:2, 1 mL/min, 220 nm, 25°C) 6.3 (*S*), 7.5 (*R*) min (>99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 2.7 Hz, 1H), 6.73 (dd, J = 8.4, 2.7 Hz, 1H), 3.78 (s, 3H), 2.83-2.77 (m, 1H), 2.70-2.65 (m, 1H), 2.54-2.49 (m, 1H), 2.30-2.20 (m, 2H), 2.12-2.07 (m, 1H), 1.97-1.91 (m, 1H), 1.79-1.73 (m, 1H), 1.72 (s, 3H), 1.61-1.55 (m, 2H), 1.35-1.24 (m, 4H), 0.88 (t, J = 6.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 157.8, 141.5, 129.6, 128.7, 112.9, 111.0, 81.2, 55.2, 35.5, 34.3, 31.3, 29.7, 28.7, 24.7, 22.3, 21.1, 13.9.

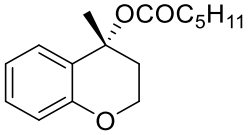


(*R*)-7-Bromo-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4c)[4]: Purified by column chromatography using Wakogel 50NH2 (hexane/EtOAc = 10:1); 56% yield; a colorless oil; $[\alpha]^{29}_D = -68$ (*c* 1.03, CH_3OH) (lit.[4] $[\alpha]^{23}_D = -59$ (*c* 0.68, CH_3OH), 99% ee, *R*); HPLC analysis CHIRALPAK IJ-3 (hexane/*i*-PrOH = 99:1, 0.5 mL/min, 220 nm, 25°C) 9.5 (*S*), 10.7 (*R*) min (>99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 2.84-2.77 (m, 1H), 2.68 (dt, *J* = 16.6, 4.5 Hz, 1H), 2.51 (td, *J* =12.5, 3.4 Hz, 1H), 2.26 (t, J = 7.4 Hz, 2H), 2.09-2.05 (m, 1H), 1.99-1.92 (m, 1H), 1.82-1.70 (m, 1H), 1.68 (s, 3H), 1.62-1.54 (m, 2H), 1.36-1.23 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 142.7, 135.4, 130.4, 130.0, 128.6, 119.6, 80.4, 35.4, 34.0, 31.2, 29.8, 29.0, 24.7, 22.4, 20.8, 13.9.

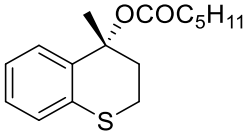


(*R*)-6-Fluoro-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4d)[4]: Purified by column chromatography using Wakogel 50NH2 (hexane/EtOAc = 10:1); 79% yield; a colorless oil; $[\alpha]^{29}_D = -31$

(*c* 0.99, CH_3OH) (lit.[4] $[\alpha]^{23}_D$ = −21 (*c* 0.82, CH_3OH), 97% ee, *R*); HPLC analysis CHIRALPAK IJ-3 (two columns connected in series, hexane/*i*-PrOH = 99:1, 0.3 mL/min, 220 nm, 15°C) 38.0 (*S*), 41.2 (*R*) min (>99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.5, 5.9 Hz, 1H), 6.86 (td, *J* = 8.5, 2.5 Hz, 1H), 6.76 (dd, *J* = 9.5, 1.6 Hz, 1H), 2.90-2.83 (m, 1H), 2.71 (dt, *J* = 16.7, 4.9 Hz, 1H), 2.53 (td, *J* = 12.3, 3.1 Hz, 1H), 2.28-2.17 (m, 2H), 2.09-2.03 (m, 1H), 1.99-1.92 (m, 1H), 1.81-1.73 (m, 1H), 1.71 (s, 3H), 1.59-1.52 (m, 2H), 1.34-1.23 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 161.5 (d, J_{C-F} = 245.6 Hz), 139.0 (d, J_{C-F} = 7.5 Hz), 136.2 (d, J_{C-F} = 3 Hz), 127.7 (d, J_{C-F} = 8.4 Hz), 114.7 (d, J_{C-F} = 20.4 Hz), 113.2 (d, J_{C-F} = 21.3 Hz), 80.6, 35.5, 34.4, 31.2, 29.7, 29.5, 24.6, 22.3, 20.7, 13.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ −115.9 (td, *J* = 8.9, 5.9 Hz, 1F).



(*R*)-4-Methylchroman-4-yl hexanoate (4e)[4]: Purified by column chromatography using Wakogel 50NH2 (hexane/EtOAc = 10:1); 70% yield; a colorless oil; $[\alpha]^{29}_D$ = +10 (*c* 1.05, CH_3OH) (lit.[4] $[\alpha]^{24}_D$ = +10 (*c* 0.62, CH_3OH), 96% ee, *R*); HPLC analysis CHIRALPAK IC-3 (hexane/*i*-PrOH = 98:2, 1 mL/min, 220 nm, 25°C) 5.3 (*R*), 7.5 (*S*) min (95% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 7.8, 1.6 Hz, 1H), 7.20-7.17 (m, 1H), 6.94-6.91 (m, 1H), 6.82 (dd, J = 8.2, 1.2 Hz, 1H), 4.33-4.29 (m, 1H), 4.20-4.16 (m, 1H), 2.68-2.61 (m, 1H), 2.34-2.19 (m, 3H), 1.89 (s, 3H), 1.61-1.54 (m, 2H), 1.34-1.22 (m, 4H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 153.8, 129.4, 127.7, 125.4, 120.3, 117.0, 76.2, 63.0, 35.5, 34.3, 31.2, 26.5, 24.7, 22.3, 13.9.



(*R*)-4-Methylthiochroman-4-yl hexanoate (4f)[4]: Purified by column chromatography using Wakogel 50NH2 (hexane/EtOAc = 10:1); 70% yield; a colorless oil; $[\alpha]^{29}_D$ = −8.4 (*c* 1.03, CH_3OH) (lit.[4] $[\alpha]^{24}_D$ = −8.4 (*c* 0.69, CH_3OH), 98% ee, *R*); HPLC analysis CHIRALPAK IC-3 (hexane/*i*-PrOH = 98:2, 1 mL/min, 220 nm, 25°C) 6.4 (*R*), 8.4 (*S*) min (97% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.9 Hz, 1H), 7.11-7.09 (m, 2H), 7.08-7.03 (m, 1H), 3.11-3.03 (m, 2H), 2.85-2.76 (m, 1H), 2.39-2.35 (m, 1H), 2.32-2.23 (m, 2H), 1.79 (s, 3H), 1.62-1.55 (m, 2H), 1.35-1.24 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 136.7, 132.3, 127.6, 126.60, 126.55, 124.1, 78.8, 35.4, 33.7, 31.2, 28.0, 24.7, 23.3, 22.3, 13.9.

7. References

1 A. L. Miller and N. B. Bowden, *J. Org. Chem.*, 2009, **74**, 4834–4840.

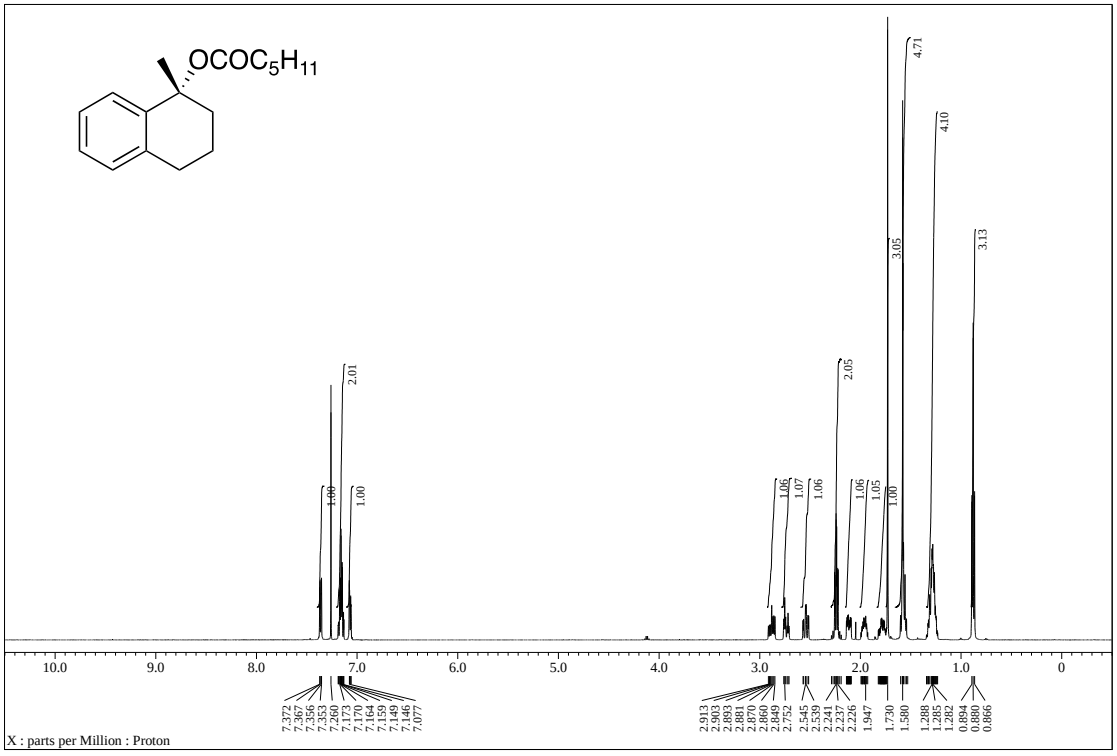
2 H. Sato, W. Hummel and H. Gröger, *Angew. Chem. Int. Ed.*, 2015, **54**, 4488–4492.

