Supporting Information

Development of the synthetic route to 5-hydroxymethyl tolterodine, a key synthetic intermediate of Toviaz, via an organic solvent-free Rh-catalyzed asymmetric 1,4-addition

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Contents

1. General experimental methods

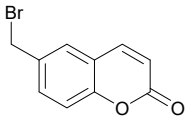
All reactions were carried out under an argon atmosphere with dry solvent under anhydrous conditions, unless otherwise noted. All solvents were purchased from KANTO CHEMICAL CO., INC. and then were stored in Schlenk flasks under an argon atmosphere. H_2O was purified by distillation prior to use. $[RhOH(cod)]_2$ was purchased from Sigma-Aldrich. M^FF-MeO-BIPHEP was prepared according to reference 8. Phenylboronic acid was purchased from Tokyo Chemical Industry Co., Ltd. and was used without purification. All other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted. For reactions that required heating or cooling, an oil bath or a low-temperature bath (EYELA PSL-1820, Tokyo Rika Kikai Co., Ltd.) was used. The light source was a standard desk lamp (non-specialized, emitting visible light) placed close to the reaction vessel, with the room lights kept on. Preparative column chromatography was carried out by using silica-gel (KANTO CHEMICAL CO., INC. 60N, 63–210 μm). Melting points were measured by using AS ONE ATM-02 and were uncorrected. The solvent of recrystallization is reported in parentheses only when the compound was purified by recrystallization as the final step. Optical rotations were recorded on a DIP-1000 polarimeter (JASCO) using a 1 cm cell and reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. IR spectra were measured at resolution 4.0 cm^{-1} or 0.1 cm^{-1} using JASCO FTIR-4200. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL JNM-ECA 500 or Bruker Avance III 500. ^1H NMR spectra were measured at 400 or 500 MHz using tetramethylsilane (TMS, δ 0 ppm) as an internal standard for $CDCl_3$ solutions or residual DMSO-d_6 (δ 2.50 ppm) as a reference. ^{13}C NMR spectra were measured at 126 MHz, and chemical shifts were given relative to $CDCl_3$ (δ 77.16 ppm) or DMSO-d_6 (δ 39.52 ppm). HPLC analyses were carried out on a JASCO LC-NET II/ADC system. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 double-focusing mass spectrometer. ICP-OES analysis was performed on an Agilent 5800.

2. Experimental section

2-1 Gram scale synthesis of (*R*)-1

Procedure for the bromination reaction of 2

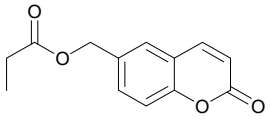
6-bromomethyl-coumarin (4) [S1,S2]



A flame-dried 100 mL Schlenk tube was flashed with argon and charged with 1,3-dibromo-5,5-dimethyl hydantoin (1.69 g, 5.90 mmol, 0.63 equiv.), CH_2Cl_2 (50.0 mL), zirconium (IV) chloride (218 mg, 0.936 mmol, 0.10 equiv.) and 6-methylcoumarin (**2**) (1.50 g, 9.36 mmol, 1.0 equiv.). The mixture was stirred at 5 °C for 17 h under illumination from a standard desk lamp and ambient room light. After addition of H_2O under air atmosphere, the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with toluene/EtOAc = 20/1 to give **4** (1.82 g, 7.61 mmol, 81% yield) as white solid. M.p. 150–151 °C (from EtOAc) (lit. [S2] M.p. 151 °C). IR (KBr): 3081, 1719, 1620, 1573, 1387, 1170, 910, 831, 631, 531 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 9.7 Hz, 1H), 7.57 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 6.46 (d, *J* = 9.7 Hz, 1H), 4.54 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.5, 153.9 143.1, 134.4, 132.7, 128.3, 119.1, 117.6, 117.4, 32.1.

Procedure for the acyloxylation of 4

(2-oxo-*2H*-chromen-6-yl)methyl propionate (5b)

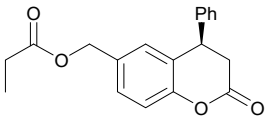


A 100 mL Schlenk tube was flashed with argon and charged with **4** (1.82 g, 7.61 mmol, 1.0 equiv.), sodium Propionate (950 mg, 9.89 mmol, 1.3 equiv.), *N,N*-dimethylformamide (36.3 mL). The mixture was stirred at 80 °C for 14 h. After addition of H_2O under air atmosphere, the reaction mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with hexane/EtOAc = 2/1 to give **5b** (1.75 g, 7.54 mmol, >99% yield) as white solid. M.p. 71–72 °C (from Et_2O). IR (KBr): 2977, 2360, 1744, 1715, 1625, 1575, 1377, 1163, 903, 821, 760, 712 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.72–7.70 (m, 1H), 7.55–7.50 (m, 2H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.45 (d, *J* =

9.5 Hz, 1H), 5.15 (s, 2H), 2.39 (q, J = 7.7 Hz, 2H), 1.17 (t, J = 7.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 160.7, 153.9, 143.3, 132.7, 132.0, 127.8, 118.9, 117.3, 117.2, 65.2, 27.7, 9.18. HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{12}O_4$: 232.0736; found: 232.0737.

Organic solvent-free Rh-catalyzed asymmetric 1,4-addition of 5b (Procedure A. Optimized procedure for the synthesis of [(*R*)-6b])

(*R*)-(2-oxo-4-phenylchroman-6-yl)methyl propionate [(*R*)-6b]

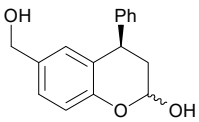


A mixture of $[RhOH(cod)]_2$ (3.43 mg, 7.52 μmol, 1.0×10^{-3} equiv.), (*R*)-M^{F}F-MeO-BIPHEP (14.0 mg, 15.1 μmol, 2.0×10^{-3} equiv.), **5b** (1.75 g, 7.54 mmol, 1.0 equiv.), 2,4,6-triphenylboroxin (7.85 g, 25.2 mmol, 3.3 equiv.) and H_2O (2.71 mL, 151 mmol, 20 equiv.) was placed in a 100 mL Schlenk tube and was stirred at 70 °C for 96 h under argon atmosphere. After addition of H_2O under air atmosphere at 0 °C, the resulting mixture was extracted with air-bubbled EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with hexane/EtOAc = 4/1 to give (*R*)-**6b** (2.10 g, 6.78 mmol, 90% yield, >99% ee) as colorless oil. $[\alpha]_D^{23.4}$= +23.3° (*c* 0.2, $CHCl_3$). IR (KBr): 3367, 3024, 2981, 2360, 1769, 1736, 1498, 1420, 1344, 1245, 1180, 1148, 1082, 889, 824, 704 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.30 (m, 4H), 7.17–7.13 (m, 3H), 6.98 (d, J = 1.7 Hz, 1H), 5.01 (s, 2H), 4.35 (t, J = 6.6 Hz, 1H) 3.12–3.00 (m, 2H), 2.33 (q, J = 7.5 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 167.5, 151.7, 140.2, 132.8, 129.4, 128.9, 128.4, 127.9, 127.7, 126.0, 117.5, 65.4, 40.8, 37.1, 27.7, 9.18. Daicel Chiralcel AD-3, hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min: t_R of (*S*)-**6b**; 30.3 min (0.3%), t_R of (*R*)-**6b**; 33.2 min (99.7%). HRMS (EI) m/z: $[M]^+$ calcd for $C_{19}H_{18}O_4$: 310.1205; found: 310.1205.

Procedure for the DIBAL reduction of (*R*)-6b

(2*R*,4*R*)- and (2*S*,4*R*)-6-(hydroxymethyl)-4-phenylchroman-2-ol [(2*R*,4*R*)- and (2*S*,4*R*)-7] [S3,S4]

(The inseparable mixture of diastereomers isolated via column chromatography showed the ratio of *ca*. 3:1, as determined by ^{1}H NMR analysis.)

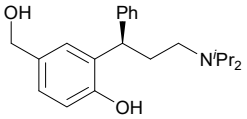


A 100 mL Schlenk tube was flushed with argon and charged with (*R*)-**6b** (2.05 g, 6.62 mmol, 1.0 equiv.) and toluene (22.0 mL). The mixture was cooled to −25 °C.

Diisobutylaluminium hydride in hexane solution (19.8 mL, 19.8 mmol, 3.0 equiv.) was added dropwise over 1.5 h. The mixture was stirred for an additional 1 h and added ethyl acetate (110 μL) and aqueous citric acid (23%, 14.7 mL) at −25 °C. The mixture was stirred overnight at room temperature. After addition of H_2O under air atmosphere, the resulting mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with CH_2Cl_2/MeOH = 29/1 to give (2*R*,4*R*)- and (2*S*,4*R*)-**7** (1.56 g, 6.10 mmol, 92% yield) as white solid. M.p. 110–111 °C (from toluene/EtOAc = 10/1) (lit. [S4] M.p. 106.5 °C (d/s, ratio 1:4)). IR (KBr): 3367, 3309, 3203, 2930, 1604, 1581, 1492, 1453, 1419, 1239, 1130, 1038, 920, 813, 700 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.35–7.32 (m, 2H), 7.27–7.24 (m, 1H), 7.21–7.19 (m, 3H), 7.06–7.02 (m, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.60 (bs, 0.75H), 6.53 (bs, 0.25H), 5.52–5.50 (m, 0.75H), 5.43–5.39 (m, 0.25H), 4.96–4.93 (m, 1H), 4.29–4.22 (m, 3H), 2.24–2.20 (m, 0.25H), 2.08–1.93 (m, 1.75H). ^{13}C NMR (126 MHz, DMSO-d_6): δ Major diastereoisomer 151.4, 144.7, 134.1, 128.8, 128.7, 127.6, 126.7, 126.4, 125.1, 116.5, 90.6, 62.8, 36.9, 36.6. Minor diastereoisomer 152.9, 144.5, 134.3, 128.7, 128.6, 127.3, 126.7, 126.4, 125.3, 116.3, 94.3, 62.7, 41.4, 39.1.

Procedure for the Ir-catalyzed reductive amination of [(2*R*,4*R*)- and (2*S*,4*R*)-7]

(*R*)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol [(*R*)-1] [S5–S7]

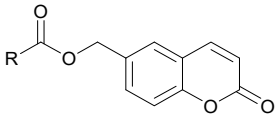


A 50 mL Schlenk tube was flushed with argon and charged with (2*R*,4*R*)- and (2*S*,4*R*)-**7** (1.56 g, 6.10 mmol, 1.0 equiv.), diisopropylamine (2.04 mL, 14.5 mmol, 2.4 equiv.), formic acid (0.660 mL, 17.4 mmol, 2.9 equiv.), THF (11.5 mL) and Cp*IrCl(8-quinolinolato) (3.08 mg, 6.07 μmol, 1.0×10^{-3} equiv.) at 0 °C. The mixture was warmed to 50 °C and stirred for 20 h. After addition of sat. $NaHCO_3$ aq. under air atmosphere, the resulting mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with CH_2Cl_2/MeOH/Et_3N = 20/1/0.2 to give (*R*)-**1** (1.90 g, 5.57 mmol, 91% yield) as pale yellow solid (lit. [S5] colorless solid, [S6] colorless oil, [S7] Gummy solid). M.p. 58–60 °C (lit. [S5] M.p. ≥50 °C). $[\alpha]_D^{24.1}$ = +15.7° (*c* 0.99, EtOH) (lit. [S5] $[\alpha]_D^{22}$ = +21.3° (*c* 1.0, EtOH)). IR (KBr): 3399, 2973, 2925, 2869, 1702, 1599, 1493, 1450, 1389, 1259, 1164, 1113, 1011, 826, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.29 (m, 4H), 7.25–7.21 (m, 1H), 7.06 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 4.49 (dd, *J* = 11.3, 4.3 Hz, 1H), 4.39 (s, 2H), 3.25–3.19 (m, 2H),

2.73–2.70 (m, 1H), 2.40–2.29 (m, 2H), 2.10–2.05 (m, 1H), 1.12 (d, J = 7.0 Hz, 6H), 1.06 (d, J = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7, 144.6, 132.9, 132.7, 128.7, 128.5, 127.6, 126.6, 126.4, 118.7, 65.6, 48.0, 42.1, 39.6, 33.4, 20.0, 19.6. The enantiomeric excess measured after conversion to (*R*)-**8** was 99.2% ee.

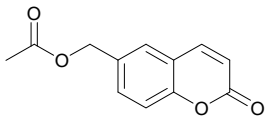
2-2 Substituent-screening studies: preparation and evaluation

General procedure for the acyloxylation of 4



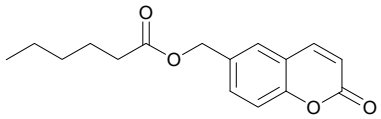
A 20 mL Schlenk tube was flashed with argon and charged with **4** (1.0 equiv.), in situ generated sodium carboxylates (1.3 equiv.), *N,N*-dimethylformamide (0.21 M). The mixture was stirred at 80 °C for 14 h. After addition of H_2O under air atmosphere, the reaction mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with hexane/EtOAc=2/1 to give **5**.

(2-oxo-*2H*-chromen-6-yl)methyl acetate (5a)



5a (251 mg, 1.15 mmol, 92% yield) as white solid from **4** (300 mg, 1.26 mmol). M.p. 109–110 °C (from Et_2O). IR (KBr): 3423, 3082, 2960, 1723, 1623, 1568, 1388, 1254, 1109, 915, 824, 757, 708 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72–7.70 (m, 1H), 7.55–7.50 (m, 2H), 7.34 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 9.2 Hz, 1H), 5.15 (s, 2H), 2.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.9, 160.6, 153.9, 143.3, 132.5, 132.0, 127.9, 118.9, 117.3, 117.2, 65.3, 21.1. HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{10}O_4$: 218.0579; found: 218.0581.

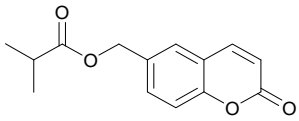
(2-oxo-*2H*-chromen-6-yl)methyl hexanoate (5c)



5c (377 mg, 1.37 mmol, 82% yield) as white solid from **4** (402 mg, 1.68 mmol). M.p. 62–63 °C (from Et_2O). IR (KBr): 3427, 2981, 2905, 1723, 1579, 1384, 1228, 1180, 1125, 965, 830, 759 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72–7.70 (m, 1H), 7.53 (dd, J = 8.6, 2.3

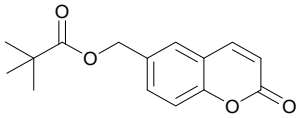
Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 9.2 Hz, 1H), 5.15 (s, 2H), 2.36 (t, J = 7.7 Hz, 2H), 1.67–1.61 (m, 2H), 1.34–1.27 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.6, 160.6, 153.9, 143.2, 132.8, 132.0, 127.8, 118.9, 117.3, 117.2, 65.1, 34.3, 31.4, 24.7, 22.4, 14.0. HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{18}O_4$: 274.1205; found: 274.1203.

(2-oxo-*2H*-chromen-6-yl)methyl isobutyrate (5d)



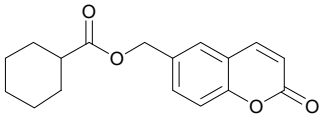
5d (317 mg, 1.29 mmol, 77% yield) as white solid from **4** (400 mg, 1.67 mmol). M.p. 63–64 °C (from Et_2O). IR (KBr): 3088, 2977, 2908, 1722, 1626, 1470, 1387, 1269, 1191,1126, 914, 761,713 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 9.7 Hz, 1H), 7.53 (dd, J = 8.6, 2.3 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 9.7 Hz, 1H), 5.15 (s, 2H), 2.65–2.57 (m, 1H), 1.19 (d, J = 7.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 160.6, 153.9, 143.3, 132.9, 131.8, 127.7, 118.9, 117.3, 117.2, 65.1, 34.1, 19.1. HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{14}O_4$: 246.0892; found: 246.0889.

(2-oxo-*2H*-chromen-6-yl)methyl pivalate (5e)



5e (412 mg, 1.58 mmol, 95% yield) as white solid from **4** (400 mg, 1.67 mmol). M.p. 93–94 °C (from Et_2O). IR (KBr): 3085,2983, 2855, 1716, 1625, 1574, 1387, 1363, 1253, 1190, 1036, 969, 760, 714 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 9.7 Hz, 1H), 7.53–7.48 (m, 2H), 7.34 (d, J = 8.1 Hz, 1H), 6.45 (d, J = 9.7 Hz, 1H), 5.14 (s, 2H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.3, 160.7, 153.9, 143.3, 133.1, 131.6, 127.4, 118.9, 117.3, 117.2, 65.2, 39.0, 27.3. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{16}O_4$: 260.1049; found: 260.1050.

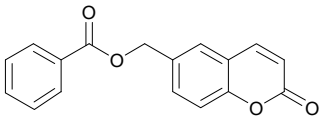
(2-oxo-*2H*-chromen-6-yl)methyl cyclohexanecarboxylate (5f)



5f (387 mg, 1.35 mmol, 81% yield) as white solid from **4** (400 mg, 1.67 mmol). M.p. 73–74 °C (from Et_2O). IR (KBr): 3431, 3076, 2925, 2861, 1722, 1624, 1448, 1384, 1248, 1170, 963, 836, 760, 715 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 9.8 Hz, 1H), 7.53–7.48 (m, 2H), 7.33 (d, J = 8.2 Hz, 1H), 6.45 (d, J = 9.8 Hz, 1H), 5.14 (s, 2H), 2.35

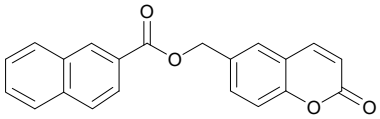
(tt, J = 11.4 Hz, 3.6 Hz, 1H), 1.94–1.91 (m, 2H), 1.74–1.77 (m, 2H), 1.66–1.63 (m, 1H), 1.49–1.41 (m, 2H), 1.32–1.18 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.9, 160.6, 153.9, 143.3, 133.0, 131.8, 127.6, 118.9, 117.3, 117.2, 65.0, 43.3, 29.1, 25.8, 25.5. HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{18}O_4$: 286.1205; found: 286.1206.

(2-oxo-*2H*-chromen-6-yl)methyl benzoate (5g)



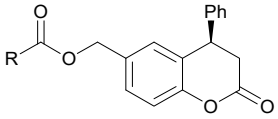
5g (116 mg, 0.412 mmol, 98% yield) as white solid from **4** (101 mg, 0.421 mmol). M.p. 102–103 °C (from Et_2O). IR (KBr): 2977, 2873, 1716, 1624, 1455, 1365, 1284, 1166, 1123, 914, 817, 711 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 9.7 Hz, 1H), 7.63 (dd, J = 8.6, 1.7 Hz, 1H), 7.60–7.57 (m, 2H), 7.46 (dd, J = 7.6 Hz, 7.3 Hz, 2H), 7.37 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 9.7 Hz, 1H), 5.41 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.4, 160.6, 153.9, 143.3, 133.4, 132.6, 132.0, 129.8, 129.7, 128.6, 127.8, 118.9, 117.3, 117.2, 65.7. HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{12}O_4$: 280.0736; found: 280.0737.

(2-oxo-*2H*-chromen-6-yl)methyl 2-naphthoate (5h)



5h (371 mg, 1.12 mmol, 89% yield) as white solid from **4** (300 mg, 1.25 mmol). M.p. 148–149 °C (from Et_2O). IR (KBr): 3439, 3068, 2885, 2363, 1726, 1623, 1455, 1373, 1282, 1222, 916, 820, 769, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.08 (dd, J = 8.6 Hz, 1.6 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.91–7.88 (m, 2H), 7.74 (d, J = 9.7 Hz, 1H), 7.68 (dd, J = 8.6 Hz, 1.7 Hz, 1H), 7.64–7.54 (m, 3H), 7.39 (d, J = 8.6 Hz, 1H), 6.47 (d, J = 9.7 Hz, 1H), 5.47 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.5, 160.6, 153.9, 143.3, 135.7, 132.6, 132.5, 132.0, 131.3, 129.4, 128.5, 128.4, 127.9, 127.8, 127.0, 126.9, 125.2, 118.9, 117.3, 117.1, 65.9. HRMS (EI) m/z: $[M]^+$ calcd for $C_{21}H_{14}O_4$: 330.0892; found: 330.0893.

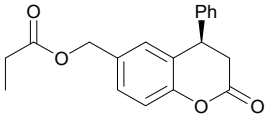
Organic solvent-free Rh-catalyzed asymmetric 1,4-addition of 5 (Procedure B. General procedures used for substituent-screening)



A mixture of $[RhOH(cod)]_2$ (0.98 mg, 2.15 μmol, 1.0×10^{-2} equiv.), (*R*)-M^{F}F-MeO-

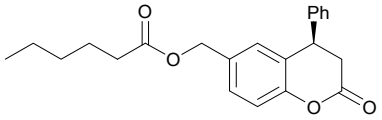
BIPHEP (3.99 mg, 4.31 μmol, 2.0×10^{-2} equiv.), **5** (0.215 mmol, 1.0 equiv.), phenylboronic acid (131 mg, 1.08 mmol, 5.0 equiv.) and H_2O (19.4 μL, 1.08 mmol, 5.0 equiv.) was placed in a 20 mL Schlenk tube and was stirred at 40 °C for 12 h under argon atmosphere. After addition of H_2O under air atmosphere at 0 °C, the resulting mixture was extracted with air-bubbled EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with hexane/EtOAc = 4/1 to give (*R*)-**6**.

