Electronic Supplementary Information (ESI) for the Synthesis of an 8-membered oxygen-containing benzo-fused heterocycle using flow technologies

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1. Experimental

1.1 General experimental detail

All batch reactions were carried out using traditional chemistry methods, glassware and apparatus found in a standard synthetic laboratory. Prior to use, all glassware was oven- or flame-dried, and specified reactions were carried out under an inert environment using either argon or nitrogen gas. Under an inert environment (nitrogen), certain drying agents were used to distill solvents. Toluene was distilled from sodium, dimethylformamide was distilled using molecular sieves (type 4A molecular sieves), acetonitrile and ethyl acetate were distilled using calcium hydride, and tetrahydrofuran was distilled using sodium with benzophenone added as an indicator.

All starting materials and solvents were purchased from fine chemical vendors and commercial sources and used without purification. The removal of solvent was performed either with the use of evaporation under a flowing stream of compressed air, or by removal under reduced pressure (approximately 20 mmHg) using a standard Heidolph rotary evaporator at temperatures between 40 °C and 90 °C, depending on solvent identity.

1.2 Flow reactors and equipment

All flow reactors and specifications are indicated in each experimental description, for convenience a general description is provided below:

1. Flow reactors:
    a. Uniqsis™ Binary Pump Module (BPM) reactor equipped with 10 mL HPLC pump heads
    b. Vapourtec™ E-series easy-Medchem 3-pump peristaltic flow reactor equipped with blue pump tubing compatible with the chosen solvents.
    c. Both reactors were fitted with standard 1/16” outer diameter and 1.0 mm inner diameter or 1/8” outer diameter and 1.5 mm inner diameter PTFE or SS tubing.
2. Coil reactors:
    a. PTFE/PFA coil reactors had a maximum operating temperature of 150 °C and maximum pressure of 362-psi (25 bar) with volumes of 10 or 14 mL (1/16” outer diameter and 1.0 mm inner diameter) and 25 or 52 mL (1/8” outer diameter and 1.5 mm inner diameter).
    b. Stainless-steel coil reactors had a maximum operating temperature of 260 °C and maximum pressure of 1000-psi (70 bar) with volumes of 2 and 20 mL (1/16” outer diameter and 1.0 mm inner diameter).
3. Packed bed reactors:
    a. Omnifit™ glass columns with enhanced PEEK adjustable end fittings and frits were used for packed bed column reactors. The columns had a maximum temperature of 150 °C and maximum pressure of 362-psi (25 bar) for the 10-mm inner diameter column reactor used.
    b. The volume of the columns was determined by packing the column with immobilized reagent and cotton at the ends of the column and sealing it with an end-cap. The column was further packed by flowing through the selected solvent until no air bubbles were observed. The column volume was determined via the difference between the dry and wet weights divided by the density of the solvent.
4. The column and coil reactors were heated using a Uniqsis™ HotCoil flow module that was fitted with the Uniqsis™ HotColumn housing for the columns and has operational temperature ranges from ambient temperature to 260 °C. A Uniqsis™ Polar Bear PLUS flow module was used for cooling with an operational temperature range of -40 °C to 150 °C.
5. Mixing chips:
    a. A 20 mL Uniqsis™ glass mixing chip was used for the ring-closing metathesis step with a maximum pressure rating of 10 bar.
6. Static mixer:
    a. A 0.5 mL Vapourtec™ static mixer was used with maximum pressure rating of 362-psi (25 bar).

7. Cartridge-based back-pressure regulators (BPR) were used with pressures set to 3 bar, 8 bar and 20 bar based on application and they were fitted with chemically resistant perfluoropolymer or Hastelloy components.