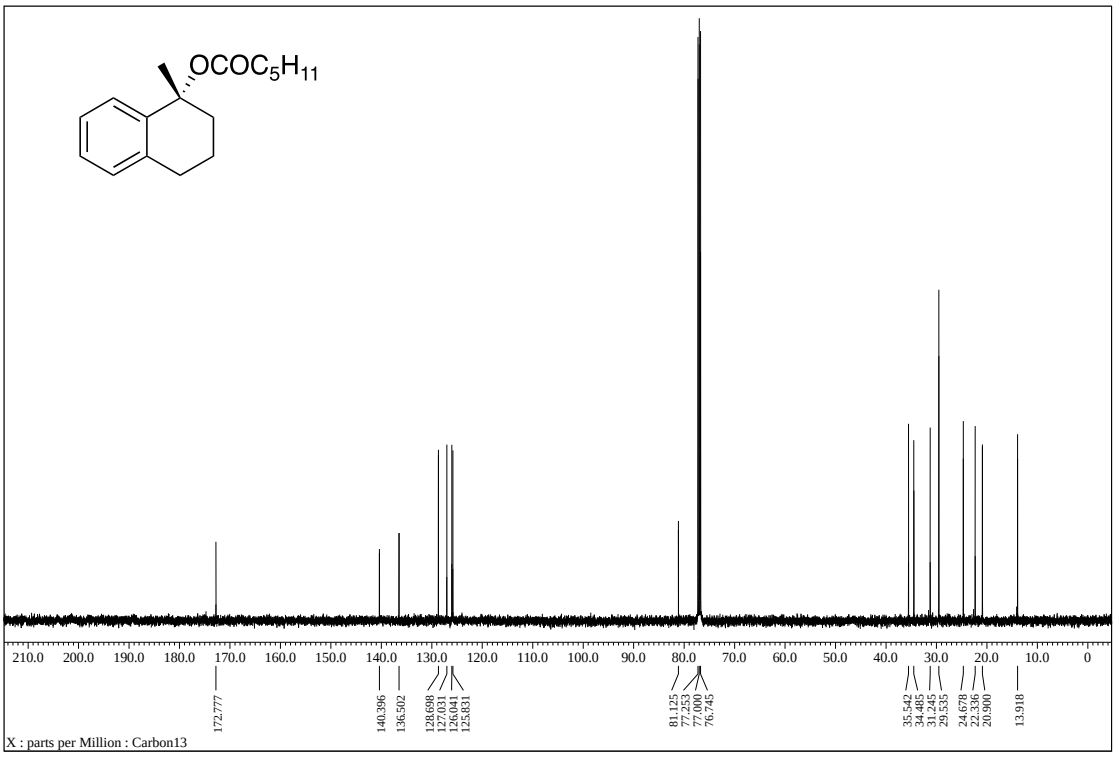
3 F. Kühn, S. Katsuragi, Y. Oki, C. Scholz, S. Akai and H. Gröger, *Chem. Commun.*, 2020, **56**,

2885–2888.
4 S. Horino, K. Wagner, A. Hummel, K. Kanomata, H. Gröger and S. Akai, *Eur. J. Org. Chem.*, 2024, **27**, e202400242.
5 C. Wolf, *Dynamic Stereochemistry of Chiral Compounds*, The Royal Society of Chemistry, Cambridge, 2008.
6 R. Ikeda, T. Nishio, K. Kanomata and S. Akai, *Chem. Pharm. Bull.*, 2024, **72**, 213–219.
7 H. Brockerhoff, *J. Biol. Chem.*, 1971, **246**, 5828–5831.
8 C. S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294–7299.
9 J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5–26.
10 J. Moon, T. Kin, K. Mizuno, S. Akai and K. Kanomata, *ChemCatChem*, 2023, **15**, e202300878.

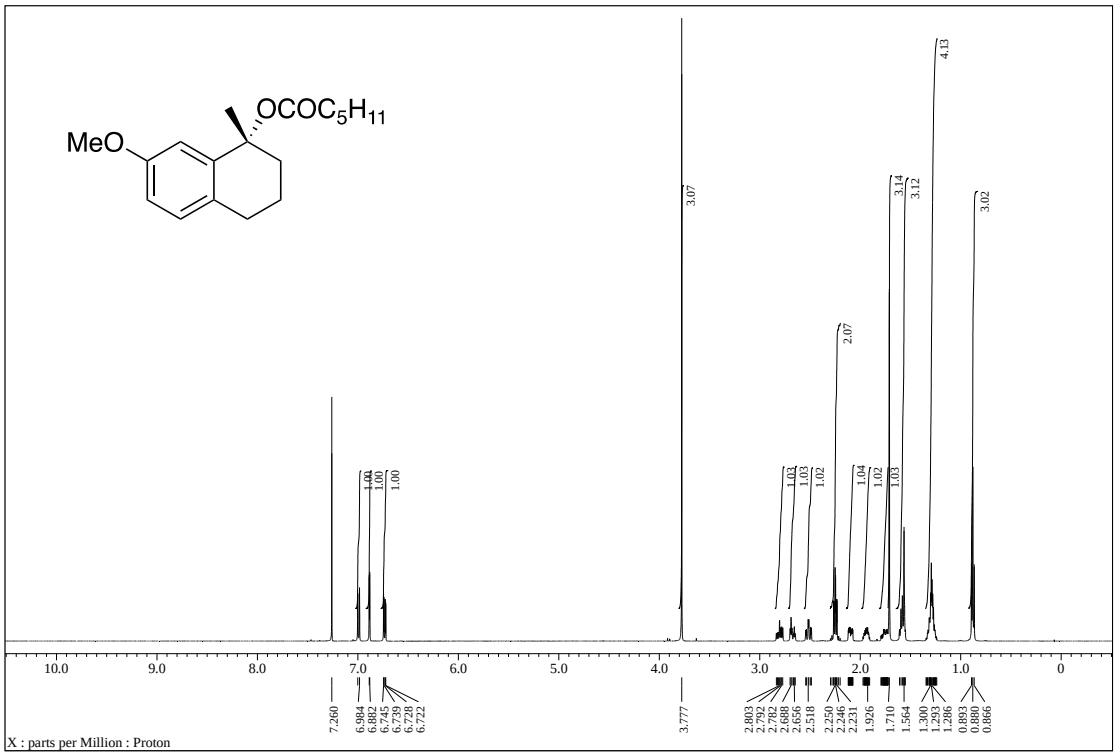
8. NMR and chiral HPLC chart

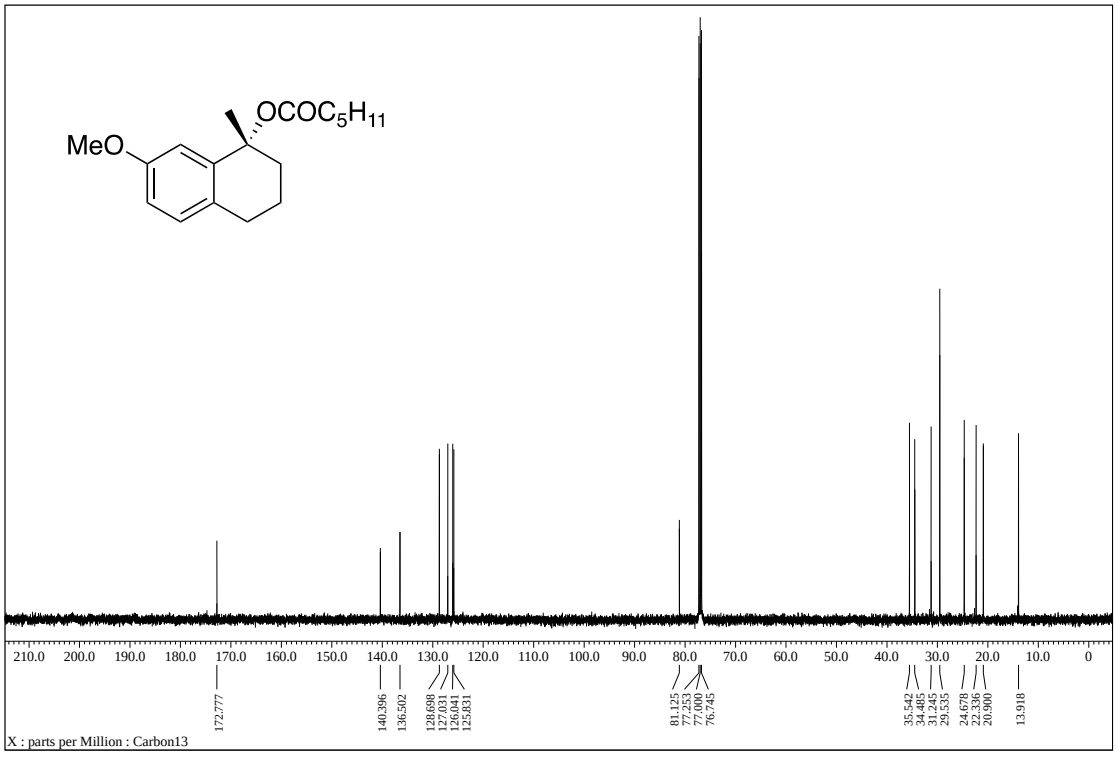
(*R*)-1-Methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4a)