(*R*)-(2-oxo-4-phenylchroman-6-yl)methyl propionate [(*R*)-6b]



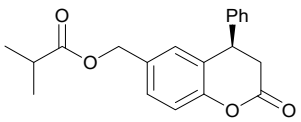
(*R*)-**6b** (63.1 mg, 0.203 mmol, 94% yield, >99% ee) was obtained as colorless oil. $[\alpha]_D^{25.0}$= +23.4° (*c* 0.2, $CHCl_3$). Daicel Chiralcel AD-3, hexane/ ^{i}PrOH = 90/10, flow rate = 0.5 mL/min: t_R of (*S*)-**6b**; 30.2 min (0.4%), t_R of (*R*)-**6b**; 33.1 min (99.6%). HRMS (EI) m/z: $[M]^+$ calcd for $C_{19}H_{18}O_4$: 310.1205; found: 310.1206.

(*R*)-(2-oxo-4-phenylchroman-6-yl)methyl hexanoate [(*R*)-6c]



(*R*)-**6c** (58.9 mg, 0.167 mmol, 78% yield, 97.4% ee) was obtained as colorless oil. $[\alpha]_D^{25.2}$= +56.8° (*c* 0.1, $CHCl_3$). IR (KBr): 2968, 2371, 1785, 1726, 1499, 1423, 1376, 1244, 1144, 965, 826, 774, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.29 (m, 4H), 7.16–7.12 (m, 3H), 6.98 (d, *J* = 1.7 Hz,1H), 5.00 (s, 2H), 4.35 (t, *J* = 6.9 Hz, 1H) 3.11–3.00 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.63–1.56 (m, 2H), 1.32–1.24 (m, 4H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.7, 167.5, 151.6, 140.2, 132.8, 129.3, 128.9, 128.4, 127.9, 127.6, 126.0, 117.5, 65.4, 40.8, 37.0, 34.3, 31.4, 24.7, 22.4, 14.0. Daicel Chiralcel AD-3, hexane/ ^{i}PrOH = 90/10, flow rate = 0.5 mL/min: t_R of (*S*)-**6c**; 24.0 min (1.3%), t_R of (*R*)-**6c**; 24.6 min (98.7%). HRMS (EI) m/z: $[M]^+$ calcd for $C_{22}H_{24}O_4$: 352.1675; found: 352.1678.

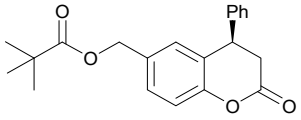
(*R*)-(2-oxo-4-phenylchroman-6-yl)methyl isobutyrate [(*R*)-6d]



(*R*)-**6d** (69.3 mg, 0.214 mmol, >99% yield, >99% ee) was obtained as colorless oil. $[\alpha]_D^{25.1}$= +12.3° (*c* 0.2, $CHCl_3$). IR (KBr): 2979, 2937, 2365, 1778, 1736, 1691, 1498,

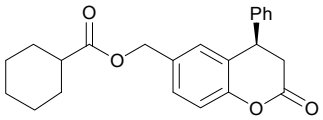
1339, 1197, 1152, 969, 824, 773, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.18 (m, 4H), 7.08–7.04 (m, 3H), 6.87 (d, *J* = 1.7 Hz,1H), 4.92 (s, 2H), 4.26 (t, *J* = 6.9 Hz, 1H) 3.02–2.92 (m, 2H), 2.49–2.43 (m, 1H), 1.05 (d, *J* = 12.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 167.5, 151.5, 140.1, 133.0, 129.3, 128.6, 128.0, 127.9, 127.6, 126.0, 117.4, 65.2, 40.7, 37.0, 34.0, 19.0. Daicel Chiralcel AD-3, hexane/ ^{i}PrOH = 90/10, flow rate = 0.5 mL/min: t_R of (*S*)-**6d**; 25.0 min (0.5%), t_R of (*R*)-**6d**; 27.3 min (99.5%). HRMS (EI) m/z: $[M]^+$ calcd for $C_{20}H_{20}O_4$: 324.1362; found: 324.1361.

(*R*)-(2-oxo-4-phenylchroman-6-yl)methyl pivalate [(*R*)-6e]



(*R*)-**6e** (67.0 mg, 0.198 mmol, 92% yield, >99% ee) was obtained as white solid. M.p. 92–94 °C (from Et_2O). $[\alpha]_D^{24.5}$= +26.7° (*c* 0.2, $CHCl_3$). IR (KBr): 2981, 2872, 1721, 1618, 1442, 1400, 1365, 1280, 1111, 1040, 978, 824, 778, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.26 (m, 4H), 7.17–7.12 (m, 3H), 6.92 (d, *J* = 1.7 Hz, 1H), 5.00 (s, 2H), 4.36–4.33 (m, 1H) 3.11–3.00 (m, 2H), 1.16 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.3, 167.6, 151.4, 140.1, 133.2, 129.3, 128.2, 127.9, 127.7, 127.6, 126.1, 117.4, 65.3, 40.7, 38.9, 37.0, 27.2. Daicel Chiralcel AD-3, hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min: t_R of (*S*)-**6e**; 18.4 min (0%), t_R of (*R*)-**6e**; 20.6min (100%). HRMS (EI) m/z: $[M]^+$ calcd for $C_{21}H_{22}O_4$: 338.1518; found: 338.1520.

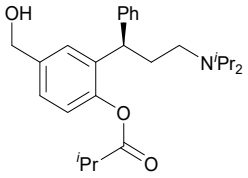
(*R*)-(2-oxo-4-phenylchroman-6-yl)methyl cyclohexanecarboxylate [(*R*)-6f]



(*R*)-**6f** (71.2 mg, 0.195 mmol, 91% yield, >99% ee) was obtained as colorless oil. $[\alpha]_D^{24.3}$= +34.3° (*c* 0.2, $CHCl_3$). IR (KBr): 2944, 2368, 1770, 1735, 1495, 1428, 1311, 1244, 1038, 969, 831, 755, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.26 (m, 4H), 7.16–7.12 (m, 3H), 6.94 (d, *J* = 1.6 Hz,1H), 5.00 (s, 2H), 4.34 (t, *J* = 6.9 Hz, 1H) 3.11–3.00 (m, 2H), 2.28 (tt, *J* = 11.3, 3.6 Hz, 1H), 1.86–1.62 (m, 5H), 1.41–1.15 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.7, 167.5, 151.4, 140.1, 133.0, 129.2, 128.5, 127.9, 127.8, 127.6, 126.0, 117.3, 65.0, 43.1, 40.7, 36.9, 29.0, 25.7, 25.4. Daicel Chiralcel AD-3, hexane/ ^{i}PrOH = 90/10, flow rate = 0.5 mL/min: t_R of (*S*)-**6f**; 28.9 min (0.4%), t_R of (*R*)-**6f**; 33.5 min (99.6%). HRMS (EI) m/z: $[M]^+$ calcd for $C_{23}H_{24}O_4$: 364.1675; found: 364.1678.

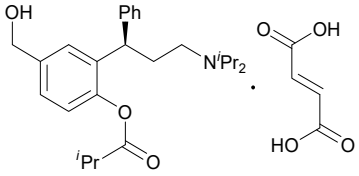
2-3 The synthesis of Toviaz

(*R*)-(+)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (Fesoterodine) [(*R*)-8] [S3,S8]



A 20 mL Schlenk tube was flushed with argon and charged with (*R*)-**1** (100 mg, 0.293 mmol, 1.0 equiv.). The material was dissolved in CH_2Cl_2 (0.7 mL) and then cooled to −10 °C and stirred for 0.5 h. A solution of isobutyryl Chloride (46.1 μL, 0.439 mmol, 1.5 equiv.) in CH_2Cl_2 (0.8 mL) was added dropwise to the stirred solution and stirred at −10 °C for 2 h. A 5 wt%/wt aqueous sodium carbonate solution (0.5 mL) was then added to the reaction, allowing the temperature to rise towards 0 °C during the addition. The resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography with hexane/EtOAc/Et_3N = 1/3/0.04 to give (*R*)-**8** (104 mg, 0.253 mmol, 86% yield, >99% ee) as colorless oil. $[\alpha]_D^{22.4}$= +2.74° (*c* 1.0, EtOH) (lit. [S8] $[I]_D^{22}$= +2.7° (*c* 1.0, EtOH)). IR (KBr): 3087, 2984, 2965, 2868, 1761, 1602, 1495, 1470, 1422, 1389, 1364, 1231, 1131, 1048, 970, 755, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 1.7 Hz, 1H), 7.27–7.24 (m, 2H), 7.22–7.20 (m, 3H), 7.17–7.14 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.65 (s, 2H), 4.11 (t, *J* = 7.8 Hz, 1H), 2.99–2.92 (m, 2H), 2.83–2.78 (m, 1H), 2.38–2.27 (m, 2H), 2.19–2.08 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 147.9, 143.9, 138.9, 136.9, 128.4, 128.0, 126.9, 126.2, 125.6, 122.6, 64.7, 48.9, 44.0, 41.9, 36.9, 34.3, 20.6, 20.6, 19.2, 19.1. Daicel Chiralcel AD-3, hexane/^{i}PrOH = 96/4 + 0.1% diethylamine, flow rate = 1.0 mL/min: t_R of (*S*)-**8**; 7.09 min (0.4%), t_R of (*R*)-**8**; 7.75 min (99.6%).

(*R*)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester hydrogen fumarate (Toviaz) [S3,S8-S12]



A 20 mL round bottom flask was charged with fumaric acid (97.0 mg, 0.836 mmol, 0.95 equiv.) and (*R*)-**8** (363 mg, 0.881 mmol, 1.0 equiv.). The material was dissolved in methyl ethyl ketone (3.7 mL) and then heated at 40 °C in a water bath with stirring for 0.5 h until complete dissolution. The flask was then removed from the water bath and the solution was allowed to cool to room temperature, after which seed crystals were added. Upon

continued stirring, a white slurry formed within several minutes. The mixture was cooled in an ice bath and stirred at 0 °C for 1 h, followed by the addition of cyclohexane (0.40 mL). Stirring was continued overnight at 0 °C. The resulting white solid was collected by filtration, washed with MEK/cyclohexane (1/4, 10 mL), and dried under reduced pressure to afford the title product (384 mg, 0.727 mmol, 83% yield) as white solid. M.p. 80–81 °C (lit. [S11] 72–78 °C). $[\alpha]_D^{25.9}$ = +6.25° (c 0.29, MeOH) (lit. [S12] $[\alpha]_D$ = +7.8° (*c* 0.3, MeOH)). IR (KBr): 3466, 2986, 2934, 2874, 2679, 2513, 1758, 1701, 1684, 1582, 1466, 1227, 1185, 1090, 981, 921, 797, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.25–7.21 (m, 4H), 7.16–7.12 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.83 (s, 2H), 4.60 (q, *J* = 13.1 Hz, 2H), 3.94 (m, 1H), 3.60 (sept, *J* = 6.6 Hz, 2H), 2.87–2.75 (m, 4H), 2.57–2.53 (m, 1H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 6.6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.8, 170.5, 147.7, 142.5, 140.6, 135.6, 134.6, 128.9, 127.7, 127.6, 126.9, 126.7, 122.3, 64.0, 54.4, 45.9, 42.0, 34.3, 31.8, 19.3, 19.1, 18.0.

3. Determination of residual rhodium content

Residual rhodium was quantified by ICP-OES at 343.488 nm using an external calibration curve, which is shown in Fig. S1. To determine the residual rhodium, 56.2 mg of (*R*)-**1** was treated with nitric acid and decomposed using a microwave-assisted sample preparation system. The resulting solution was diluted to 50 mL, and the rhodium content was quantified by ICP-OES. The average of five consecutive measurements indicated a residual rhodium level of 0.020 ppm.

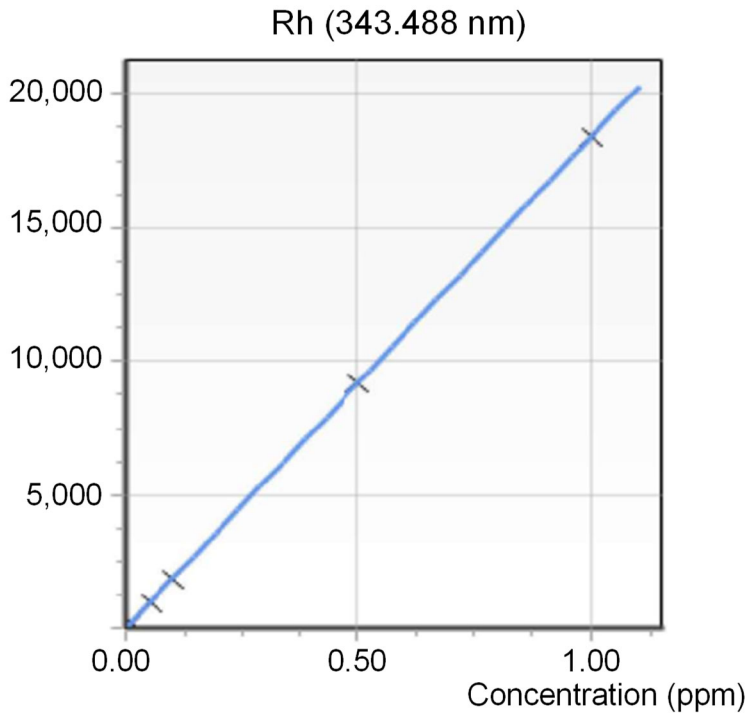
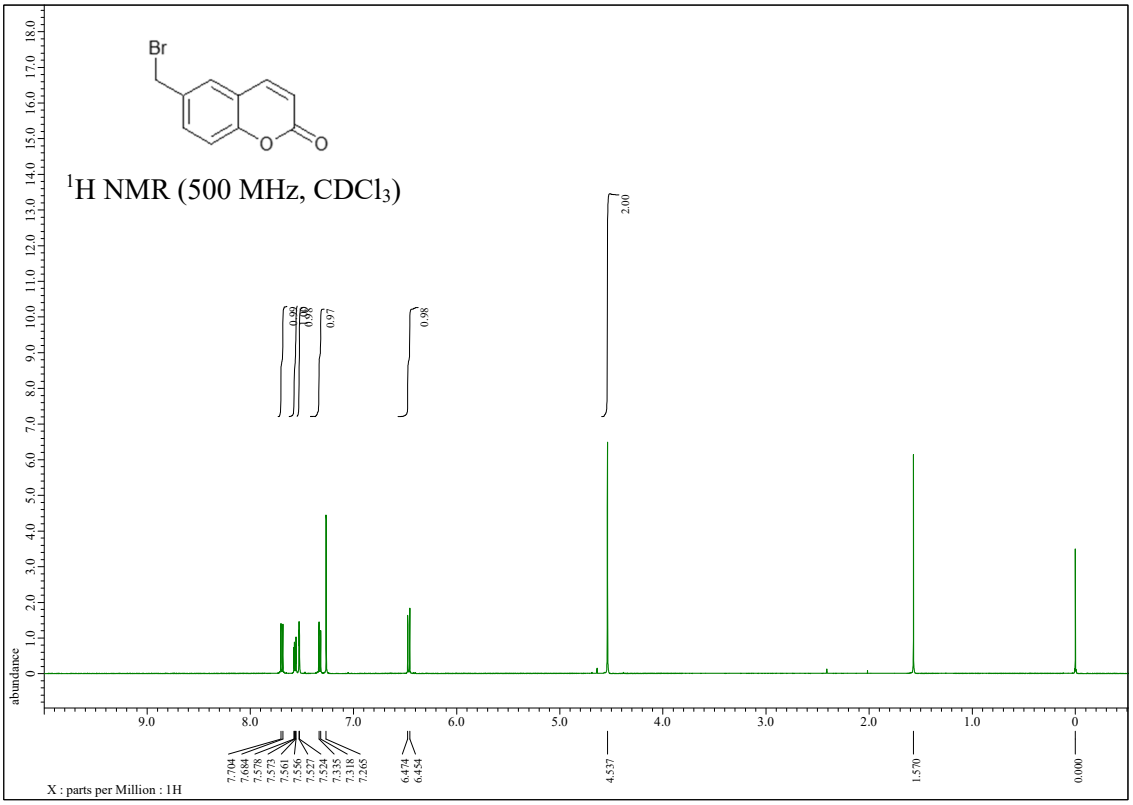


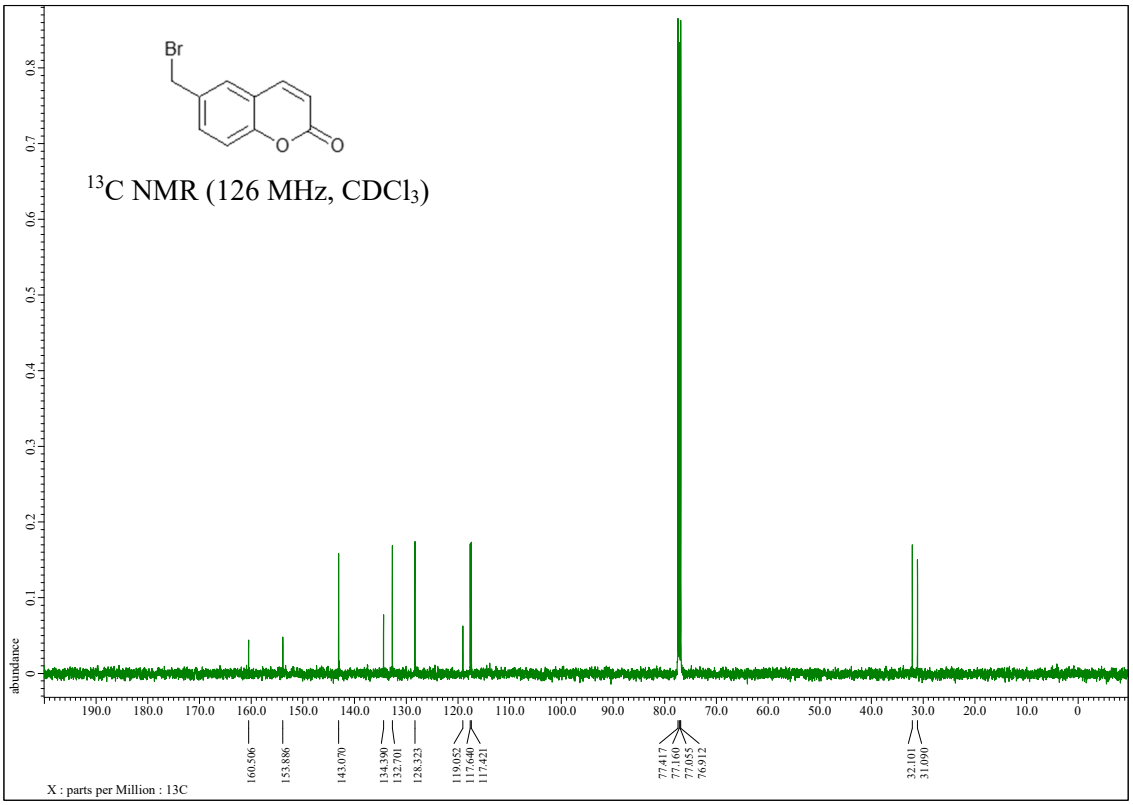
Fig. S1 calibration curve

4. NMR charts

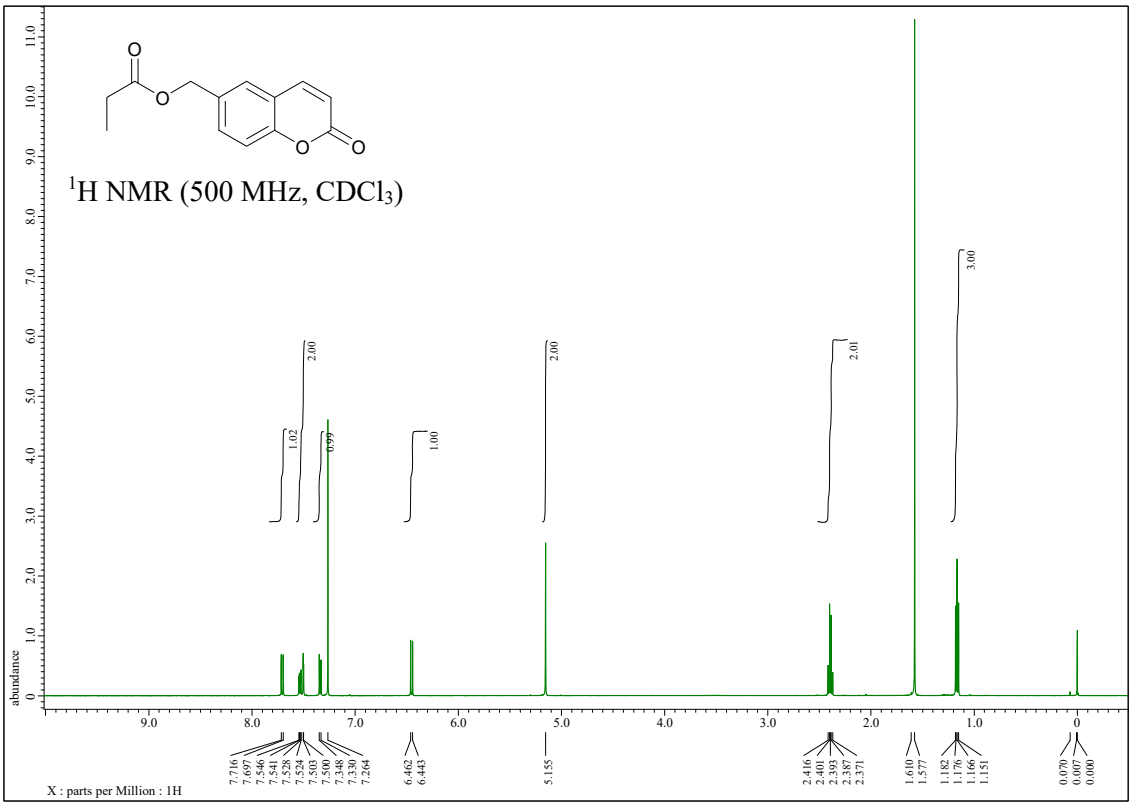
^{1}H NMR of 6-bromomethyl-coumarin (**4**)