1.3 Characterisation and purification

1. Purification: Isolated yields were obtained by performing column chromatography using Merck silica gel 60 (0.040–0.063 mm) as the stationary phase. Mobile phase eluents are indicated in in each experimental description.
2. Nuclear Magnetic Radiance (NMR) were performed using a Bruker Ultrashield AVANCE-III spectrometer.
    a. Splitting and multiplicity patterns are reported as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), doublet of triplet (dt), quartet (q), multiplet (m) and broad singlet (bs). Coupling constants, J, were reported in Hertz (Hz). Chemical shifts δ, are reported in parts per million (ppm).
    b. ^{1}H NMR were recorded at 300 and 400 MHz and chemical shifts were reported in the following order: chemical shift (δH, ppm); coupling constants (J, Hz); multiplicity; number or protons; proton assignment and all signals are referenced relative to deuterated chloroform ($CDCl_3$) at 7.27 ppm.
    c. ^{13}C NMR were recorded at 75MHz and 101 MHz and chemical shifts were reported in the following order: chemical shift (δC, ppm); assignment and all signals are referenced relative to $CDCl_3$ at 77.36 ppm.
3. Thin Layer Chromatography (TLC)
    a. Reaction progress was monitored by TLC or HPLC.
    b. The reported retention factor (R_f) values were obtained from TLC analysis carried out on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F254).
4. Fourier-transform Infrared (FTIR) spectroscopy was performed on a Bruker Alpha Platinum ATR spectrometer instrument.
    a. Functional group signals were reported as wavenumbers (cm^{-1}) in the range of 400 – 3000 cm^{-1}.
5. High-performance liquid chromatography (HPLC) analysis was performed with an Agilent Infinity model and 1260-diode-array dector (DAD, G7115 A).
    a. The injection volume was set to 2.0 µL and the column oven was set to 35 °C and DAD data were reported at wavelengths of 210 and 260 nm. An Agilent Poroshell 120 EC-C18 column (695975-902, 100 × 4.6 mm inner diameter, 2.7-µm particles) was used.
    b. Samples were prepared using analytical grade acetonitrile to approximate concentrations relating to each method.
6. High-resolution mass spectra (HRMS) were recorded on a Waters Synapt G2 Mass Spectrometer at 70 eV and 200 mA.
    a. For analysis, the instrument was operated under the following conditions: a capillary voltage of 2.8 kV (positive mode), a sampling cone (ramped from 20 V – 40 V), an extraction cone of 4 V, a source temperature of 100 °C, a desolvation temperature of 200 °C, cone gas of 100 $L.h^{-1}$, desolvation gas of 500 $L.h^{-1}$, inert gas source: nitrogen.
    b. Samples were prepared in analytical grade acetonitrile to an approximate concentration of 10 $µg.mL^{-1}$.

1.4 Nomenclature

1. Compound were named according to IUPAC nomenclature and ChemDraw Ultra 12.0 was used for naming, and numbering was chosen as a matter of convenience.
2. NMR FID's were processed and analyzed using MestreNova 12.0

1.5 Overall percentage yield and time calculations

Table 1: Calculations of overall percentage yield and total reaction time for batch and flow conditions compared to literature values

Approach	Overall percentage yield	Total reaction time
Van Otterlo and co-workers	(0.99×0.75×0.86×0.77×0.52)×100 = 25.6 %	20+64+18+12+20+2 =136 hours
Flow	(0.93×0.98×0.86×0.93×0.92×0.55) ×100 = 36.9 %	(15×3) +25 (20×2) =110 minutes

1.6 Reactor setup for each step

Figure 1: Phenolic allylation (potassium carbonate approach) setup using Uniqsis Binary Pump

Figure 2: Claisen rearrangement setup using Uniqsis Binary Pump

Figure 3: Protection (potassium hydroxide) setup using Uniqsis Binary Pump

Figure 4: Reduction (polymer supported sodium borohydride approach) using Uniqsis Binary Pump

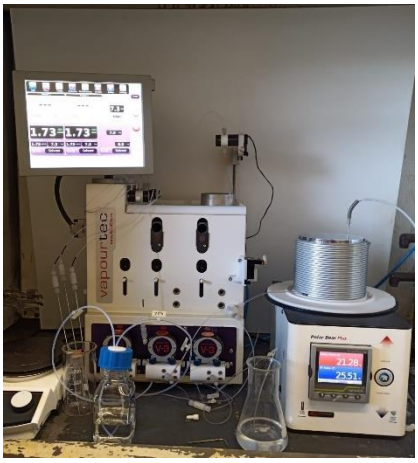


Figure 5: Reduction (sodium borohydride solution approach) using Vapourtec peristaltic pumps