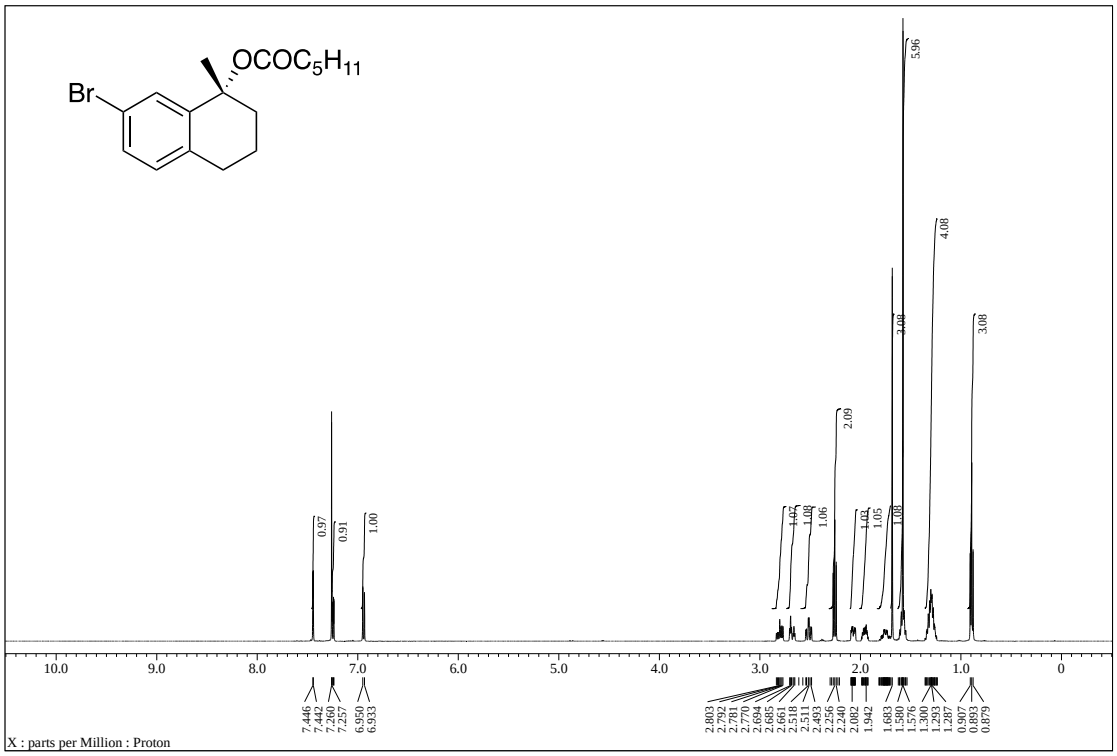


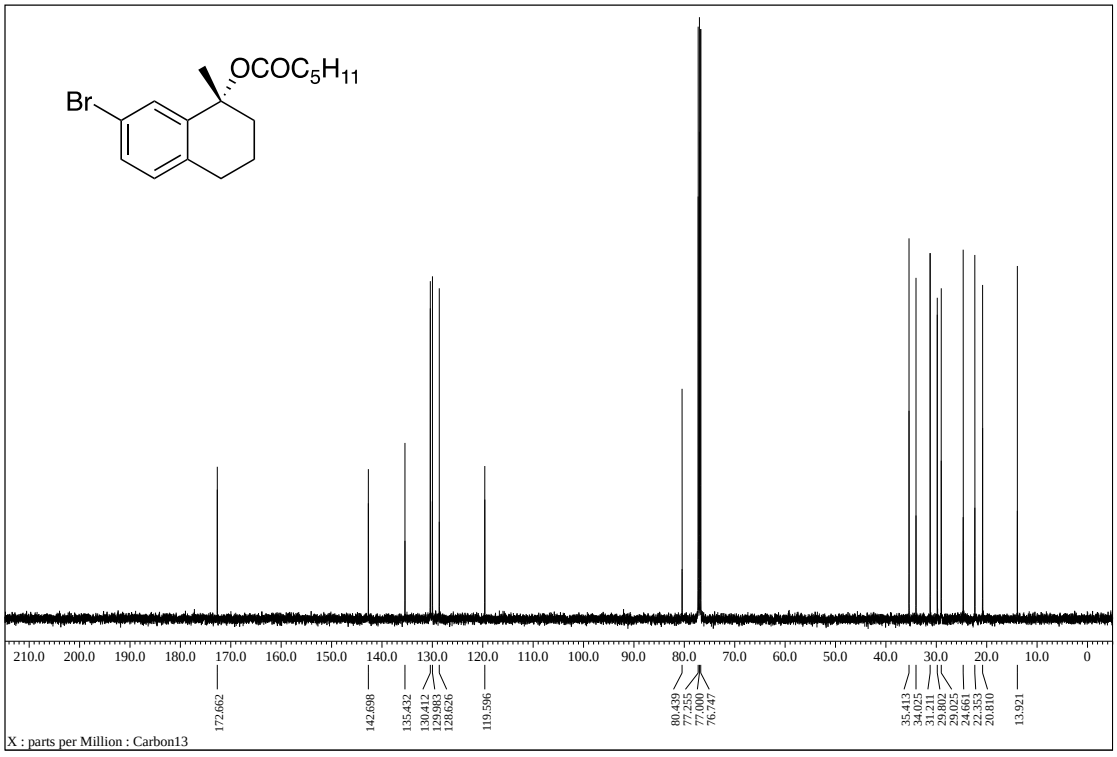
(*R*)-7-Methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4b)



