Catalytic Asymmetric Conjugate Addition of Grignard Reagents to Coumarins – Synthesis of Versatile Chiral Building Blocks

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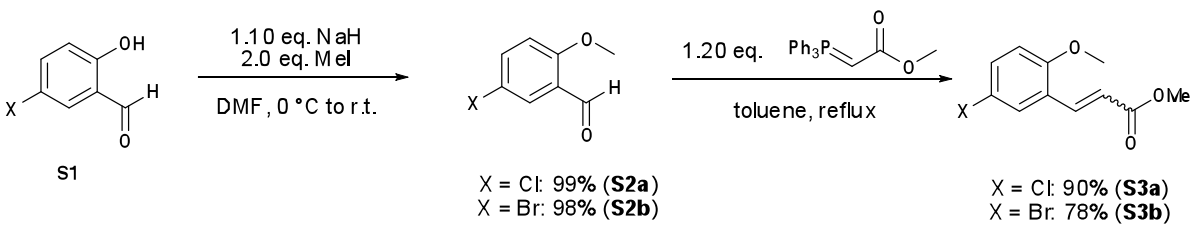
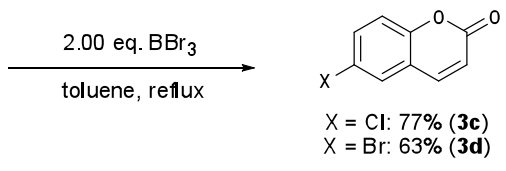
Supporting Information

1. General

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60,0.25 mm. Components were visualized by UV and cerium/molybdenum staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI^+) or a LTQ Orbitrap XL (ESI^+). ^1H, ^{19}F and ^{13}C NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively), a Varian VXR300 (300 and 75 MHz, respectively) or a Varian Gemini 200, using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^1H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantiomeric excesses (*ee* values) were determined by HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector and chiral columns as indicated. *Ee*s were determined by comparison of the racemic mixture with the corresponding chiral compounds or the mixtures of both R and S enantiomers. All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. CH_2Cl_2 was dried and distilled over calcium hydride, THF and Et_2O were dried and distilled over Na/benzophenone. Toluene was dried and distilled over Na. MTBE was dried and distilled over CaH_2. CuBr•SMe_2 was purchased from Sigma-Aldrich, and used without further purification. Grignard reagents were purchased from Sigma-Aldrich (MeMgBr, EtMgBr, *n*-HexMgBr, *i*-BuMgBr), all other Grignard reagents were prepared from the corresponding bromides with Mg in Et_2O. All Grignard reagents were titrated using *s*-BuOH and catalytic amounts of 1,10-phenanthroline before use. **L1** was prepared according to literature,[1] **L2-L5** were purchased from Sigma-Aldrich. All coumarins were commercially available, **3c** and **3d** were prepared (see below).

2.) Synthesis of starting materials

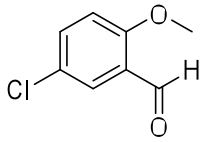




General Procedure for the methylation of salicylic aldehydes (synthesis of S2)

The corresponding salicylic aldehyde **S1** (1.00 eq.) was dissolved in DMF (Volume: 100 mL/10 mmol) and the solution cooled to 0 °C. Then, 1.00 eq. sodium hyride (as 60% suspension in mineral oil) was added slowly and the reaction mixture was stirred for 15 min at 0 °C (or until gas evolution ceased, respectively). Then, 2.00 eq. methyl iodide was added dropwise, and the reaction mixture was allowed to warm to 21 °C. When TLC showed full consumption of the starting material, the reaction was quenched by addition of water (100 mL/10 mmol). The mixture was washed with water and brine (50 mL / 10 mmol each), extracted with EtOAc (2x 50 mL / 10 mmol) and the organic phases was dried over $MgSO_4$. The crude product was used without further purification.

5-chloro-2-methoxybenzaldehyde (S2a)

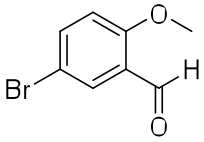


S2a

Following the general procedure for methylation of salicylic aldehydes, 2.167 g 5-chloro-2-methoxybenzaldehyde **S2a** (12.70 mmol, 99 % yield) was isolated as a pale yellow solid from the reaction of 5-chloro-2-hydroxybenzaldehyde (2.00 g, 12.77 mmol) with methyl iodide (1.597 ml, 25.5 mmol).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.64 (s, 1H), 7.46 – 7.34 (m, 1H), 6.87 (d, J = 8.8 Hz, 1H), 3.84 (s, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ 188.12, 160.07, 135.16, 127.53, 126.00, 125.37, 113.18, 55.79.
HR-MS: (ESI^+) calculated for $C_8H_8ClO_2$ [$M+H^+$]: 171.0207, found: 171.0204.

5-bromo-2-methoxybenzaldehyde (S2b)



S2b

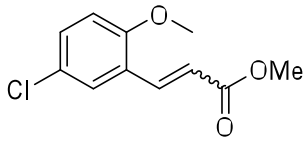
Following the general procedure for methylation of salicylic aldehydes, 2.097 g 5-bromo-2-methoxybenzaldehyde **S2b** (9,75 mmol, 98 % yield) was isolated as a pale yellow solid from the reaction of 5-bromo-2-hydroxybenzaldehyde (2.00 g, 9.95 mmol) with methyl iodide (1.244 ml, 19.90 mmol).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.83 (d, J = 2.6 Hz, 1H), 7.56 (dd, J = 8.9, 2.6 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 3.86 (s, 3H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 188.13, 160.57, 138.12, 130.70, 125.83, 113.63, 113.19, 55.82.
HR-MS: (ESI^+) calculated for $C_8H_8BrO_2$ [$M+H^+$]: 214.9702, found: 214.9696.

General procedure for the Wittig reaction of methyl 2-(triphenylphosphoranylidene)acetate with salicylic aldehydes

Salicylic aldehyde **S2** (1.00 eq.) was dissolved in toluene (Volume: 50 mL/ 10 mmol), and 1.20 eq. methyl 2-(triphenylphosphoranylidene)acetate was added to the mixture. This was heated to 110 °C until TLC showed full conversion of the starting material. After cooling, diethylether (50 mL/10 mmol) was added to precipitate any triphenylphosphinoxide, which was subsequently filtered off. All volatiles were removed under reduced pressure to give the crude products, which were purified by column chromatography (SiO_2, pentane/EtOAc 8:2) to yield **S3** as a mixture of E/Z isomers.

Methyl 3-(5-chloro-2-methoxyphenyl)acrylate (S3a)

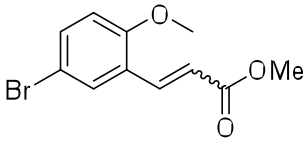


S3a

Following the general procedure for the Wittig reaction with salicylic aldehydes, 2.384 g methyl 3-(5-chloro-2-methoxyphenyl)acrylate **S3a** (10.52 mmol, 90 % yield) was isolated as a white solid from the reaction of 5-chloro-2-methoxybenzaldehyde **S2a** (2.00 g, 11.72 mmol) with methyl 2-(triphenylphosphoranylidene)acetate (4.70 g, 14.07 mmol). (R_f = 0.80 in pentane/EtOAc 8:2).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.2 Hz, 1H), 7.41 (d, *J* = 2.6 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.45 (d, *J* = 16.2 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ 167.25, 156.61, 138.50, 130.70, 129.68, 127.97, 125.57, 124.64, 119.30, 112.28, 55.62, 51.50.
HR-MS: (ESI$^+$) calculated for $C_{11}H_{12}ClO_3$ [M+H$^+$]: 227.0470, found: 227.0465.

Methyl 3-(5-bromo-2-methoxyphenyl)acrylate (S3b)



S3b

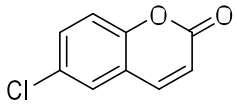
Following the general procedure for the Wittig reaction with salicylic aldehydes, 1.977 g methyl 3-(5-bromo-2-methoxyphenyl)acrylate **S3b** (7.29 mmol, 78 % yield) was isolated as a white solid from the reaction of 5-bromo-2-methoxybenzaldehyde **S2b** (2.00 g, 9.30 mmol) with methyl 2-(triphenylphosphoranylidene)acetate (3.73 g, 11.16 mmol). (R_f = 0.65 in pentane/EtOAc 8:2).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.87 (d, *J* = 16.2 Hz, 1H), 7.57 (d, *J* = 2.5 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.46 (d, *J* = 16.2 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 167.32, 157.14, 138.52, 138.49, 133.68, 130.99, 125.20, 119.39, 112.85, 112.78, 55.66, 51.61.
HR-MS: (ESI$^+$) calculated for $C_{11}H_{12}BrO_3$ [M+H$^+$]: 270.9964, found: 270.9969.

General procedure for the synthesis of coumarin derivatives 3c, 3d from methyl acrylates

According to a modified literature procedure,[2] 1.00 eq. methyl acrylate **S3** was dissolved in toluene (Volume: 50 mL/ 5 mmol) and the mixture cooled to 0 °C. Then, 2.00 eq. boron tribromide was added dropwise. The reaction mixture was heated to 110 °C for 4h. After cooling to room temperature, water (50 mL / 5 mmol) was added and the aqueous layer was extracted twice with $CHCl_3$ (30 mL / 5 mmol). After drying over $MgSO_4$ and removal of all volatiles under reduced pressure, the crude mixture was purified by column chromatography (SiO_2, pentane/EtOAc 8:2) to yield the desired coumarins **3c** or **3d**.

6-chloro-2H-chromen-2-one (3c)

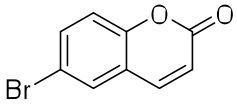


3c

Following the general procedure for the synthesis of coumarin derivatives from esters, 0.613 g 6-chloro-2H-chromen-2-one **3c** (3.40 mmol, 77 % yield) was isolated as a pale yellow solid from the reaction of methyl 3-(5-chloro-2-methoxyphenyl)acrylate **S3a** (1.00 g, 4.41 mmol) with boron tribromide (0.834 ml, 8.82 mmol). (R_f = 0.75 in pentane/EtOAc 8:2).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.63 (d, *J* = 9.6 Hz, 1H), 7.44 (dt, *J* = 4.9, 2.3 Hz, 2H), 7.30 – 7.18 (m, 1H), 6.44 (d, *J* = 9.6 Hz, 1H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 159.94, 152.32, 142.15, 131.65, 129.58, 127.05, 119.72, 118.20, 117.74.
HR-MS: (ESI^+) calculated for $C_9H_6ClO_2$ [$M+H^+$]: 181.0051, found: 181.0051.

6-bromo-2H-chromen-2-one (3d)



3d

Following the general procedure for the synthesis of coumarin derivatives from esters, 0.522 g 6-bromo-2H-chromen-2-one **3d** (2.320 mmol, 63 % yield) was isolated as an orange solid from the reaction of methyl 3-(5-bromo-2-methoxyphenyl)acrylate **S3b** (1.00 g, 3.69 mmol) with boron tribromide (0.697 ml, 7.38 mmol). (R_f = 0.90 in pentane/EtOAc 8:2).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.68 – 7.55 (m, 3H), 7.29 – 7.15 (m, 1H), 6.45 (d, *J* = 9.6 Hz, 1H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 164.90, 159.88, 142.04, 134.54, 130.13, 120.28, 118.60, 117.83, 116.94.
HR-MS: (ESI^+) calculated for $C_9H_6BrO_2$ [$M+H^+$]: 224.9546, found: 224.9548.

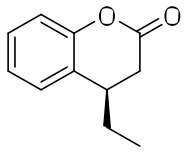
3. General Procedure for the asymmetric Cu-catalyzed conjugate addition of Grignard reagents to Coumarins

Copper Bromide dimethyl sulfide complex (5.0 mol %) and 5.5 mol % (R,S_{Fe})-reverse Josiphos (**L4**) were dissolved in MTBE (Volume: 15 mL / 1 mmol substrate) and the mixture was stirred at room temperature for 15 min. Then, the mixture was cooled to -72 °C and subsequently 2.5 eq. of the appropriate Grignard reagent was added. The mixture stirred for and additional 10 min at -72 °C. Then, a solution of 1.00 eq. of the appropriate coumarin **1** or **3** in MTBE (Volume: 5 mL / 1 mmol) was added dropwise over a period of 1 h. The reaction mixture was stirred until TLC showed full conversion. Then, the reaction was quenched by adding HCl solution in Et_2O (2.0 mL / 1 mmol substrate) at -72 °C. Then, 20 mL / 1 mmol saturated aqueous NH_4Cl solution was added at low temperature and the reaction mixture was allowed to warm to room temperature. Then, it was diluted with Et_2O (30 mL / 1 mmol). After washing two times with aqueous saturated NH_4Cl solution (2x 50 mL / 1 mmol) and reextraction of the aqueous layer with Et_2O (20 mL / 1 mmol), the combined organic layers were dried over $MgSO_4$. All volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, EtOAc/Pentane) to yield **2** or **4**.

General Procedure for the synthesis of racemic products of the Cu-catalyzed conjugate addition to Coumarins

1.00 eq. of the appropriate coumarin (0,485 mmol) and 30.0 mol % copper bromide dimethyl sulfide complex (0.030 g, 0.145 mmol) and 60.0 mol % triphenylphosphine (0.076 g, 0.291 mmol) were dissolved in MTBE (Volume: 15 ml), cooled to -40 °C and stirred for 10 min. Then, 2.50 eq. of the appropriate Grignard reagent (1.212 mmol) was added dropwise. The reaction mixture was stirred overnight at -40 °C. Then, the reaction was quenched by addition of 2.0 mL HCl in Et_2O (2N). Then, 20 mL saturated aqueous NH_4Cl solution was added at low temperature and the reaction mixture was allowed to warm to room temperature. Then, it was diluted with Et_2O (30 mL). After washing two times with aqueous saturated NH_4Cl solution (2x 50 mL) and reextraction of the aqueous layer with Et_2O (20 mL), the combined organic layers were dried over $MgSO_4$. All volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, EtOAc/Pentane) to yield the desired compounds.

(R)-4-ethylchroman-2-one (2a)



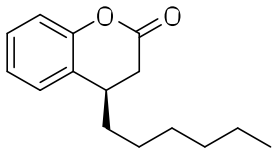
2a

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.135 g (R)-4-ethylchroman-2-one **2a** (0.768 mmol, 96% yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) with ethylmagnesium bromide solution (3.0 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.68 in pentane/EtOAc 10:1, 95% *ee*).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 7.21 – 7.15 (m, 1H), 7.11 (dd, *J* = 10.7, 4.2 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.78 (qd, *J* = 15.8, 4.9 Hz, 2H), 1.64 (tdd, *J* = 14.0, 11.3, 6.2 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.48, 151.22, 128.17, 127.84, 126.42, 124.20, 117.00, 36.52, 34.35, 27.50, 11.11.
HR-MS: (ESI^+) calculated for $C_{11}H_{12}O_2Na$ [$M+Na^+$]: 199.0730, found: 199.0730.
$[\alpha]_D^{20}$ = 53.6 (c = 1.0 in $CHCl_3$)
$[\alpha]_D^{20}$ = 114.6 (c = 1.0 in C_6H_6)
The two $[\alpha]_D^{20}$ values have been used for determination of the absolute configuration by comparison with literature data.[3, 4]
ee determination by chiral HPLC (Chiralpak AD: n-heptane/2-propanol 95:5, 40 °C isotherm, 220 nm), retention times: 8.3 min (major), 8.9 min (minor).

(R)-4-hexylchroman-2-one (2c)

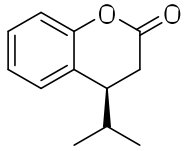


2c

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.177 g (R)-4-hexylchroman-2-one **2c** (0.760 mmol, 95 % yield) was isolated as a pale yellow solid from the reaction of 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) with n-hexylmagnesium bromide solution (2.0 molar in Et_2O) (1.00 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.78 in pentane/EtOAc 10:1, 99% *ee*).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.30 – 6.95 (m, 4H), 3.04 – 2.87 (m, 1H), 2.81 – 2.61 (m, 2H), 1.66 – 1.45 (m, 2H), 1.44 – 1.02 (m, 8H), 0.84 (t, *J* = 6.4 Hz, 3H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.26, 151.09, 127.99, 127.65, 126.72, 124.10, 116.85, 34.94, 34.54, 34.47, 31.47, 28.94, 26.44, 22.41, 13.88.
HR-MS: (ESI^+) calculated for $C_{15}H_{20}O_2Na$ [$M+Na^+$]: 255.1356, found: 255.1356.
$[\alpha]_D^{20}$ = 47.6 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 10.5 min (minor), 12.4 min (major).

(S)-4-isopropylchroman-2-one (2d)



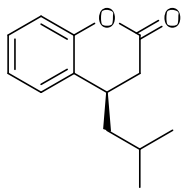
2d

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.145 g (S)-4-isopropylchroman-2-one **2d** (0.760 mmol, 95 % yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) with isopropylmagnesium bromide solution (1.5 molar in Et_2O) (1.33 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.90 in pentane/EtOAc 10:1, 63% *ee*).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 1H), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.11 – 7.04 (m, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 2.85 (dd, *J* = 10.7, 8.9 Hz, 1H), 2.78 – 2.63 (m, 2H), 1.82 (dd, *J* = 13.5, 6.7 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.65, 151.46, 128.84, 128.09, 125.30, 123.87, 116.81, 41.61, 32.05, 31.96, 20.00, 19.00.
HR-MS: (ESI^+) calculated for $C_{12}H_{15}O_2$ [$M+H^+$]: 191.1067, found: 191.1066.
$[\alpha]_D^{20}$ = 21.6 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 15.5 min (major), 17.2 min (minor).

(R)-4-isobutylchroman-2-one (2e)

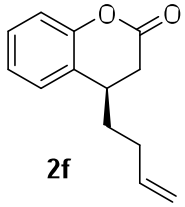


2e

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.118 g (R)-4-isobutylchroman-2-one **2e** (0.576 mmol, 72 % yield) was isolated as a pale yellow solid from the reaction of 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) with isobutylmagnesium bromide solution (2.0 molar in Et_2O) (1.00 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.78 in pentane/EtOAc 10:1, 93% *ee*).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 1H), 7.20 – 7.15 (m, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 3.07 (dd, *J* = 5.3, 3.9 Hz, 1H), 2.76 (ddd, *J* = 19.5, 15.8, 4.7 Hz, 2H), 1.63 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.42 (dtd, *J* = 21.2, 13.9, 7.5 Hz, 2H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.34, 151.20, 128.12, 127.48, 127.17, 124.25, 117.09, 43.62, 34.69, 32.76, 24.84, 22.59, 22.22.
HR-MS: (ESI^+) calculated for $C_{13}H_{17}O_2$ [$M+H^+$]: 205.1223, found: 205.1223.
$[\alpha]_D^{20}$ = 72.0 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 13.8 min (major), 15.4 min (minor).

(R)-4-(but-3-enyl)chroman-2-one (2f)

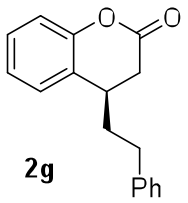


2f

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.106 g (R)-4-(but-3-en-1-yl)-3,4-dihydronaphthalen-2(1H)-one **2f** (0.528 mmol, 66 % yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) with butenylmagnesium bromide solution (2.38 molar in Et_2O) (0.84 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.85 in pentane/EtOAc 10:1, 93% *ee*).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.38 – 6.93 (m, 4H), 5.93 – 5.62 (m, 1H), 5.24 – 4.83 (m, 2H), 3.10 – 2.93 (m, 1H), 2.91 – 2.61 (m, 2H), 2.25 – 1.95 (m, 2H), 1.79 – 1.55 (m, 2H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.20, 151.23, 137.18, 128.27, 127.76, 126.42, 124.26, 117.09, 115.61, 34.57, 34.28, 33.51, 30.54.
HR-MS: (ESI^+) calculated for $C_{13}H_{14}O_2Na$ [$M+Na^+$]: 225.0886, found: 225.0884.
$[\alpha]_D^{20}$ = 72.6 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OD-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 210 nm), retention times: 20.4 min (minor), 21.6 min (major).

(R)-4-phenethylchroman-2-one (2g)

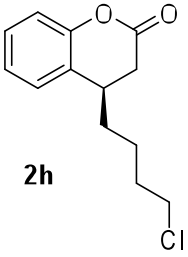


2g

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.126 g (R)-4-phenethylchroman-2-one **2g** (0.499 mmol, 73% yield) was isolated as an orange solid from the reaction of 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) with phenylethylmagnesium bromide solution (1.50 molar in Et_2O) (1.14 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.65 in pentane/EtOAc 10:1, 94% *ee*).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 3H), 7.25 – 7.04 (m, 6H), 3.11 – 2.98 (m, 1H), 2.90 – 2.80 (m, 2H), 2.79 – 2.58 (m, 2H), 2.04 – 1.85 (m, 2H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.06, 151.17, 140.68, 128.39, 128.25, 128.14, 127.68, 126.30, 126.01, 124.23, 117.02, 35.86, 34.48, 34.35, 32.56.
HR-MS: (ESI^+) calculated for $C_{17}H_{16}O_2Na$ [$M+Na^+$]: 275.1043, found: 275.1042.
$[\alpha]_D^{20}$ = 57.0 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak AD: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 8.3 min (minor), 9.0 min (major).

(R)-4-(4-chlorobutyl)chroman-2-one (2h)

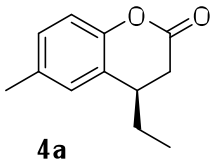


2h

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.075 g (R)-4-(4-chlorobutyl)chroman-2-one **2h** (0.315 mmol, 46 % yield) was isolated as a yellow oil from the reaction of 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) with (4-chlorobutyl)magnesium bromide solution (2.30 molar in Et_2O) (0.744 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.65 in pentane/EtOAc 10:1, 98% *ee*).

The product contains traces of dehalogenated product.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.11 (td, *J* = 7.4, 1.1 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 3.52 (dt, *J* = 6.5, 5.1 Hz, 2H), 2.99 (dd, *J* = 5.8, 3.8 Hz, 1H), 2.80 (ddd, *J* = 19.7, 15.9, 4.8 Hz, 2H), 1.77 (ddd, *J* = 7.7, 6.1, 3.7 Hz, 2H), 1.68 – 1.52 (m, 4H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.20, 151.21, 128.39, 127.79, 126.33, 124.35, 117.18, 44.58, 35.10, 34.75, 33.87, 32.25, 24.05.
HR-MS: (ESI^+) calculated for $C_{13}H_{16}O_2$ [$M+H^+$]: 239.0833, found: 239.0842.
$[\alpha]_D^{20}$ = 84.6 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 26.0 min (major), 27.0 min (minor).

(R)-4-ethyl-6-methylchroman-2-one (4a)

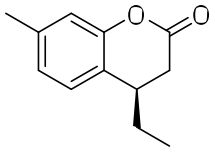


4a

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.140 g (R)-4-ethyl-6-methylchroman-2-one **4a** (0.736 mmol, 92 % yield) was isolated as a pale yellow oil from the reaction of 6-methyl-2H-chromen-2-one **3a** (0.128 g, 0.8 mmol) with ethylmagnesium bromide solution (3.00 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.85 in pentane/EtOAc 10:1, 94% *ee*).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.09 – 6.85 (m, 3H), 2.90 – 2.78 (m, 1H), 2.77 – 2.61 (m, 2H), 2.30 (s, 3H), 1.70 – 1.44 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.51, 149.05, 133.63, 128.50, 128.15, 126.03, 116.53, 36.42, 34.26, 27.43, 20.59, 11.00.
HR-MS: (ESI^+) calculated for $C_{12}H_{15}O_2$ [$M+H^+$]: 191.1067, found: 191.1067.
$[\alpha]_D^{20}$ = 19.0 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 15.8 min (major), 17.3 min (minor).

(R)-4-ethyl-7-methylchroman-2-one (4b)

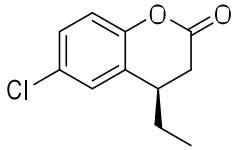


3b

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.141 g (R)-4-ethyl-7-methylchroman-2-one **4b** (0.741 mmol, 93 % yield) was isolated as a pale yellow oil from the reaction of 7-methyl-2H-chromen-2-one **3b** (0.128 g, 0.8 mmol) with ethylmagnesium bromide solution (3.00 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.70 in pentane/EtOAc 10:1, 97% *ee*).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 7.7 Hz, 1H), 6.90 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.84 (s, 1H), 2.89 – 2.81 (m, 1H), 2.74 (qd, *J* = 15.7, 4.9 Hz, 2H), 2.31 (s, 3H), 1.59 (qt, *J* = 13.9, 7.2 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.54, 151.05, 138.28, 127.47, 124.84, 123.22, 117.30, 36.09, 34.45, 27.50, 20.89, 11.00.
HR-MS: (ESI^+) calculated for $C_{12}H_{15}O_2$ [$M+H^+$]: 191.1067, found: 191.1062.
$[\alpha]_D^{20}$ = 37.0 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 16.9 min (major), 18.2 min (minor).