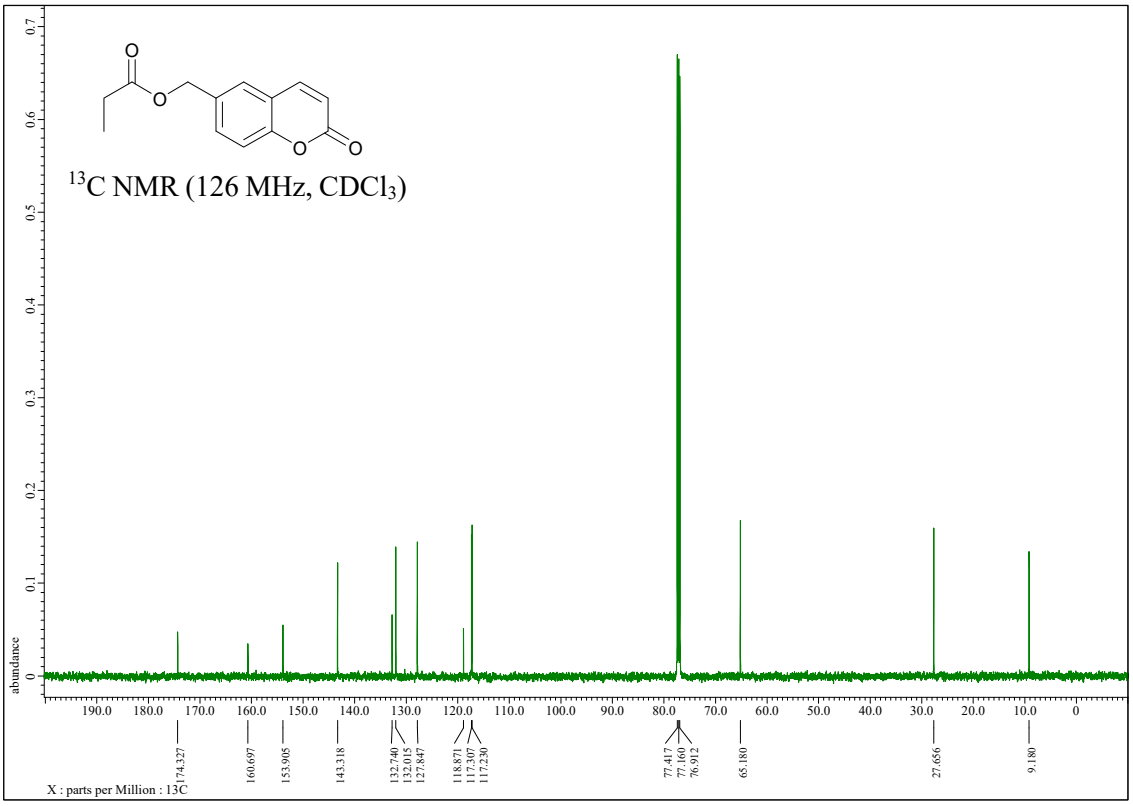
^{13}C NMR of 6-bromomethyl-coumarin (**4**)



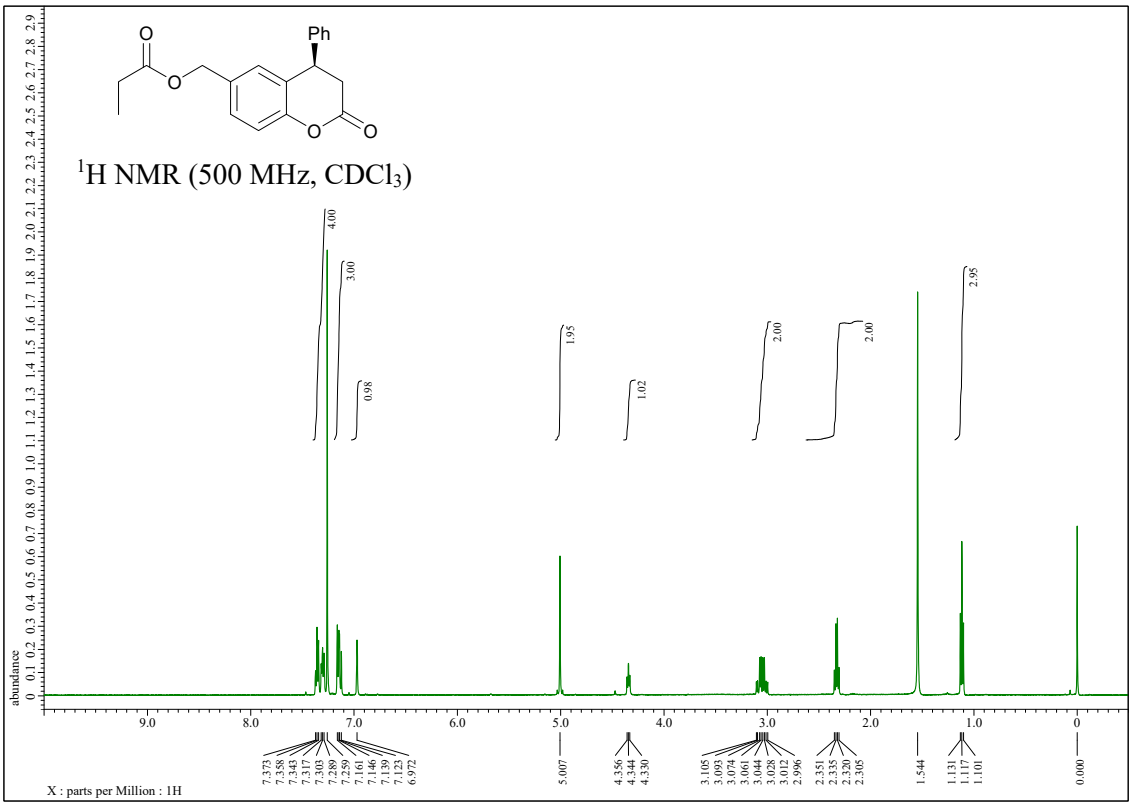
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl propionate (**5b**)



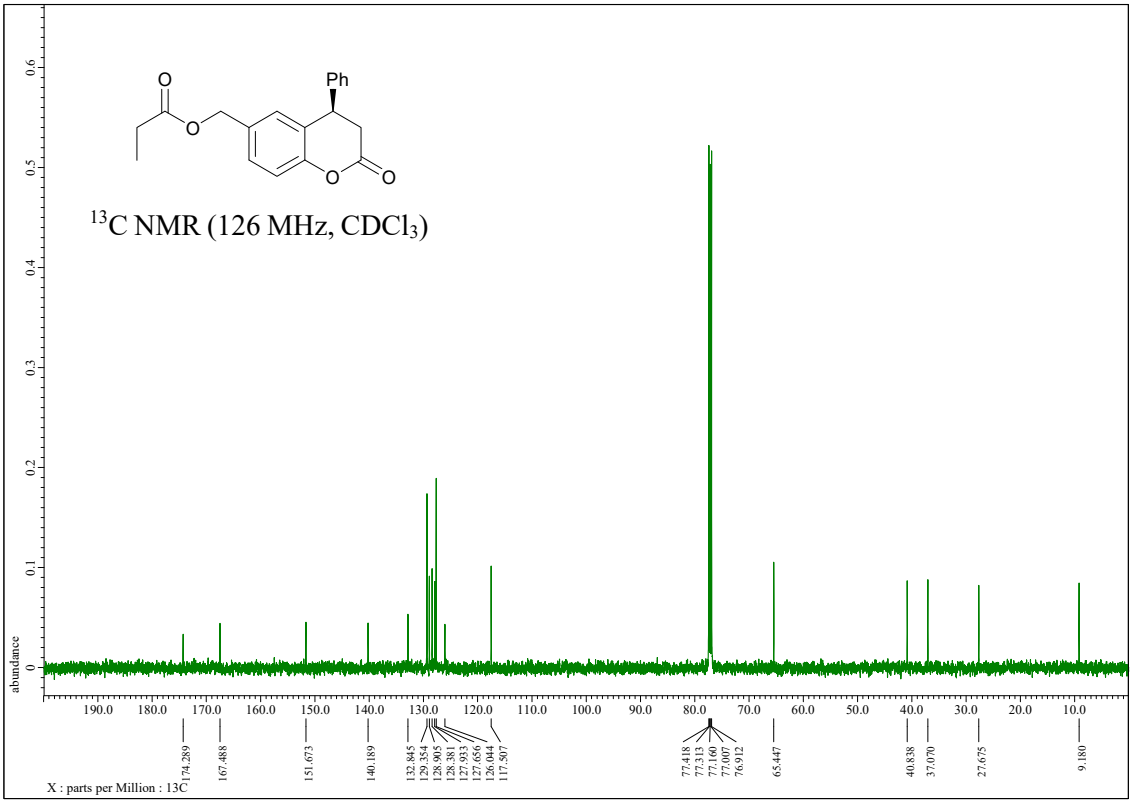
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl propionate (**5b**)



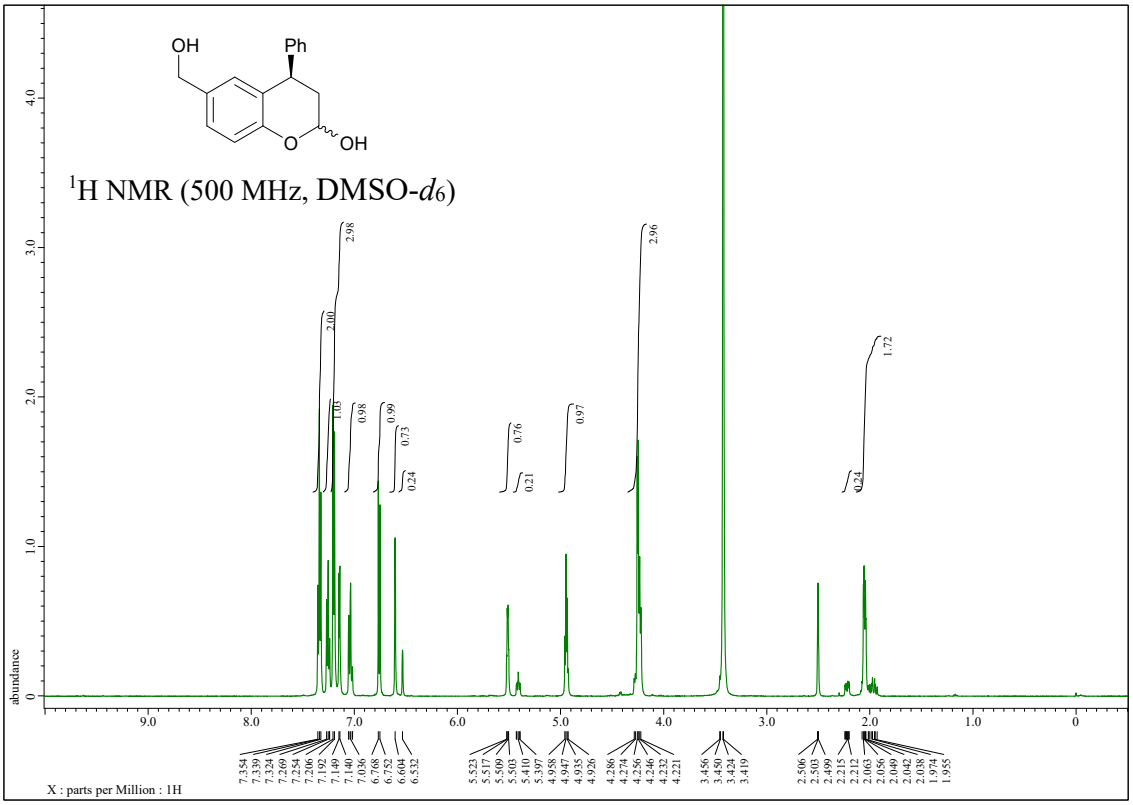
^{1}H NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl propionate [(*R*)-**6b**]



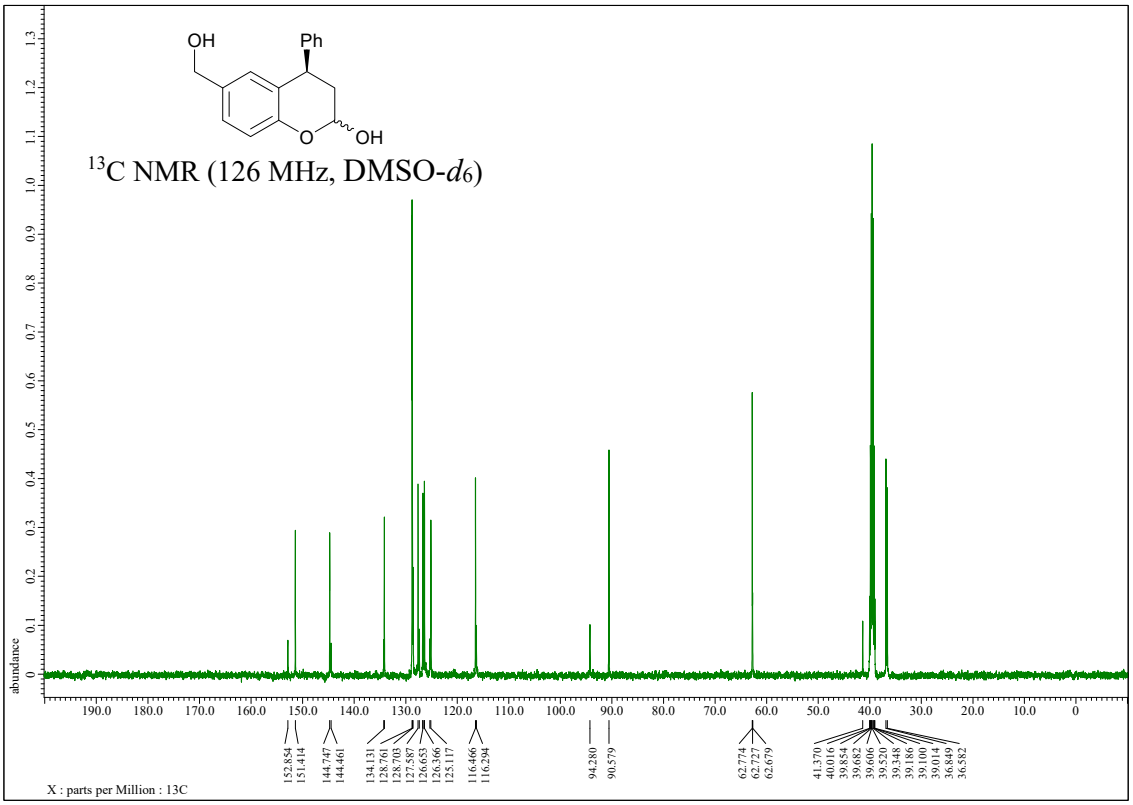
^{13}C NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl propionate [(*R*)-**6b**]



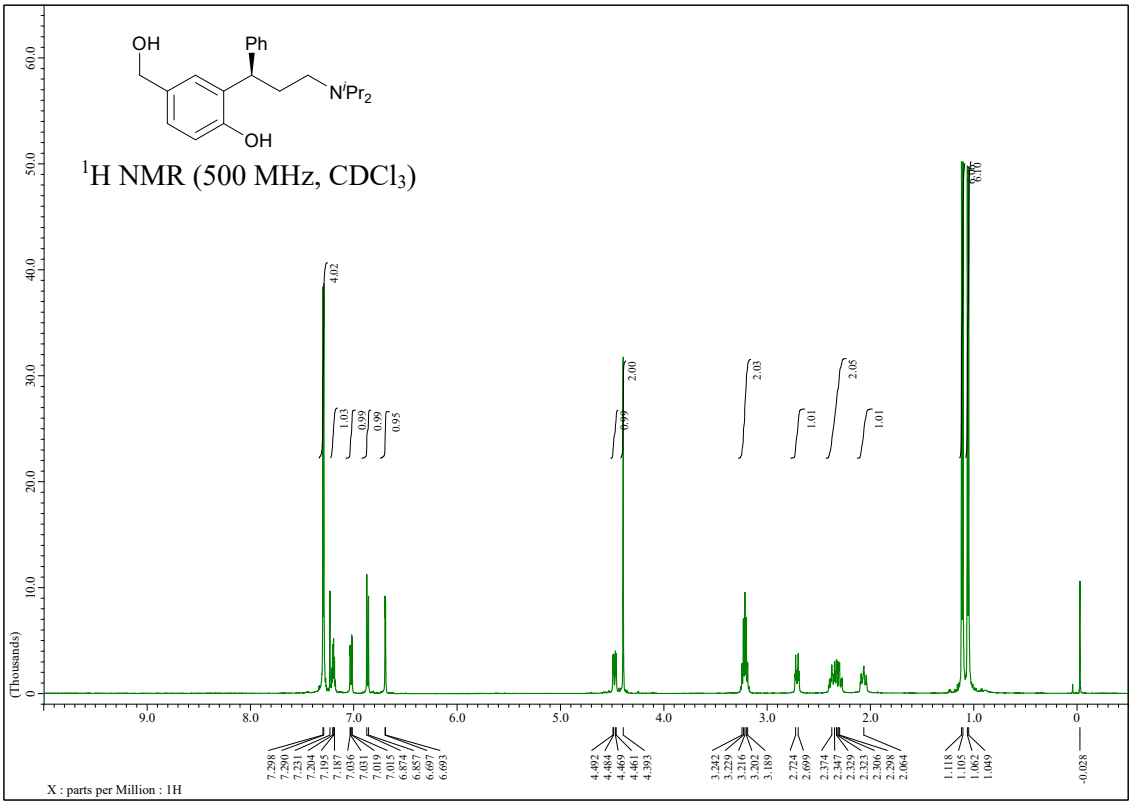
^{1}H NMR of (2*R*,4*R*)- and (2*S*,4*R*)-6-(hydroxymethyl)-4-phenylchroman-2-ol [(2*R*,4*R*)- and (2*S*,4*R*)-**7**]



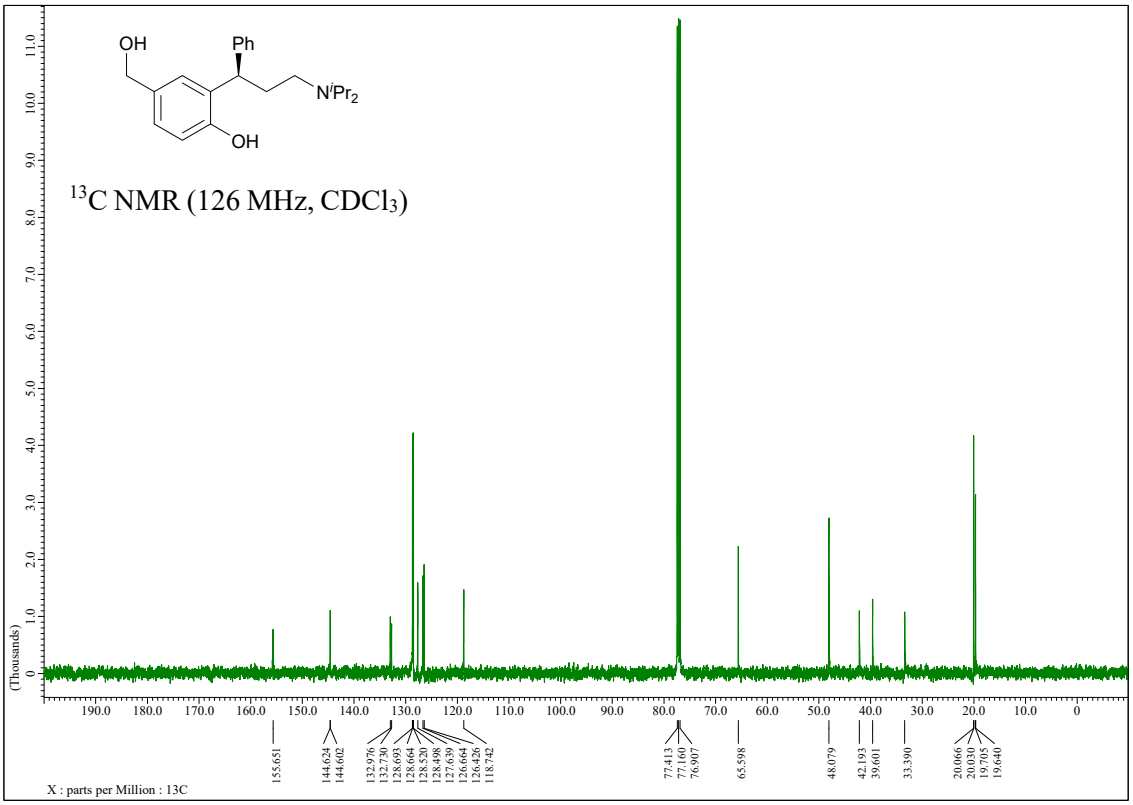
^{13}C NMR of (2*R*,4*R*)- and (2*S*,4*R*)-6-(hydroxymethyl)-4-phenylchroman-2-ol [(2*R*,4*R*)- and (2*S*,4*R*)-**7**]