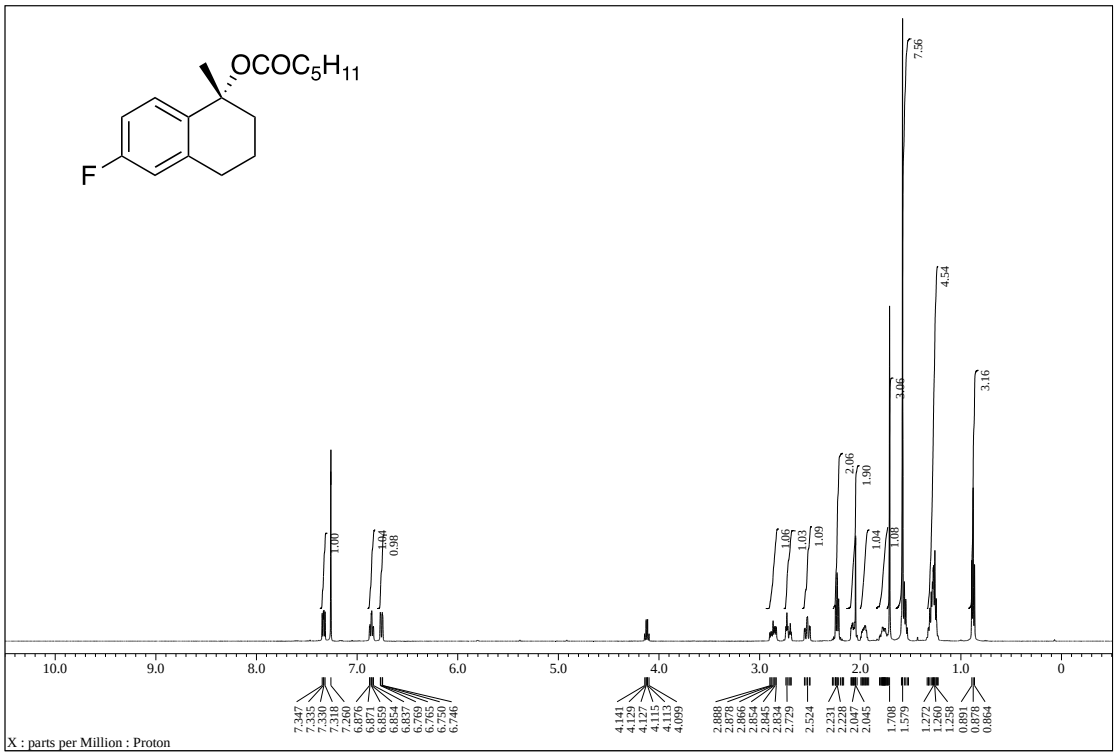


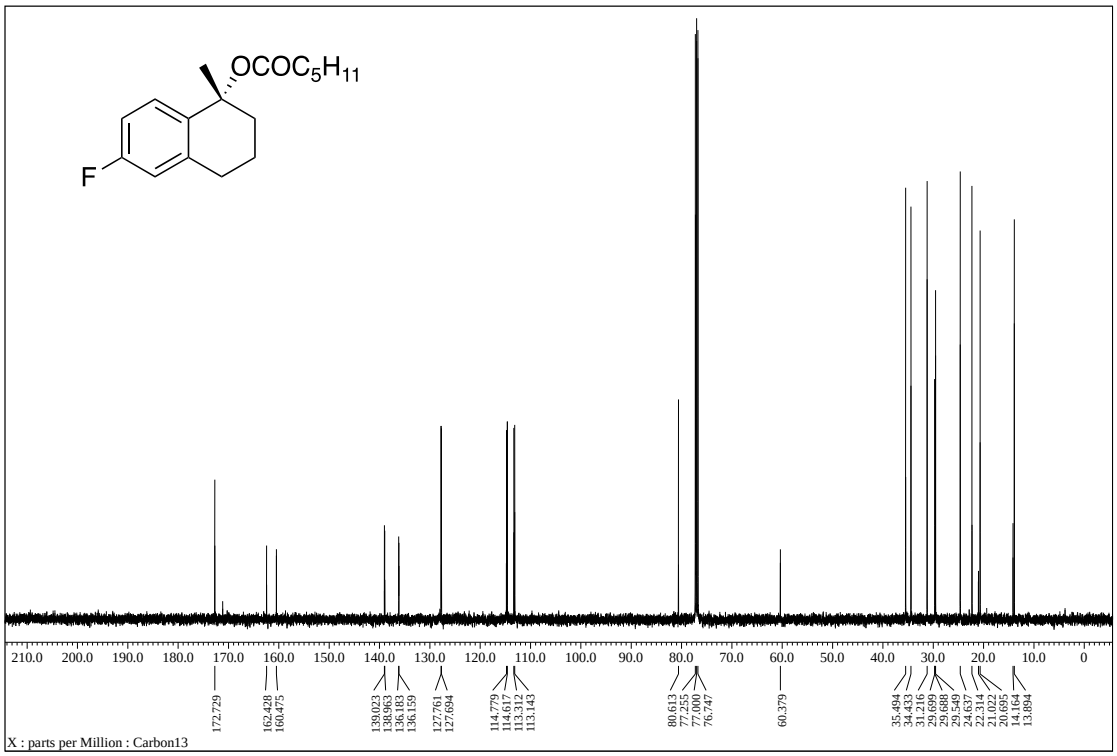
(*R*)-7-Bromo-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4c)

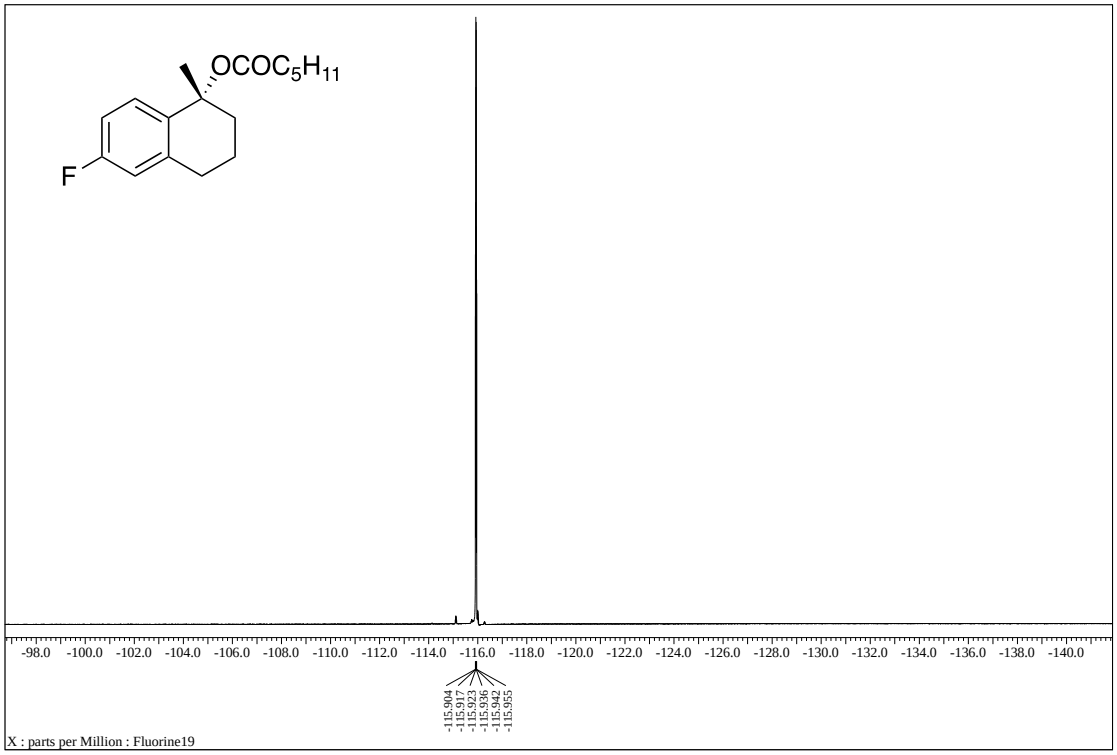




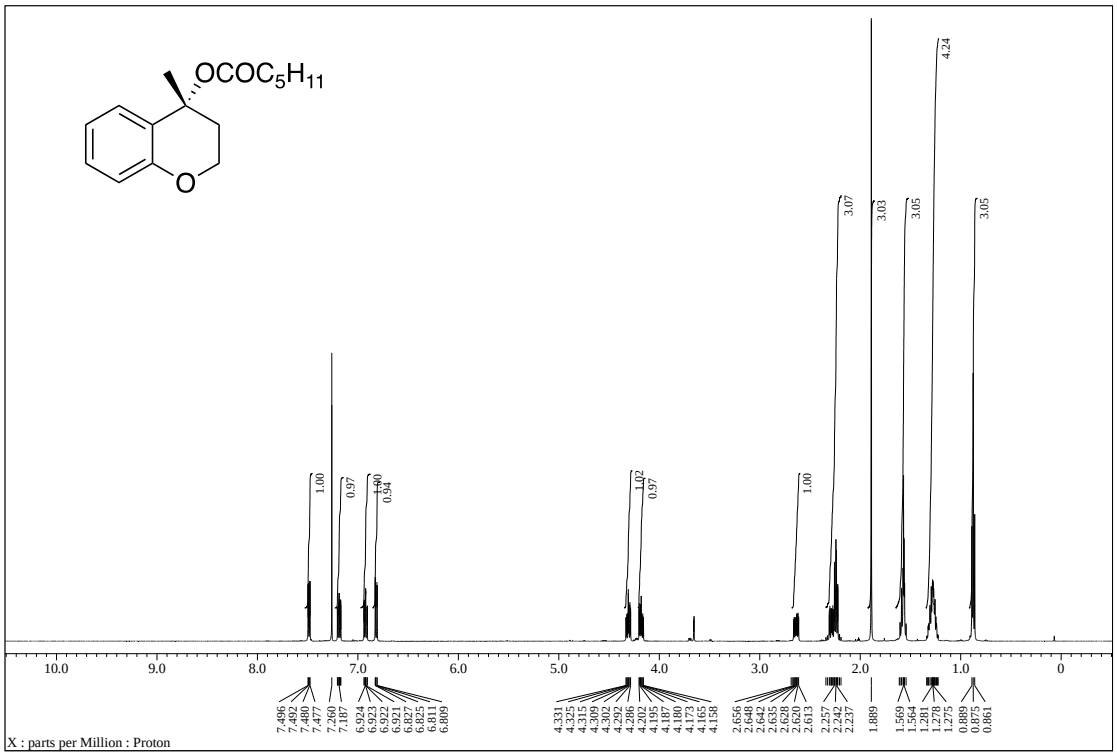
(*R*)-6-Fluoro-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4d)