(R)-6-chloro-4-ethylchroman-2-one (4c)

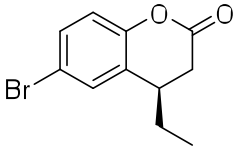


4c

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.135 g (R)-6-chloro-4-ethylchroman-2-one **4c** (0.641 mmol, 80 % yield) was isolated as an orange oil from the reaction of 6-chloro-2H-chromen-2-one **3c** (0.144 g, 0.8 mmol), which was added as a solution in 7 mL MTBE/CH_2Cl_2 (5:2), with ethylmagnesium bromide solution (3.00 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.55 in pentane/EtOAc 10:1, 95% *ee*).

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 2.93 – 2.83 (m, 1H), 2.82 – 2.66 (m, 2H), 1.73 – 1.47 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ 167.55, 149.73, 129.16, 128.09, 127.57, 118.27, 97.86, 36.36, 33.81, 27.23, 10.91.
HR-MS: (ESI^+) calculated for $C_{11}H_{12}ClO_2$ [$M+H^+$]: 211.0520, found: 211.0517.
$[\alpha]_D^{20}$ = 16.8 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 27.0 min (major), 33.1 min (minor).

(R)-6-bromo-4-ethylchroman-2-one (4d)



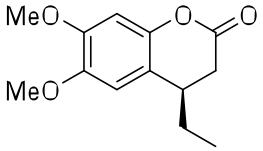
4d

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.175 g (R)-6-bromo-4-ethylchroman-2-one **4d** (0.686 mmol, 86 % yield) was isolated as a yellow oil from the reaction of 6-bromo-2H-chromen-2-one **3d** (0.180 g, 0.8 mmol), which was added as a solution in 8 mL MTBE/CH_2Cl_2 (5:3), with ethylmagnesium bromide solution (3.00 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.55 in pentane/EtOAc 10:1, 96% *ee*).

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.41 – 7.23 (m, 2H), 6.90 (d, *J* = 8.5 Hz, 1H), 2.94 – 2.81 (m, 1H), 2.81 – 2.61 (m, 2H), 1.60 (td, *J* = 14.5, 7.0 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (50 MHz, $CDCl_3$) δ 167.44, 150.25, 131.04, 130.48, 128.54, 118.67, 116.68, 36.31, 33.80, 27.26, 10.93.
HR-MS: (ESI$^+$) calculated for $C_{11}H_{12}BrO_2$ [M+H$^+$]: 255.0015, found: 255.0010.
$[\alpha]_D^{20}$ = 5.40 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 24.1 min (major), 28.4 min (minor).

(R)-4-ethyl-6,7-dimethoxychroman-2-one (4e)

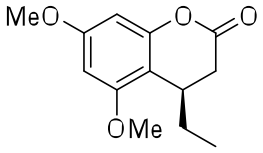


4e

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.063 g (R)-4-ethyl-6,7-dimethoxychroman-2-one **4e** (0.267 mmol, 55 % yield) was isolated as a brown oil from the reaction of 6,7-dimethoxy-2H-chromen-2-one **3e** (0.100 g, 0.485 mmol), which was added as a solution in 5.0 mL MTBE/CH_2Cl_2 (1:1), with ethylmagnesium bromide solution (3.00 molar in Et_2O) (0.404 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 8:2, R_f = 0.50 in pentane/EtOAc 8:2, 64% *ee*).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.60 (s, 1H), 3.85 (d, *J* = 3.3 Hz, 6H), 2.88 – 2.63 (m, 3H), 1.60 (dd, *J* = 13.2, 6.6 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.56, 148.72, 145.46, 145.00, 117.27, 110.41, 101.28, 56.41, 56.07, 36.34, 34.49, 27.80, 11.12.
HR-MS: (ESI$^+$) calculated for $C_{13}H_{17}O_4$ [M+H$^+$]: 237.1121, found: 237.1118.
$[\alpha]_D^{20}$ = 20.8 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 32.0 min (major), 44.1 min (minor).

(R)-4-ethyl-5,7-dimethoxychroman-2-one (4f)



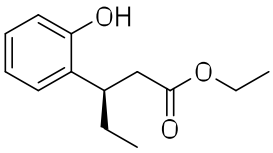
4f

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.125 g (R)-4-ethyl-5,7-dimethoxychroman-2-one **4f** (0.528 mmol, 66 % yield) was isolated as a pale yellow solid from the reaction of 5,7-dimethoxy-2H-chromen-2-one **3f** (0.165 g, 0.8 mmol), which was added as a solution in 5.0 mL MTBE/CH_2Cl_2 (1:1), with ethylmagnesium bromide solution (3.00 molar in Et_2O) (0.667 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 8:2, R_f = 0.75 in pentane/EtOAc 8:2, 48% *ee*).

^{1}H NMR: (201 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 7.8, 2.3 Hz, 2H), 3.78 (d, *J* = 6.2 Hz, 6H), 3.30 – 3.08 (m, 1H), 2.71 (qd, *J* = 15.9, 4.1 Hz, 2H), 1.66 – 1.33 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.64, 159.96, 157.28, 152.52, 107.63, 94.69, 93.82, 55.53, 55.42, 33.82, 30.22, 27.30, 11.03.
HR-MS: (ESI$^+$) calculated for $C_{13}H_{17}O_4$ [M+H$^+$]: 237.1121, found: 237.1121.
$[\alpha]_D^{20}$ = 10.6 (c = 1.0 in $CHCl_3$)

ee determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 24.0 min (major), 27.4 min (minor).

(R)-ethyl 3-(2-hydroxyphenyl)pentanoate (6)

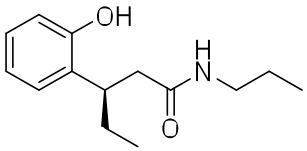


6

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.020 mmol) and 3.0 mol% reverse Josiphos **L4** (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and the mixture was stirred at room temperature for 15 min. Then, the mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 molar, 0.800 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. Then, a solution of 1.00 eq. 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.00 eq. ethanol (0.234 ml, 4.00 mmol) were added and the reaction mixture was warmed to room temperature and stirred at that temperature for 5 h. Then, the reaction was quenched by adding saturated NH_4Cl solution (50 mL) and the reaction mixture was diluted with Et_2O (50 mL). After separation of the organic phase it was dried over $MgSO_4$ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.55 in pentane/EtOAc 10:1, 95% *ee*) to yield (R)-ethyl-3-(2-hydroxyphenyl)pentanoate **6** (0.154 g, 0.693 mmol, 87 %) as a colourless oil.

^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.19 – 6.98 (m, 3H), 6.96 – 6.82 (m, 2H), 4.30 – 3.91 (m, 2H), 3.36 (dtd, *J* = 13.1, 7.6, 5.3 Hz, 1H), 2.70 (qd, *J* = 16.4, 7.3 Hz, 2H), 1.89 – 1.59 (m, 2H), 1.18 (t, *J* = 7.22 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 174.74, 154.14, 130.49, 127.22, 120.78, 117.03, 60.86, 40.90, 35.98, 27.77, 13.92, 12.02.
HR-MS: (ESI^+) calculated for $C_{13}H_{18}O_3Na$ [$M+Na^+$]: 245.1148, found: 245.1149.
$[\alpha]_D^{20}$ = -2.0 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 210 nm), retention times: 76.2 min (minor), 80.0 min (major).

(R)-3-(2-hydroxyphenyl)-N-propylpentanamide (7)



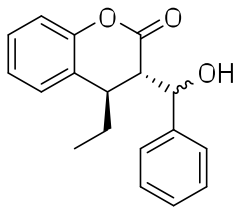
7

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.020 mmol) and 3.0 mol% reverse Josiphos **L4** (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and the mixture stirred at room temperature for 15 min. The mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 molar, 0.800 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. Next, a solution of

1.00 eq. 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.00 eq. propan-1-amine (0.329 ml, 4.00 mmol) were added and the reaction mixture was warmed up to room temperature and stirred at that temperature for 16 h. The reaction was quenched by adding saturated NH_4Cl solution (50 mL) and the reaction mixture was diluted with Et_2O (50 mL). After separation of the organic phase it was dried over $MgSO_4$ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO_2, pentane/EtOAc 1:1, R_f = 0.60 in pentane/EtOAc 1:1, 96% *ee*) to yield (R)-3-(2-hydroxyphenyl)-N-propylpentanamide **7** (0.154 g, 0.656 mmol, 82 %) as a colourless oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.71 (s (br), 1H), 7.12 – 7.02 (m, 2H), 6.94 – 6.83 (m, 2H), 6.26 (s (br), 1H), 3.34 (dd, *J* = 11.5, 7.3 Hz, 1H), 3.07 (dd, *J* = 13.3, 6.7 Hz, 2H), 2.65 (dd, *J* = 15.3, 4.3 Hz, 1H), 2.45 (dd, *J* = 15.3, 10.2 Hz, 1H), 1.72 (td, *J* = 14.2, 6.5 Hz, 2H), 1.48 – 1.28 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ 173.76, 154.50, 130.74, 127.19, 127.01, 120.50, 117.24, 43.32, 41.32, 36.21, 27.77, 22.33, 12.15, 11.03.
HR-MS: (ESI$^+$) calculated for $C_{14}H_{22}NO_2$ [M+H$^+$]: 236.1645, found: 236.1644.
$[\alpha]_D^{20}$ = -38.4 (c = 1.0 in $CHCl_3$)
ee determination by chiral HPLC (Chiralpak AB-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 25.9 min (minor), 32.4 min (major).

(3S,4R)-4-ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one (8)



8

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.020 mmol) and 3.0 mol% reverse Josiphos **L4** (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and stirred at room temperature for 15 min. The mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 molar, 0.800 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. A solution of 1.00 eq. 2H-chromen-2-one **1** (0.117 g, 0.8 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.00 eq. benzaldehyde (0.405 ml, 4.00 mmol) were added and the reaction mixture was warmed up to room temperature and stirred at that temperature for 4 h. Then, the reaction was quenched by adding saturated aq. NH_4Cl solution (50 mL) and the reaction mixture was diluted with Et_2O (50 mL). After separation of the organic phase it was dried over $MgSO_4$ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO_2, toluene/MeOH 30:1, R_f = 0.45 (major), 0.35 (minor) in toluene/MeOH 30:1) to yield (3S,4R)-4-ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one **8** (0.176 g, 0.624 mmol, 78 %) as a colourless oil.

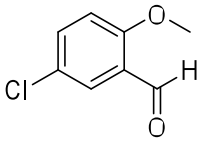
Product **8** was isolated as a mixture of 2 diastereomers (ratio 3:1), signals are assigned where resolved.
^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.48 – 6.92 (m, 9H, major + minor), 4.59 (d, *J* = 9.4 Hz, 1H, major), 4.43 (d, *J* = 10.0 Hz, 1H, minor), 3.27 – 3.03 (m, 2H, major + minor), 2.73 (s (br), 1H, major + minor), 2.24 (t, *J* = 7.3 Hz, 1H, minor), 1.49 (qd, *J* = 14.4, 7.3 Hz, 2H, major + minor), 0.90 (t, *J* = 7.3 Hz, 3H, major), 0.77 (t, *J* = 7.3 Hz, 3H, minor).
^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.46 (minor), 167.92 (major), 150.48 (minor), 150.45 (major), 140.77 (major), 140.47 (minor), 129.22, 128.87 (minor), 128.83 (major), 128.61 (major), 128.55 (minor), 128.36, 128.31 (minor), 128.26 (major), 128.09, 127.38, 126.80, 126.34, 125.89, 124.87, 124.32 (minor), 124.26 (major), 116.64 (minor), 116.34 (major), 72.58 (mjaor), 64.91 (minor), 53.93 (major), 53.29 (minor), 39.70 (minor), 39.07 (major), 28.59 (major), 28.18 (minor), 11.07 (major), 10.87 (minor).
HR-MS: (ESI^+) calculated for $C_{18}H_{18}O_3Na$ [$M+Na^+$]: 305.1148, found: 305.1149.
$[\alpha]_D^{20}$ = 72.4 (c = 1.0 in $CHCl_3$)

4. References

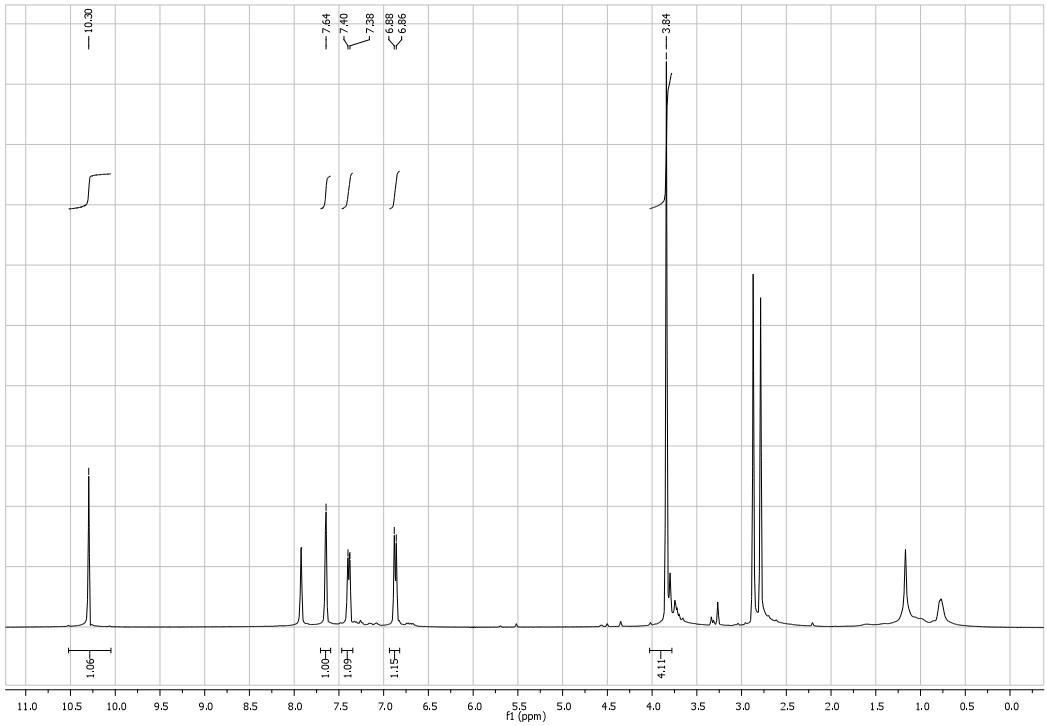
1. Smith, C. R.; Mans, D. J.; RajanBabu, T. V. *Org. Synth.* **2008** 85, 238.
2. Dubuffet, T.; Loutz, A.; Lavielle, G. *Synth. Commun.* **1999,** 29, 929-936.
3. Meyers, A. I.; Whitten, C. E. *Tetrahedron Lett.* **1976**, 1947-1950.
4. Stephan, E.; Rocher, R.; Aubouet, J.; Pourcelot, G.; Cresson, P. *Tetrahedron: Asymmetry* **1994,** 5, 41-44.

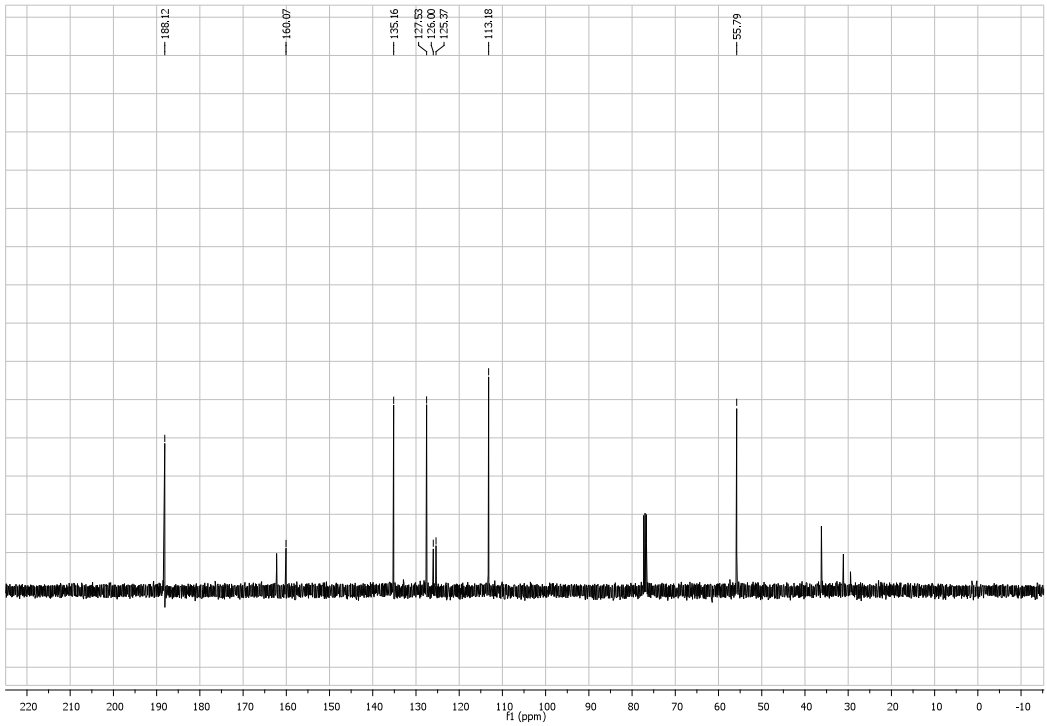
5. NMR spectra and HPLC traces

5-chloro-2-methoxybenzaldehyde (S2a)

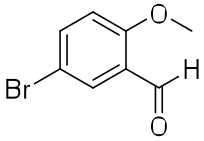


S2 a

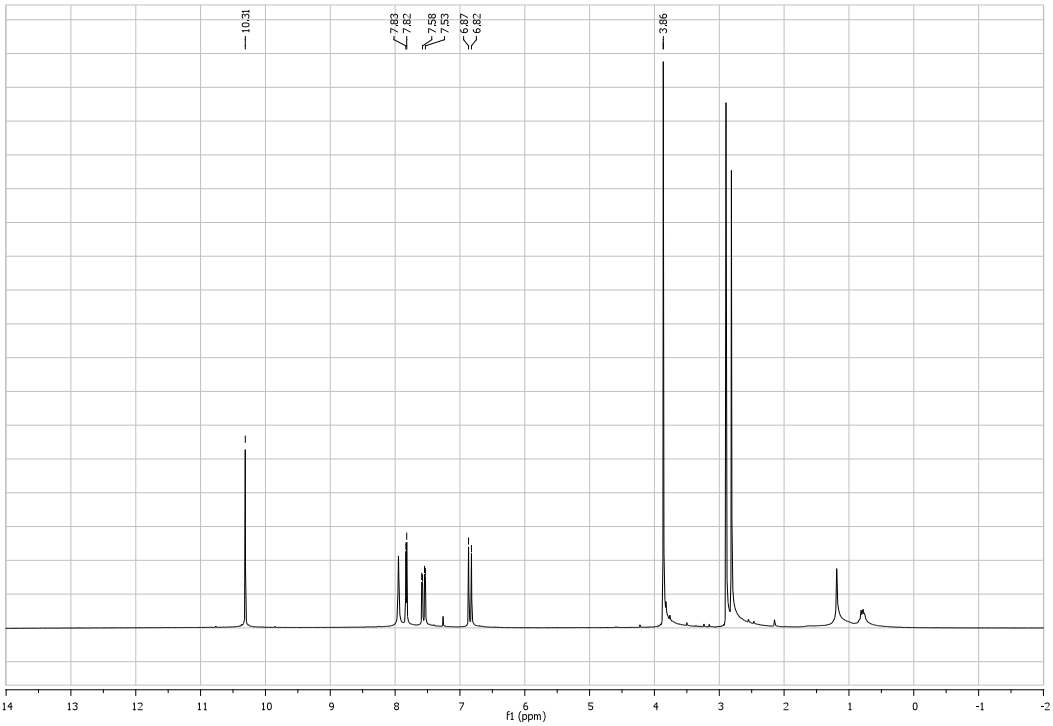


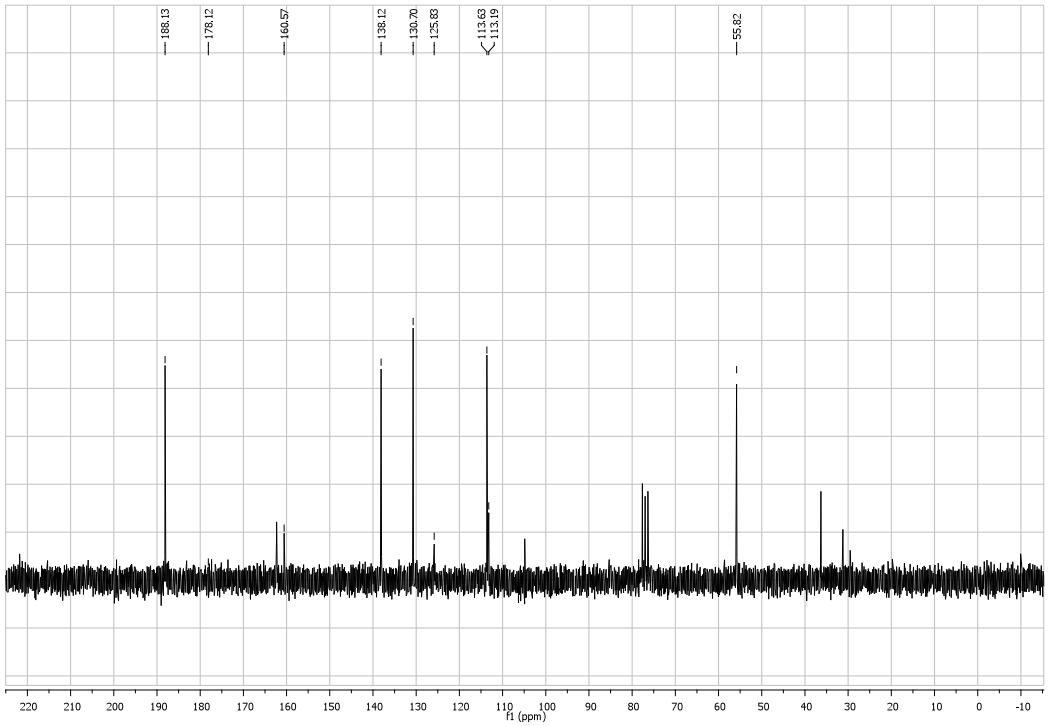


5-bromo-2-methoxybenzaldehyde (S2b)