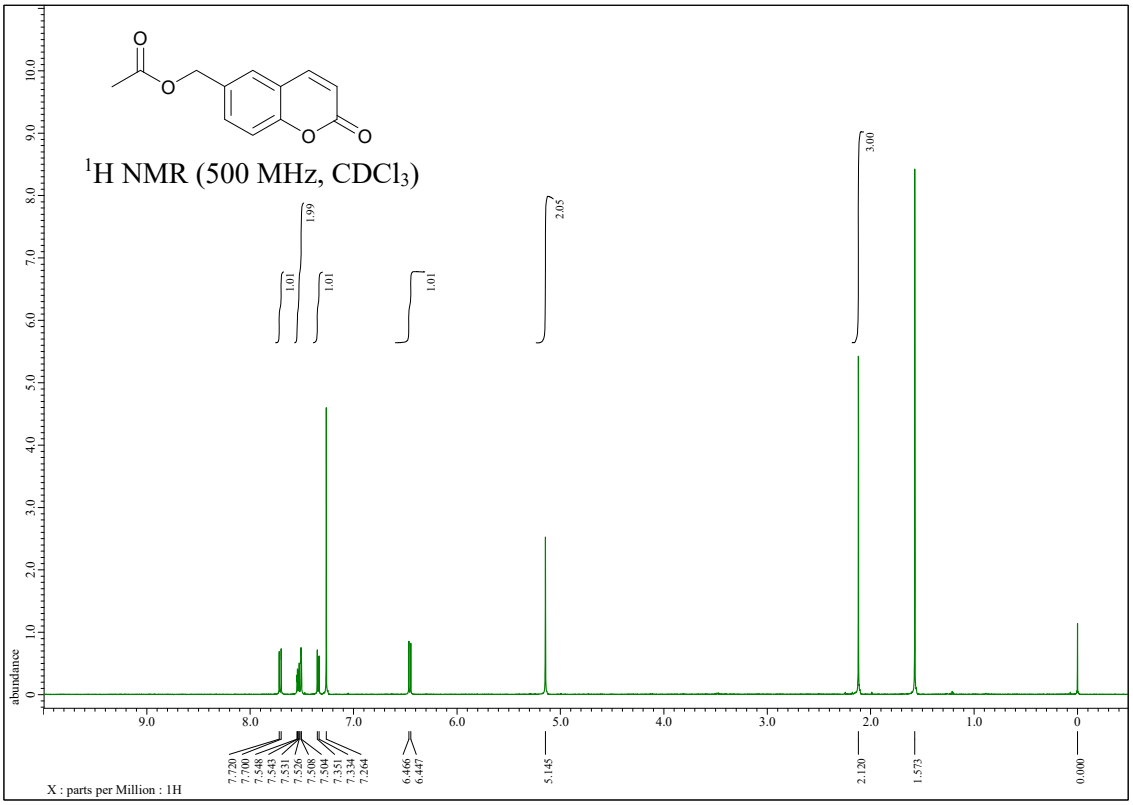
^{1}H NMR of (*R*)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol [(*R*)-**1**]



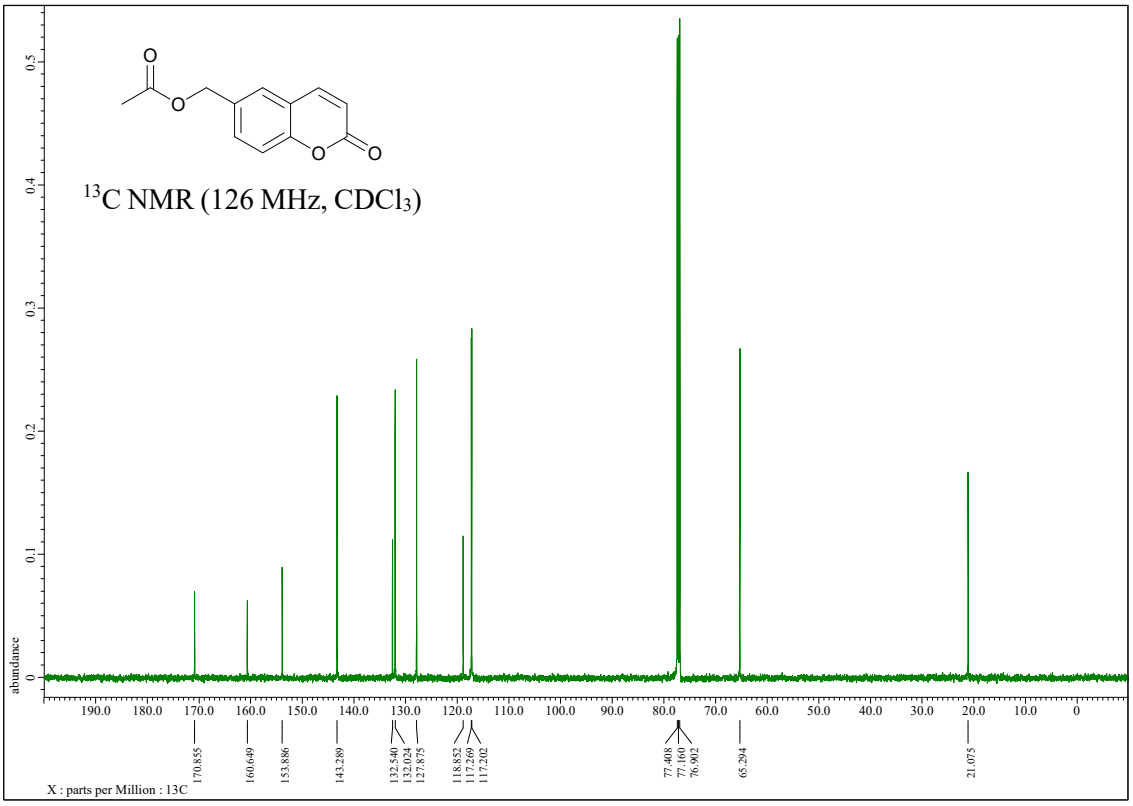
^{13}C NMR of (*R*)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol [(*R*)-**1**]



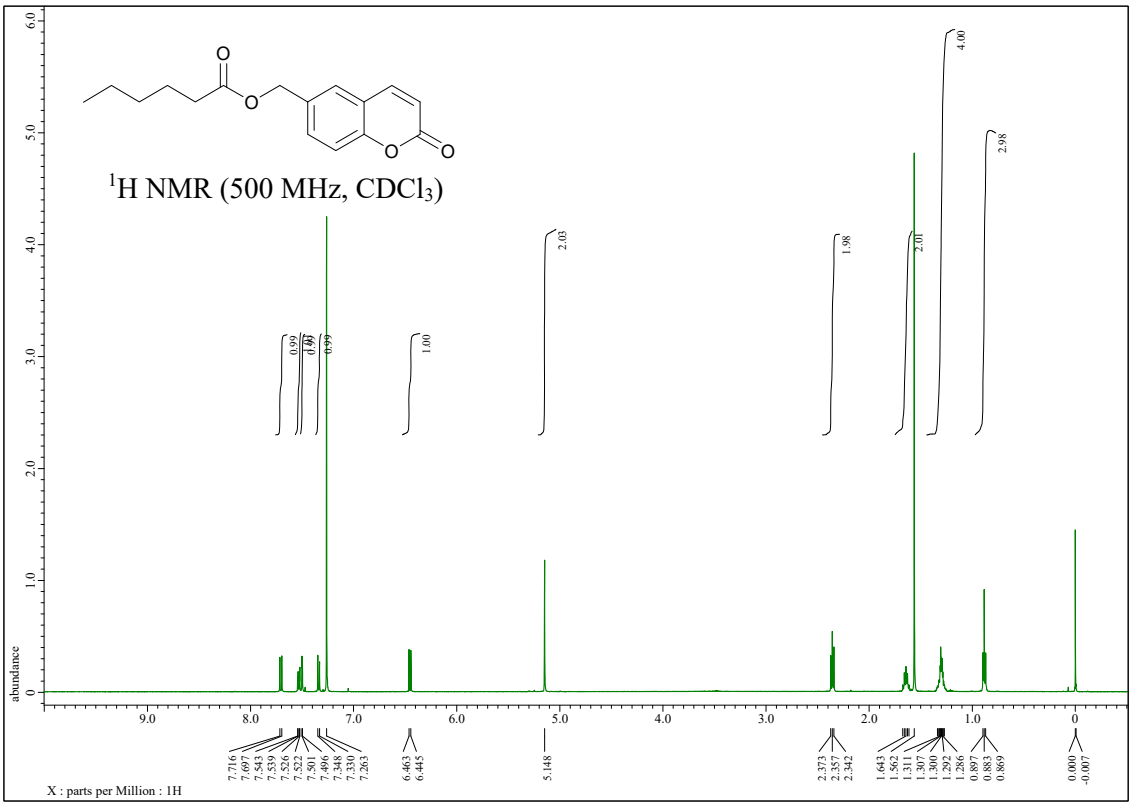
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl acetate (**5a**)



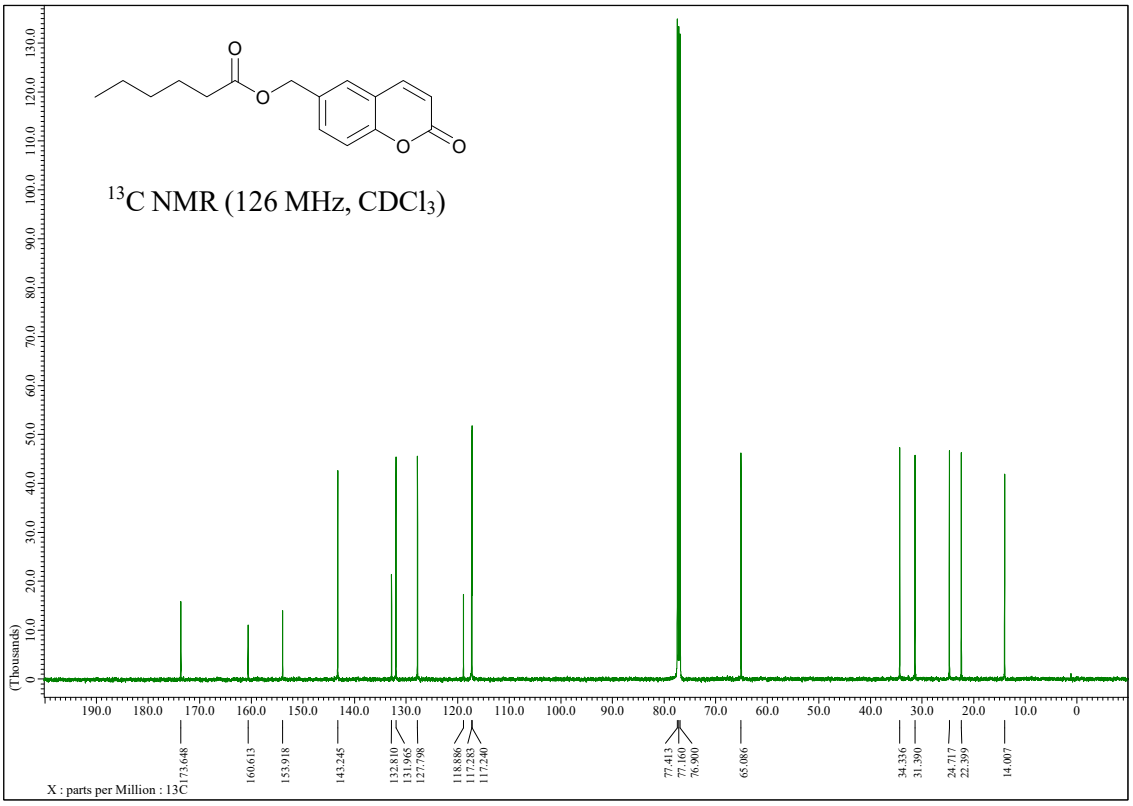
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl acetate (**5a**)



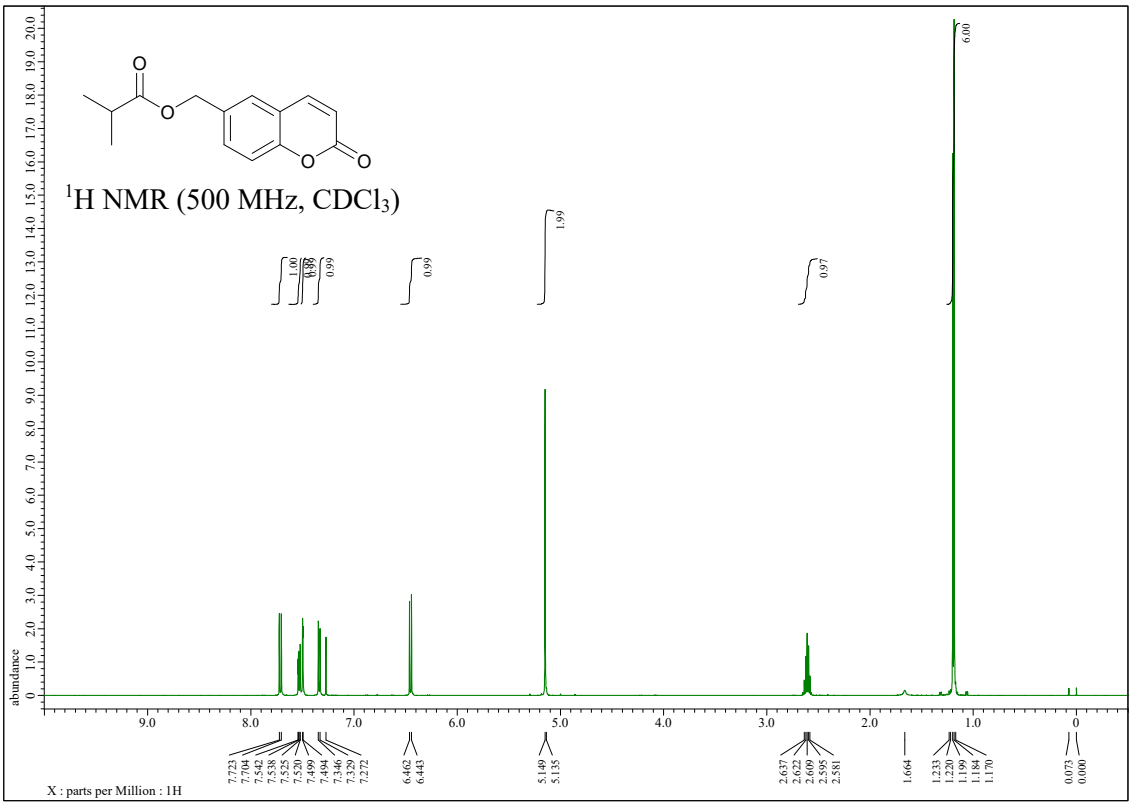
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl hexanoate (**5c**)



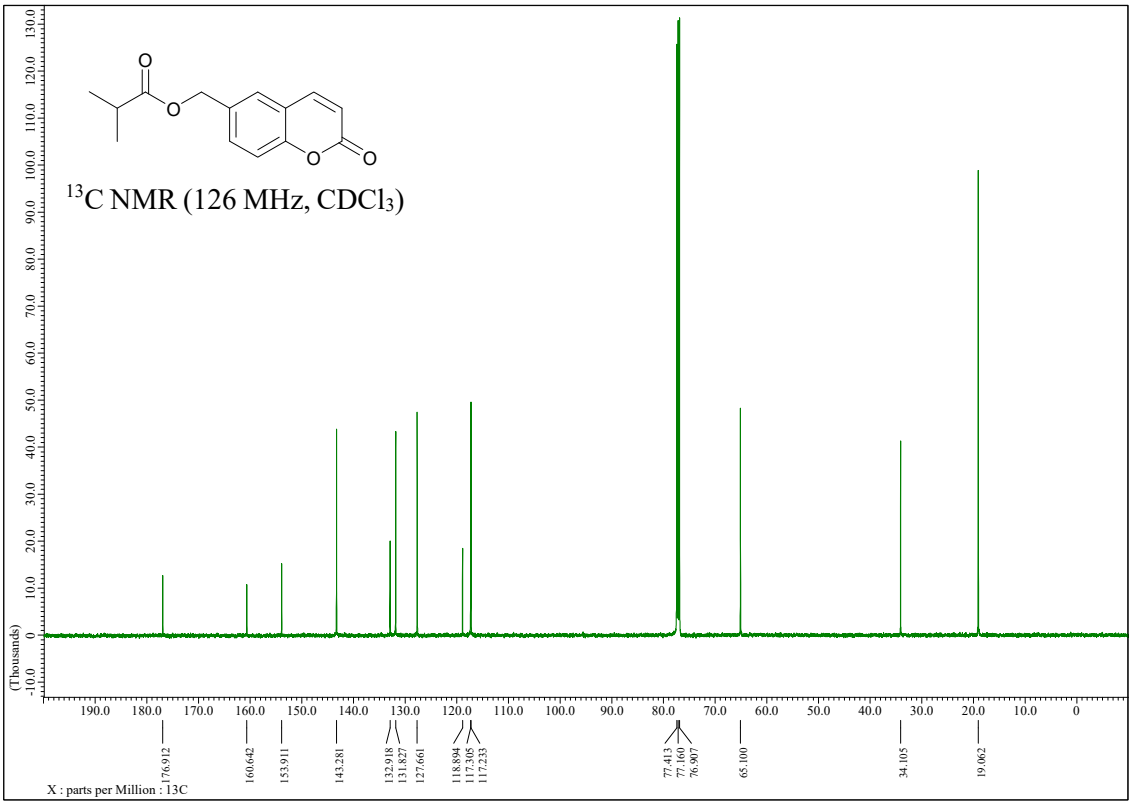
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl hexanoate (**5c**)



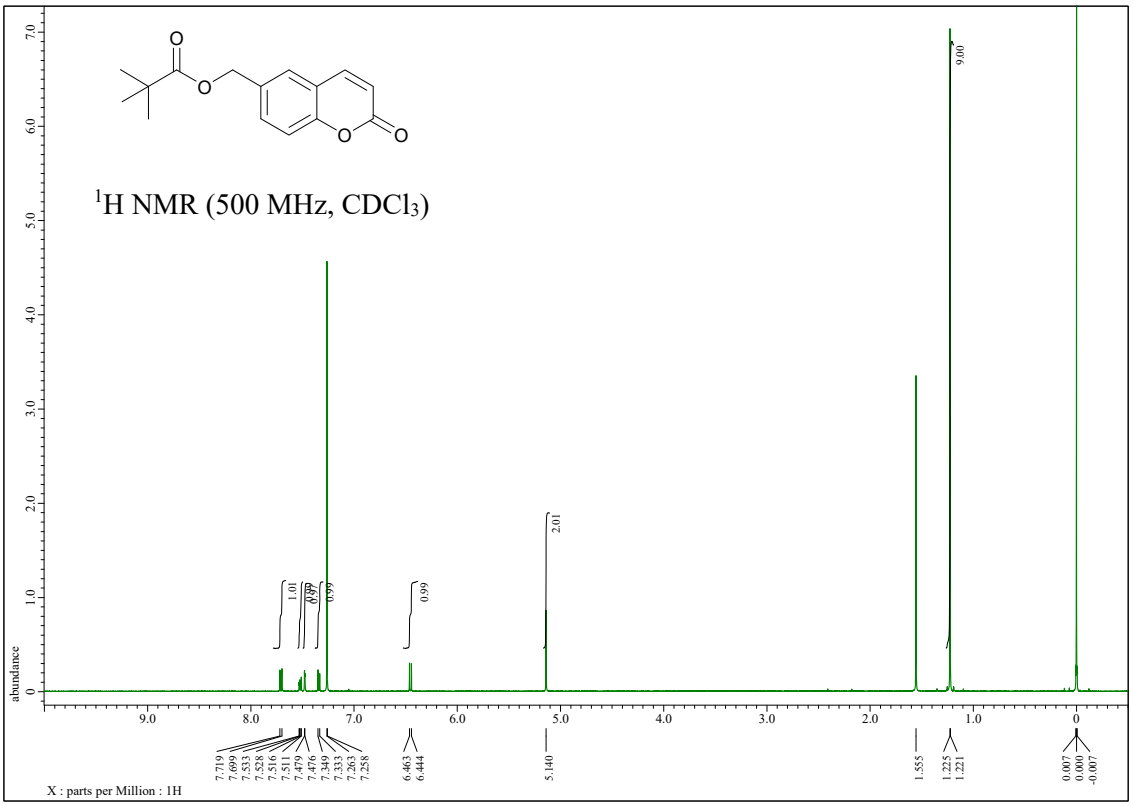
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl isobutyrate (**5d**)