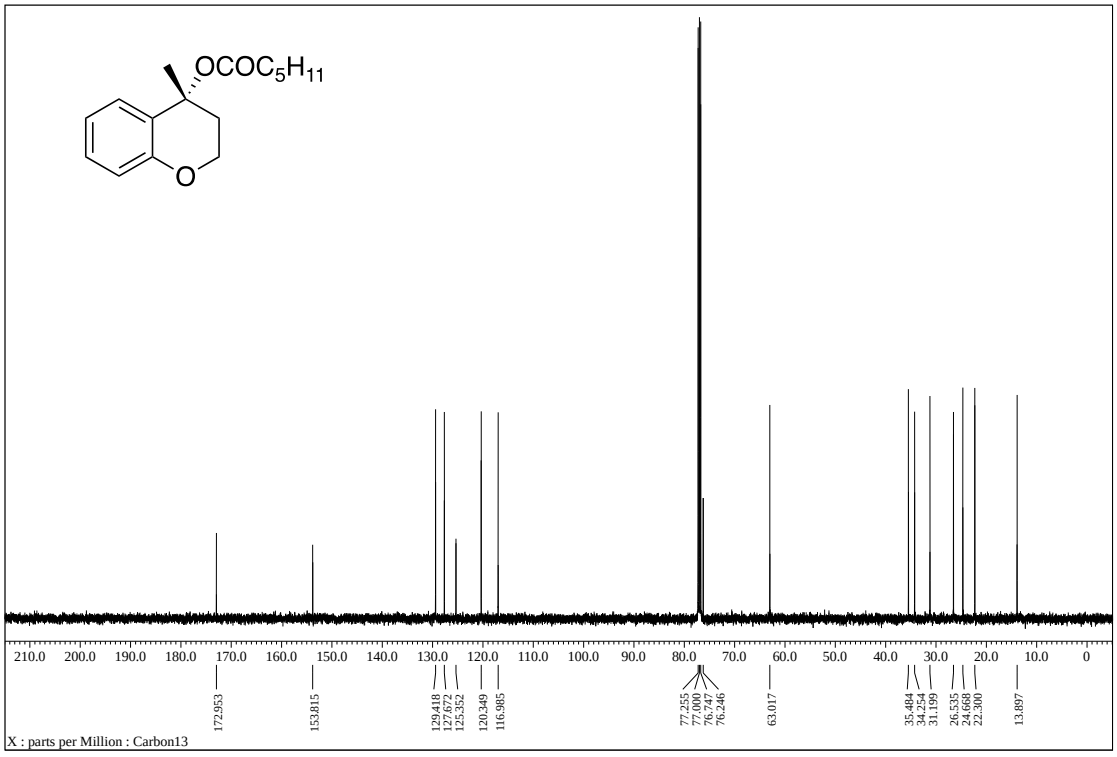




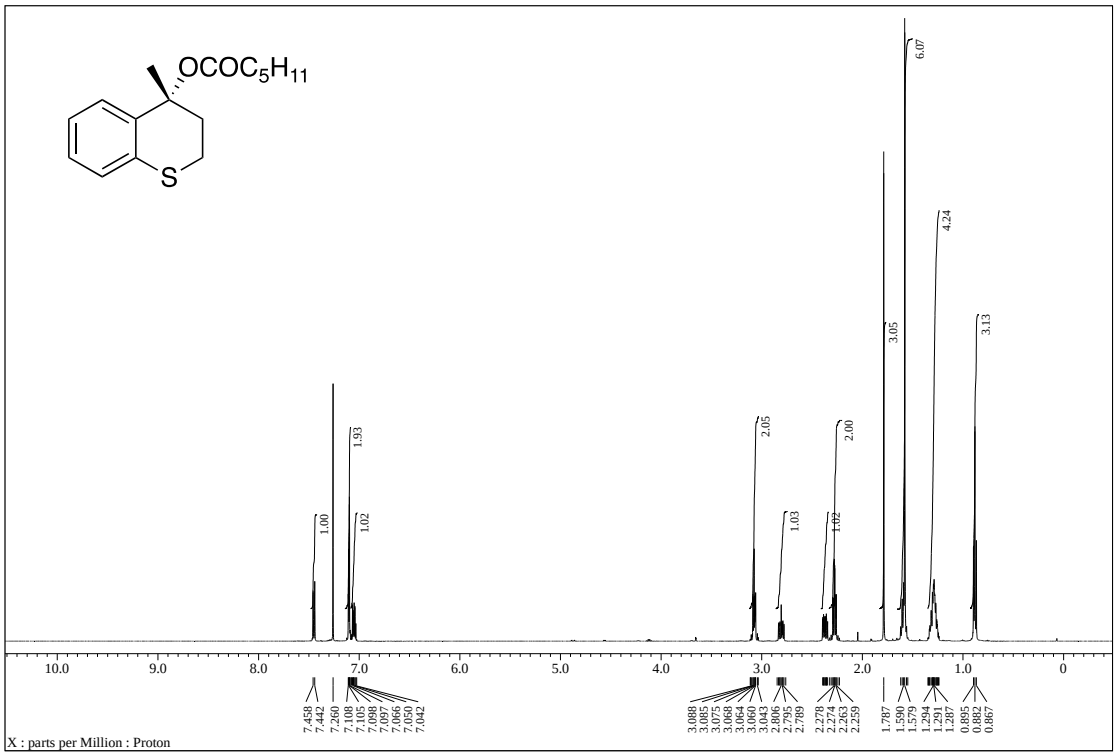

OCOC5H11
F
-98.0 -100.0 -102.0 -104.0 -106.0 -108.0 -110.0 -112.0 -114.0 -116.0 -118.0 -120.0 -122.0 -124.0 -126.0 -128.0 -130.0 -132.0 -134.0 -136.0 -138.0 -140.0
-115.904
-115.917
-115.923
-115.936
-115.942
-115.955
X : parts per Million : Fluorine19

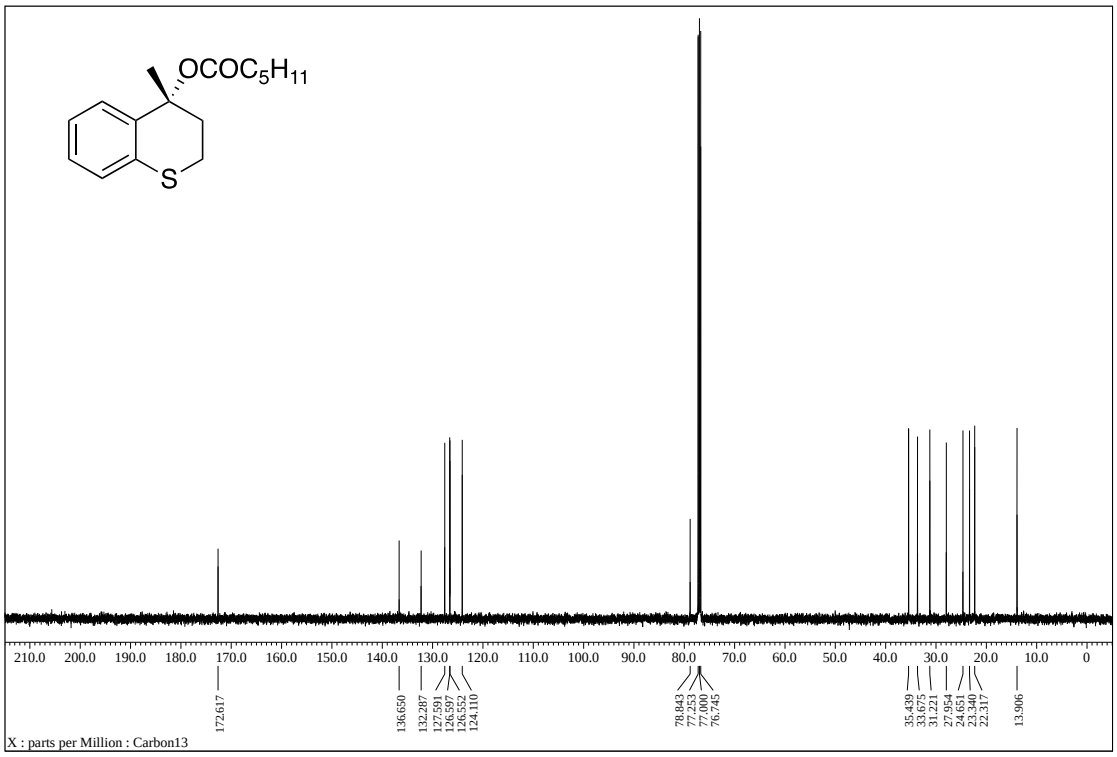
(*R*)-4-Methylchroman-4-yl hexanoate (4e)