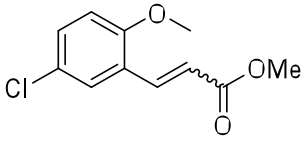


S2b

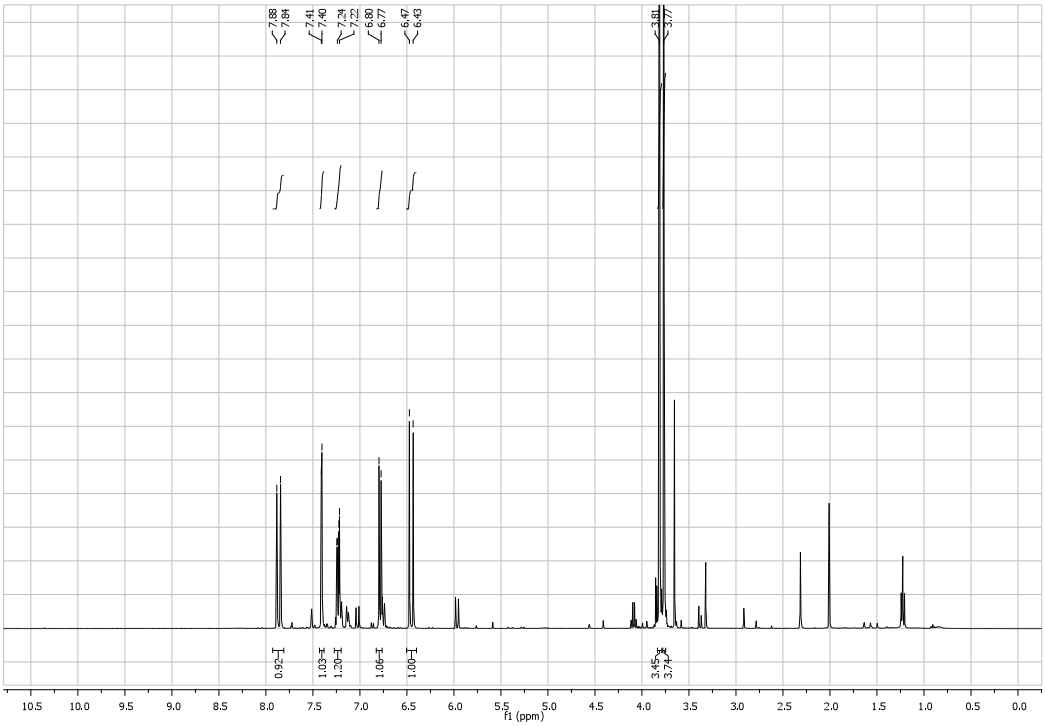


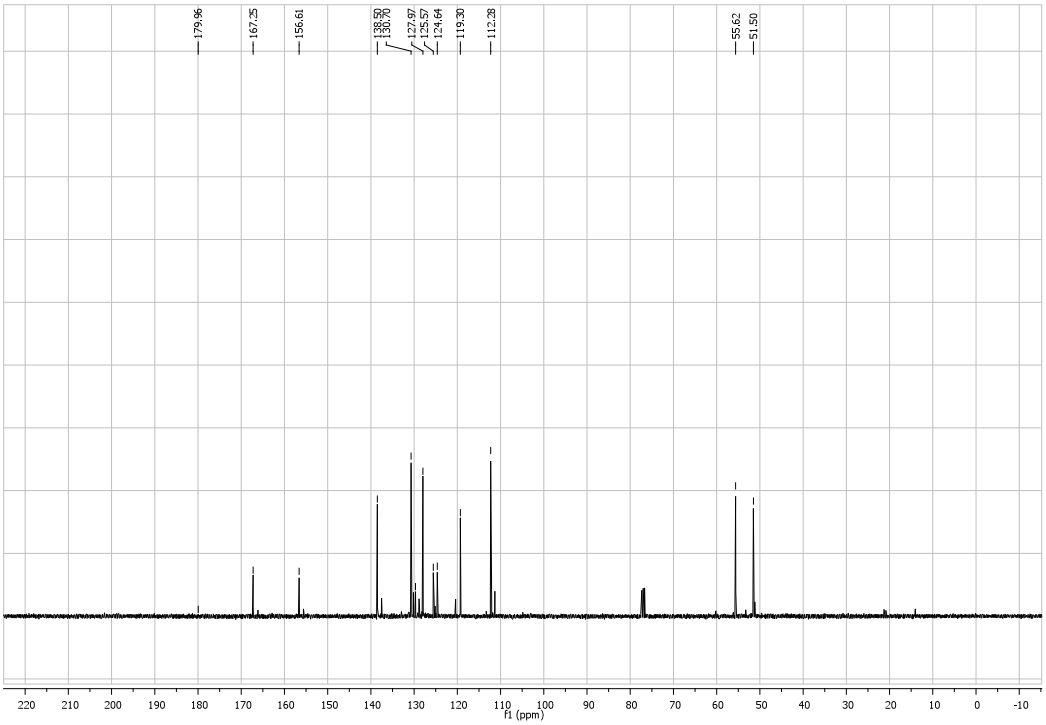


Methyl 3-(5-chloro-2-methoxyphenyl)acrylate (S3a)

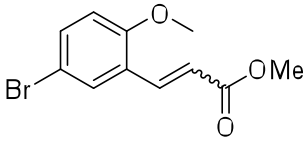


S3a

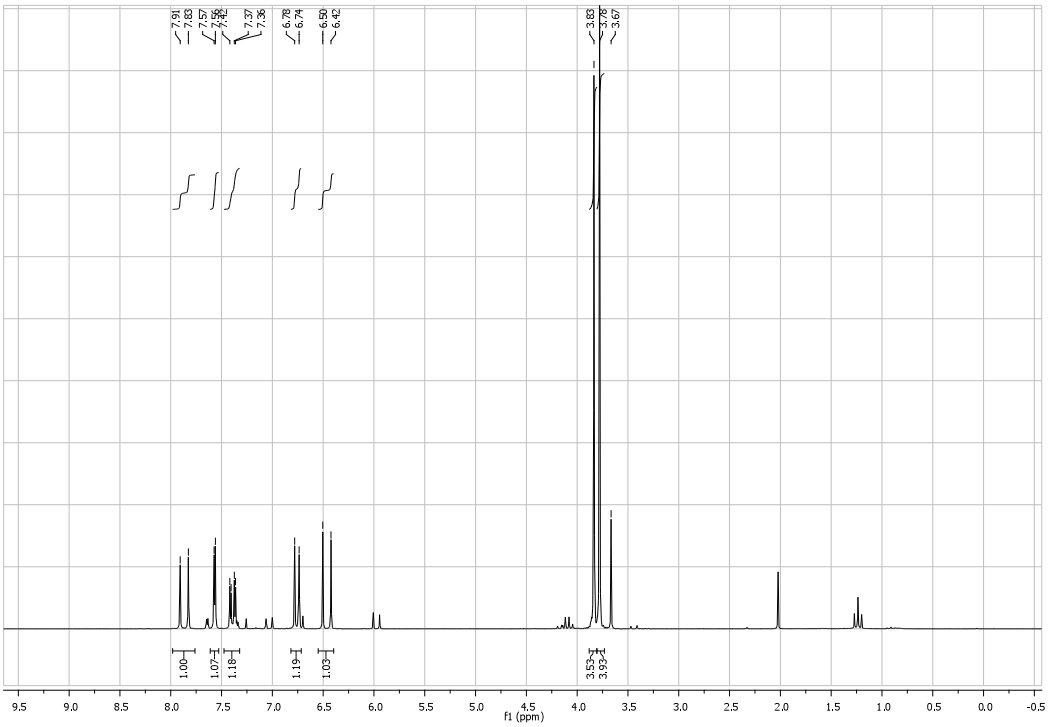


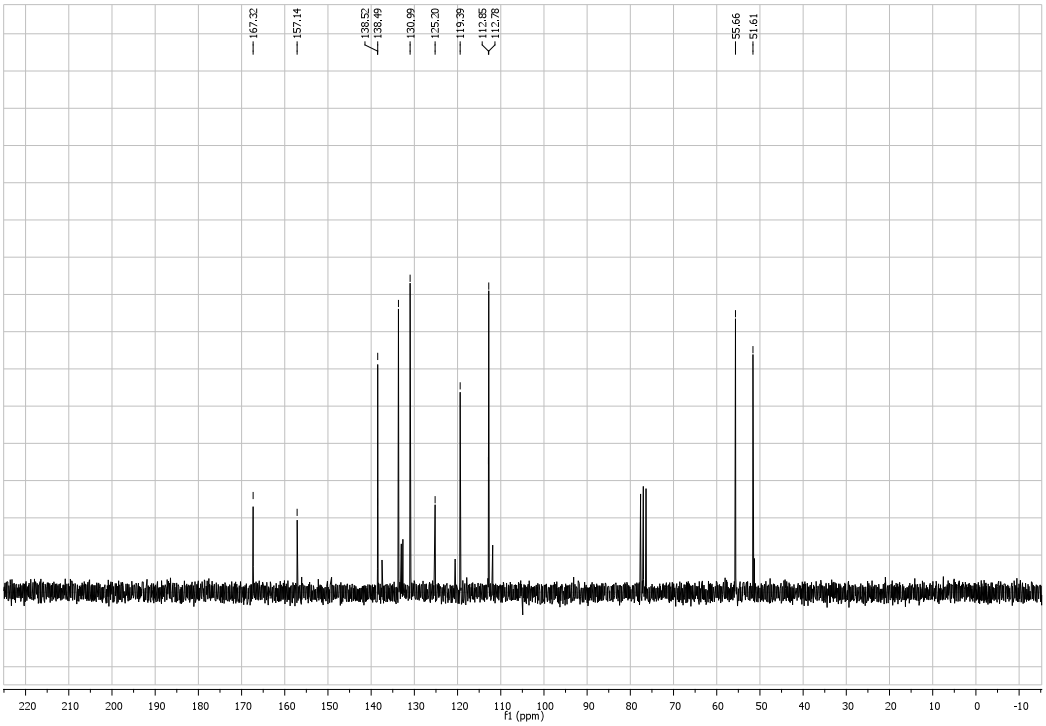


Methyl 3-(5-bromo-2-methoxyphenyl)acrylate (S3b)

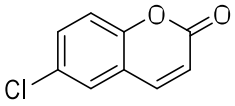


S3b

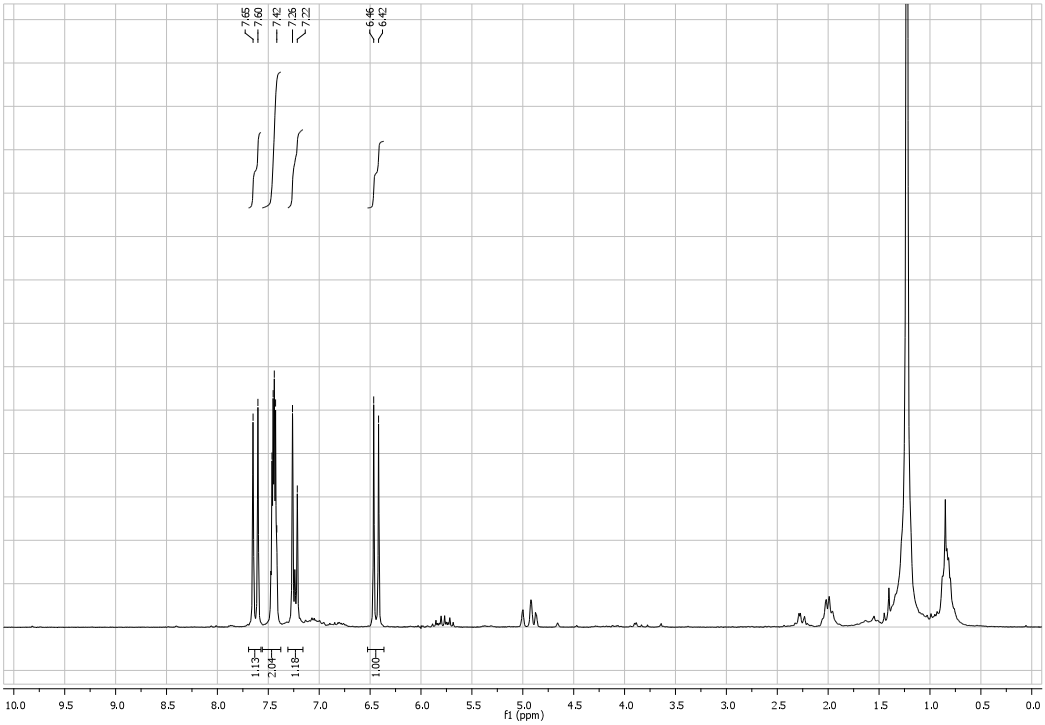


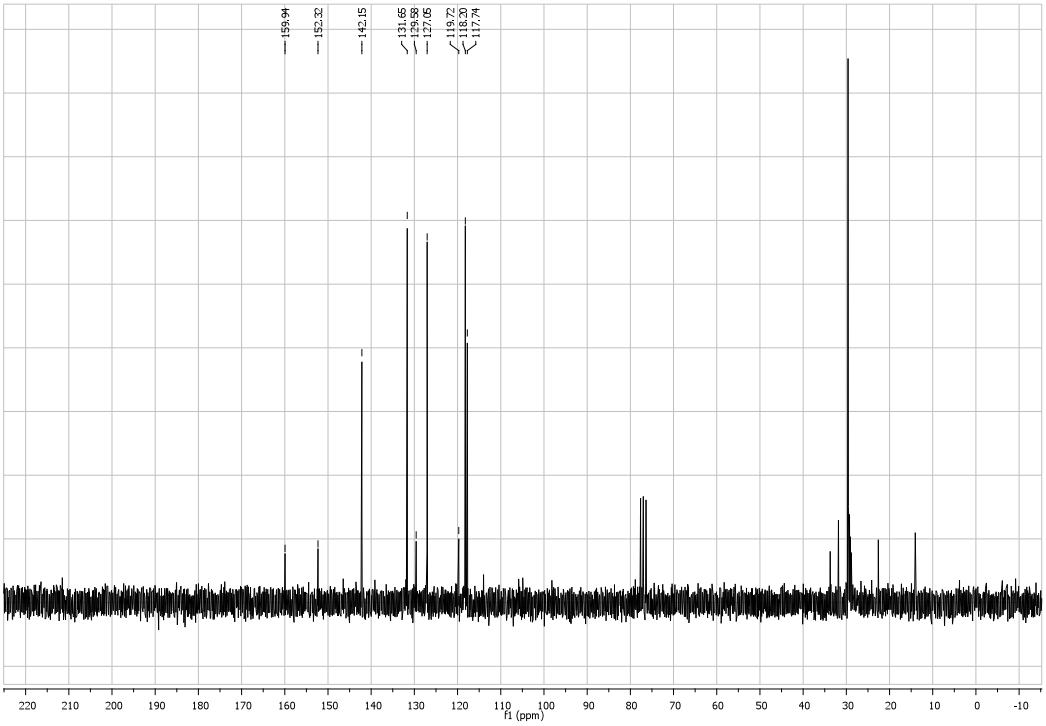


6-chloro-2H-chromen-2-one (3c)

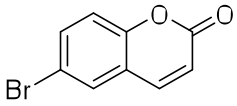


3c

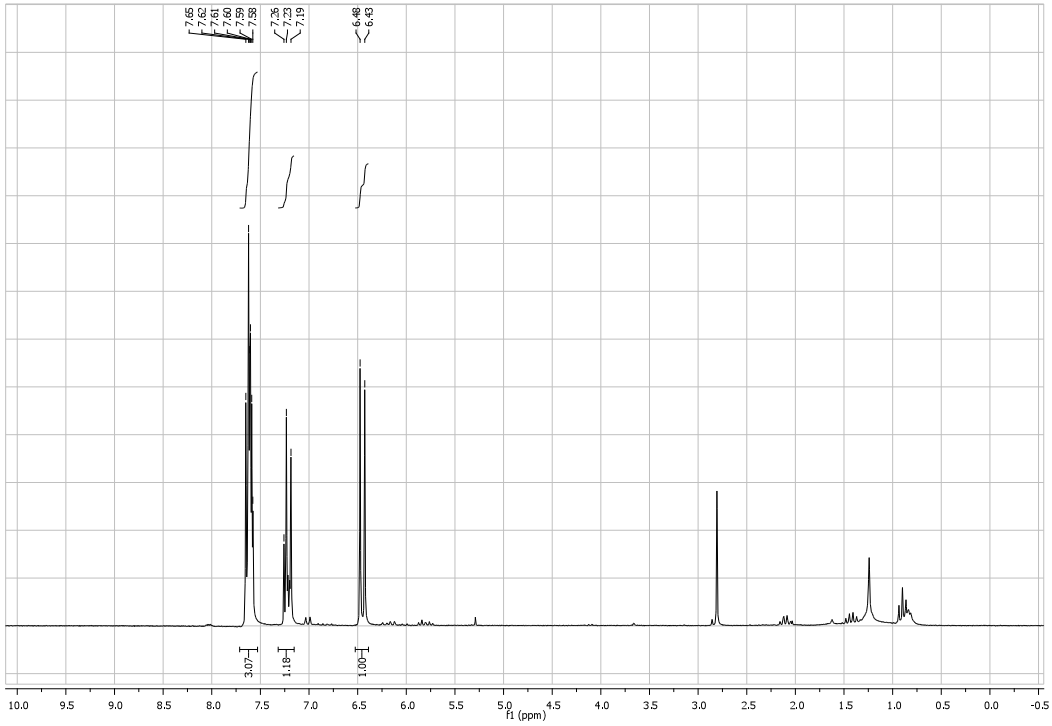


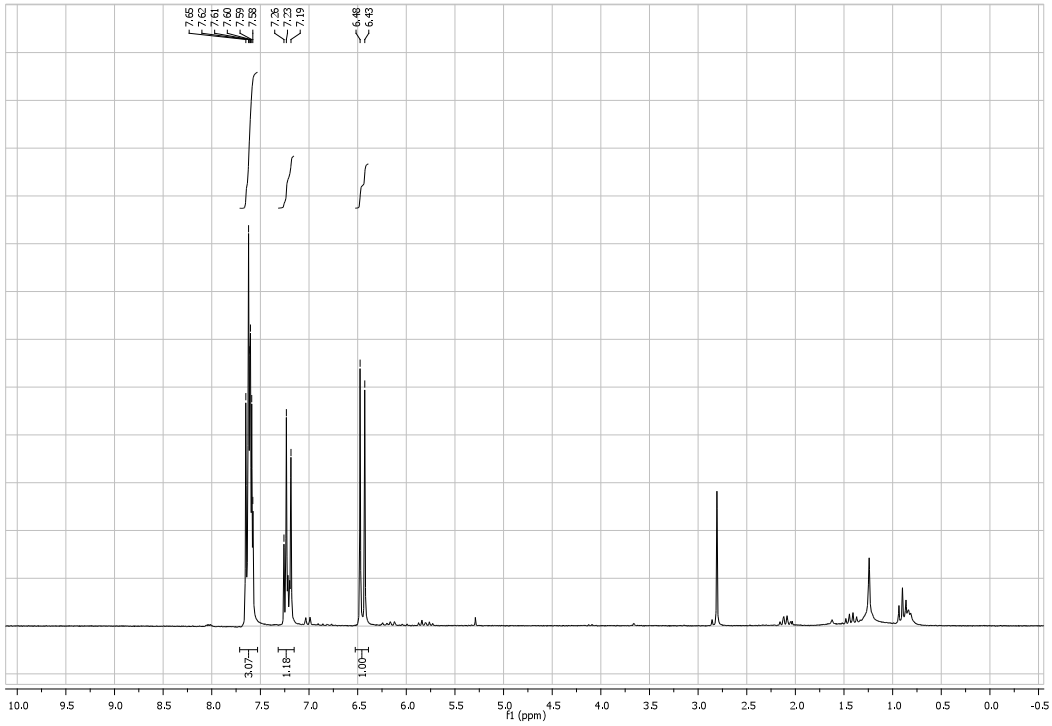


6-bromo-2H-chromen-2-one (3d)

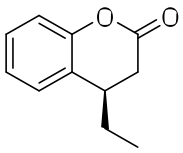


3d

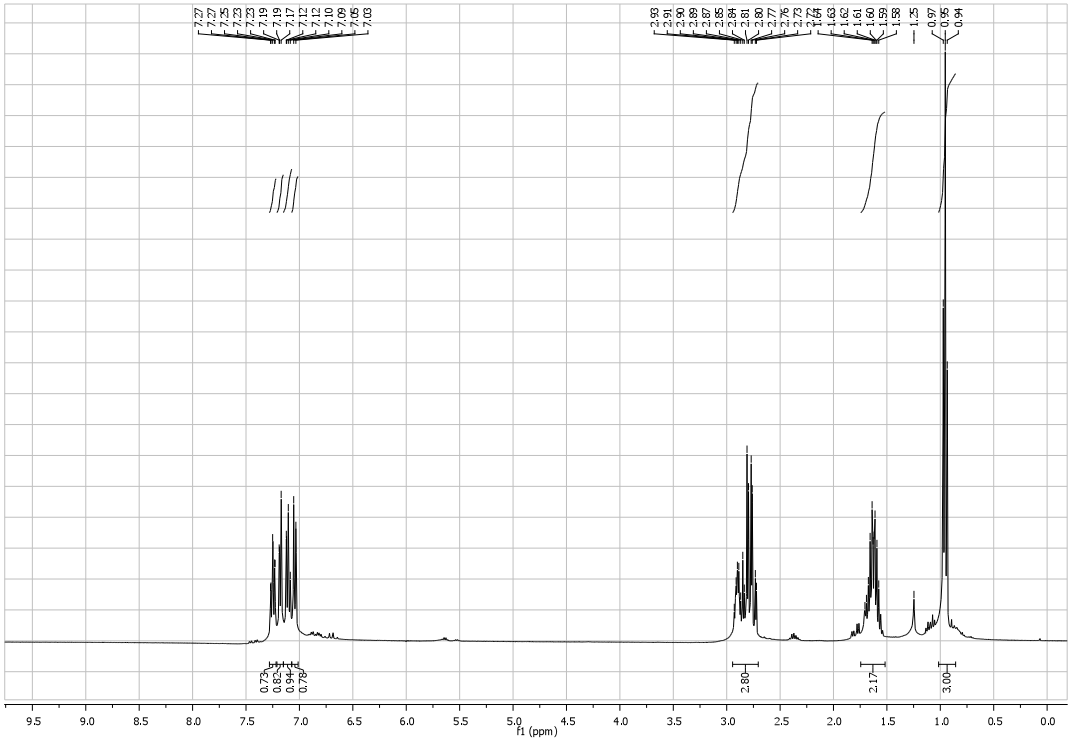


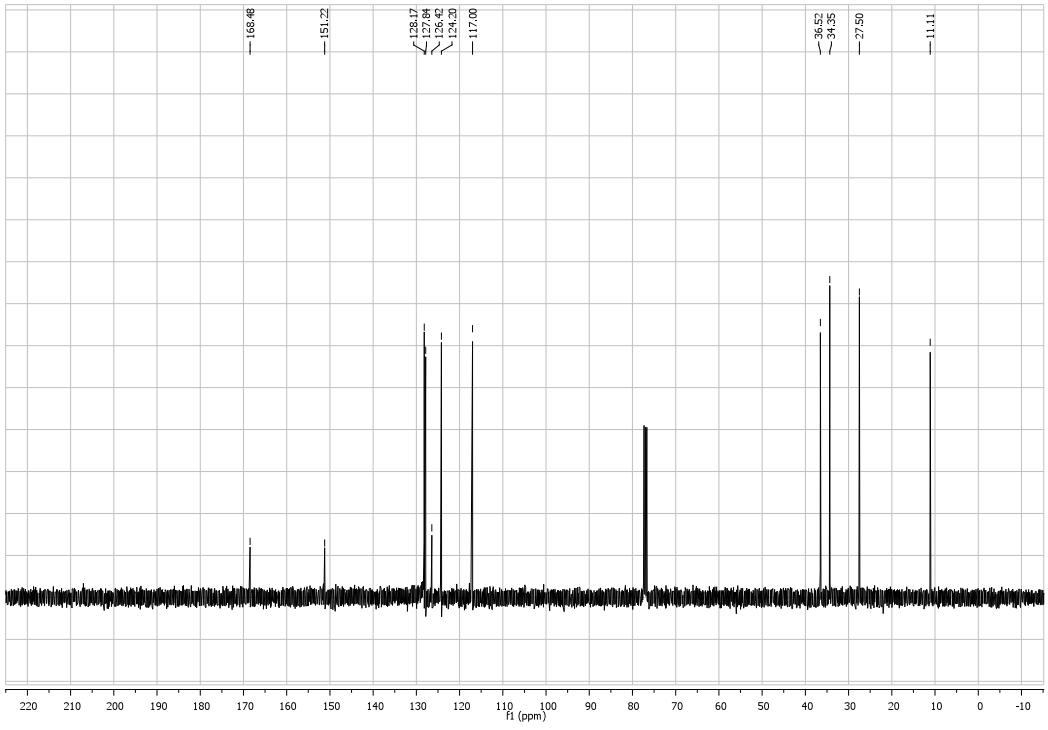


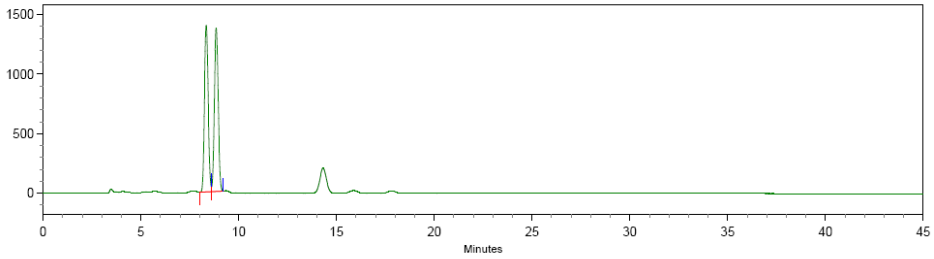
(R)-4-ethylchroman-2-one (2a)



2a







1: 210 nm, 8 nm

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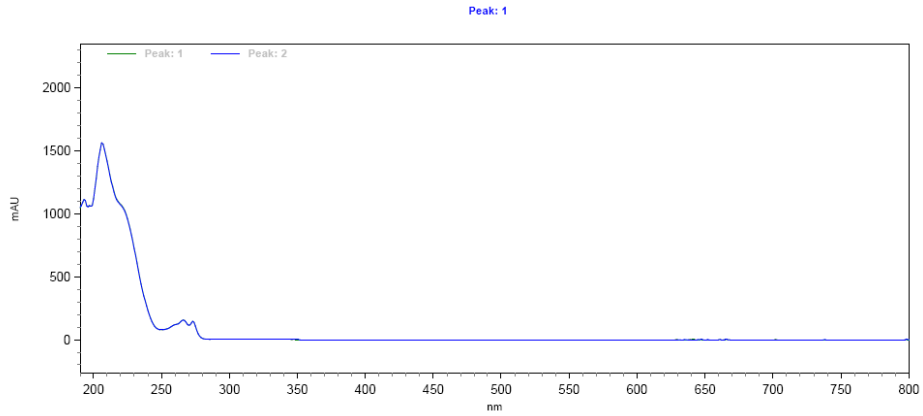