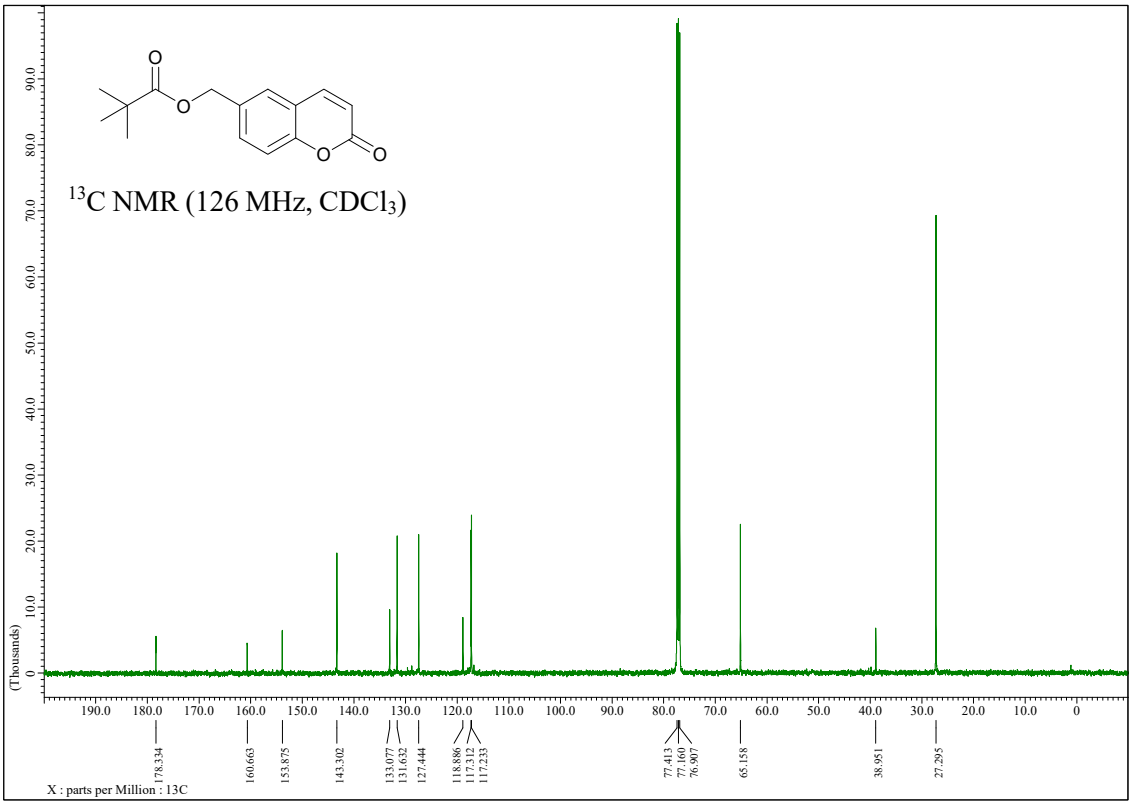
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl isobutyrate (**5d**)



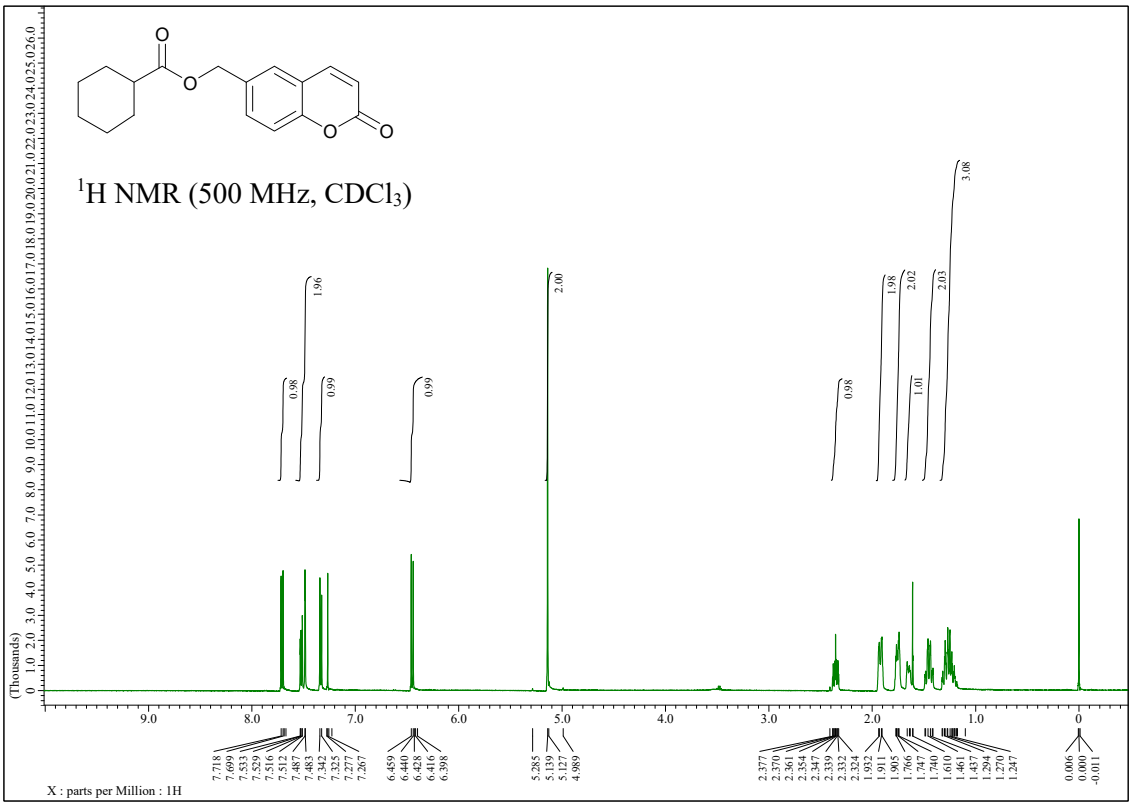
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl pivalate (**5e**)



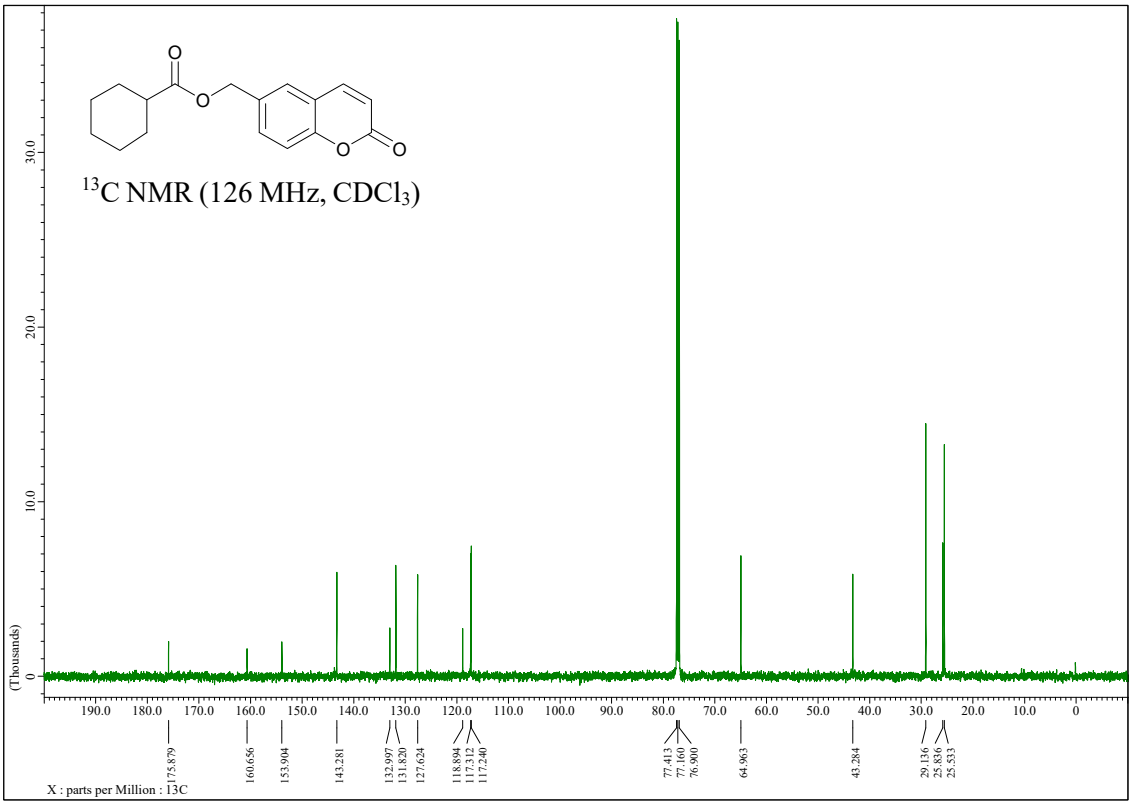
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl pivalate (**5e**)



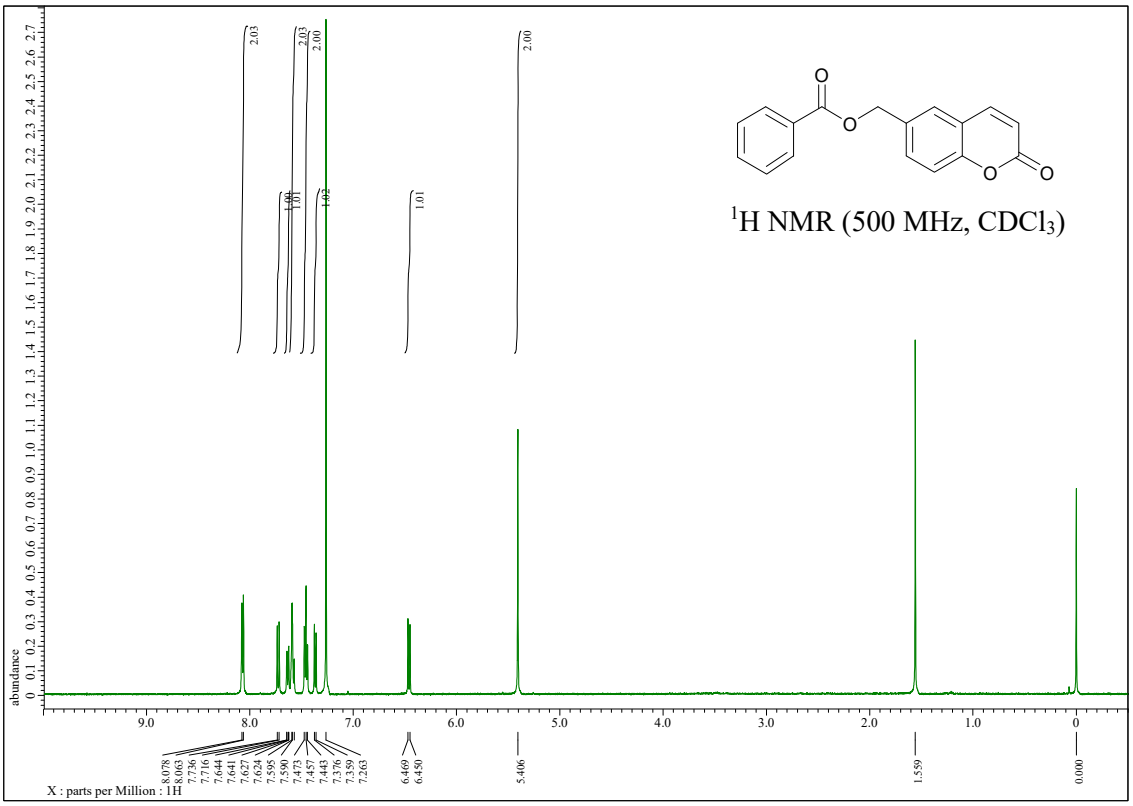
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl cyclohexanecarboxylate (**5f**)



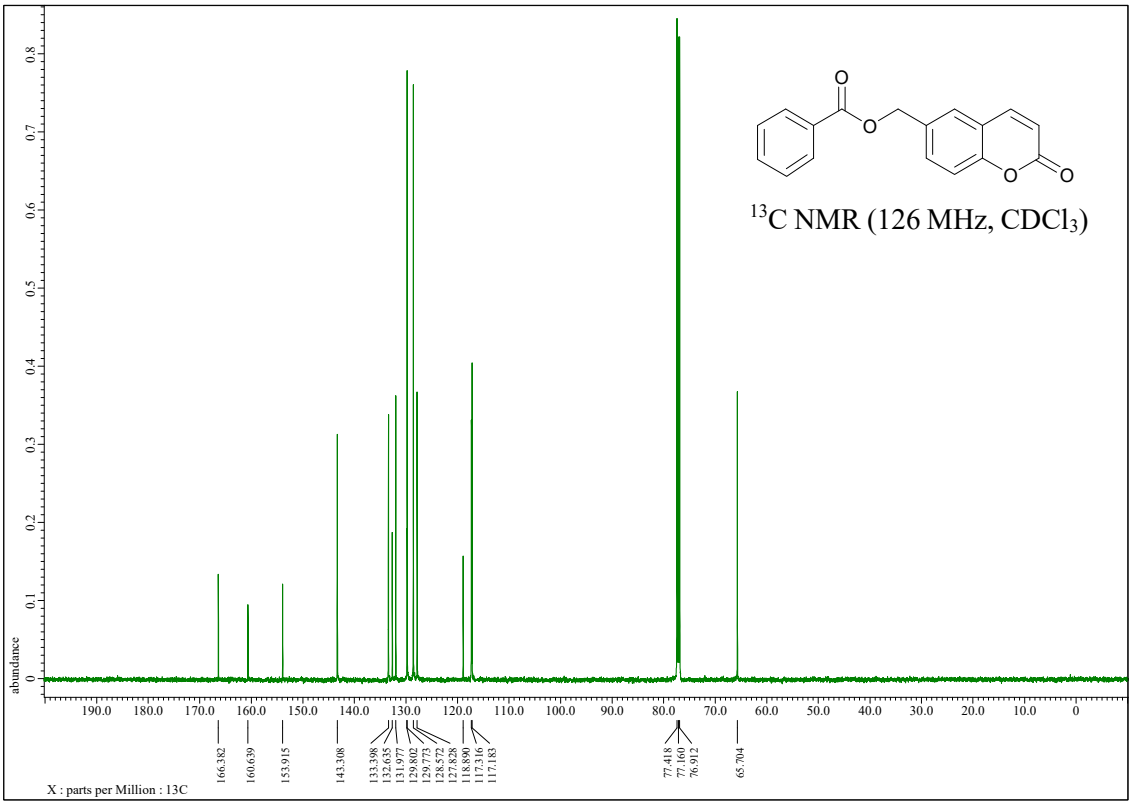
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl cyclohexanecarboxylate (**5f**)



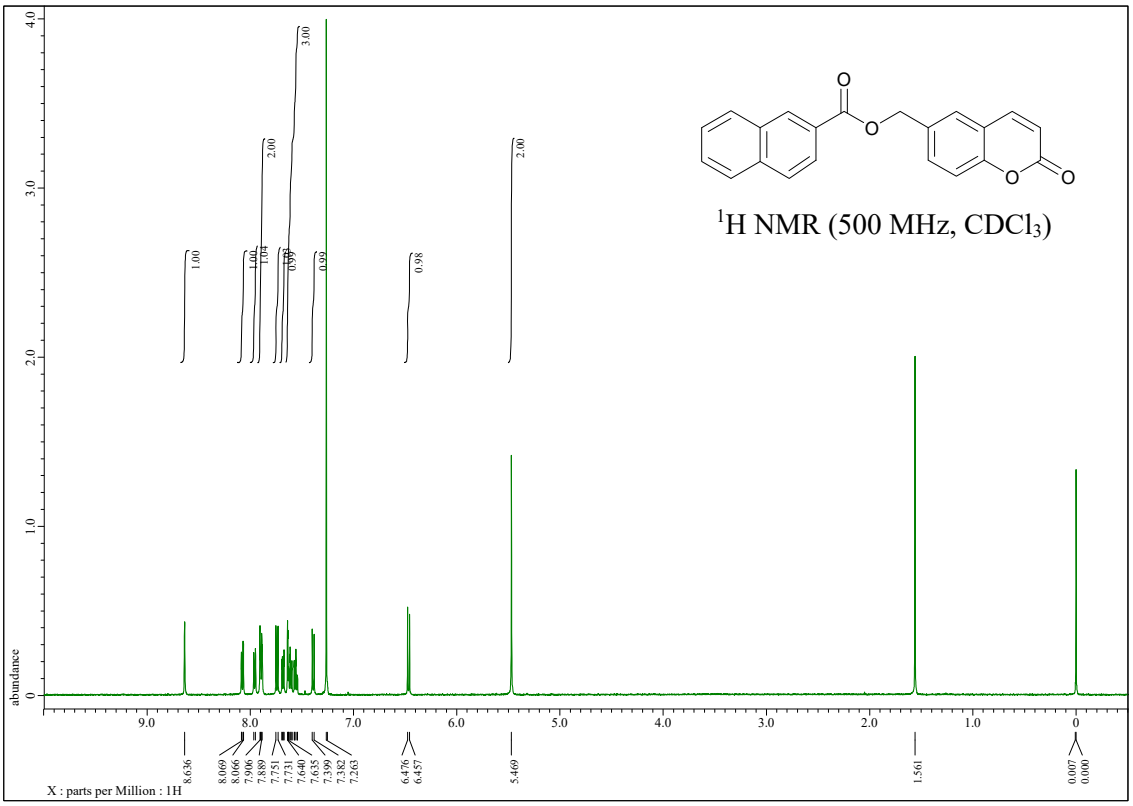
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl benzoate (**5g**)



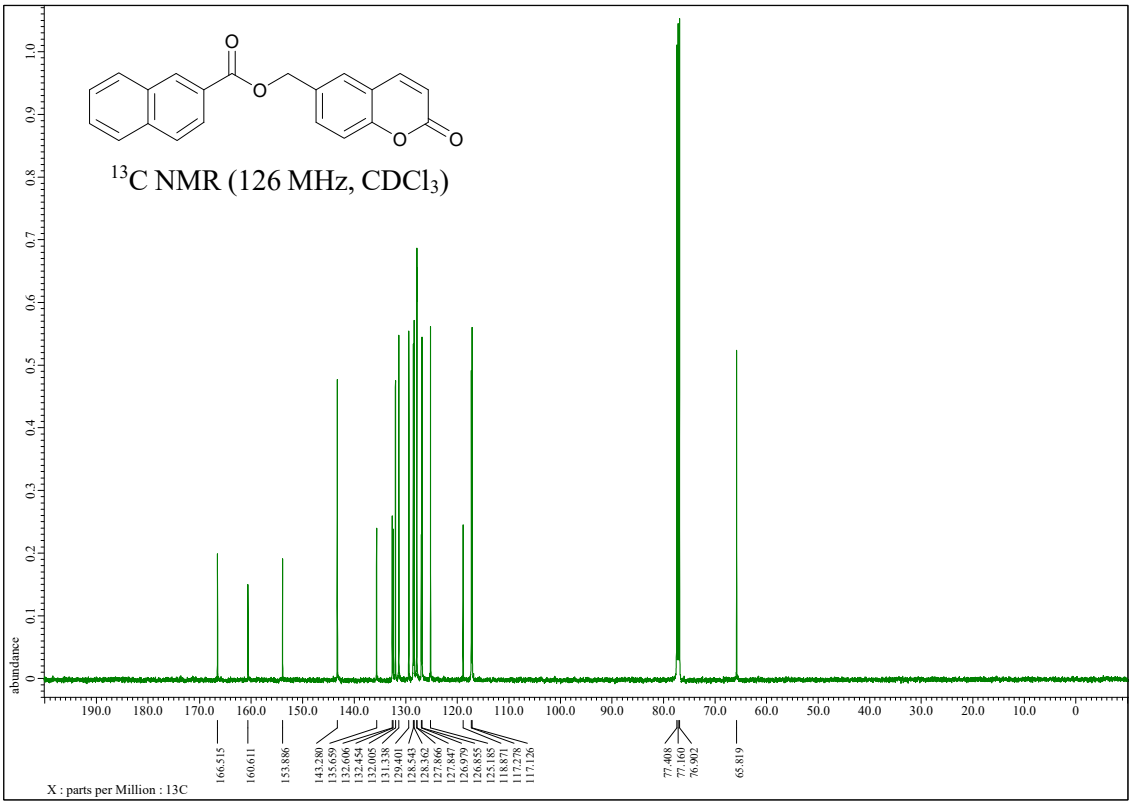
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl benzoate (**5g**)