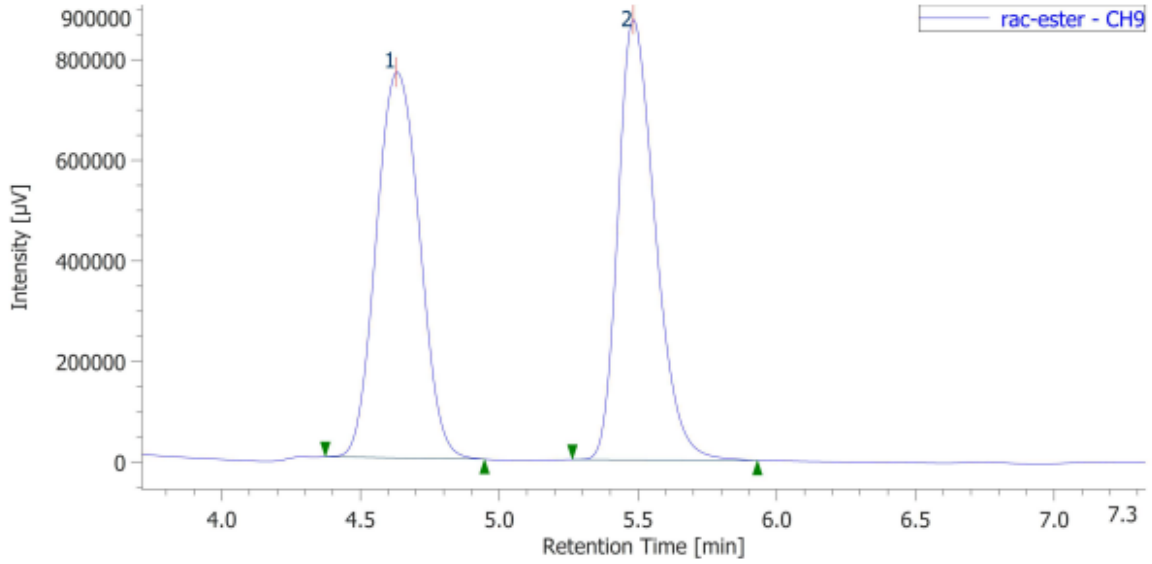
(*R*)-4-Methylthiochroman-4-yl hexanoate (4f)

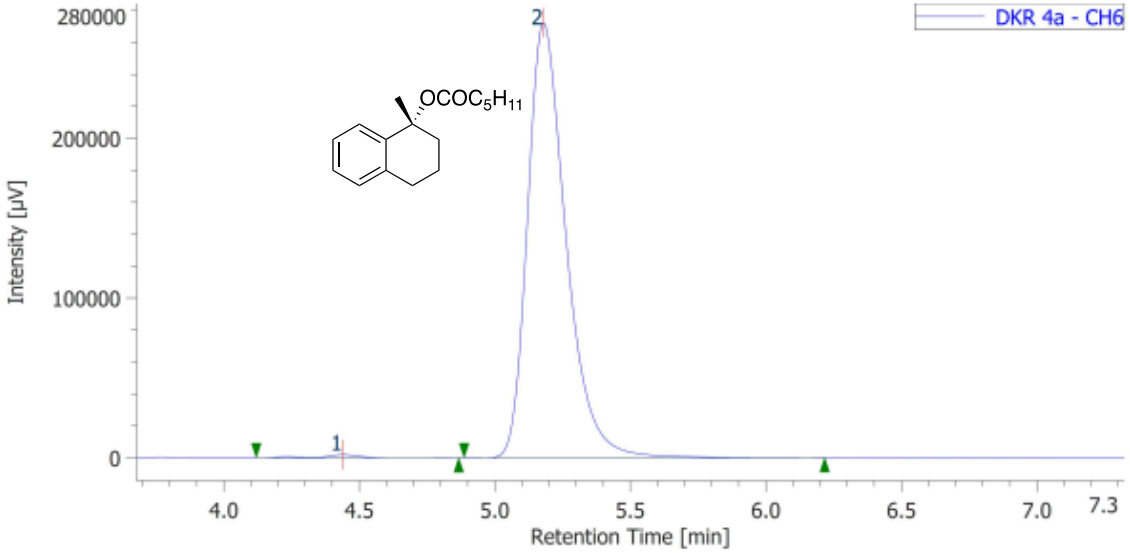




Chiral HPLC chart

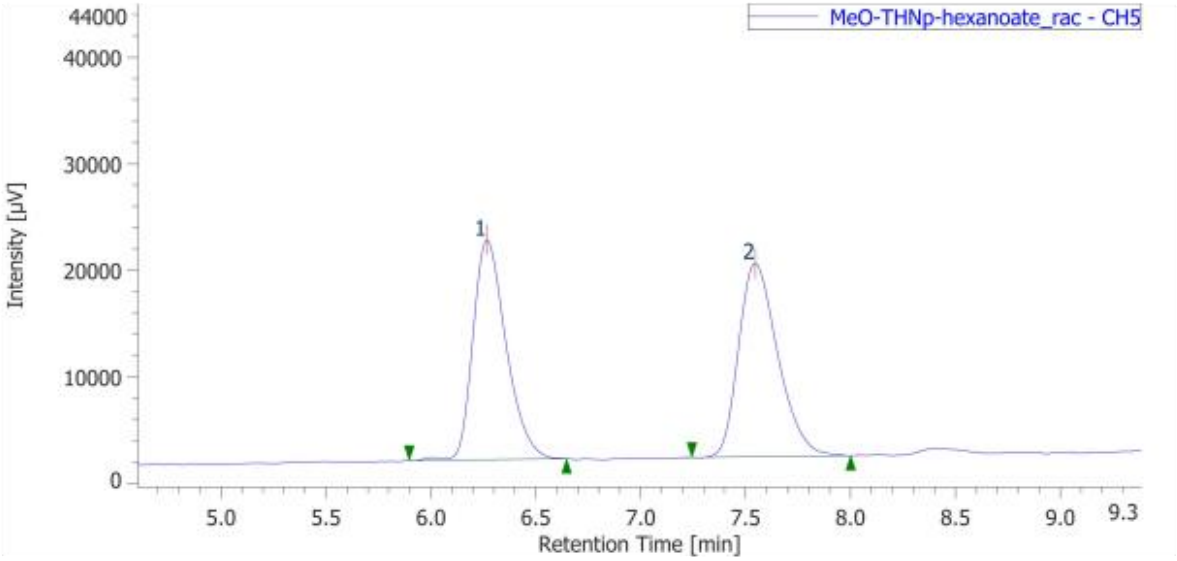
1-Methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4a)

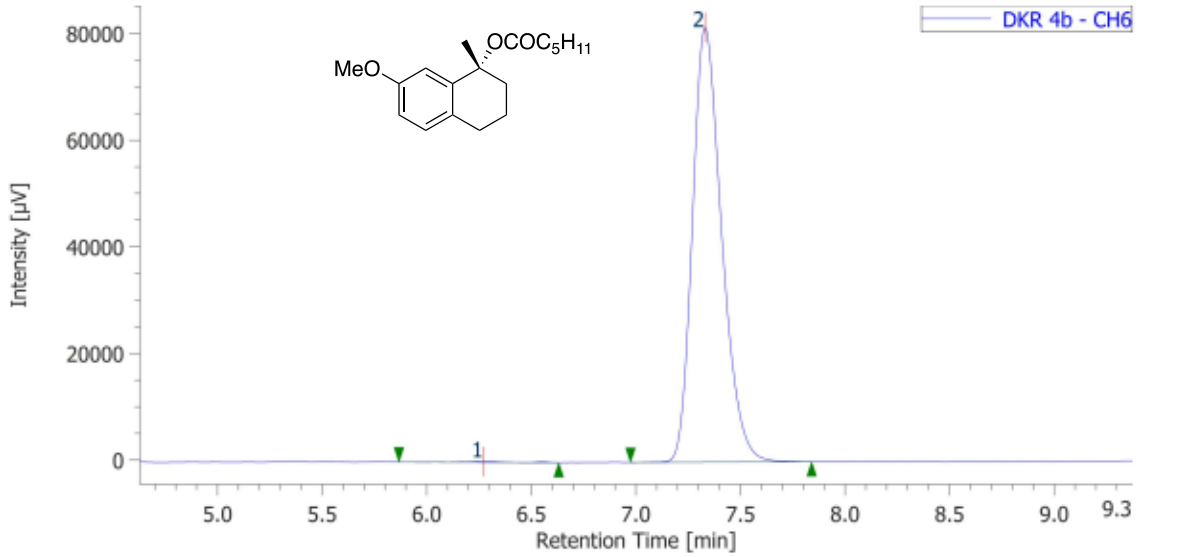




#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	4.440	19043	1973	0.702	0.719	N/A	9122	3.397	0.762	
2	Unknown	6	5.180	2694518	272233	99.298	99.281	N/A	6821	N/A	1.368	