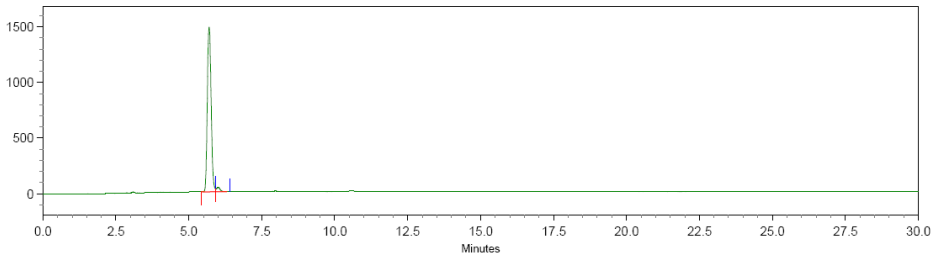

1: 210 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	5.696	13595789	97.67
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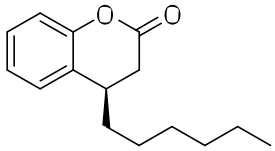
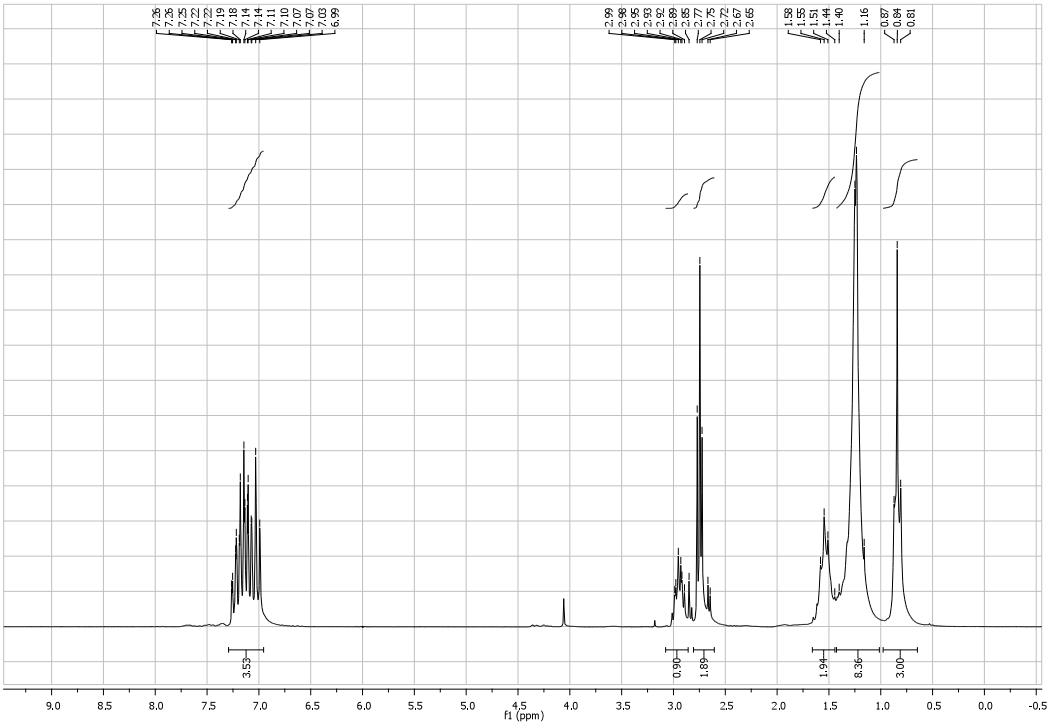
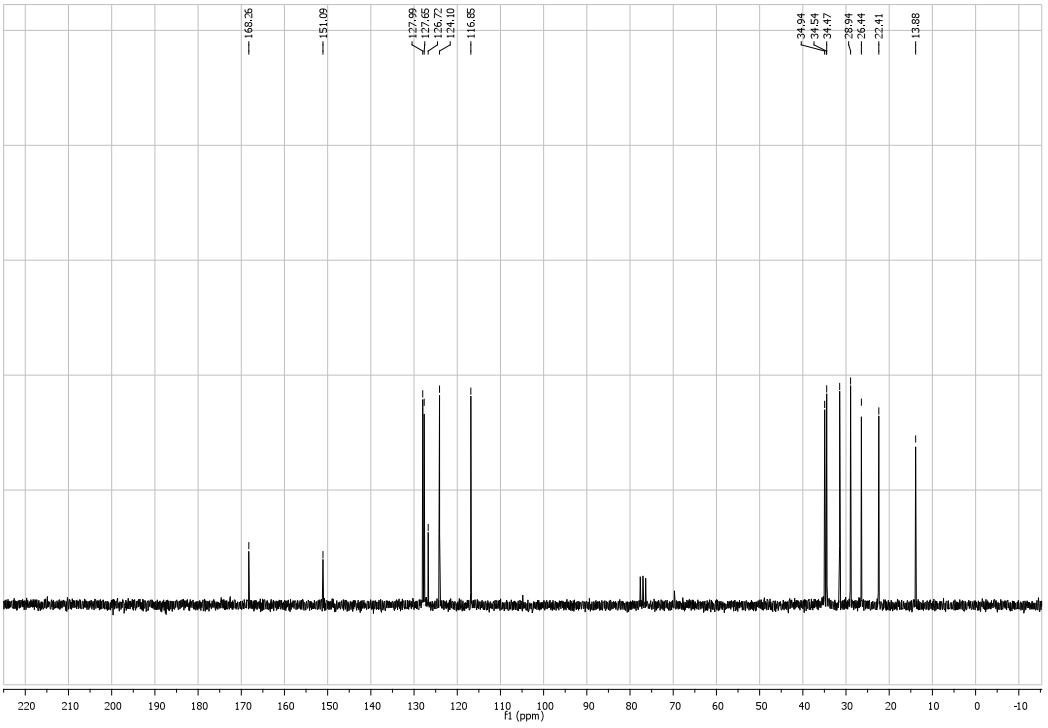
Totals			13919492	100.00

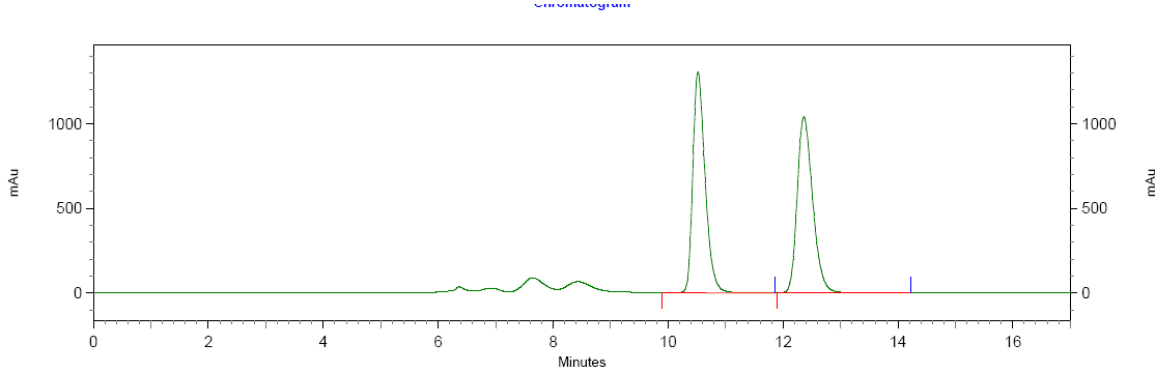
(R)-4-hexylchroman-2-one (2c)



2c







1: 210
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
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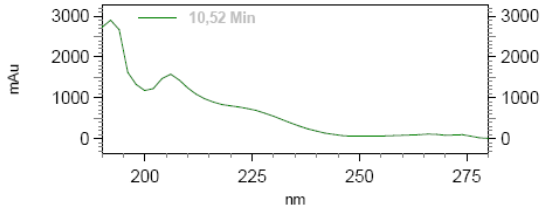
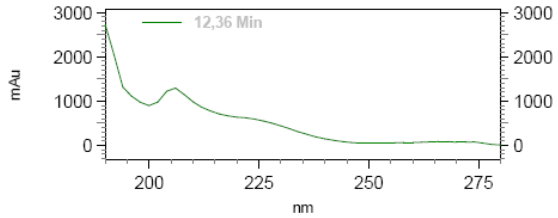
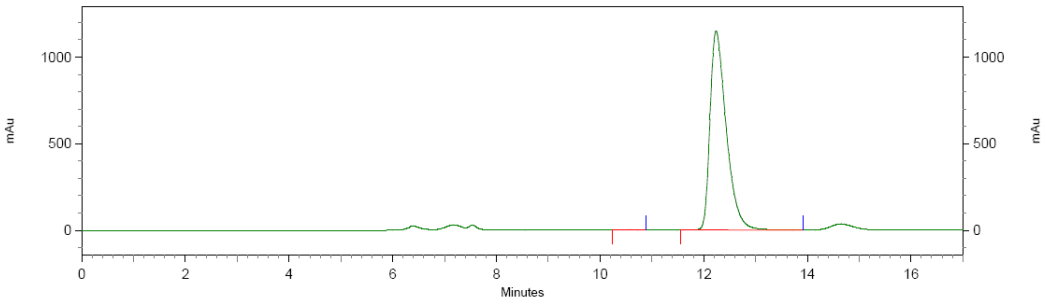
2	Peak @ 12,364 Minutes	12,364	19532524	50,091
Totals			38993864	100,000



Retention time: 10,520 Min
Peak name: Peak @ 10,520 Minutes
Lambda max: 267
Lambda min: 253



Retention time: 12,364 Min
Peak name: Peak @ 12,364 Minutes
Lambda max: 267
Lambda min: 253



1: 210
nm, 2 nm
Results

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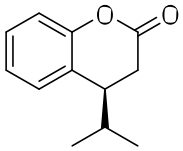
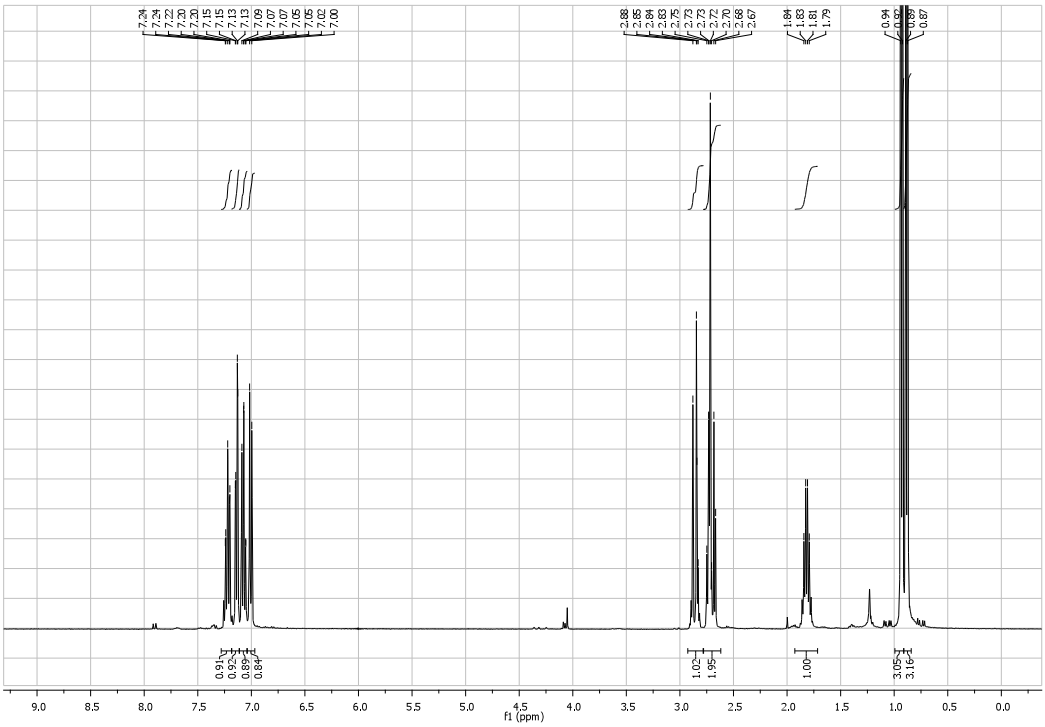
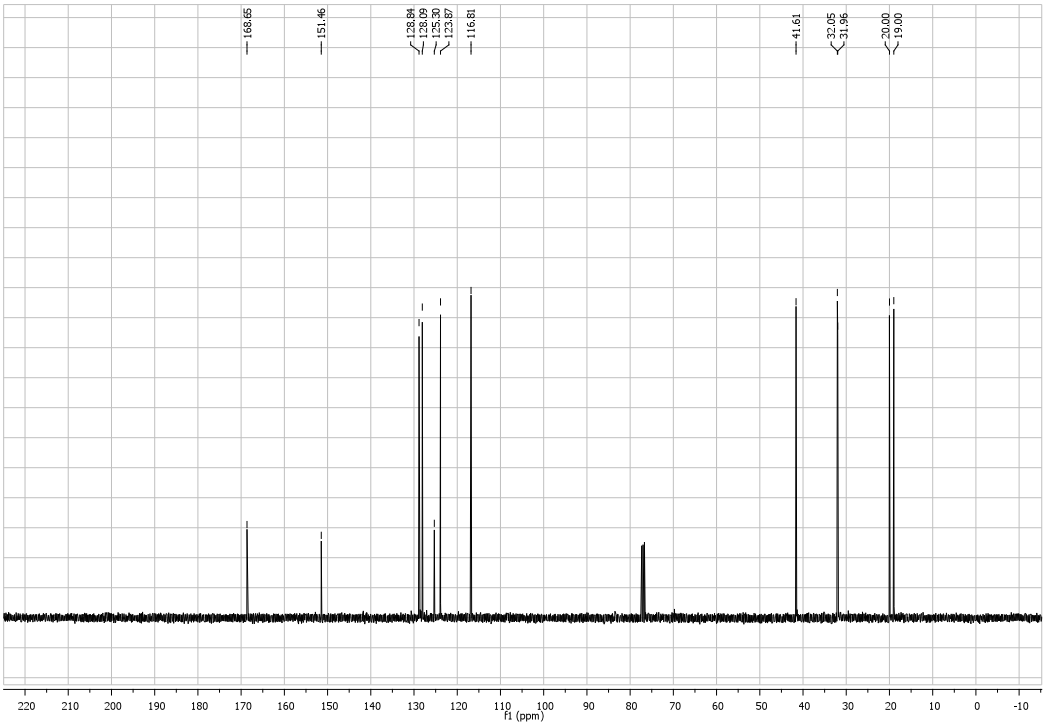
1	Peak @ 10,556 Minutes	10,556	40265	0,161
2	Peak @ 12,240 Minutes	12,240	24943841	99,839
Totals			24984106	100,000

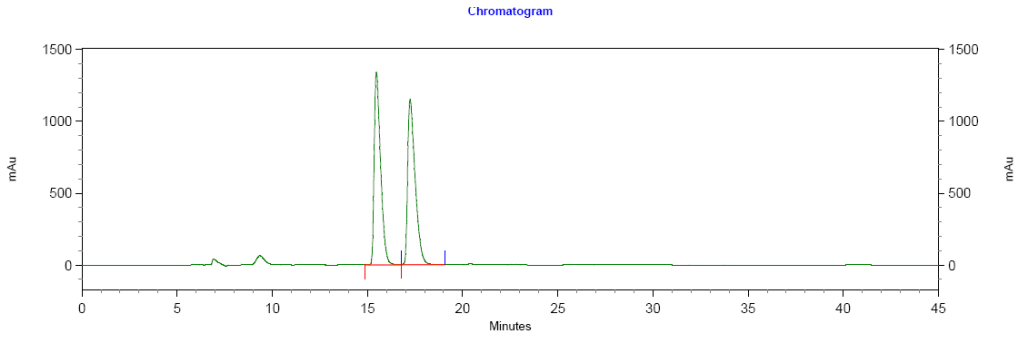
(S)-4-isopropylchroman-2-one (2d)



2d







1: 210
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
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2	Peak @ 17,240 Minutes	17,240	31619694	50,178
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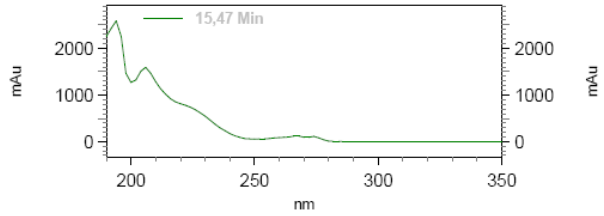
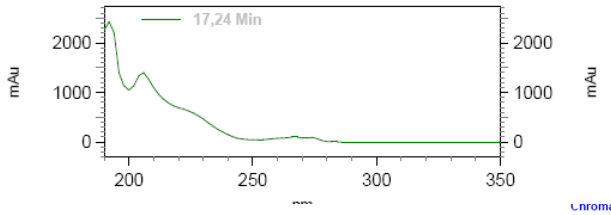
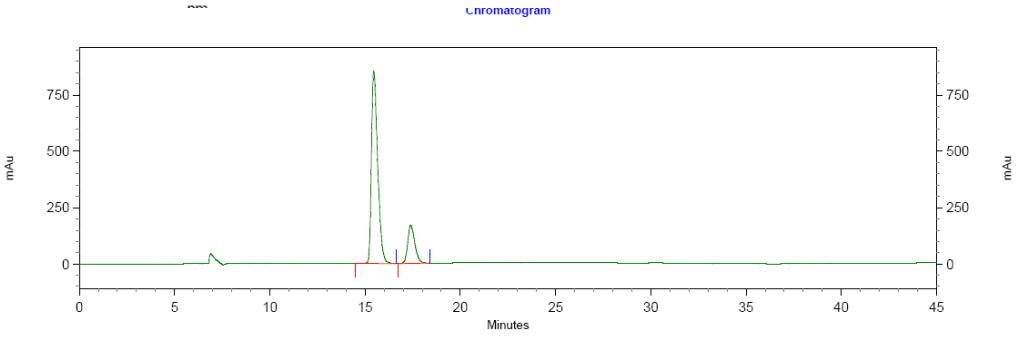


Retention time: 15,468 Min
Peak name: Peak @ 15,468 Minutes
Lambda max: 268, 321
Lambda min: 301, 252



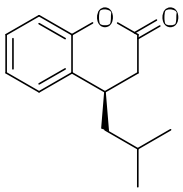
Retention time: 17,240 Min
Peak name: Peak @ 17,240 Minutes
Lambda max: 268, 321
Lambda min: 301, 252



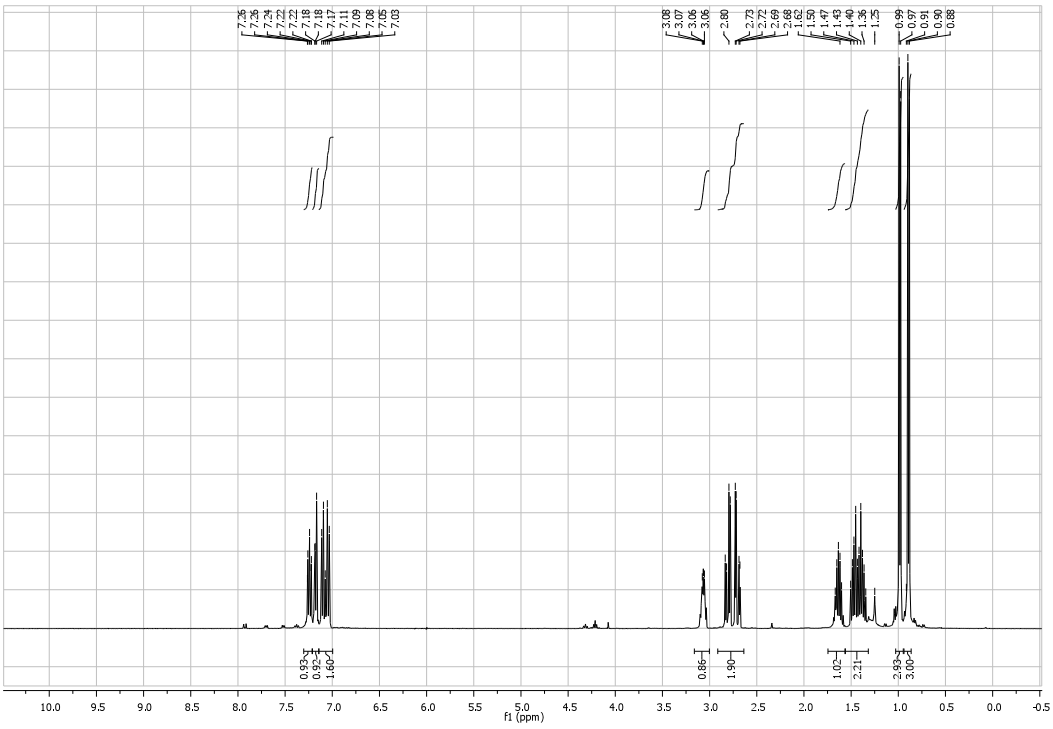
1: 210
nm, 2 nm
Results

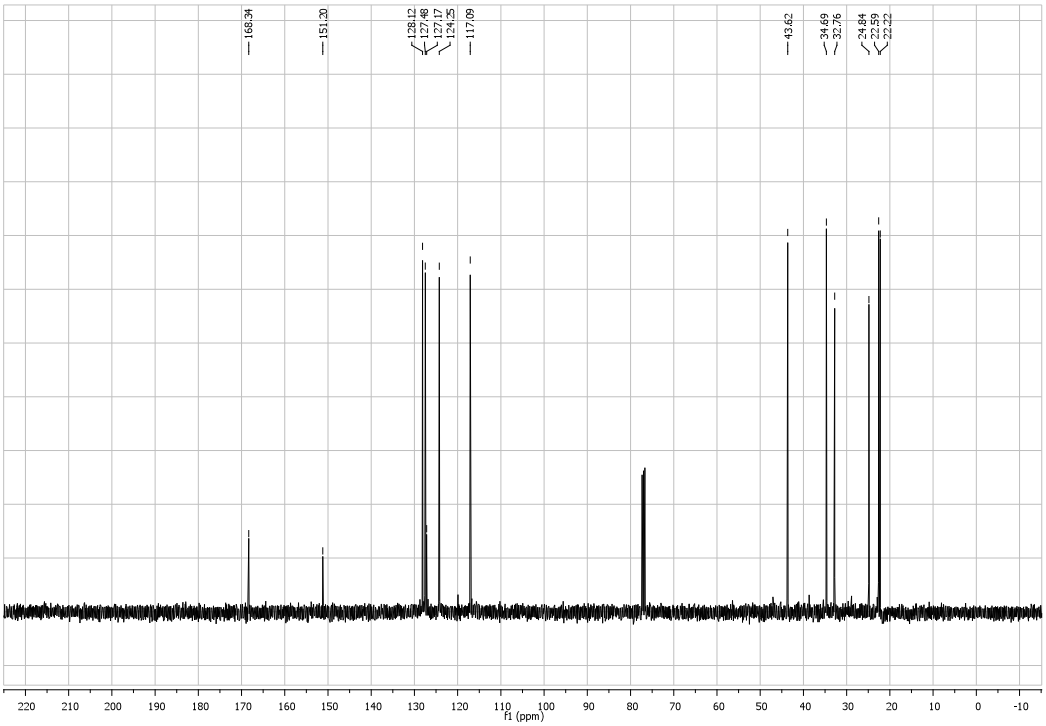
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 15,456 Minutes	15,456	19497953	81,579
2	Peak @ 17,400 Minutes	17,400	4402627	18,421
Totals			23900580	100,000

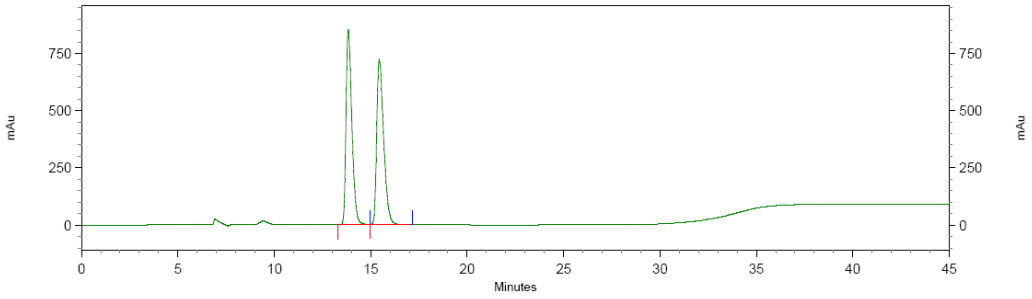
(R)-4-isobutylchroman-2-one (2e)