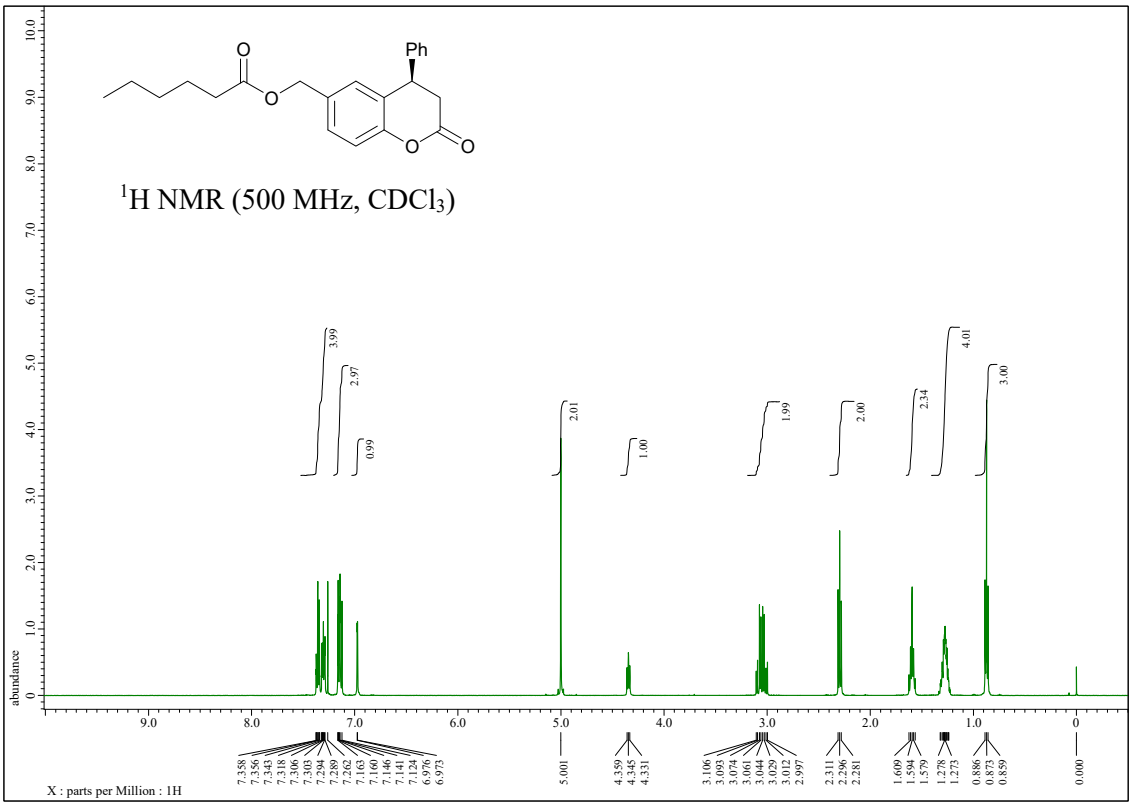
^{1}H NMR of (2-oxo-*2H*-chromen-6-yl)methyl 2-naphthoate (**5h**)



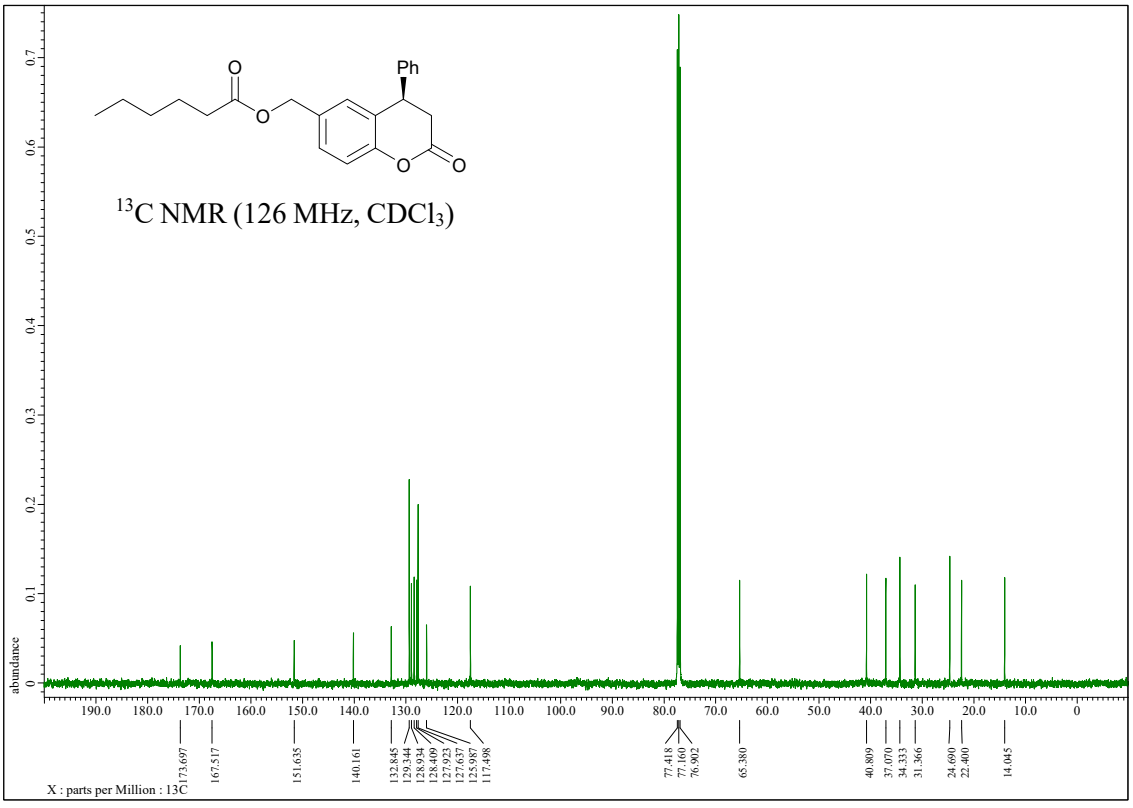
^{13}C NMR of (2-oxo-*2H*-chromen-6-yl)methyl 2-naphthoate (**5h**)



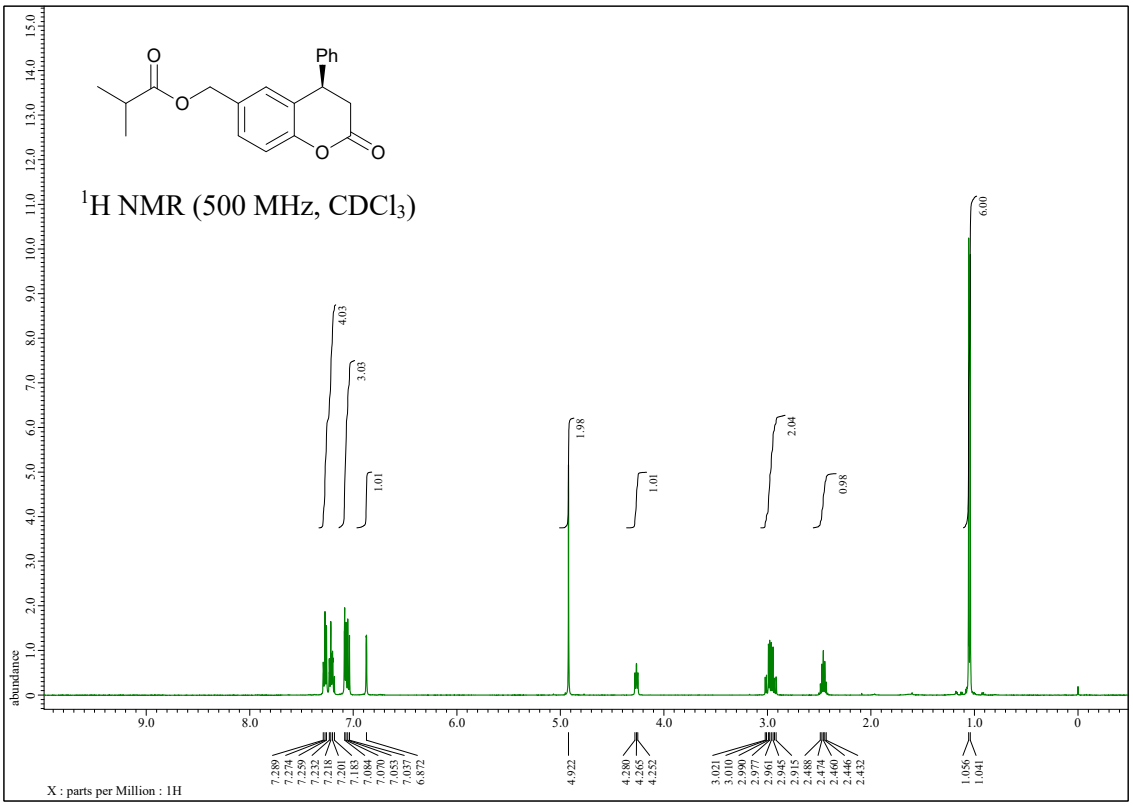
^{1}H NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl hexanoate [(*R*)-**6c**]



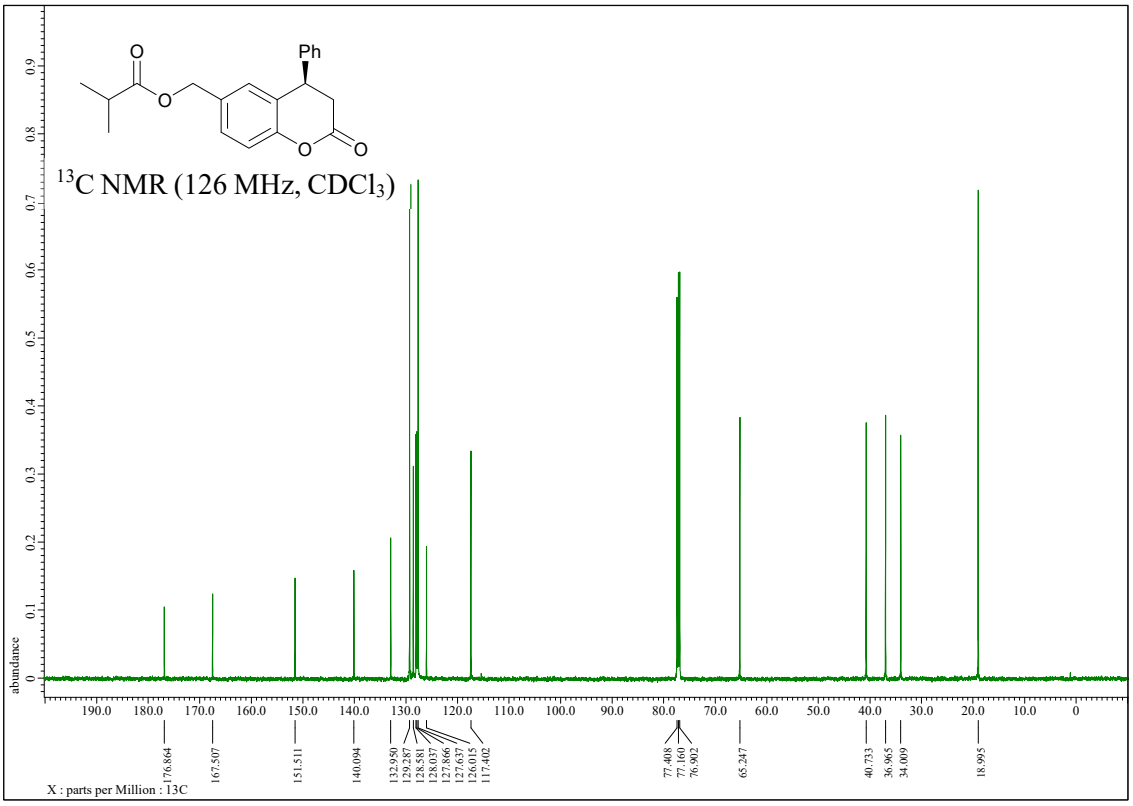
^{13}C NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl hexanoate [(*R*)-**6c**]



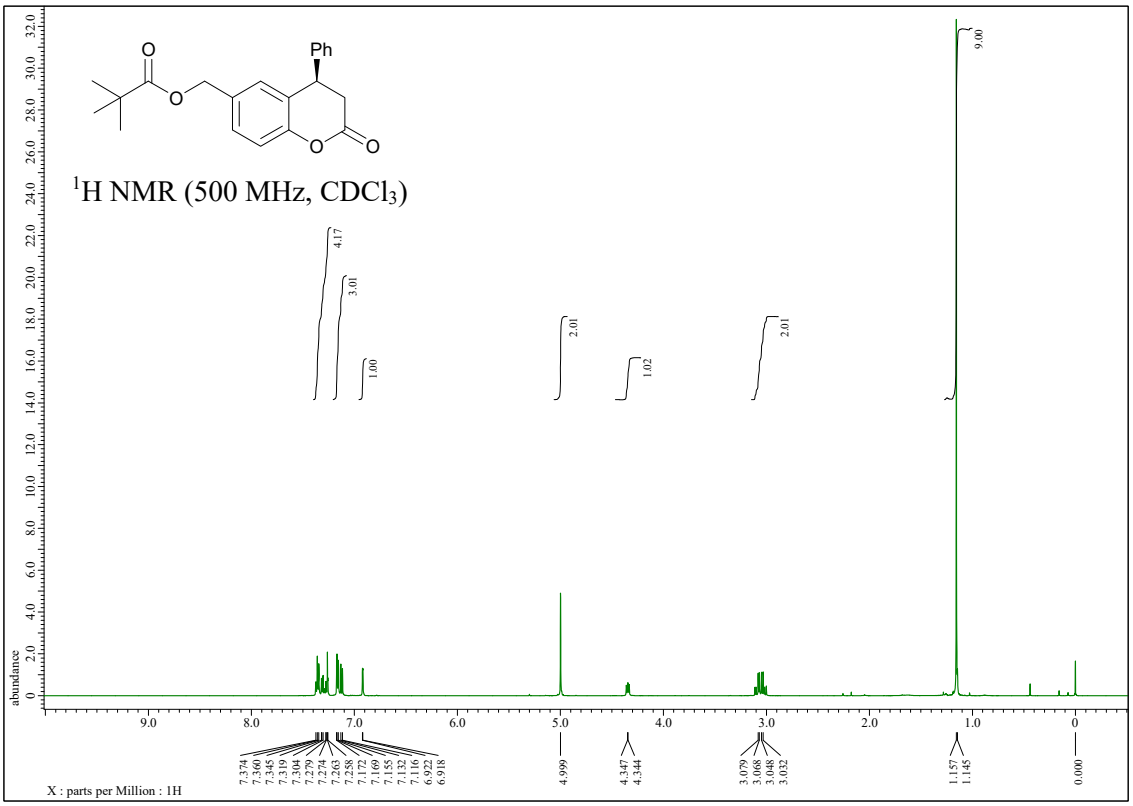
^{1}H NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl isobutyrate [(*R*)-**6d**]



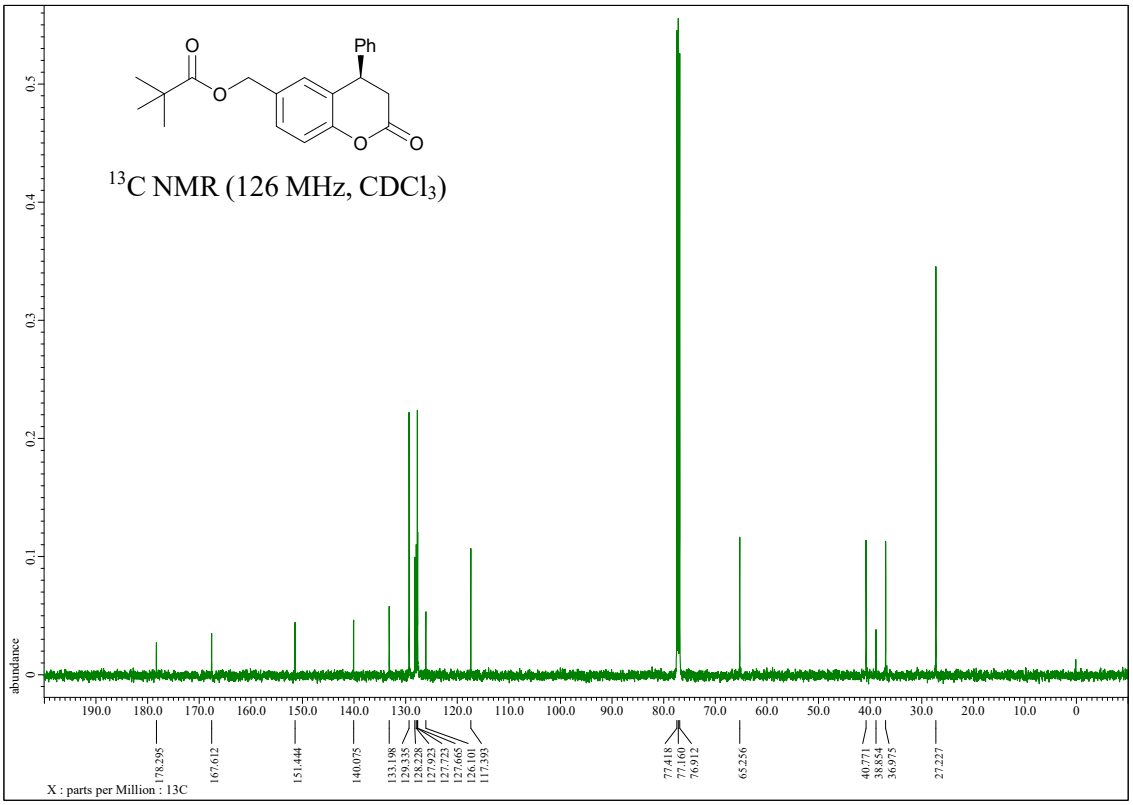
^{13}C NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl isobutyrate [(*R*)-**6d**]



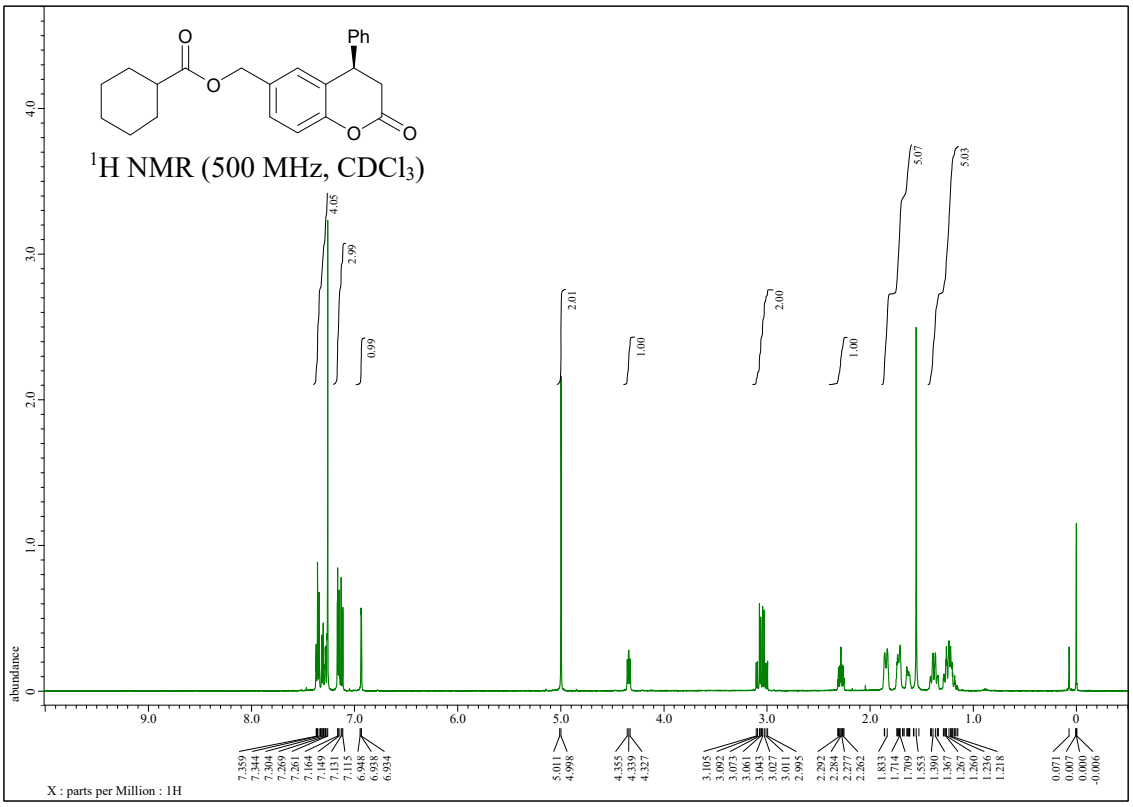
^{1}H NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl pivalate [(*R*)-**6e**]



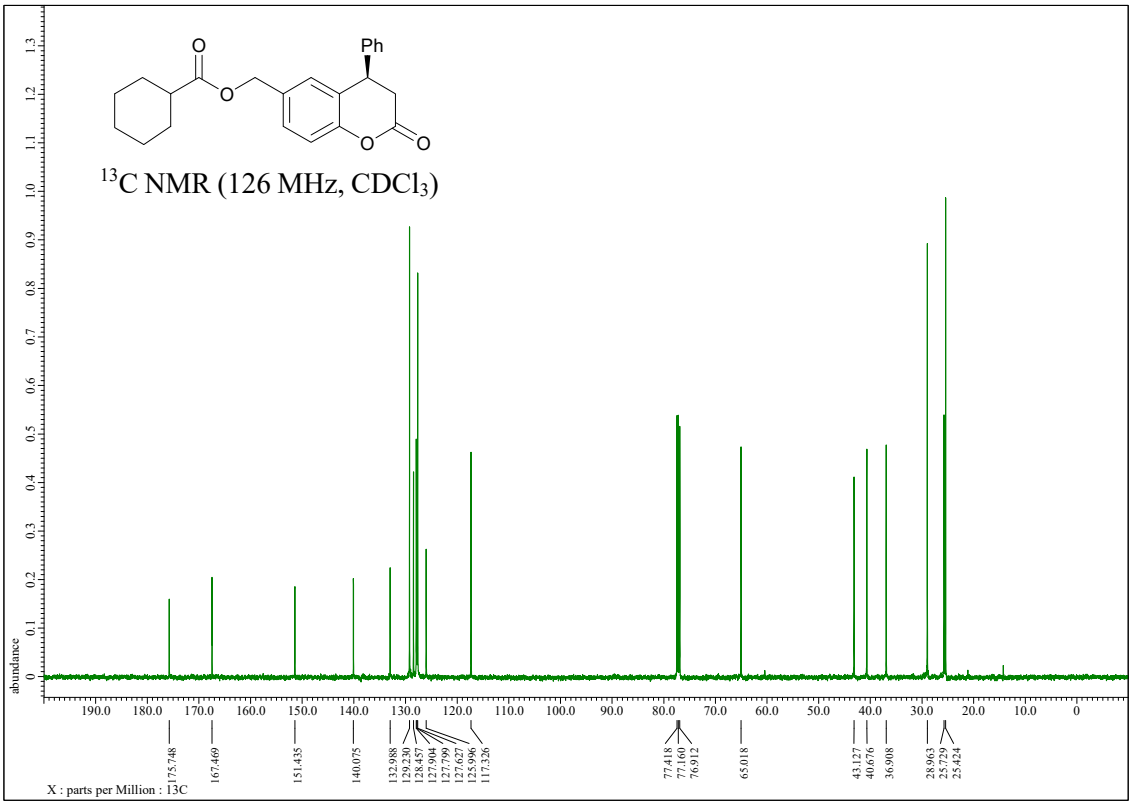
^{13}C NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl pivalate [(*R*)-**6e**]