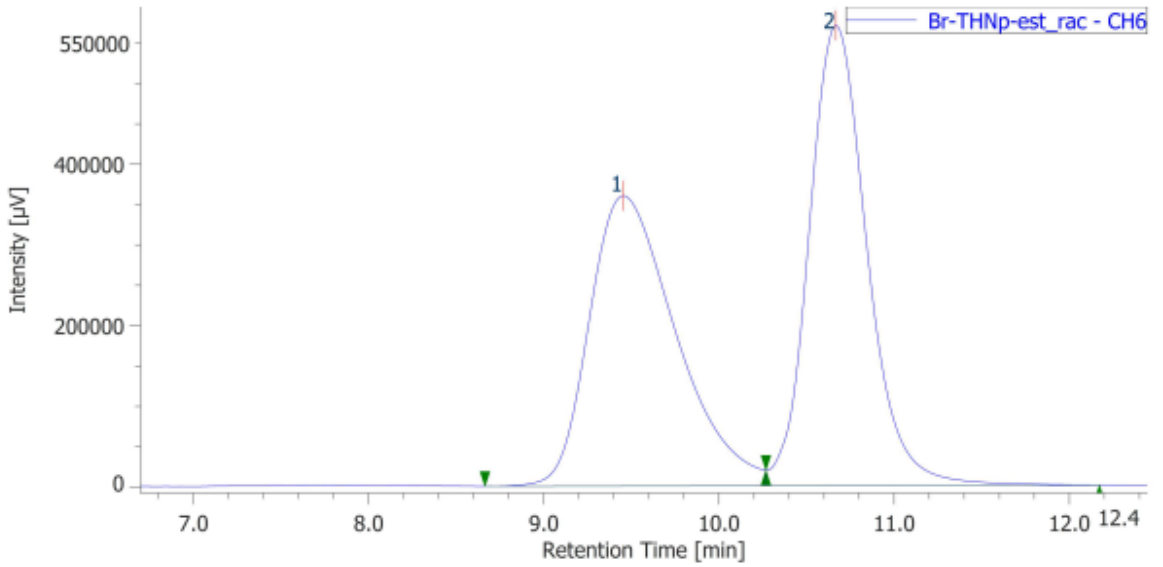
7-Methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4b)

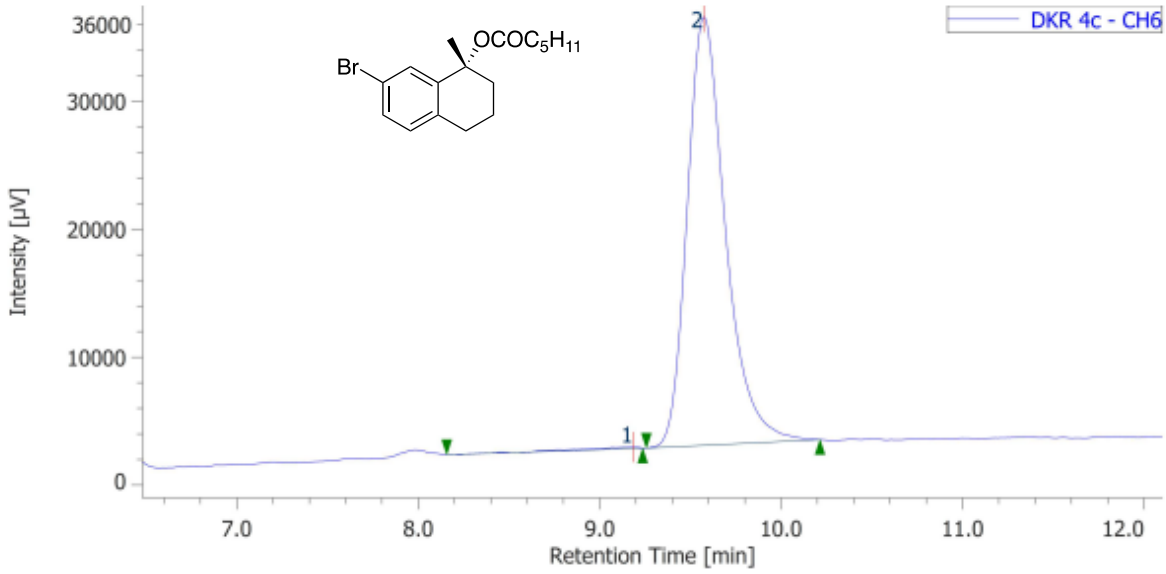




#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	6.273	1679	146	0.211	0.179	N/A	1714	2.467	1.232	
2	Unknown	6	7.330	792758	81508	99.789	99.821	N/A	13473	N/A	1.282	

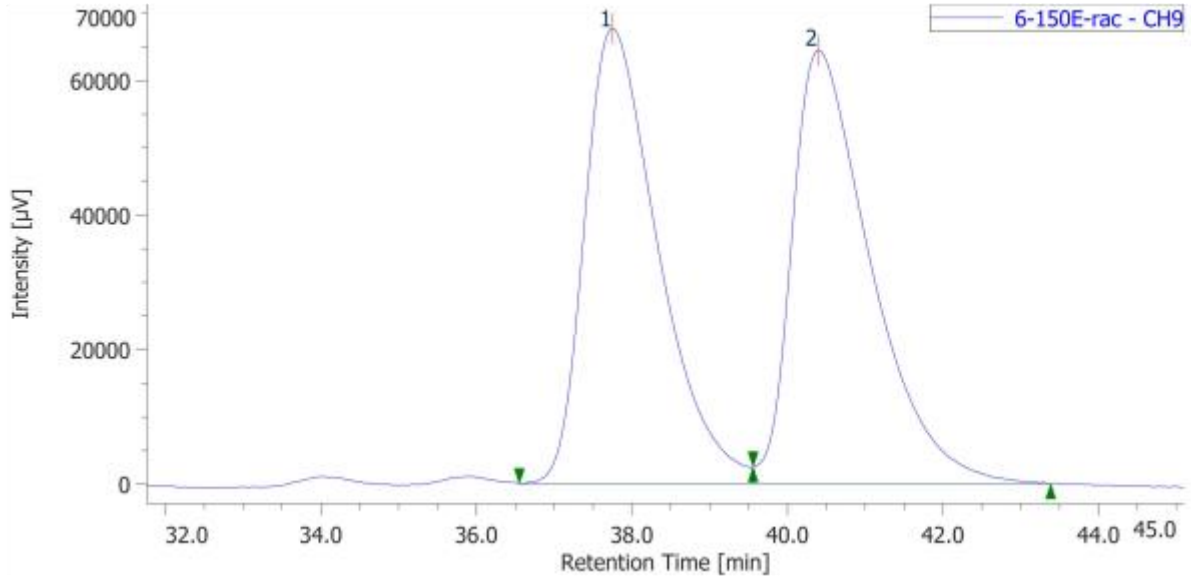
7-Bromo-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4c)

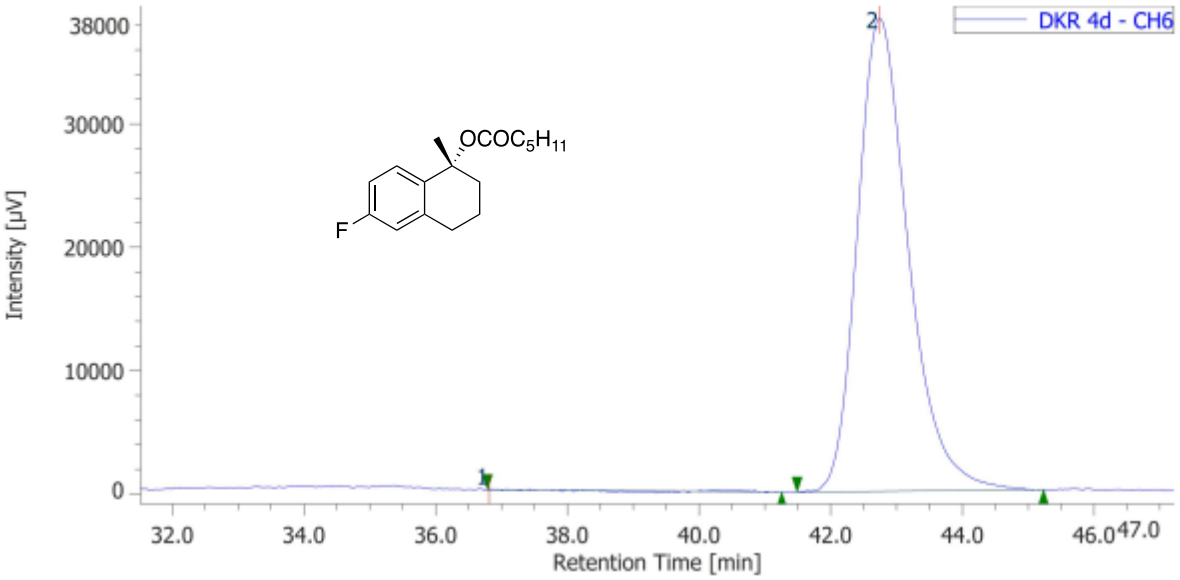




#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	9.187	2807	102	0.568	0.303	N/A	771	0.458	0.526	
2	Unknown	6	9.573	491499	33454	99.432	99.697	N/A	10618	N/A	1.336	