2e







1: 210
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
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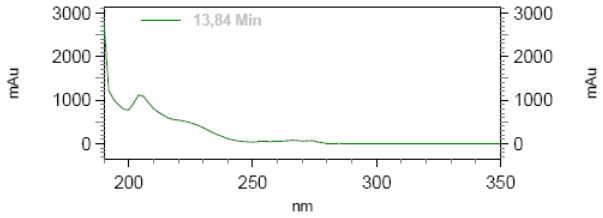
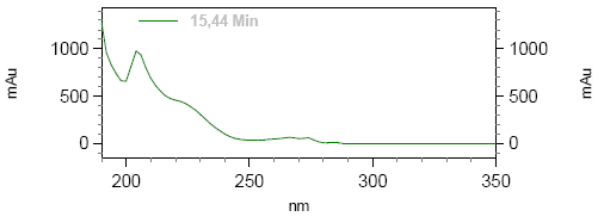
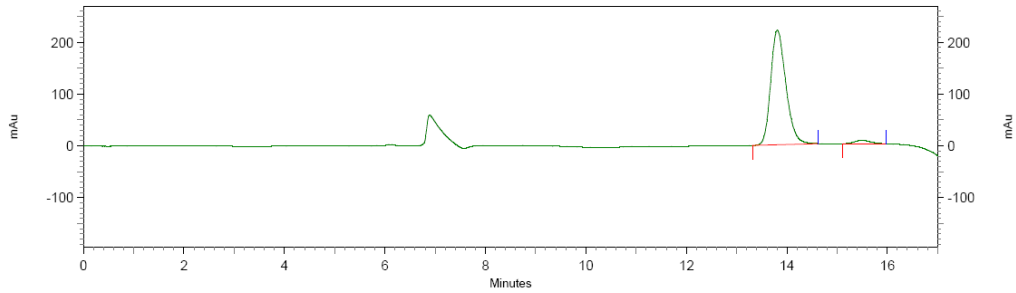
Totals			36213473	100,000



Retention time: 13,836 Min
Peak name: Peak @ 13,836 Minutes
Lambda max: 203, 267, 317
Lambda min: 300, 252, 201



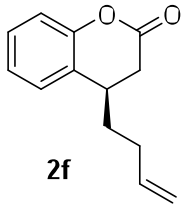
Retention time: 15,444 Min
Peak name: Peak @ 15,444 Minutes
Lambda max: 204, 267, 317
Lambda min: 301, 252, 200



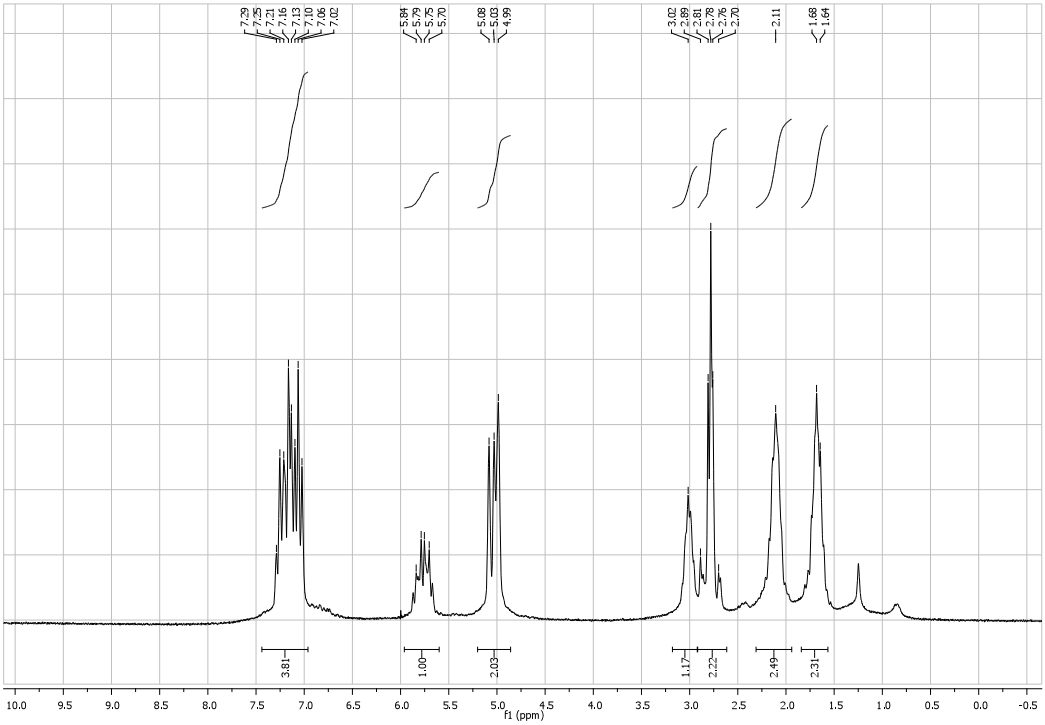
1: 210
nm, 2 nm
Results

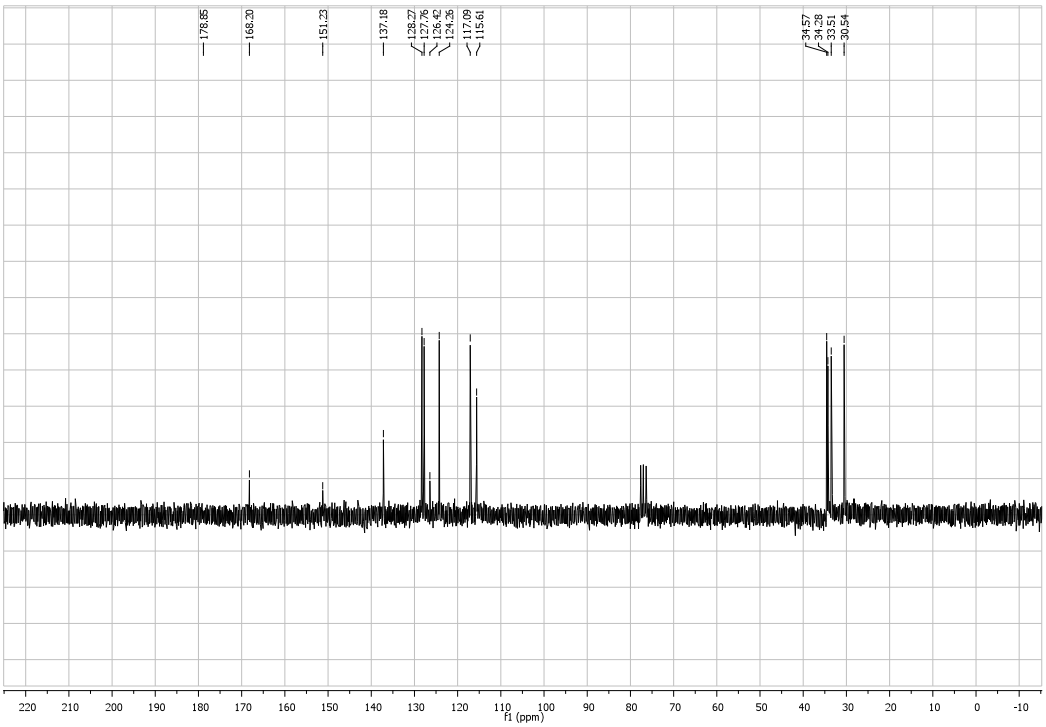
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 13,808 Minutes	13,808	4644890	96,730
2	Peak @ 15,496 Minutes	15,496	157031	3,270
Totals			4801921	100,000

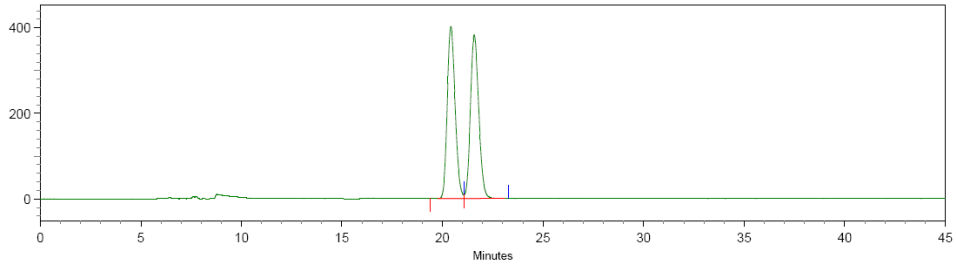
(R)-4-(but-3-enyl)chroman-2-one (2f)



2f

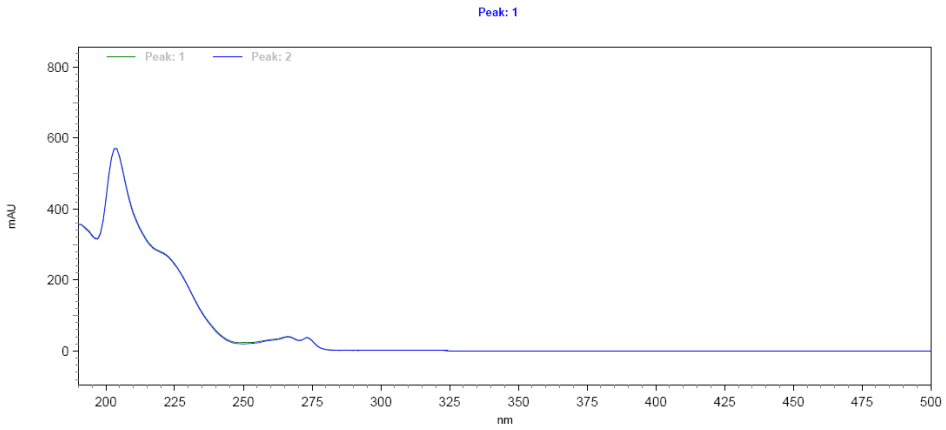


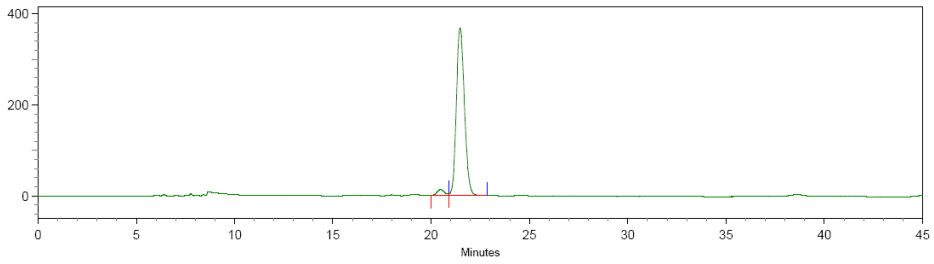




1: 210 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	20.416	10992857	49.95
2	2	21.579	11015585	50.05
Totals			22008442	100.00

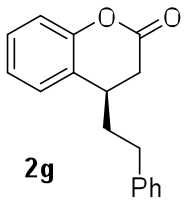




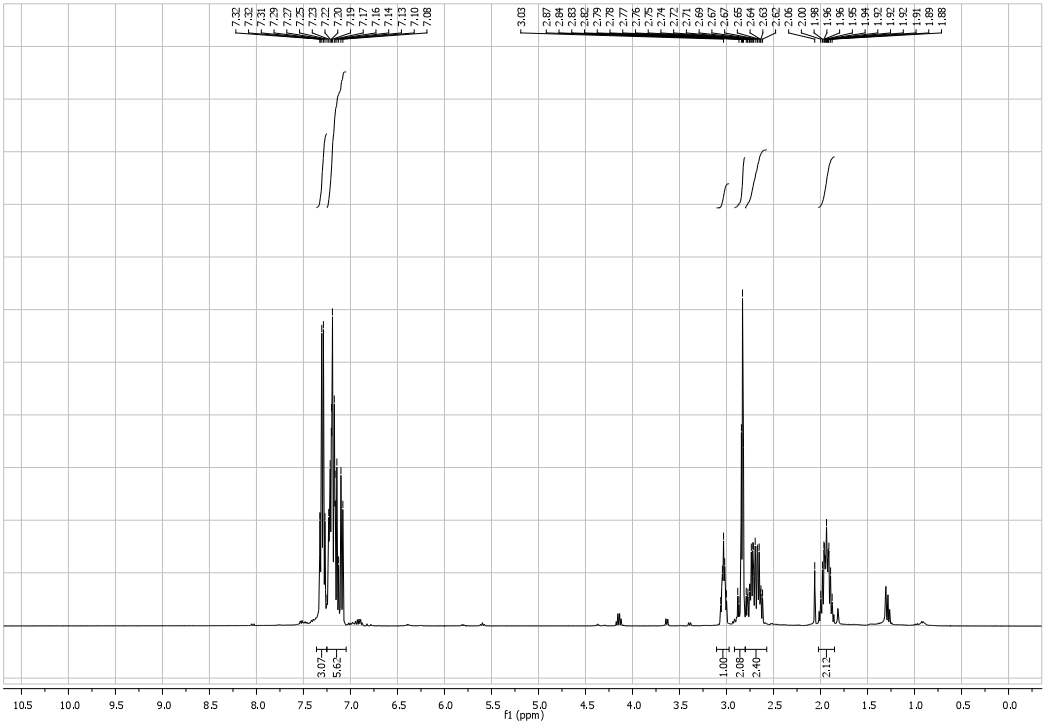
1: 210 nm, 8 nm

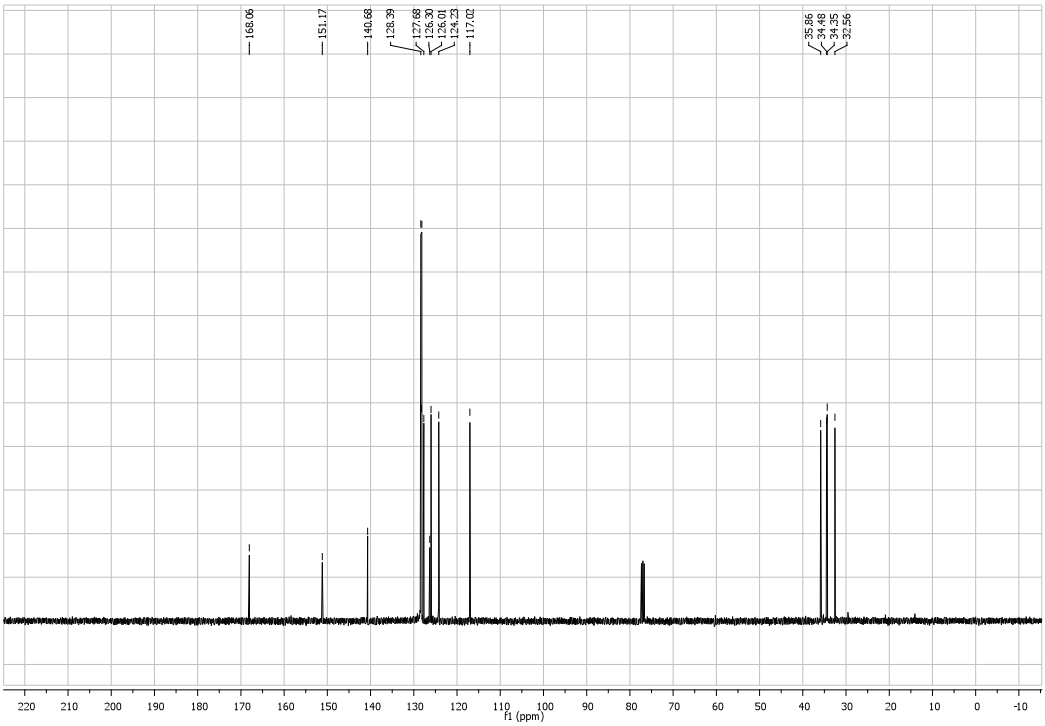
Pk #	Name	Retention Time	Area	Area Percent
1	1	20.480	368749	3.38
2	2	21.472	10552647	96.62
Totals			10921396	100.00

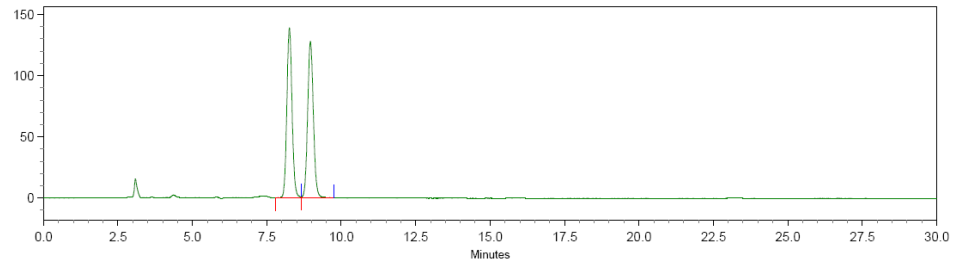
(R)-4-phenethylchroman-2-one (2g)



2g



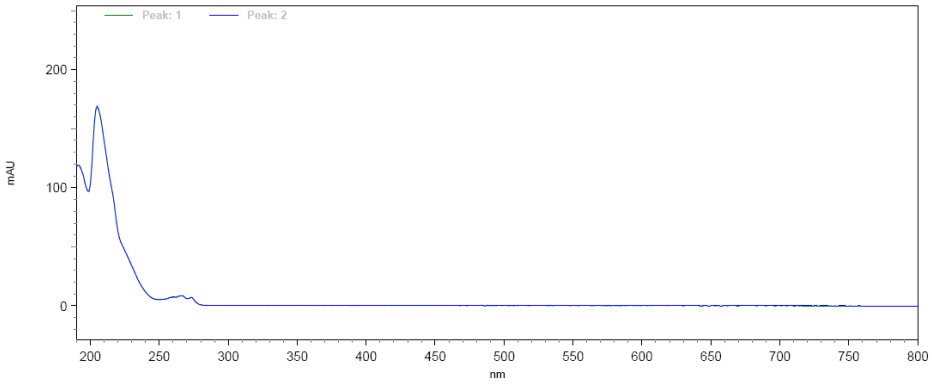


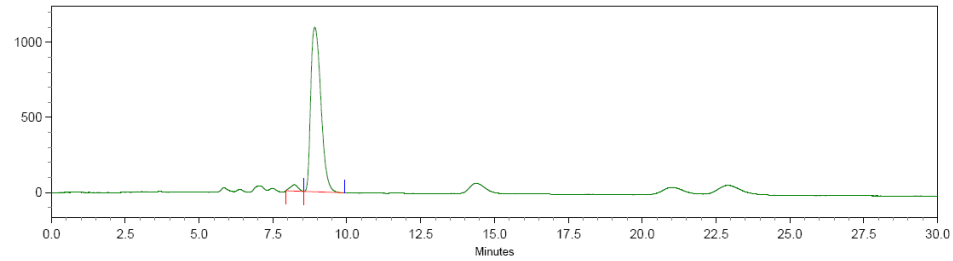


1: 210 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	1	8.256	1692015	49.86
2	2	8.960	1701779	50.14
Totals			3393794	100.00

Peak: 1



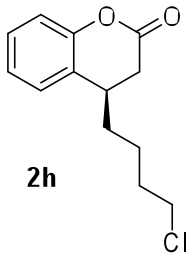


1: 210 nm, 8 nm

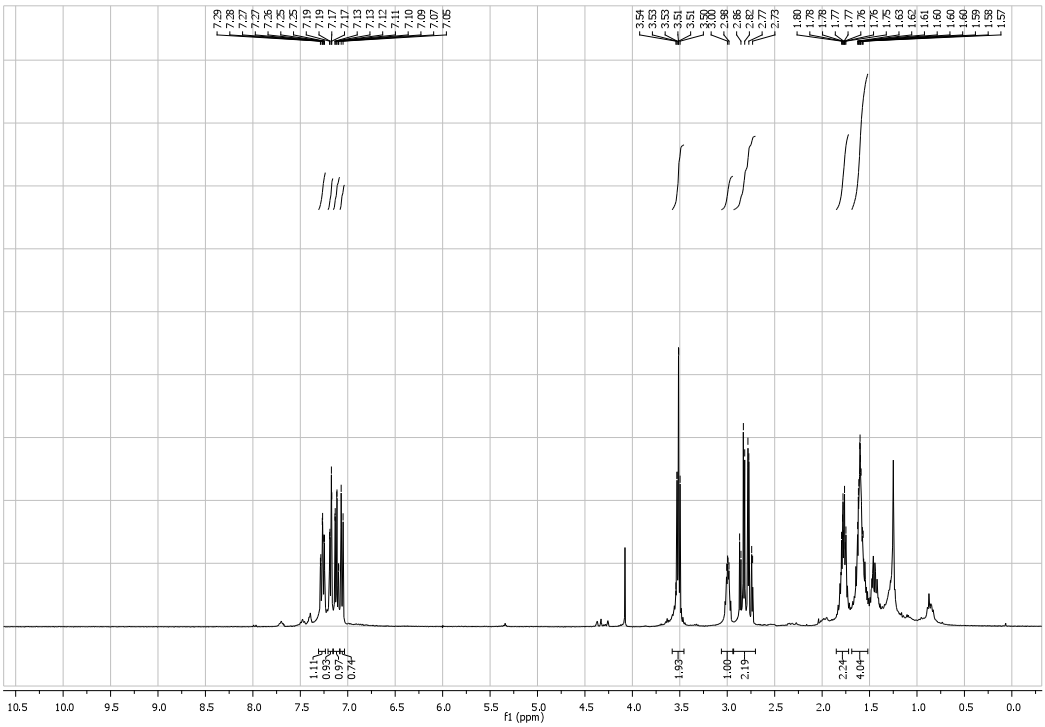
Pk #	Name	Retention Time	Area	Area Percent
1	1	8.224	768520	2.85
2	2	8.917	26233032	97.15
Totals			27001552	100.00

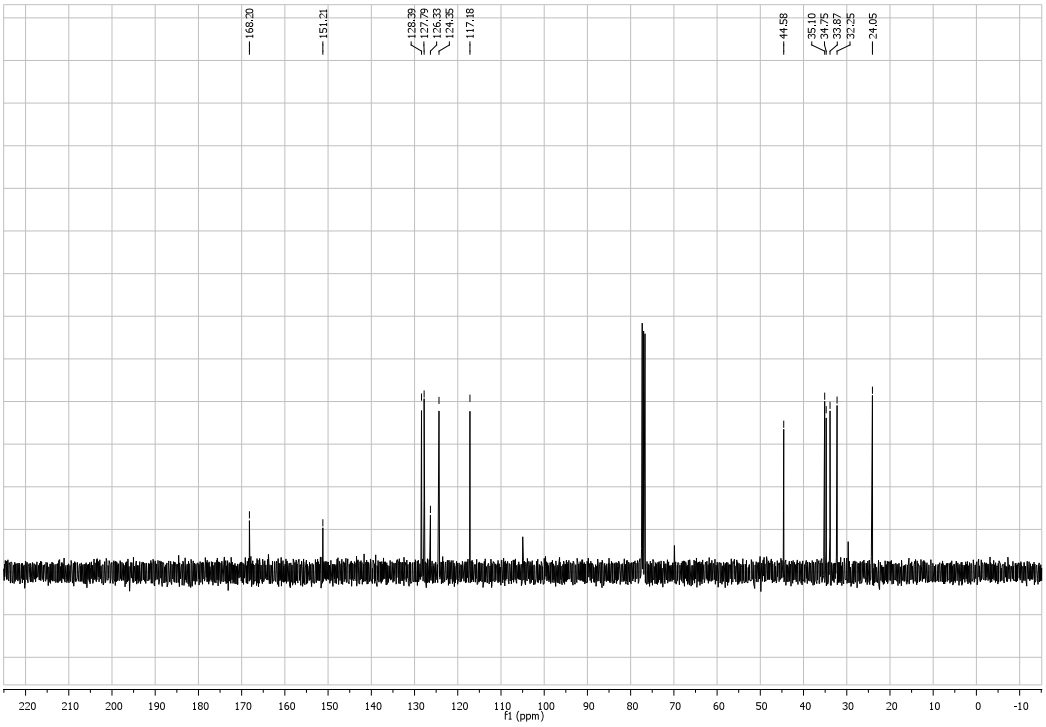
Peak: 1

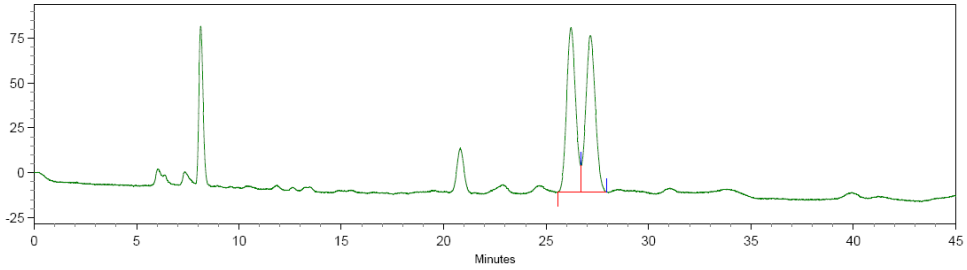
(R)-4-(4-chlorobutyl)chroman-2-one (2h)