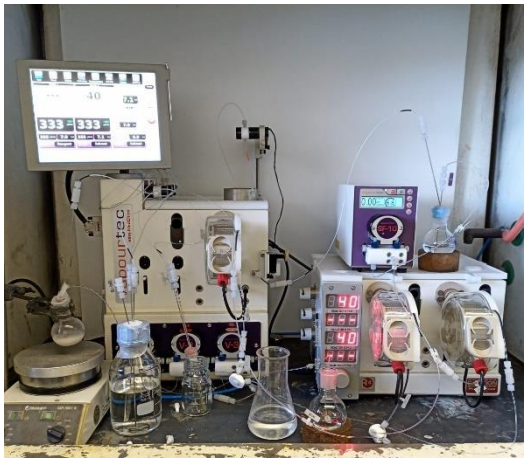


Figure 6: Second allylation (sodium hydride approach using standalone) using Vapourtec peristaltic pumps

Figure 7: Second allylation (sodium hydride approach using recycling approach) setup using Vapourtec peristaltic pumps

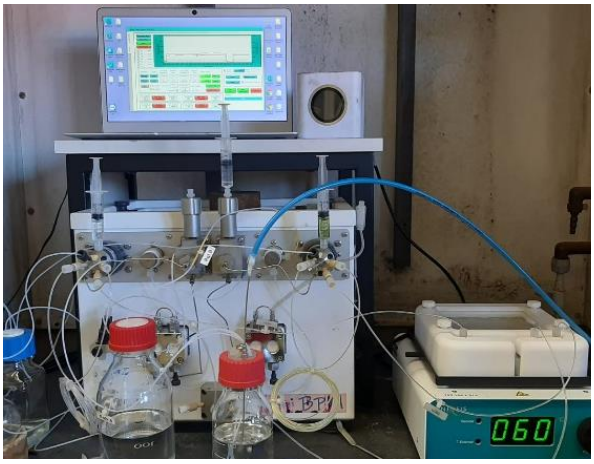
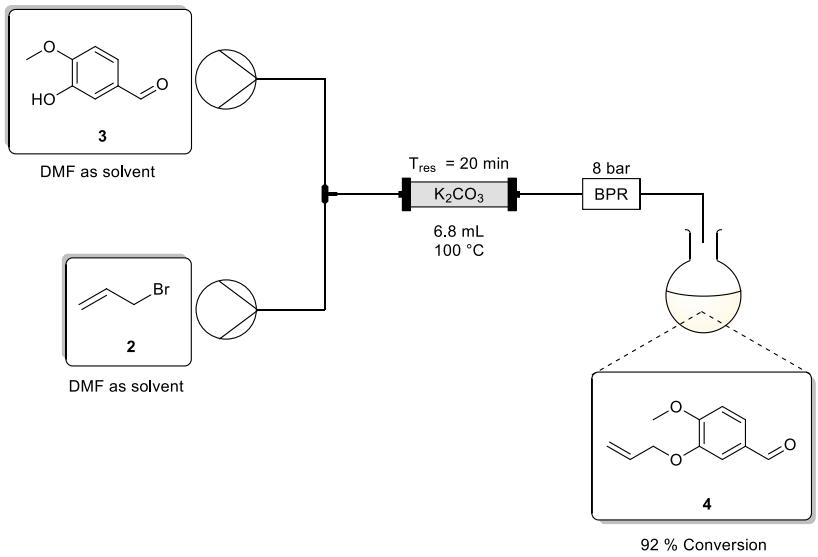


Figure 8: RCM setup using Uniqsis Binary Pump

2. Additional data related to main article.

2.1 Phenolic allylation using potassium carbonate



Scheme 1: Flow synthesis for the first allylation of isovanillin **3** using potassium carbonate