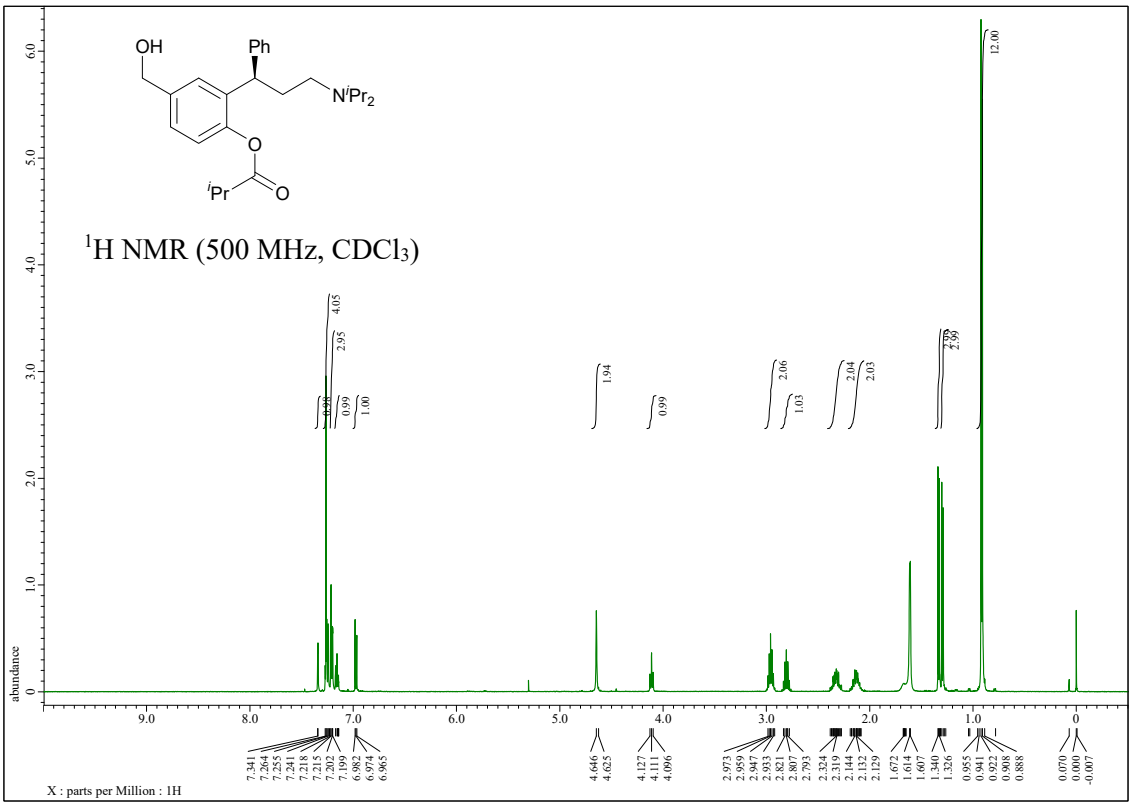
^{1}H NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl cyclohexanecarboxylate [(*R*)-**6f**]



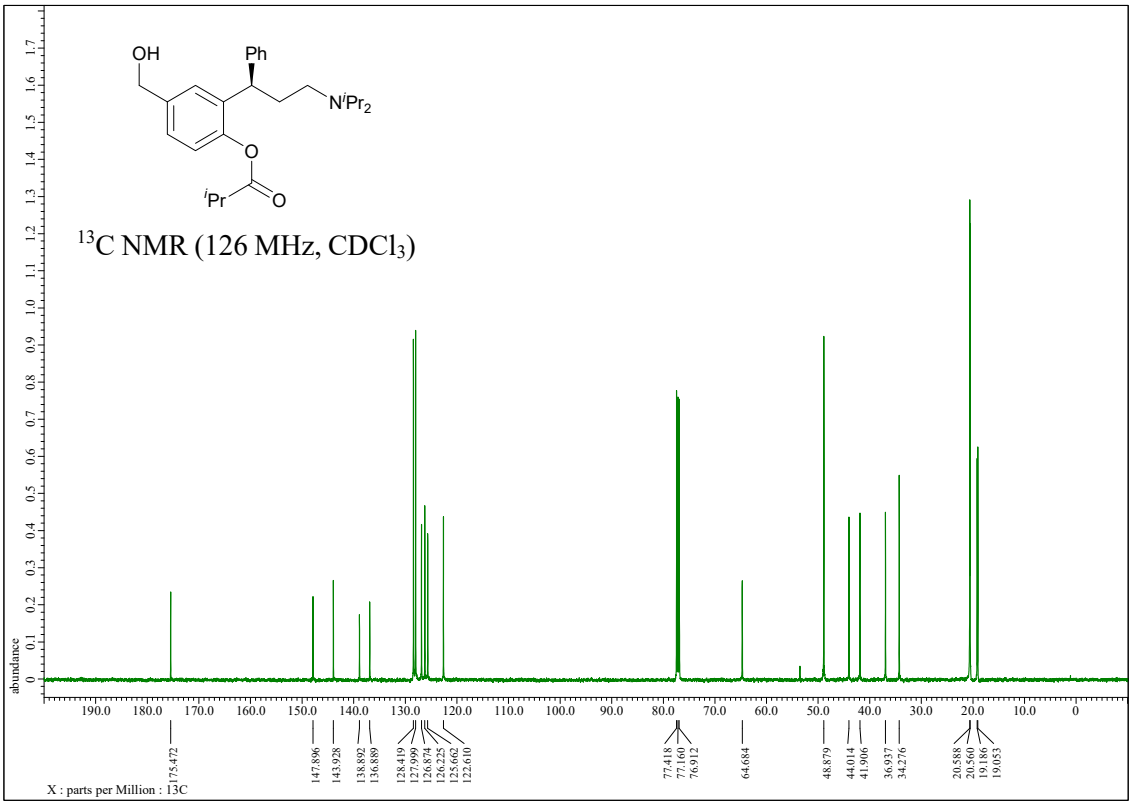
^{13}C NMR of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl cyclohexanecarboxylate [(*R*)-**6f**]



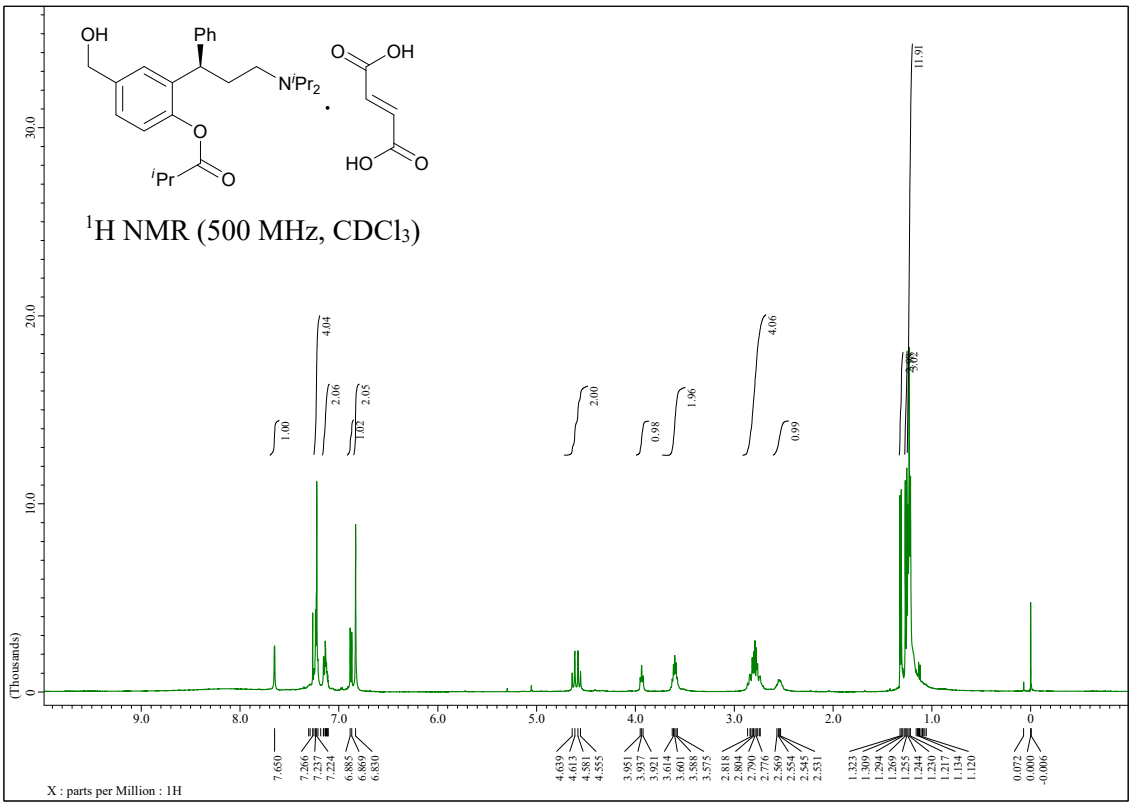
^{1}H NMR of (*R*)-(+)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (Fesoterodine) [(*R*)-**8**]



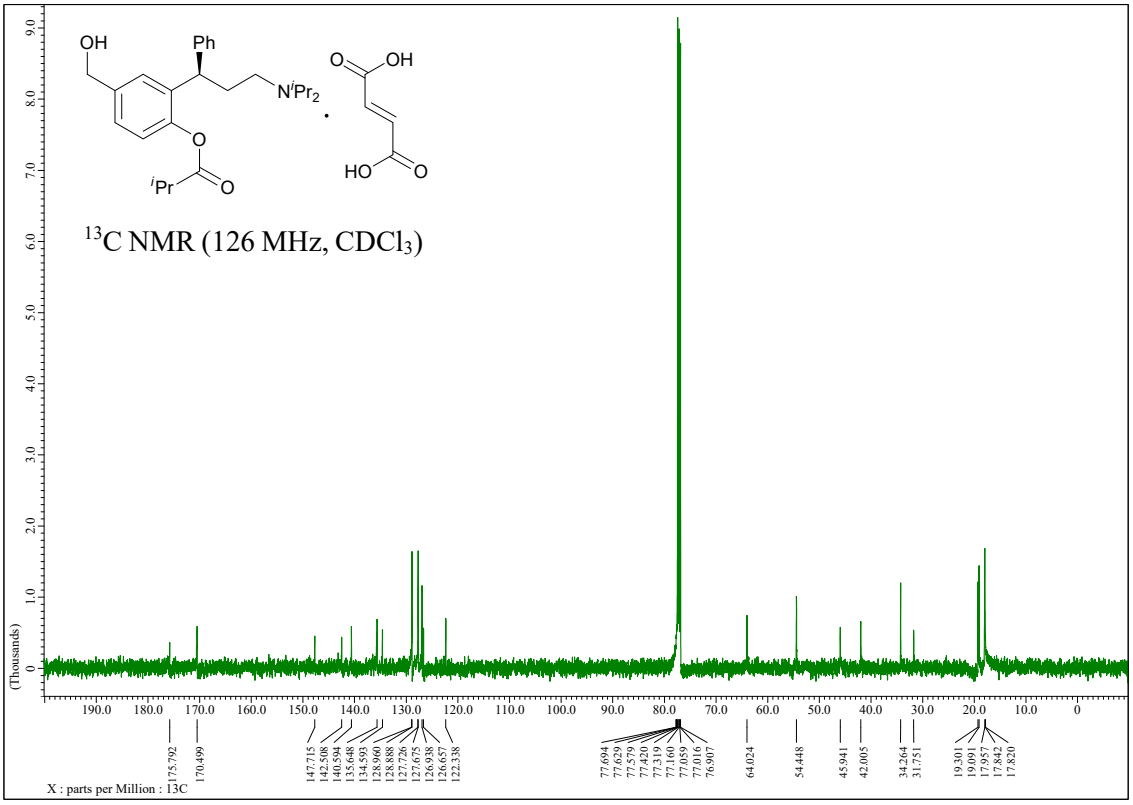
^{13}C NMR of (*R*)-(+)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (Fesoterodine) [(*R*)-**8**]



^{1}H NMR of (*R*)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester hydrogen fumarate (Toviaz)

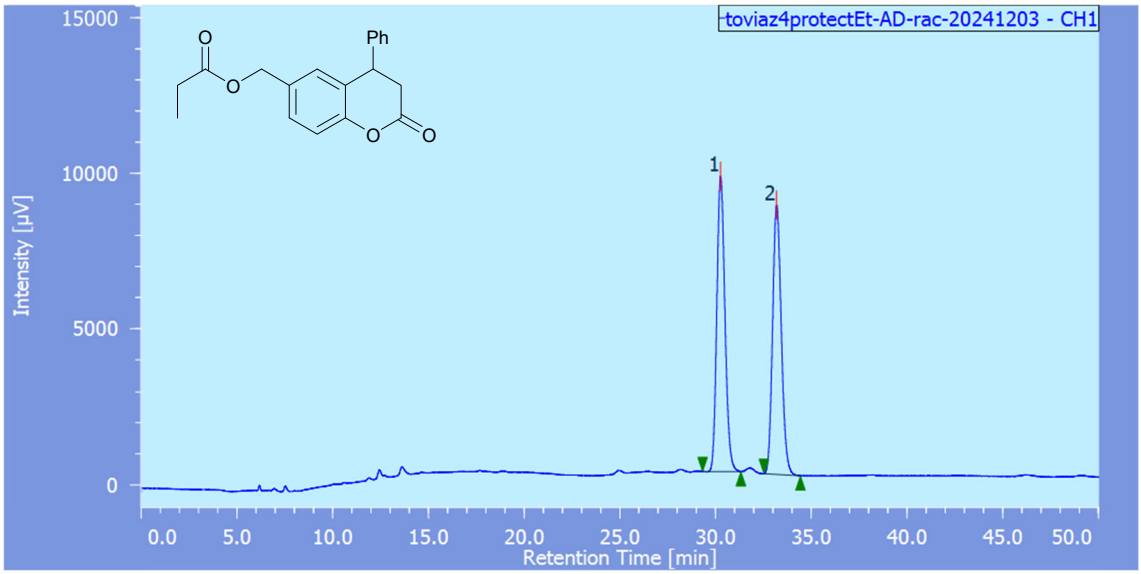


^{13}C NMR of (*R*)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester hydrogen fumarate (Toviaz)



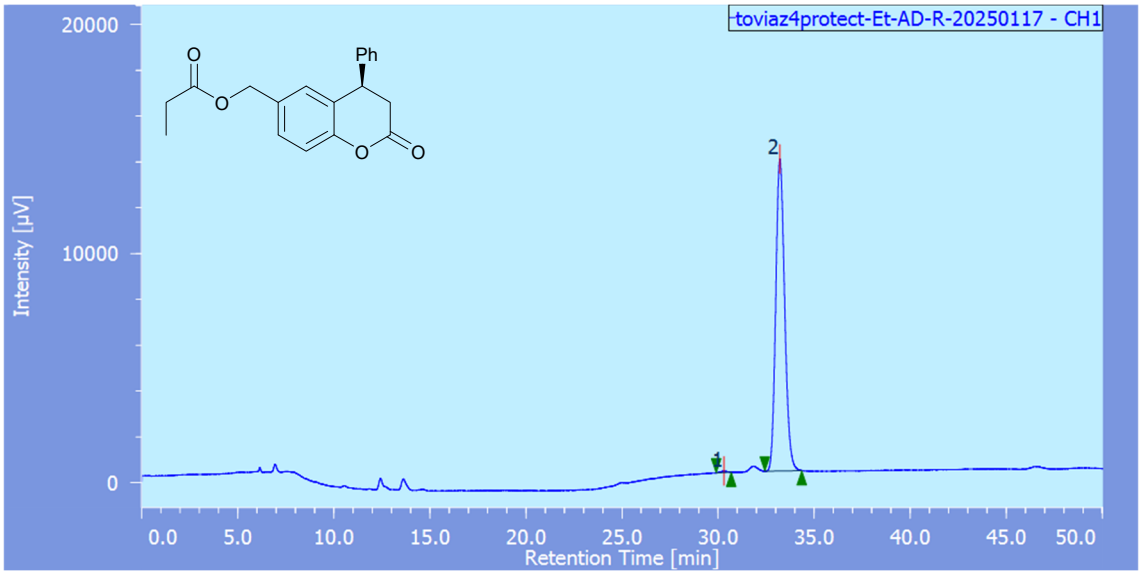
5. Chiral HPLC charts

HPLC chart of (±)-(2-oxo-4-phenylchroman-6-yl)methyl propionate [(±)-**6b**]



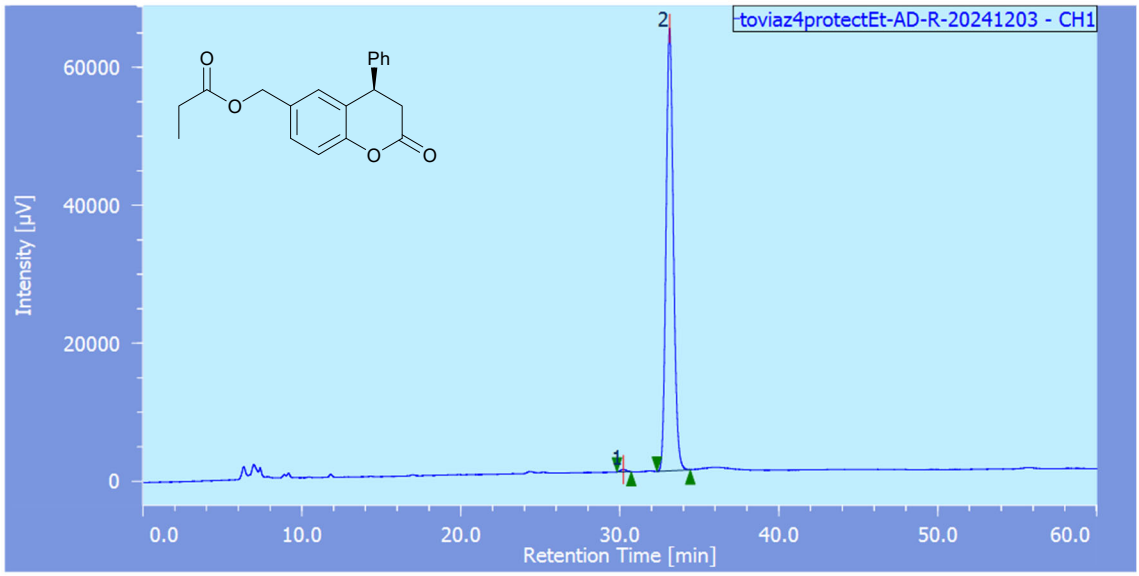
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	30.253	277852	9454	50.513
2	33.177	272210	8621	49.487

HPLC chart of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl propionate [(*R*)-**6b**]
(Product obtained by Procedure A)



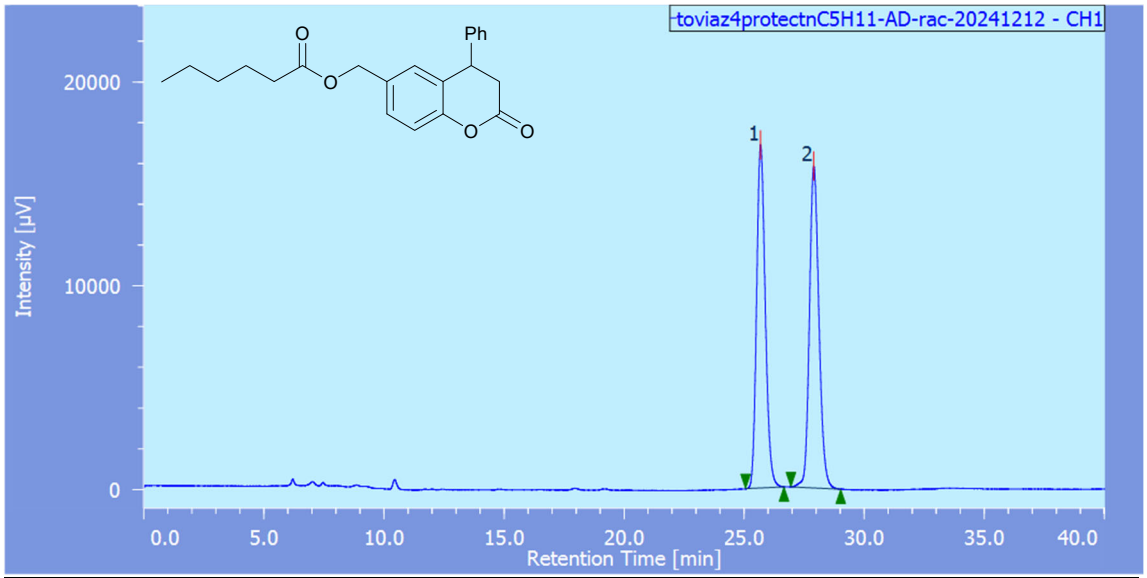
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	30.303	1506	65	0.343
2	33.207	437812	13611	99.657