2h

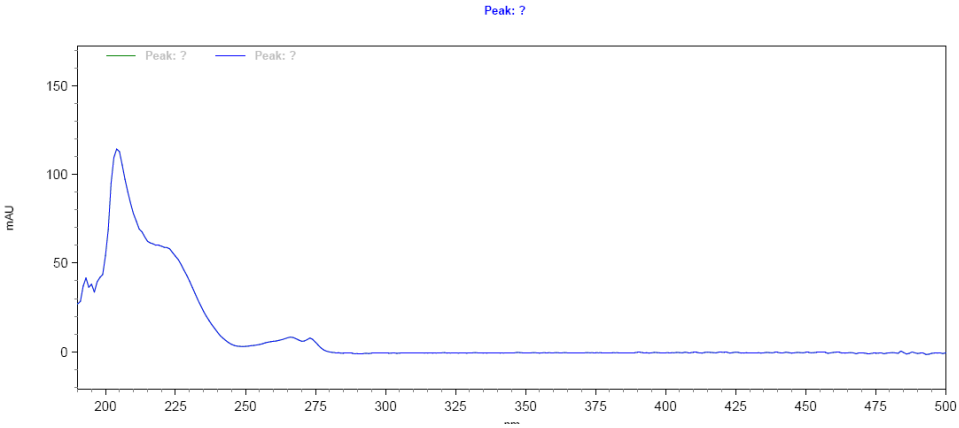


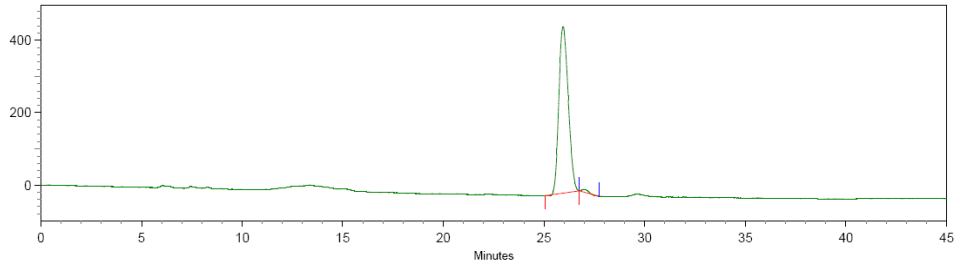




1: 210 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1	?	26.208	2813195	49.65
2	?	27.157	2852447	50.35
Totals			5665642	100.00

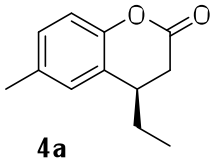




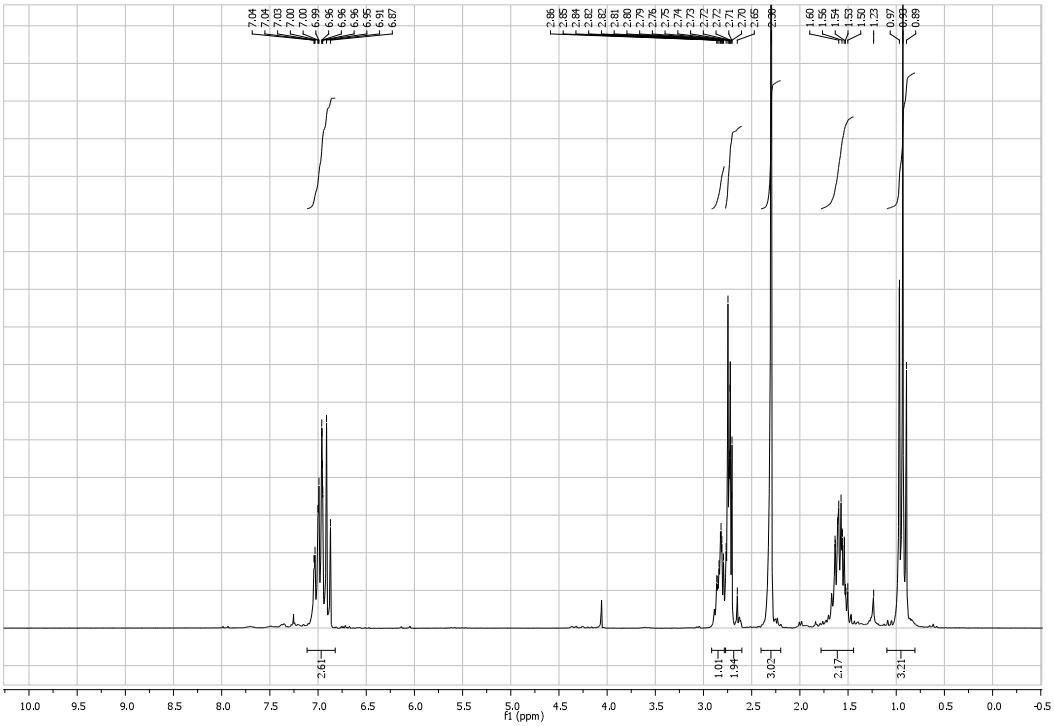
1: 210 nm, 8 nm

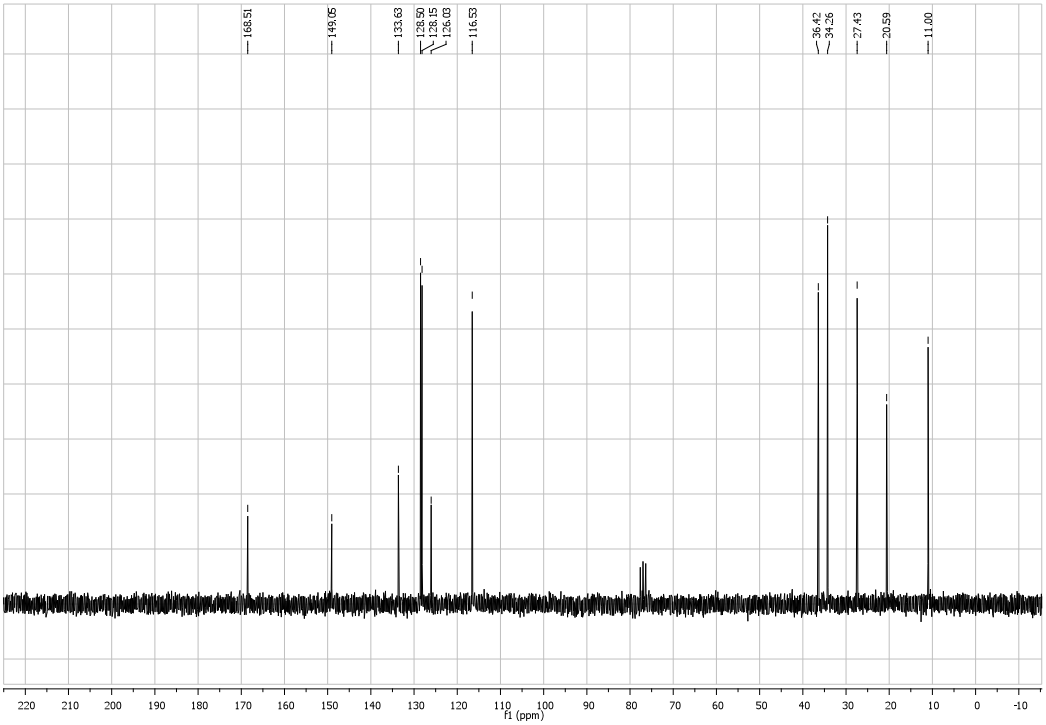
Pk #	Name	Retention Time	Area	Area Percent
1	?	25.952	14938105	98.93
2	?	26.987	161227	1.07
Totals			15099332	100.00

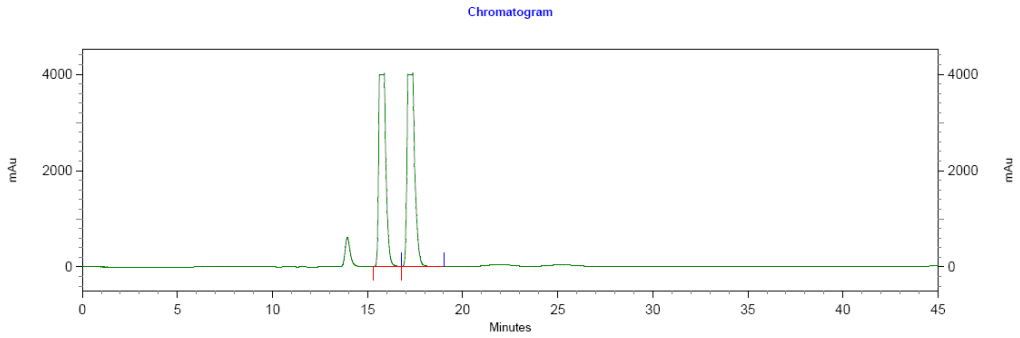
(R)-4-ethyl-6-methylchroman-2-one (4a)



4a

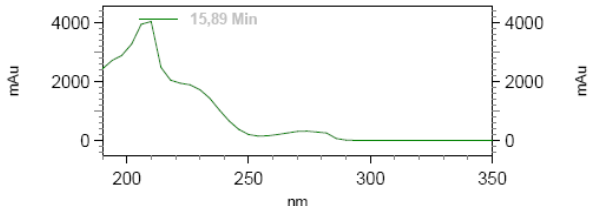




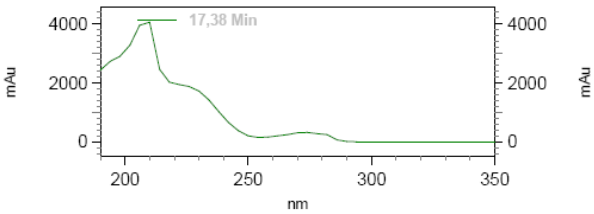


1: 210
nm, 2 nm
Results

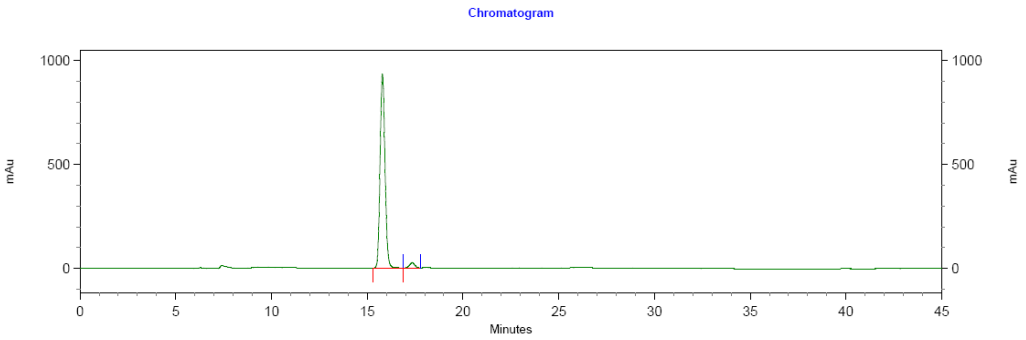
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 15,888 Minutes	15,888	104862215	48,076
2	Peak @ 17,384 Minutes	17,384	113257593	51,924
Totals			218119808	100,000



Retention time: 15,888 Min
Peak name: Peak @ 15,888 Minutes
Lambda max: 203, 271, 315
Lambda min: 313, 261



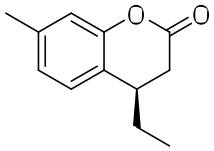
Retention time: 17,384 Min
Peak name: Peak @ 17,384 Minutes
Lambda max: 203, 271, 315
Lambda min: 313, 261



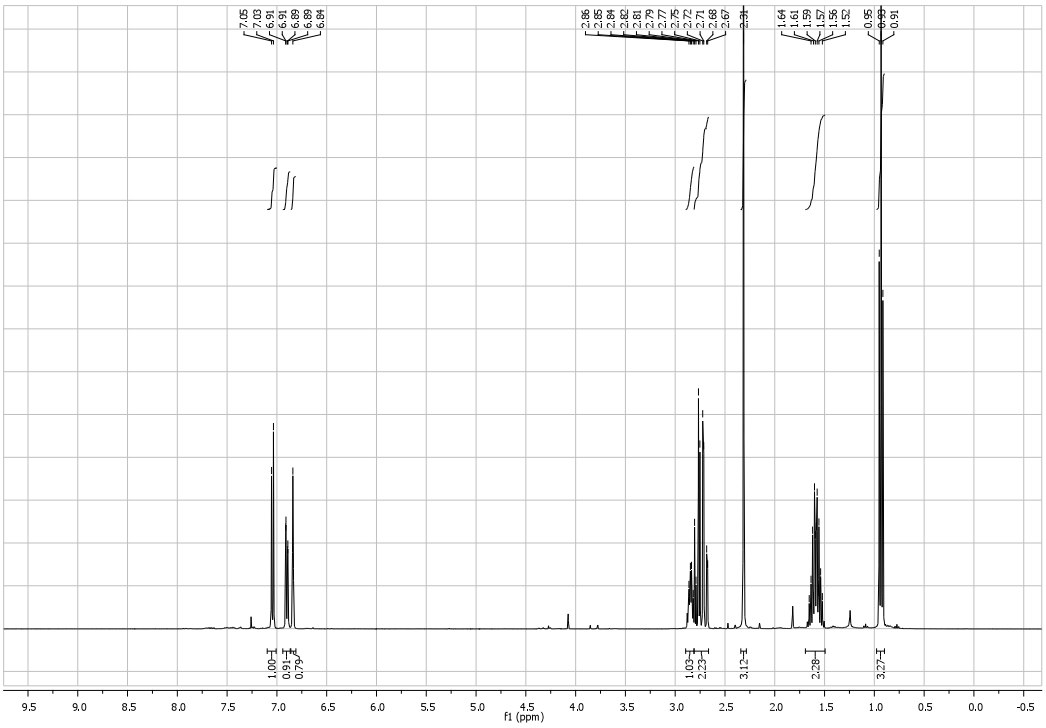
1: 210
nm, 2 nm
Results

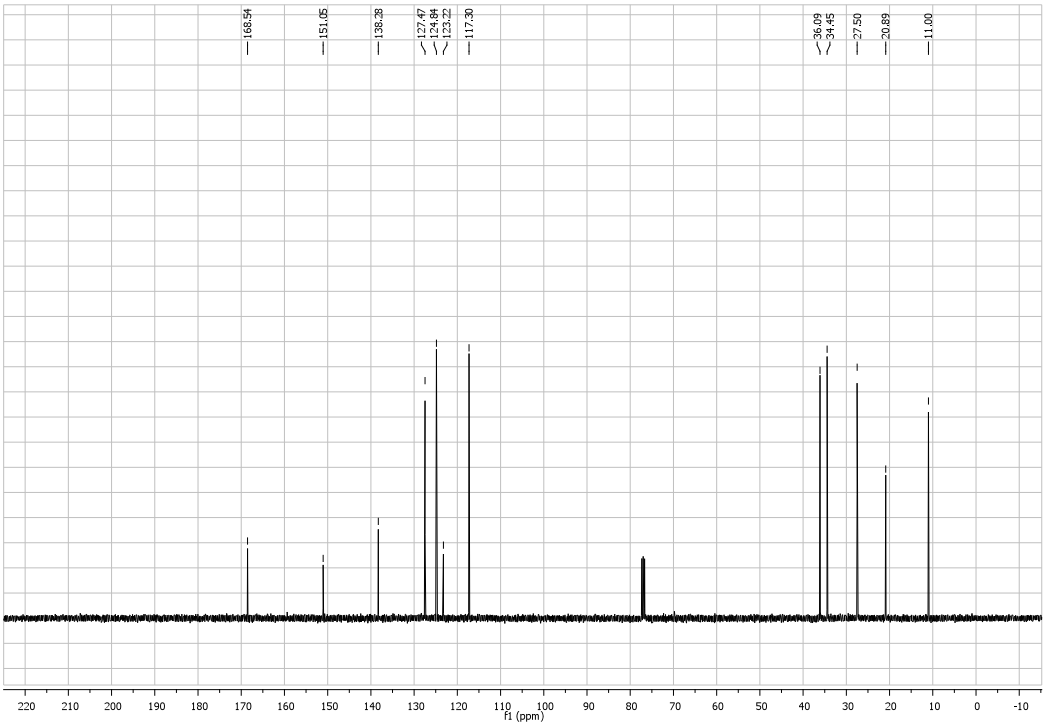
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 15,792 Minutes	15,792	16633365	97,134
2	Peak @ 17,340 Minutes	17,340	490793	2,866
Totals			17124158	100,000

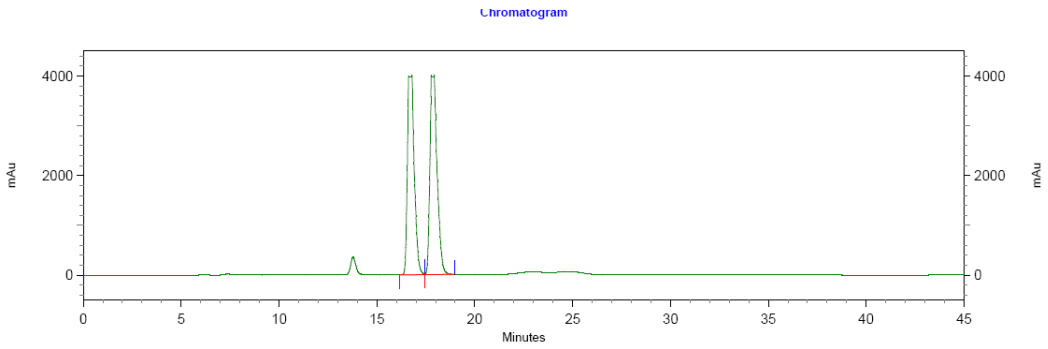
(R)-4-ethyl-7-methylchroman-2-one (4b)



3b

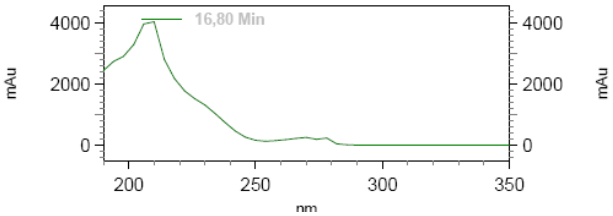




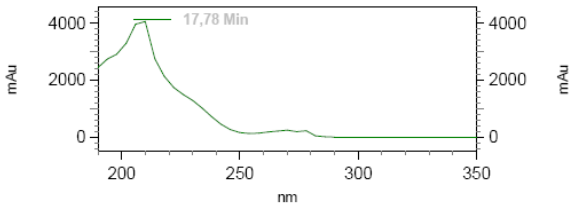


1: 210
nm, 2 nm
Results

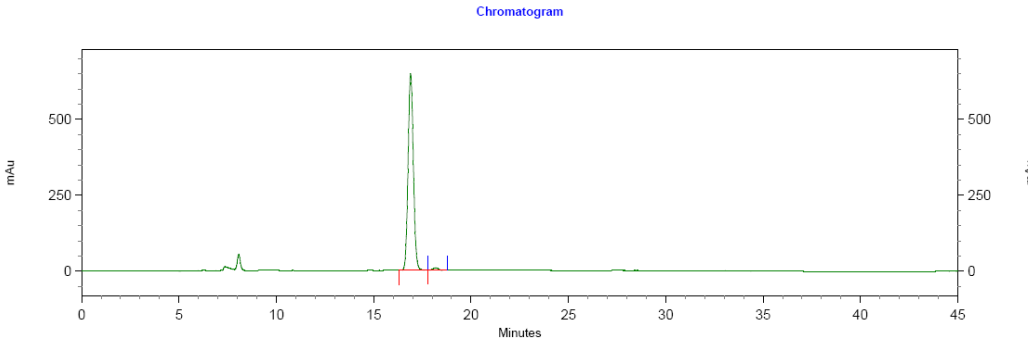
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 16,800 Minutes	16,800	97583622	48,785
2	Peak @ 17,776 Minutes	17,776	102443923	51,215
Totals			200027545	100,000



Retention time: 16,800 Min
Peak name: Peak @ 16,800 Minutes
Lambda max: 204, 266
Lambda min: 261



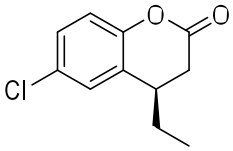
Retention time: 17,776 Min
Peak name: Peak @ 17,776 Minutes
Lambda max: 204, 266
Lambda min: 261



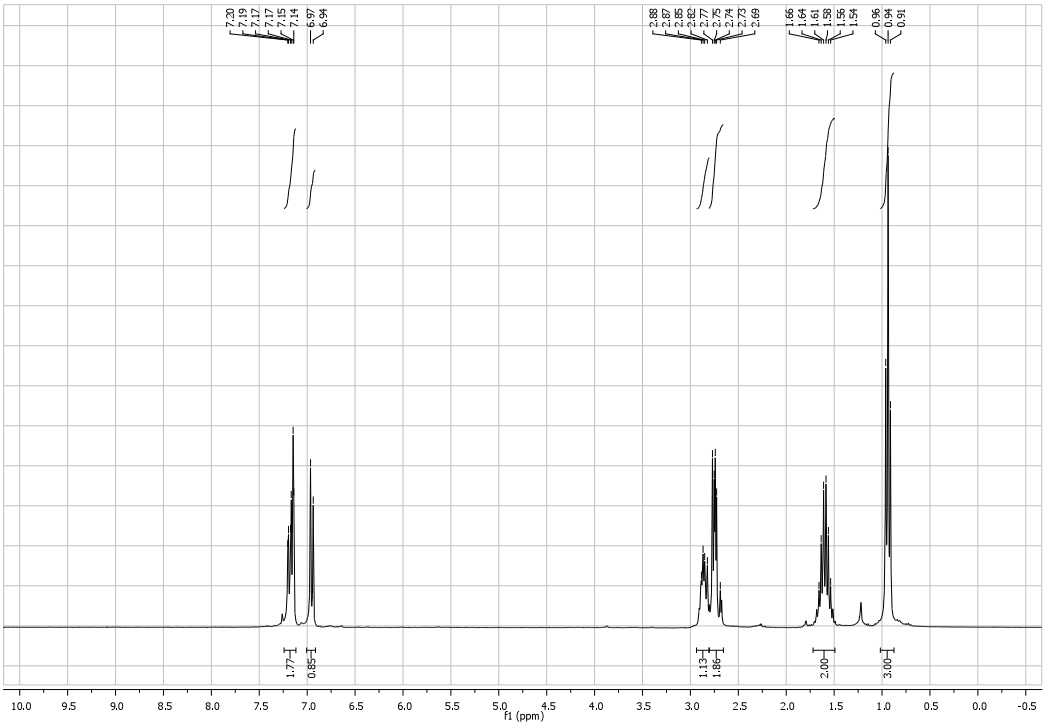
1: 210
nm, 2 nm
Results

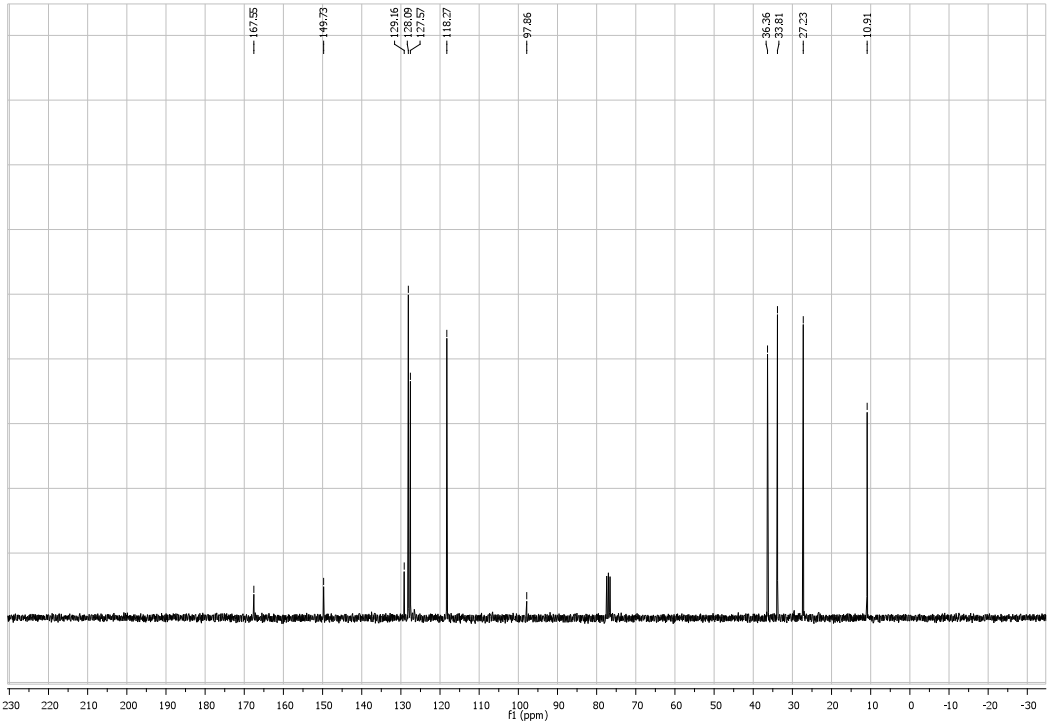
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 16,900 Minutes	16,900	12275155	98,536
2	Peak @ 18,180 Minutes	18,180	182436	1,464
Totals			12457591	100,000