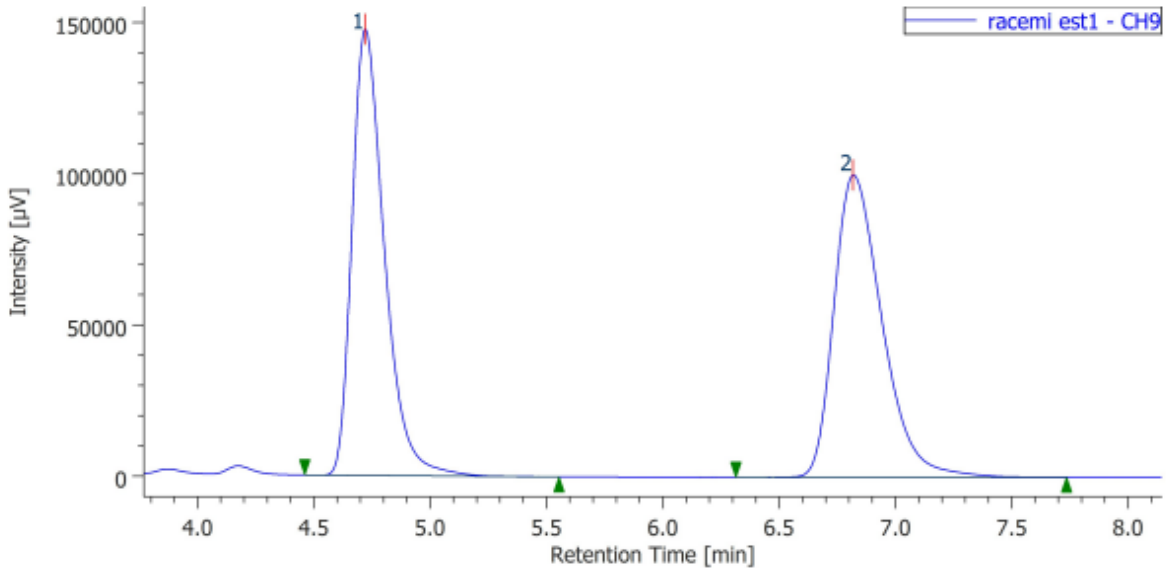
6-Fluoro-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl hexanoate (4d)

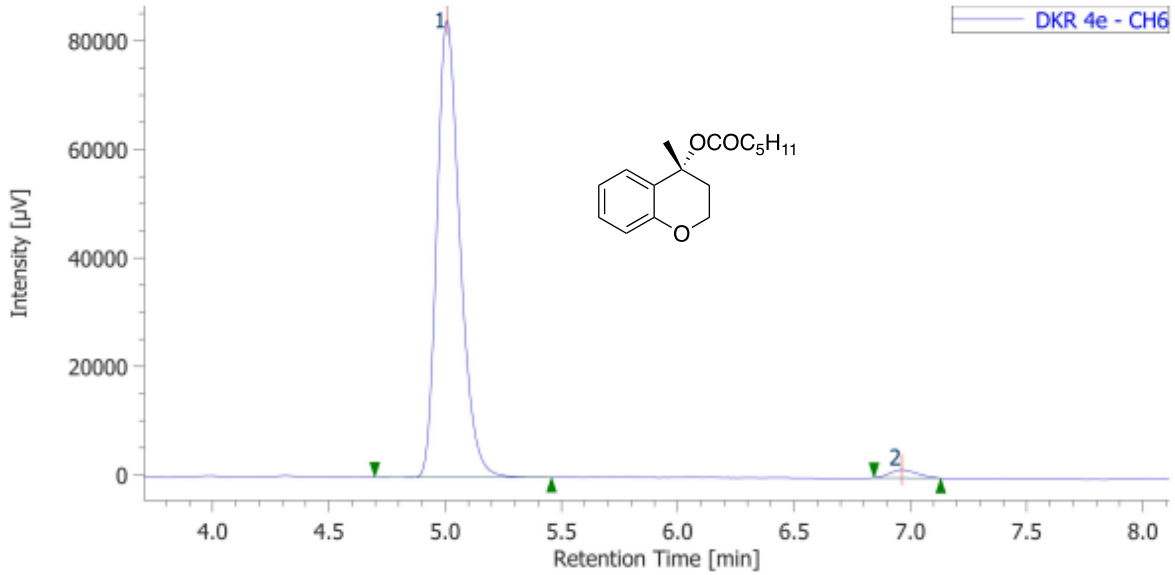




#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	36.813	4868	51	0.235	0.133	N/A	451	1.428	85.989	
2	Unknown	6	42.733	2068180	38319	99.765	99.867	N/A	15392	N/A	1.329	

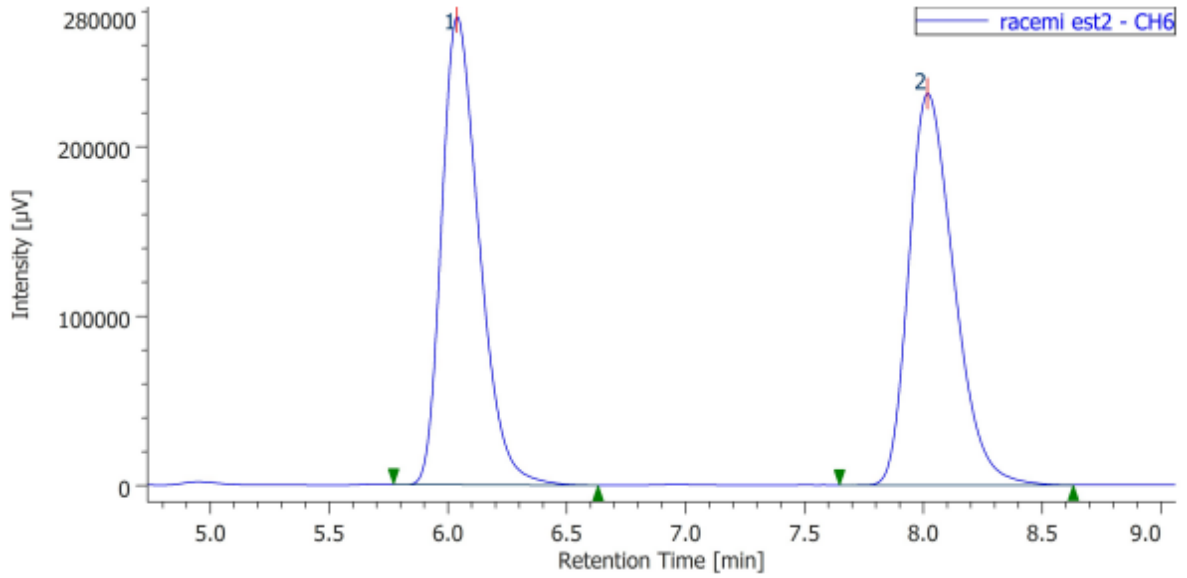
4-Methylchroman-4-yl hexanoate (4e)

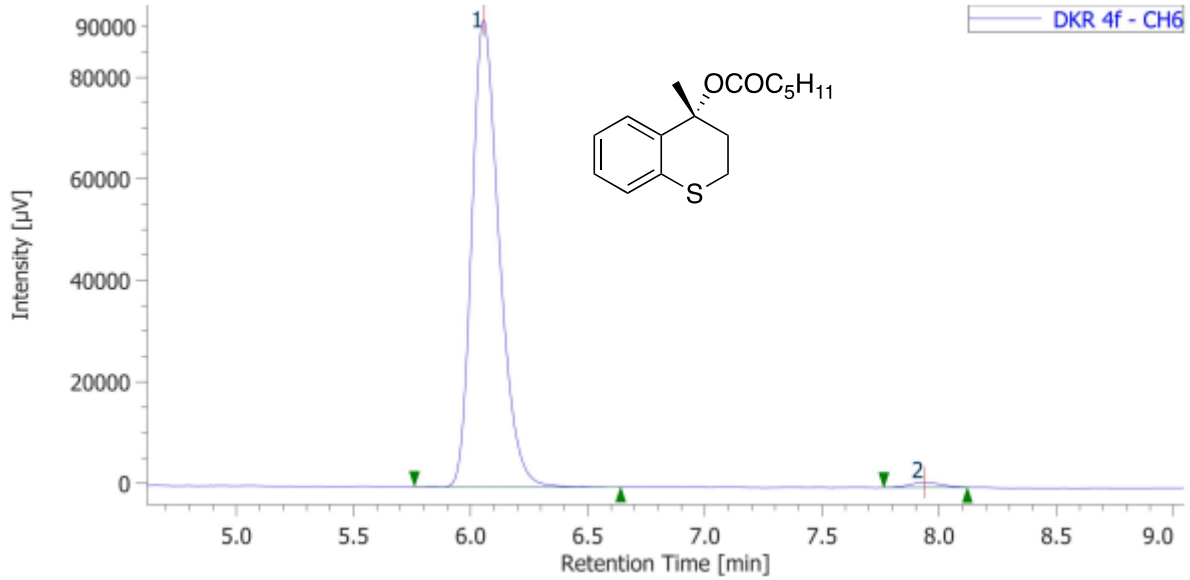




#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	5.007	578279	84251	97.950	98.265	N/A	12704	9.850	1.292	
2	Unknown	6	6.963	12101	1487	2.050	1.735	N/A	15931	N/A	1.205	

4-Methylthiochroman-4-yl hexanoate (4f)





#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	6.057	746354	91840	98.776	98.946	N/A	13264	8.069	1.275	
2	Unknown	6	7.937	9252	978	1.224	1.054	N/A	15276	N/A	1.084	