HPLC chart of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl propionate [(*R*)-**6b**]
(Product obtained by Procedure B)



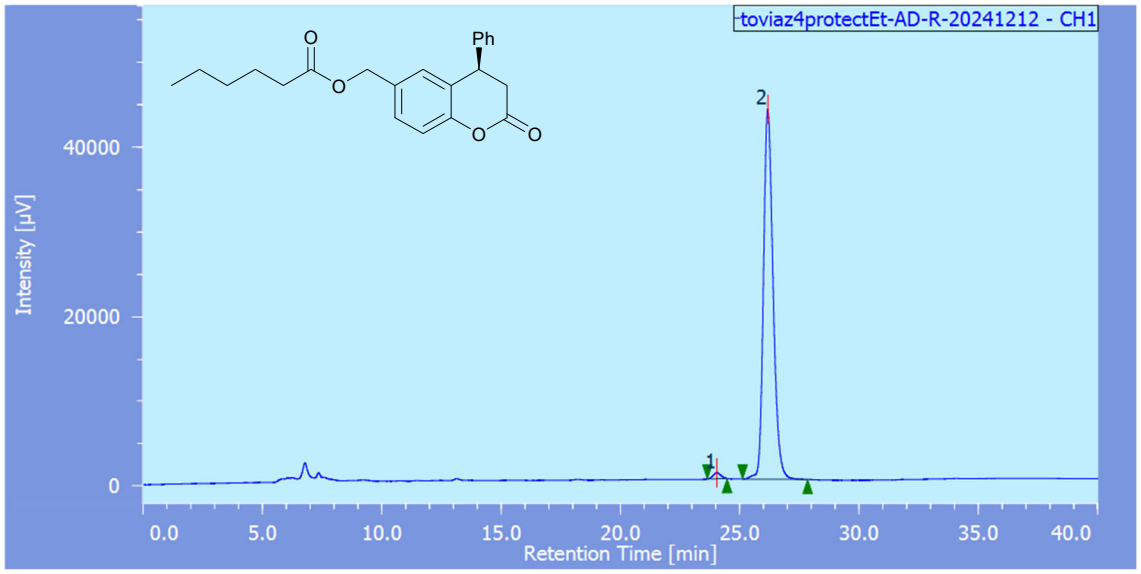
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	30.220	9064	346	0.438
2	33.123	2058872	64061	99.562

HPLC chart of (±)-(2-oxo-4-phenylchroman-6-yl)methyl hexanoate [(±)-**6c**]



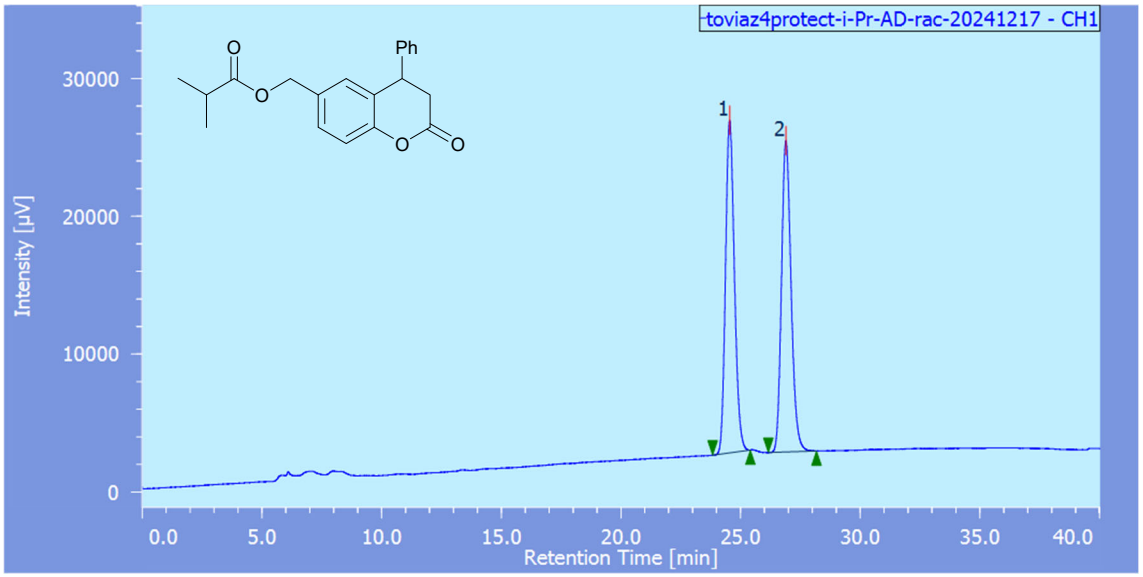
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	25.677	423349	16827	49.376
2	27.893	434051	15790	50.624

HPLC chart of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl hexanoate [(*R*)-**6c**]



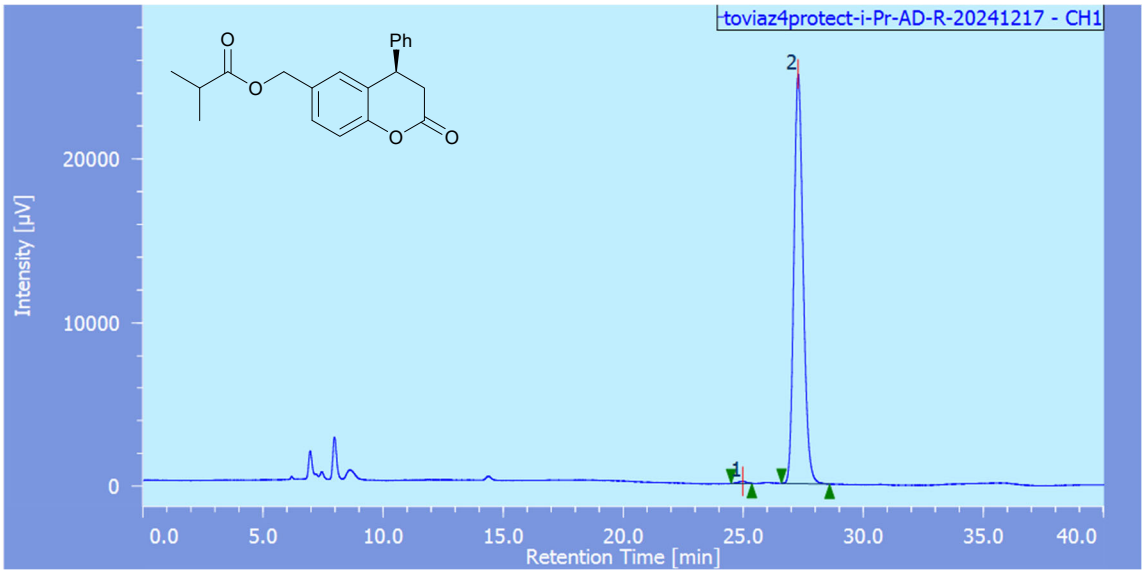
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	24.037	16215	703	1.307
2	26.170	1224733	43681	98.693

HPLC chart of (±)-(2-oxo-4-phenylchroman-6-yl)methyl isobutyrate [(±)-**6d**]



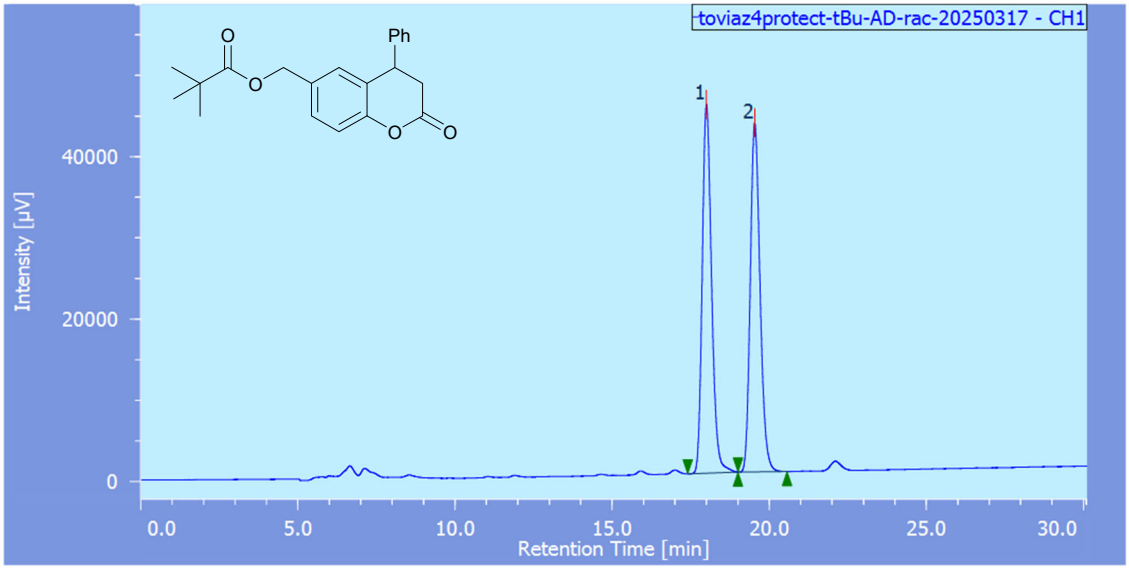
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	24.533	622805	24121	49.724
2	26.887	629730	22571	50.276

HPLC chart of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl isobutyrate [(*R*)-**6d**]



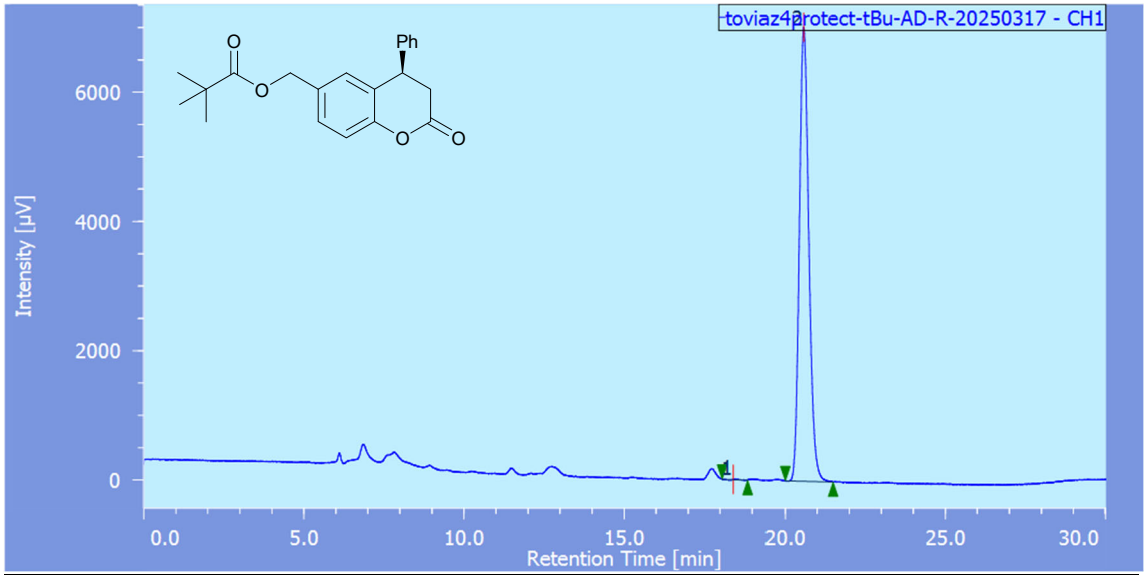
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	24.973	3154	131	0.467
2	27.280	671842	24991	99.533

HPLC chart of (±)-(2-oxo-4-phenylchroman-6-yl)methyl pivalate [(±)-**6e**]



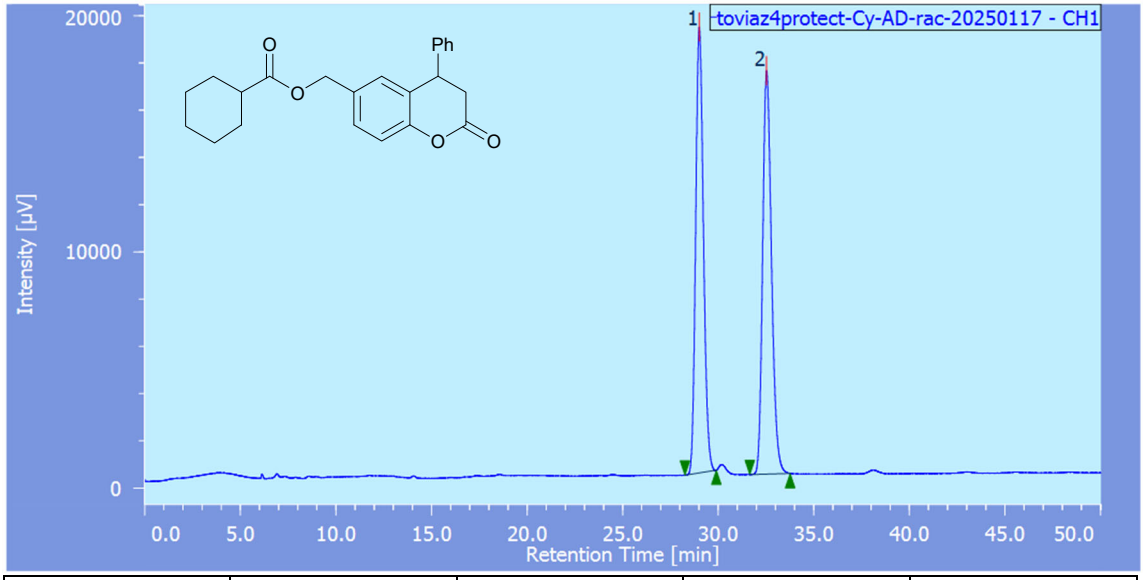
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	17.997	936796	45356	50.206
2	19.533	929105	42955	49.794

HPLC chart of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl pivalate [(*R*)-**6e**]



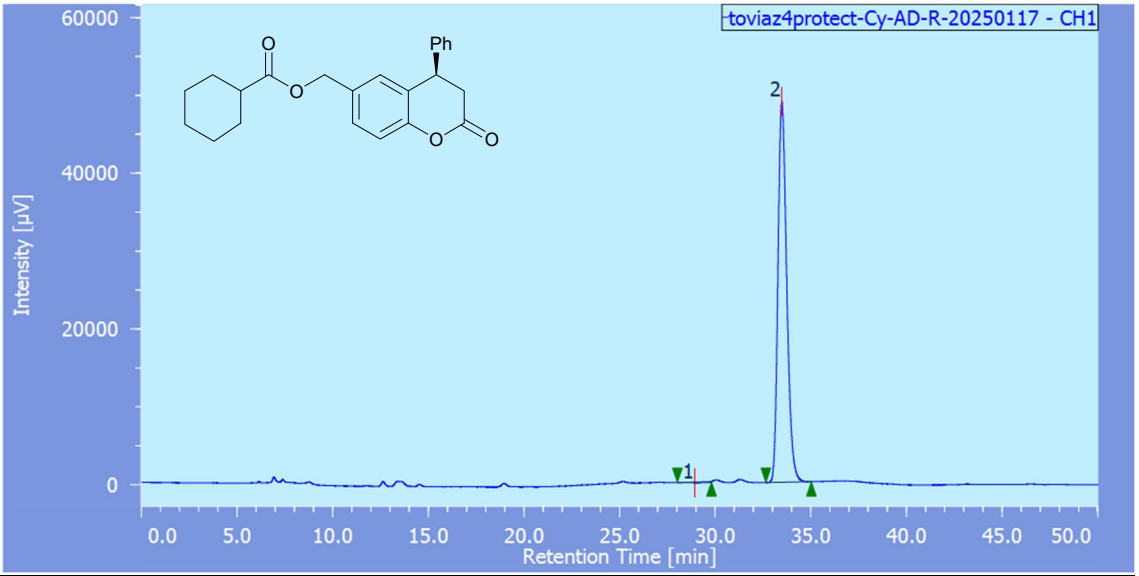
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	18.407	59	9	0.041
2	20.573	144451	7019	99.959

HPLC chart of (±)-(2-oxo-4-phenylchroman-6-yl)methyl cyclohexanecarboxylate [(±)-**6f**]



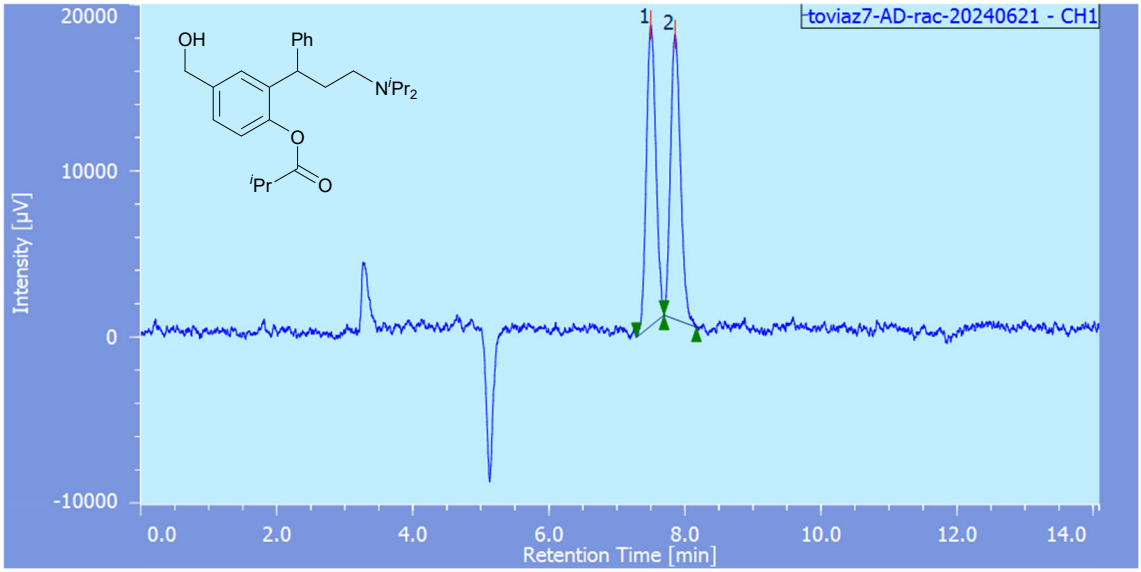
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area-
1	29.000	533244	18864	49.269
2	32.520	549072	17066	50.731

HPLC chart of (*R*)-(2-oxo-4-phenylchroman-6-yl)methyl cyclohexanecarboxylate [(*R*)-**6f**]



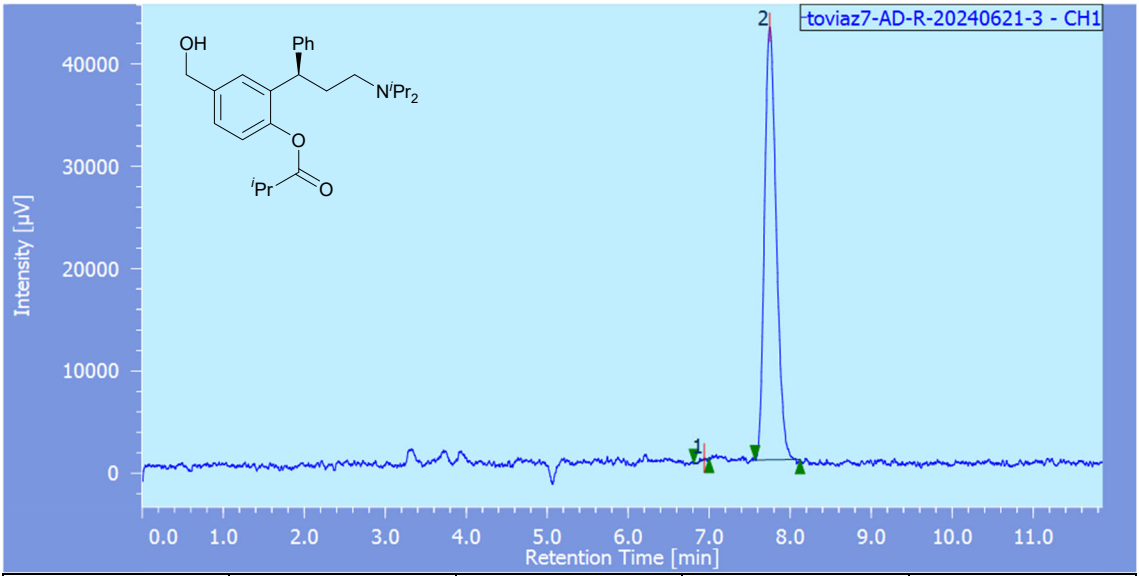
#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	28.927	6857	88	0.439
2	33.473	1554578	48889	99.561

HPLC chart of (±)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (Fesoterodine) [(±)-**8**]



#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	6.953	188526	21405	50.124
2	7.277	187596	20259	49.876

HPLC chart of (*R*)-(+)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (Fesoterodine) [(*R*)-**8**]



#	t_R [min]	Area [μV·sec]	Hight [μV]	Area%
1	7.087	1603	368	0.376
2	7.747	424532	42239	99.624

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