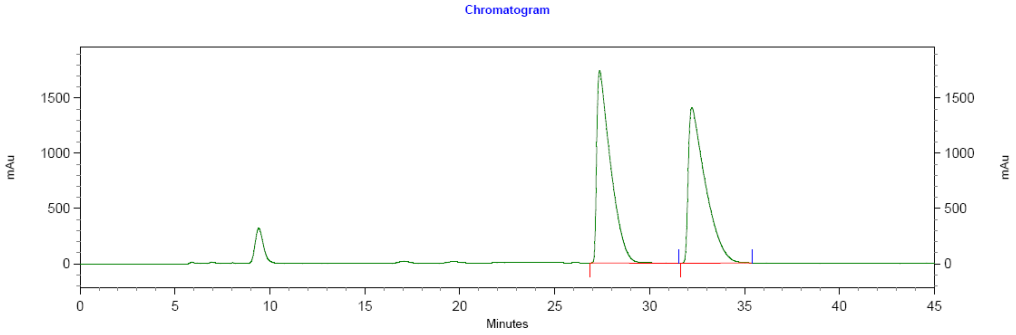
(R)-6-chloro-4-ethylchroman-2-one (4c)



4c

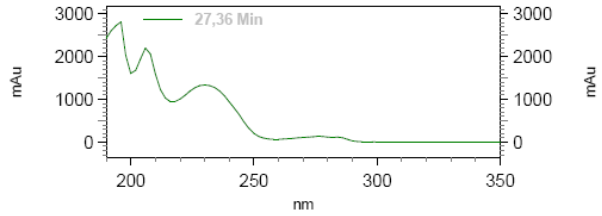




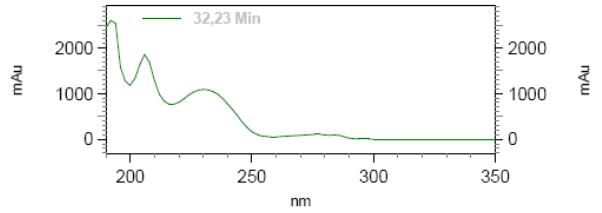


1: 210
nm, 2 nm
Results

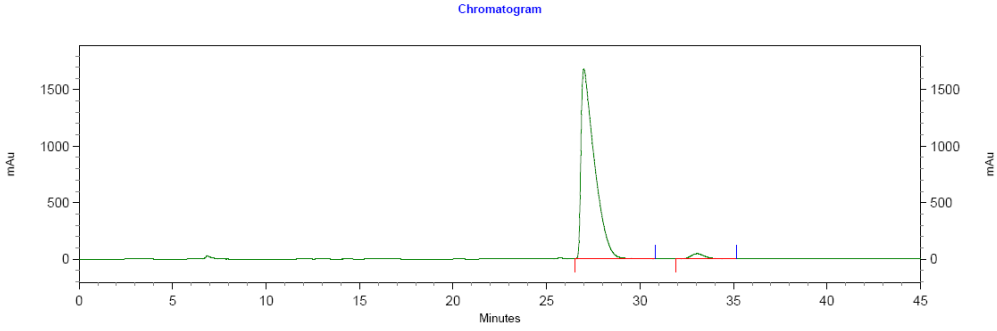
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 27,364 Minutes	27,364	88081245	49,953
2	Peak @ 32,228 Minutes	32,228	88246655	50,047
Totals			176327900	100,000



Retention time: 27,364 Min
Peak name: Peak @ 27,364 Minutes
Lambda max: 190, 230, 277
Lambda min: 261, 219



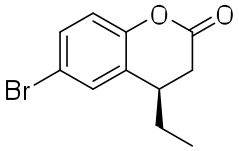
Retention time: 32,228 Min
Peak name: Peak @ 32,228 Minutes
Lambda max: 230, 277
Lambda min: 261, 219



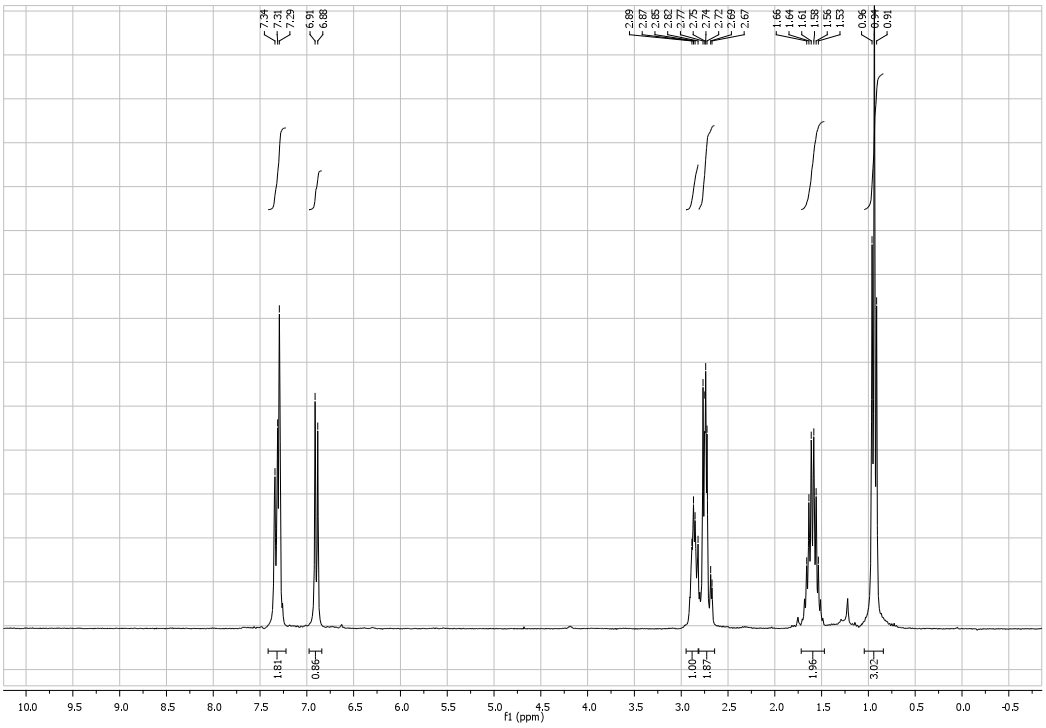
1: 210
nm, 2 nm
Results

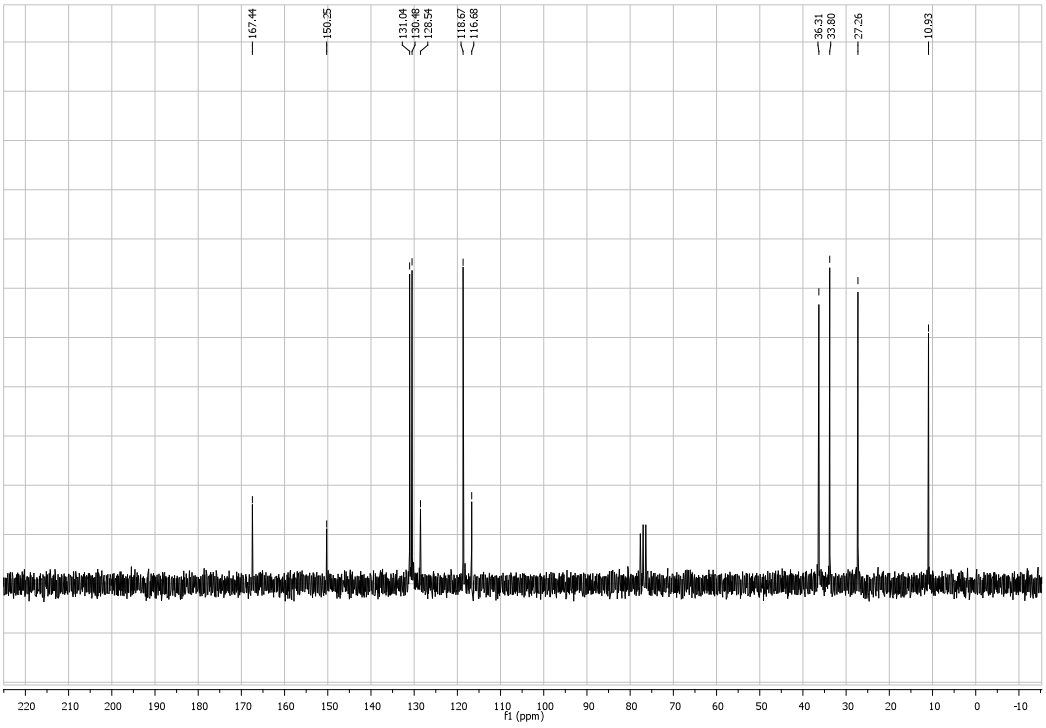
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 27,000 Minutes	27,000	83688317	97,310
2	Peak @ 33,052 Minutes	33,052	2313122	2,690
Totals			86001439	100,000

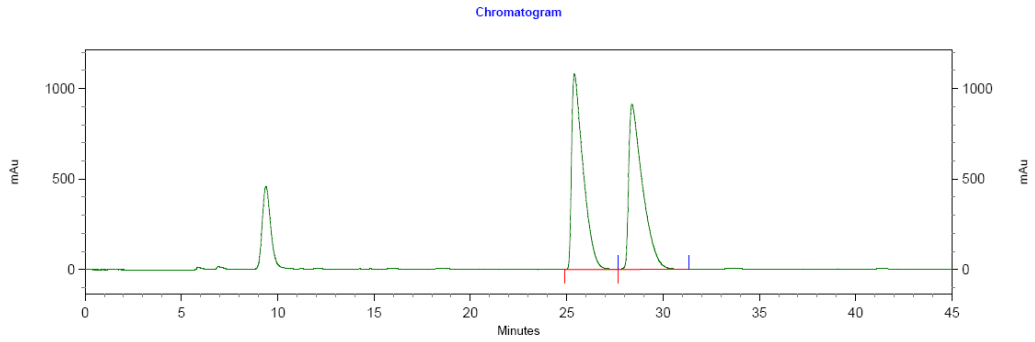
(R)-6-bromo-4-ethylchroman-2-one (4d)



4 d

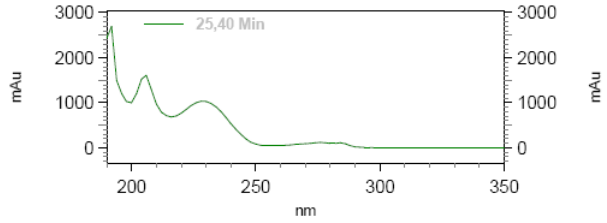




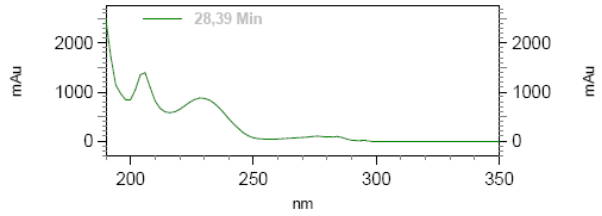


1: 210
nm, 2 nm
Results

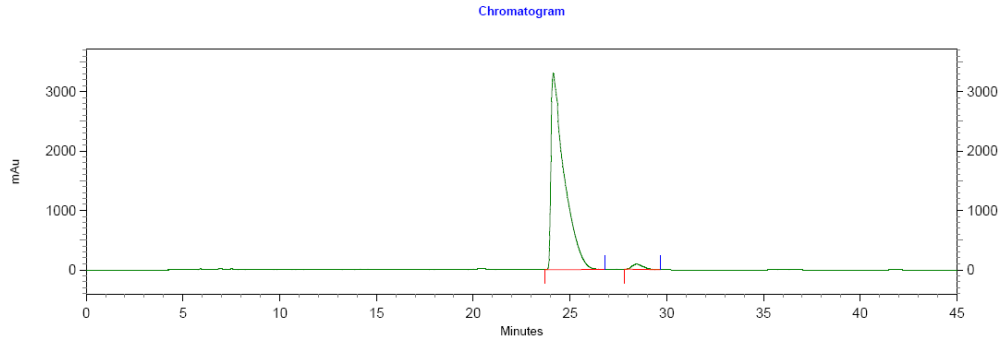
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 25,404 Minutes	25,404	44806839	49,770
2	Peak @ 28,392 Minutes	28,392	45221605	50,230
Totals			90028444	100,000



Retention time: 25,404 Min
Peak name: Peak @ 25,404 Minutes
Lambda max: 229, 278, 319
Lambda min: 308, 258, 217



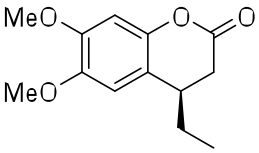
Retention time: 28,392 Min
Peak name: Peak @ 28,392 Minutes
Lambda max: 203, 229, 278
Lambda min: 307, 258, 217



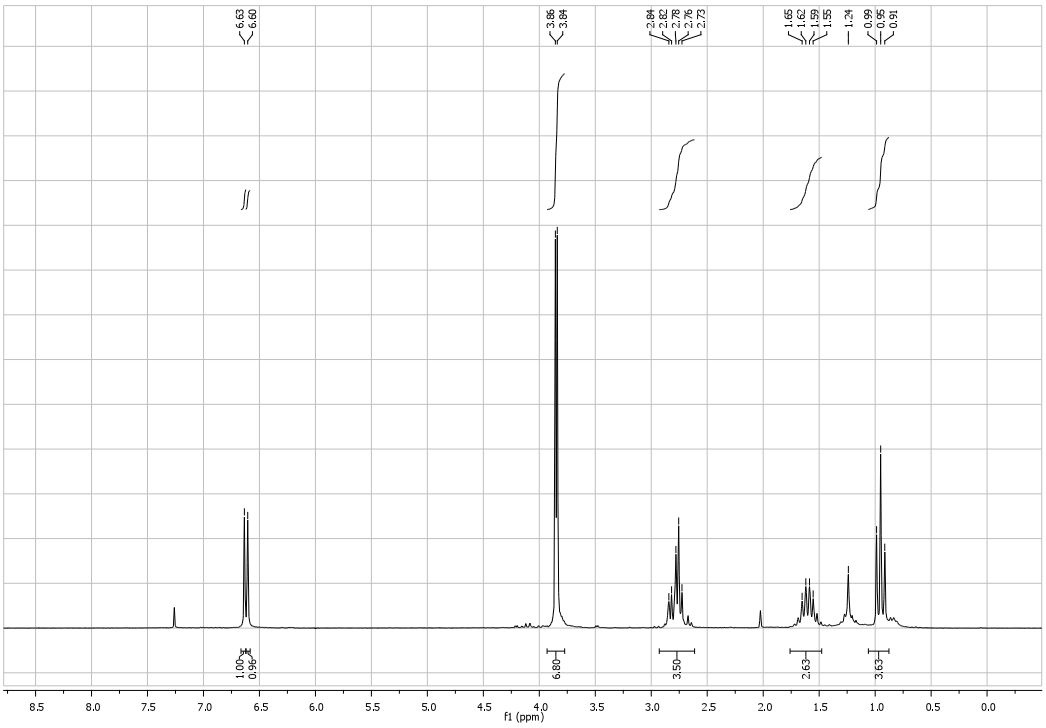
1: 210
nm, 2 nm
Results

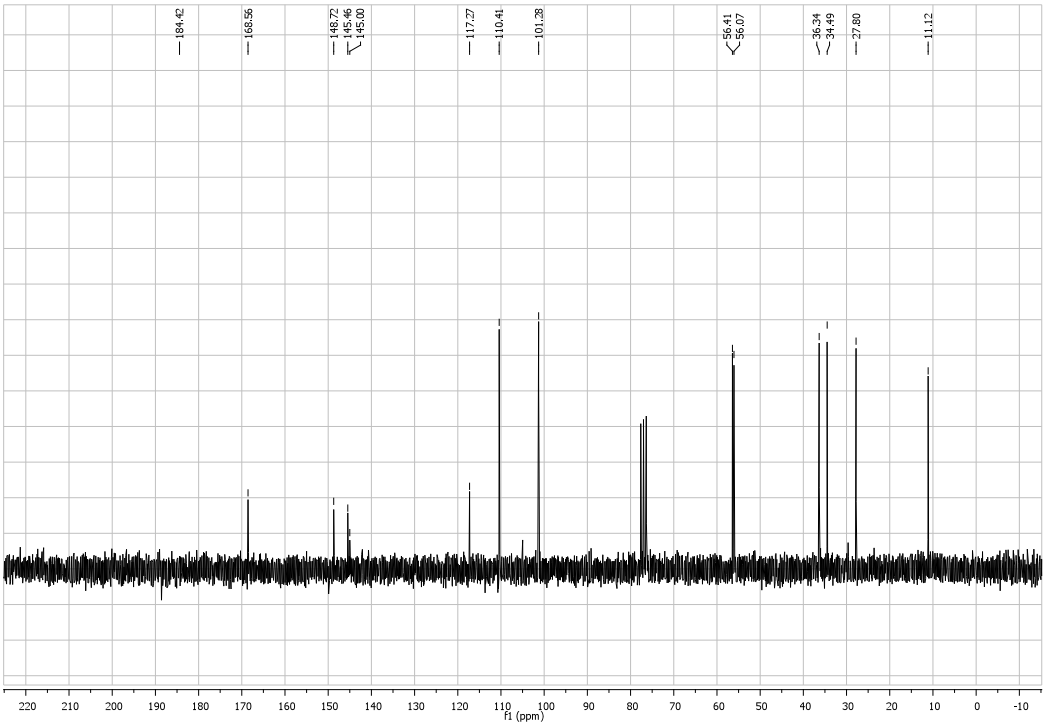
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 24,140 Minutes	24,140	155827537	97,747
2	Peak @ 28,444 Minutes	28,444	3592045	2,253
Totals			159419582	100,000

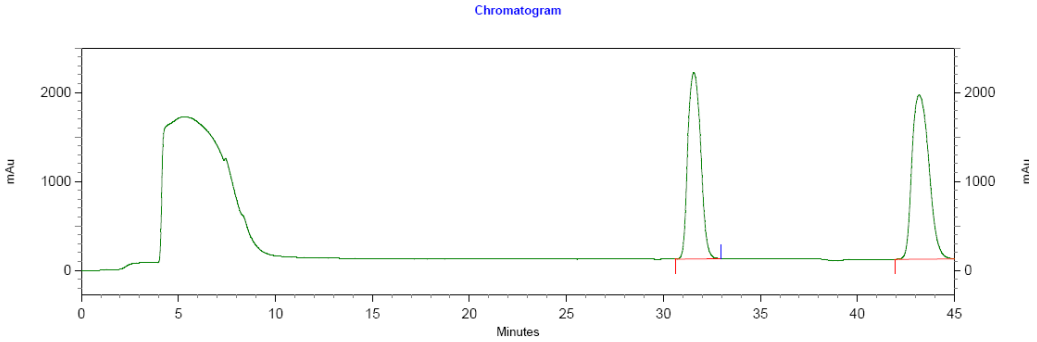
(R)-4-ethyl-6,7-dimethoxychroman-2-one (4e)



4e

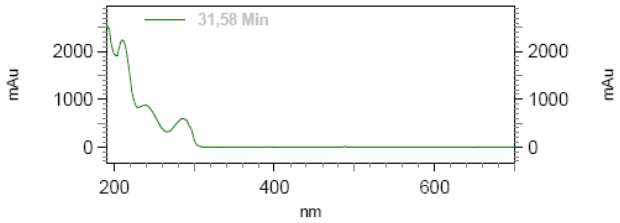




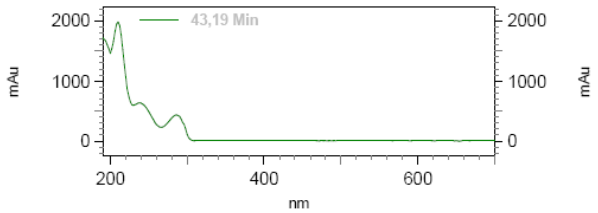


1: 210
nm, 2 nm
Results

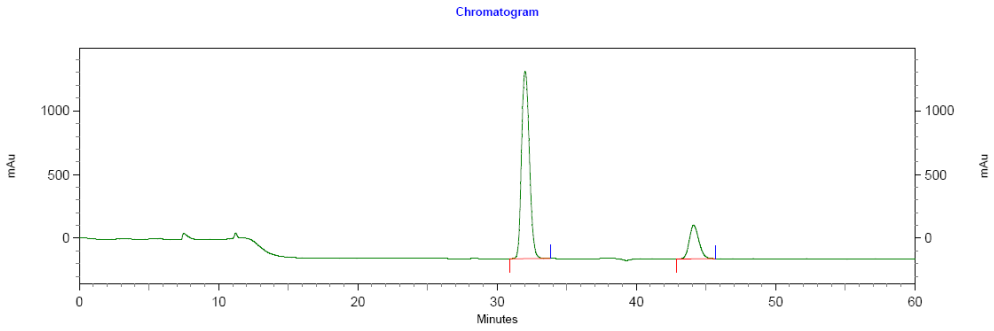
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 31,580 Minutes	31,580	96508099	46,372
2	Peak @ 43,188 Minutes	43,188	111608377	53,628
Totals			208116476	100,000



Retention time: 31,580 Min
Peak name: Peak @ 31,580 Minutes
Lambda max: 209, 237, 285
Lambda min: 654, 353, 359



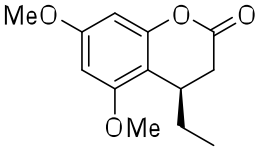
Retention time: 43,188 Min
Peak name: Peak @ 43,188 Minutes
Lambda max: 209, 237, 285
Lambda min: 654, 349, 379



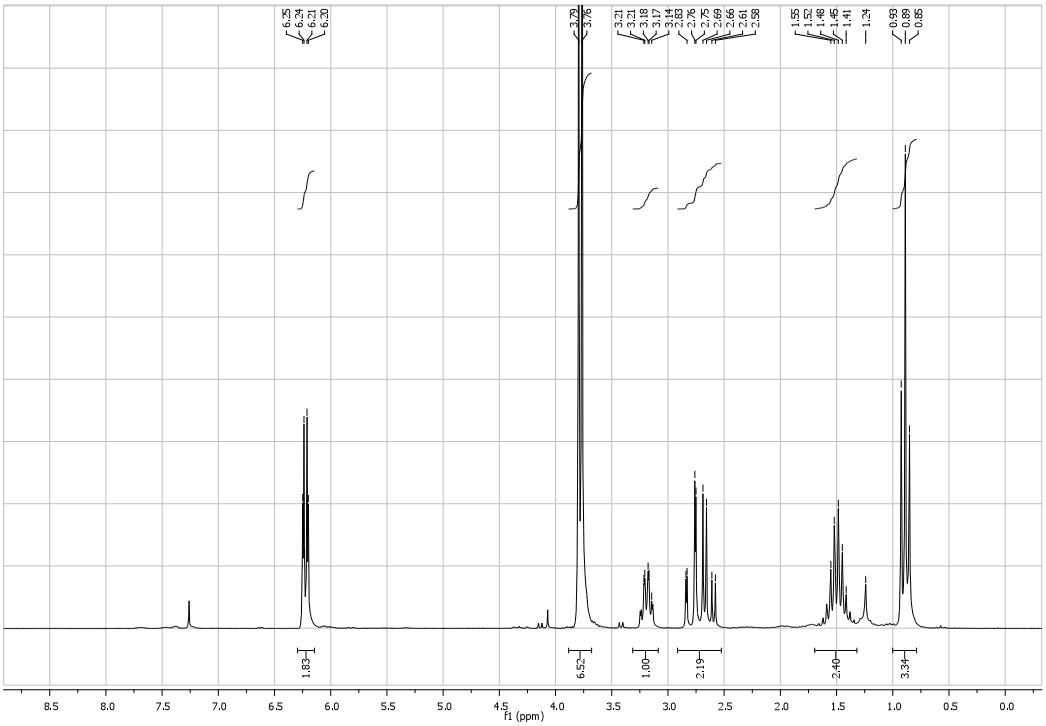
1: 210
nm, 2 nm
Results

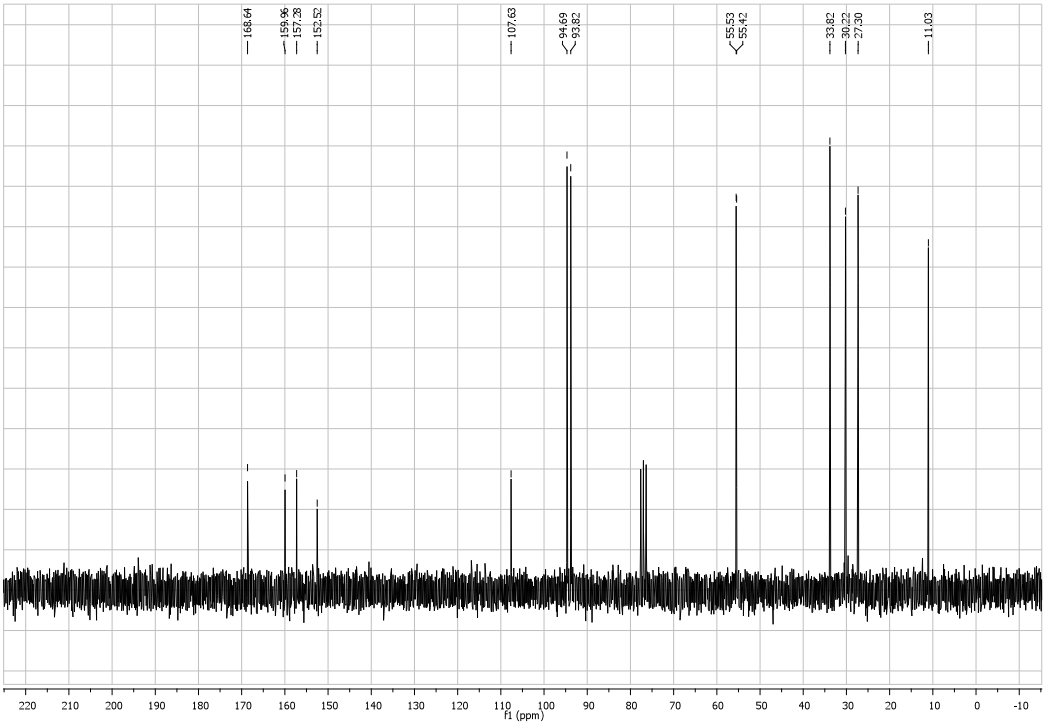
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 32,008 Minutes	32,008	57728692	81,879
2	Peak @ 44,112 Minutes	44,112	12775857	18,121
Totals			70504549	100,000