Table 2: Flow screens for the allylation of isovanillin **3** using potassium carbonate

Entry No	Reaction scale (g)	Solvent	Base	Allyl Bromide (equiv.)	Temperature (°C)	Residence time (min)	LC Conversion (%)
1[a]	0.50	ACN	K_2CO_3	2.5	80	30	0.0
2	0.25	ACN	DBU	2.5	80	30	67.0[b]
3	0.23	DMF	K_2CO_3	3.0	80	30	84.0 [b]
4	0.25	DMF	K_2CO_3	2.5	80	30	60.0
5	0.25	DMF	K_2CO_3	2.0	80	30	53.0
6	0.25	DMF	K_2CO_3	1.5	80	30	51.0
7	0.25	DMF	K_2CO_3	1.0	80	30	32.0
8	0.12	DMF	K_2CO_3	3.0	80	30	79.0
9	0.12	DMF	K_2CO_3	3.0	100	30	70.0
10	0.12	DMF	K_2CO_3	3.0	80	45	89.0
11	0.12	DMF	K_2CO_3	3.0	80	20	88.0
12 [c]	**0.12**	**DMF**	**K_2CO_3**	**3.0**	**100**	**20**	**92.0**
13	0.12	DMF	K_2CO_3	3.0	80	15	89.0

[a] Precipitation, reaction terminated, [b] Isolated yield, [c] Isolated yield (85%)

2.2 Claisen rearrangement using DMF

Table 3: Flow screens for the Claisen rearrangement when performed in DMF

Entry No	Reaction Scale (g)	Temperature (°C)	Residence time (min)	Isolated Yield (%)
1	0.1036	150	40	4
2	0.1025	180	40	13
3	0.1048	200	40	30
5	0.0999	240	40	49
6	0.1045	220	60	87*
7	0.0985	240	60	99
8	0.1065	240	50	94
9	0.0996	240	45	100

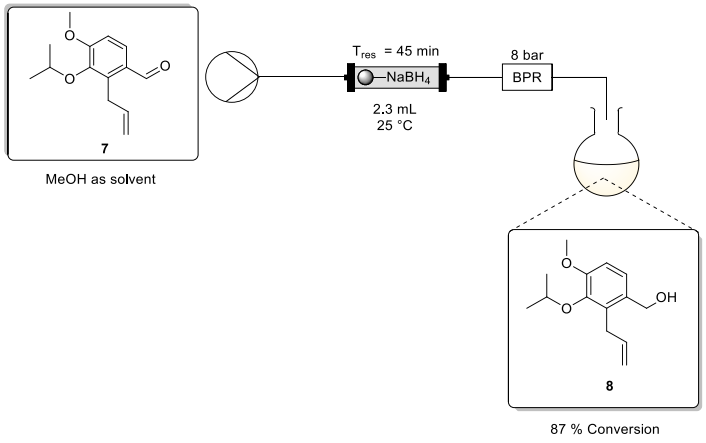
* Aborted due to reactor fouling

2.3 *Iso*-propyl protection using potassium hydroxide in aqueous methanol

Table 4: Flow screens for the *Iso*-propyl protection using potassium hydroxide in aqueous methanol