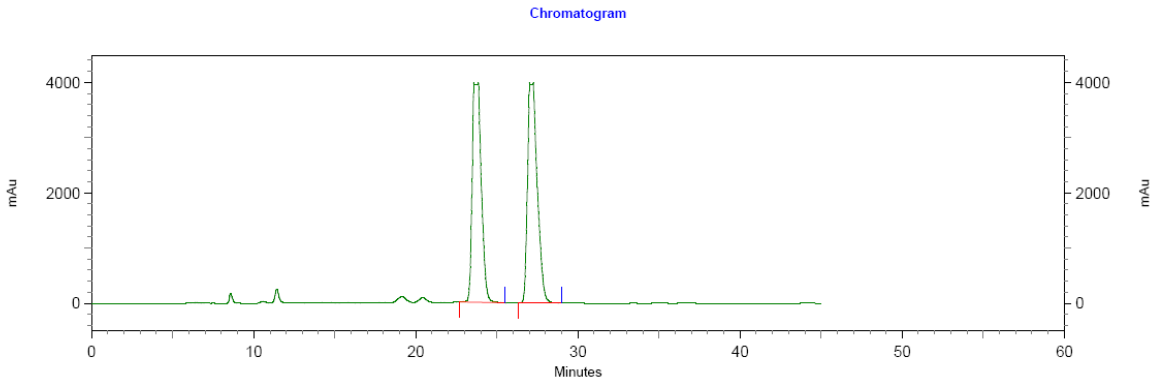
(R)-4-ethyl-5,7-dimethoxychroman-2-one (4f)



4f

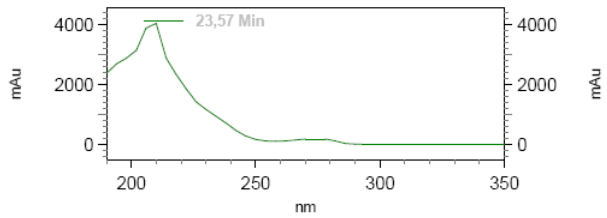




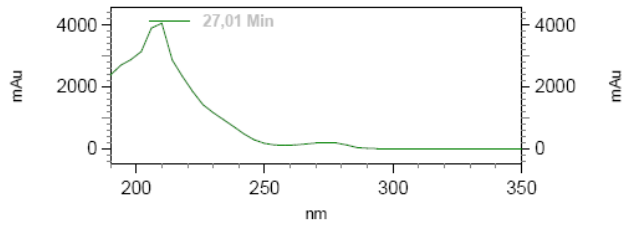


1: 210
nm, 2 nm
Results

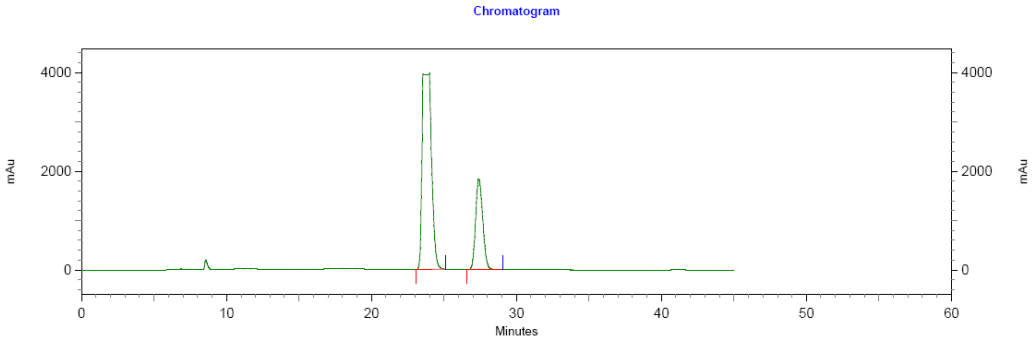
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 23,568 Minutes	23,568	154537832	48,275
2	Peak @ 27,008 Minutes	27,008	165581498	51,725
Totals			320119330	100,000



Retention time: 23,568 Min
Peak name: Peak @ 23,568 Minutes
Lambda max: 205, 268, 324
Lambda min: 313, 265



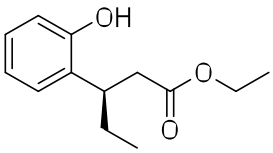
Retention time: 27,008 Min
Peak name: Peak @ 27,008 Minutes
Lambda max: 205, 268, 326
Lambda min: 312, 265



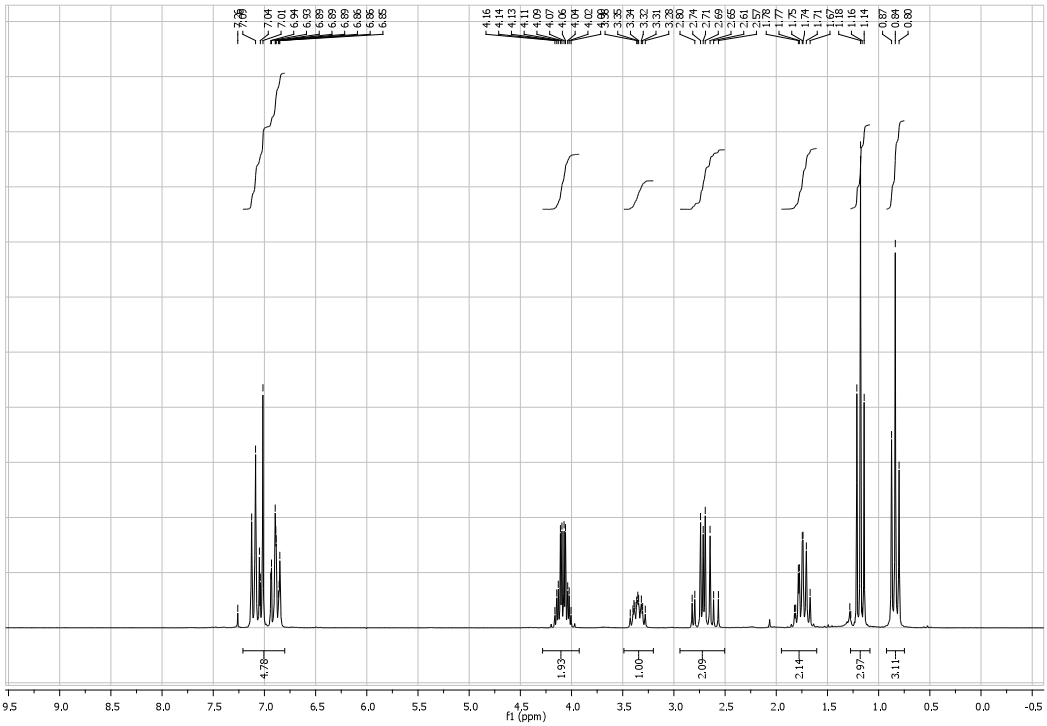
1: 210
nm, 2 nm
Results

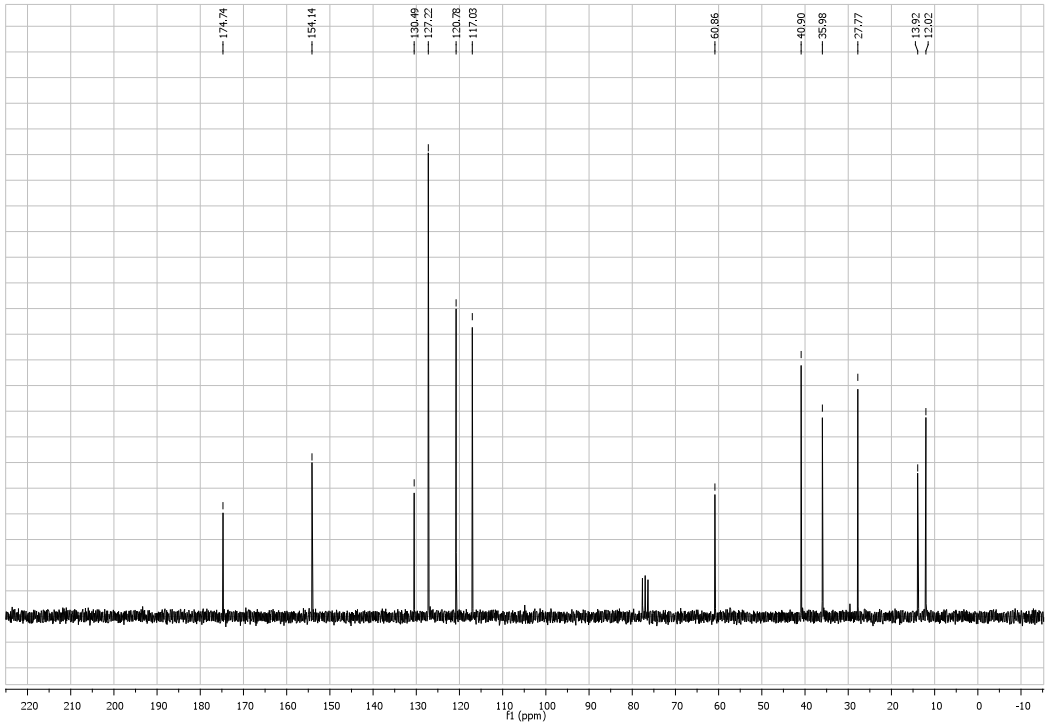
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 24,004 Minutes	24,004	179332368	74,004
2	Peak @ 27,408 Minutes	27,408	62996163	25,996
Totals			242328531	100,000

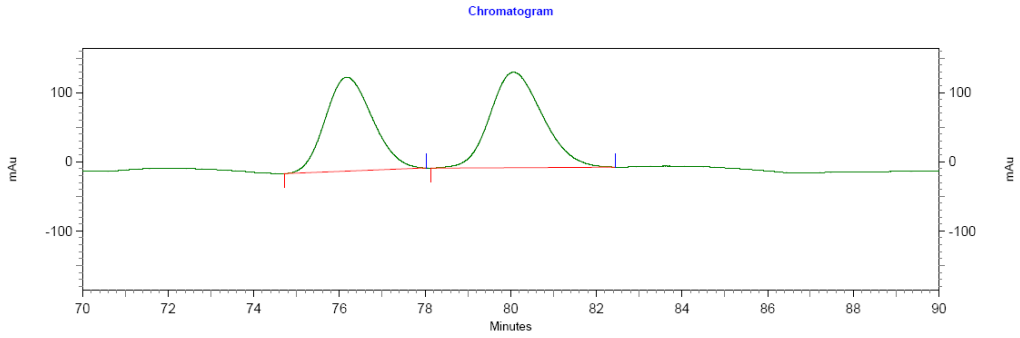
(R)-ethyl 3-(2-hydroxyphenyl)pentanoate (6)



6

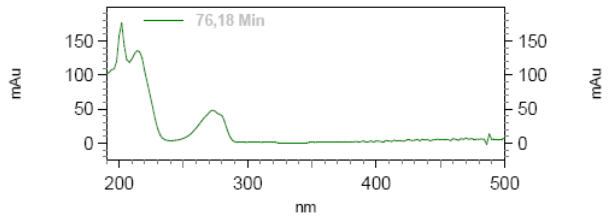




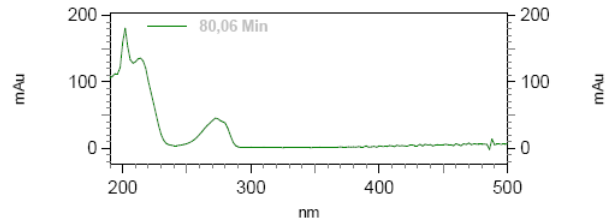


1: 210
nm, 2 nm
Results

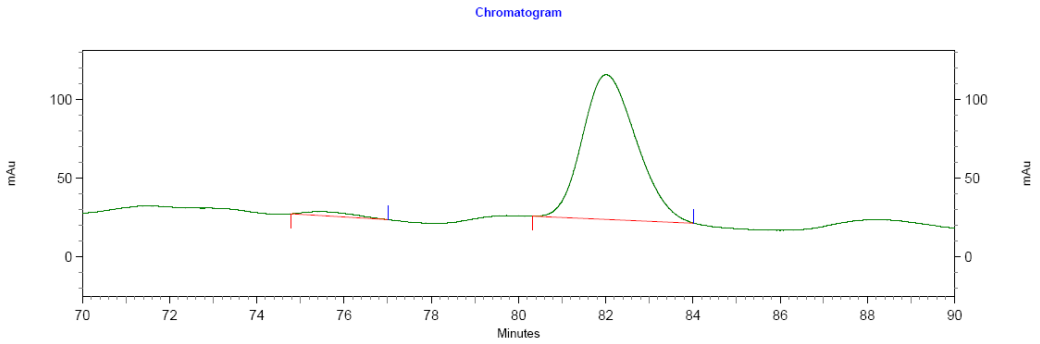
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 76,180 Minutes	76,180	10354685	46,807
2	Peak @ 80,064 Minutes	80,064	11767576	53,193
Totals			22122261	100,000



Retention time: 76,180 Min
Peak name: Peak @ 76,180 Minutes
Lambda max: 203, 273, 473
Lambda min: 335, 298, 242



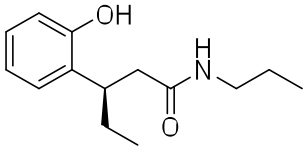
Retention time: 80,064 Min
Peak name: Peak @ 80,064 Minutes
Lambda max: 204, 273, 473
Lambda min: 335, 298, 242



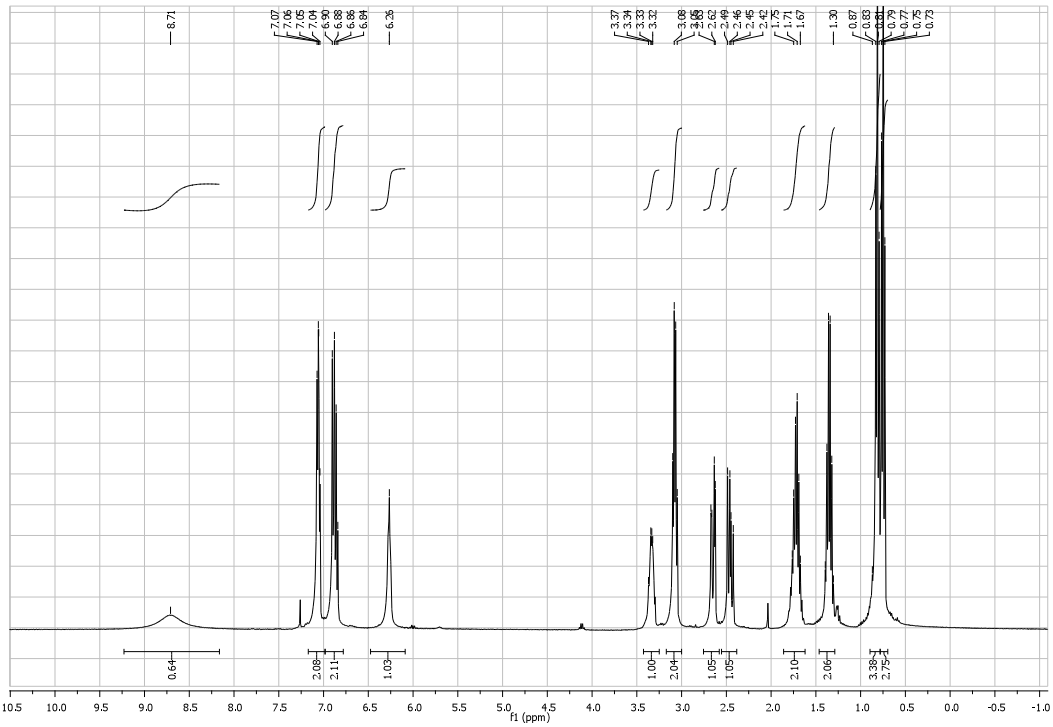
1: 210
nm, 2 nm
Results

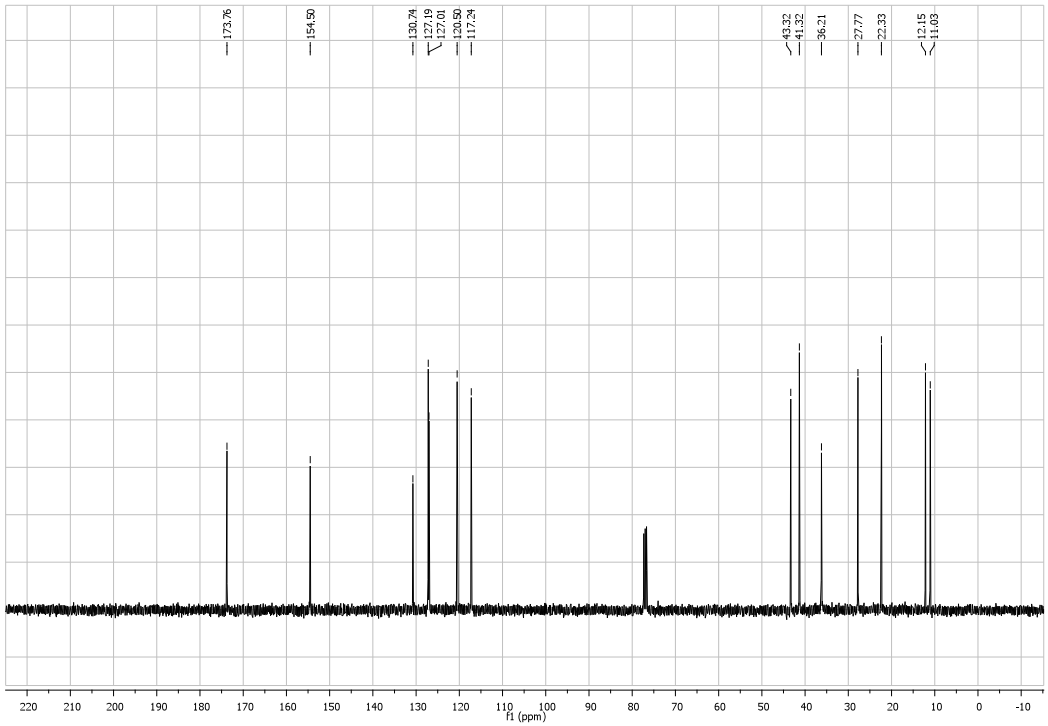
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 75,384 Minutes	75,384	210098	2,586
2	Peak @ 82,012 Minutes	82,012	7913271	97,414
Totals			8123369	100,000

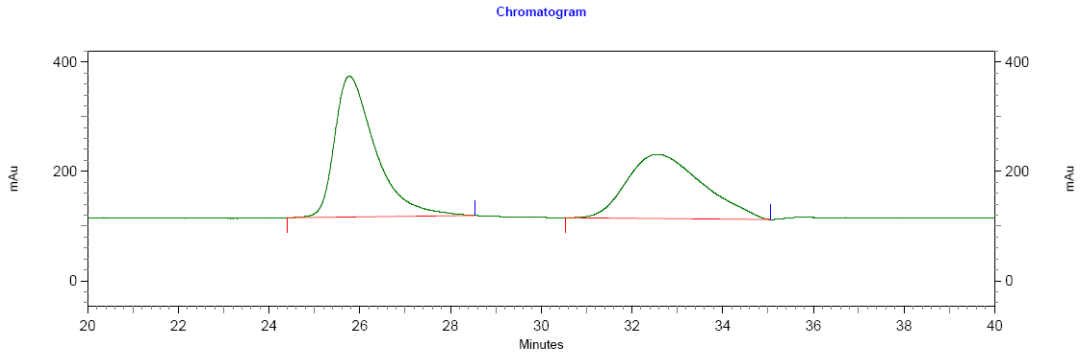
(R)-3-(2-hydroxyphenyl)-N-propylpentanamide (7)



7

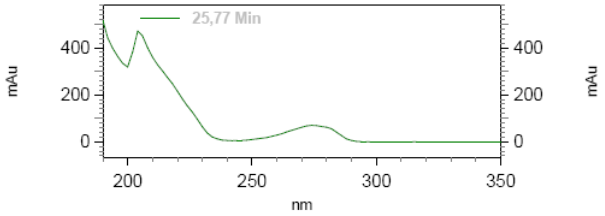




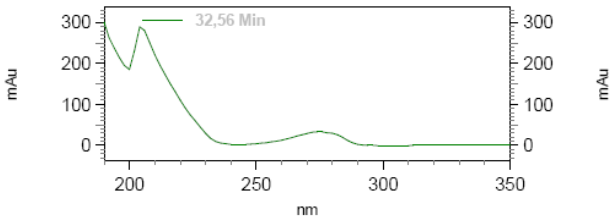


1: 210
nm, 2 nm
Results

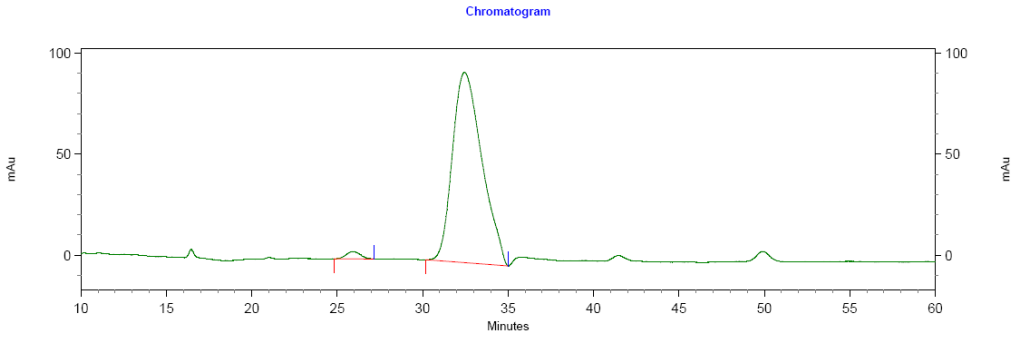
Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 25,768 Minutes	25,768	16110388	54,200
2	Peak @ 32,564 Minutes	32,564	13613462	45,800
Totals			29723850	100,000



Retention time: 25,768 Min
Peak name: Peak @ 25,768 Minutes
Lambda max: 205, 275, 326
Lambda min: 305, 348, 244



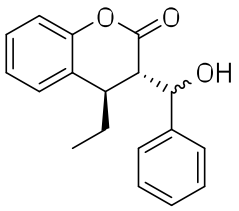
Retention time: 32,564 Min
Peak name: Peak @ 32,564 Minutes
Lambda max: 205, 275, 339
Lambda min: 304, 342, 244



1: 210
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 25,924 Minutes	25,924	213761	1,860
2	Peak @ 32,448 Minutes	32,448	11280307	98,140
Totals			11494068	100,000

(3S,4R)-4-ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one (8)



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