Entry No	Reaction scale (mL)	Solvent	Conc [M]	2-Bromopropane (equiv.)	KOH (equiv.)	Temperature (°C)	Residence time (min)	LC Conversion (%)
1	2.13	MeOH	0.4	2.00	1.80	80	35	43.97
2	2.13	MeOH	0.4	2.00	1.80	80	30	36.51
3	2.13	MeOH	0.4	2.00	1.80	80	25	24.39
4	2.13	MeOH	0.4	2.00	1.80	80	20	25.28
5	2.13	MeOH	0.4	2.00	1.80	80	15	23.73
6	2.13	MeOH	0.4	2.00	1.80	80	10	18.32
7	2.13	MeOH	0.4	2.00	1.80	80	5	10.24
8	**5.00**	**MeOH**	**0.2**	**2.50**	**1.80**	**120**	**25**	**68.53**
9	5.00	MeOH	0.2	2.00	1.50	120	25	64.68
10	5.00	MeOH	0.2	2.50	1.80	120	20	63.56
11	5.00	MeOH	0.2	2.00	1.50	130	25	61.74
12	5.00	MeOH	0.2	2.50	1.80	100	20	59.21
13	5.00	MeOH	0.2	2.50	1.80	100	25	59.02
14	5.00	MeOH	0.4	2.50	1.80	120	25	58.85
15	5.00	MeOH	0.2	2.50	1.80	120	15	57.81
16	5.00	MeOH	0.2	2.50	2.50	120	30	55.05
17	5.00	MeOH	0.2	2.50	1.80	120	30	53.39
18	5.00	MeOH	0.4	2.00	1.50	120	25	51.54
19	5.00	MeOH	0.2	2.50	2.50	120	45	51.34
20	5.00	MeOH	0.4	2.00	1.50	130	25	49.35
21	5.00	MeOH	0.2	2.50	1.80	120	35	47.13
22	2.00	MeOH	0.2	1.00	1.80	120	25	44.54
23	2.00	MeOH	0.2	5.00	1.80	120	25	58.51
24	5.00	**DMF**	0.2	2.50	2.00	80	20	55.68
25	5.00	**DMF**	0.2	2.50	2.00	120	25	48.62
26	2.00	ACN	0.2	2.50	1.80	100	10	33.96
27	2.00	ACN	0.2	2.50	1.80	100	20	50.16
28	2.00	ACN	0.1	2.50	1.80	100	20	39.78
29	**2.00**	**ACN**	**0.2**	**2.50**	**1.80**	**100**	**25**	**86.04**
30	2.00	ACN	0.2	2.50	1.80	100	30	75.67
31	2.00	ACN	0.1	2.50	1.80	100	30	41.07

2.4 Aldehyde reduction using polymer supported sodium borohydride



Scheme 2: Flow synthesis of the aldehyde reduction using polymer supported sodium borohydride

Table 5: Flow screens for the aldehyde reduction using polymer supported sodium borohydride

Entry No	Reaction scale (g)	Concentration [M]	Solvent	Residence Time (min)	LC Conversion (%)
1	0.15	0.20	MeOH	25	59.8
2	0.15	0.20	MeOH	30	69.5
3	0.15	0.80	MeOH	30	44.9
4	0.15	0.20	MeOH	60	68.0
5	0.15	0.80	MeOH	60	63.4
6	0.15	0.50	MeOH	45	80.4
7[a]	**0.15**	**0.50**	**MeOH**	**45**	**87.2**

[a] 68 % Isolated yield on 0.15-gram scale

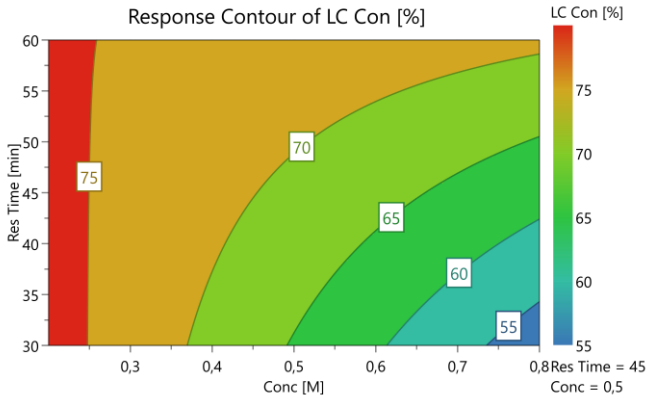


Figure 9: Representation of a 3-D contour plot for aldehyde reduction flow experiments using polymer supported sodium borohydride

2.5 Second Allylation design of experiment data

Table 6: Second allylation screening approach-DoE Design-Full Factorial Screening

Screening approach-DoE Design-Full Factorial Screening					
Name	**Abbreviation**	**Units**	**Type**	**Use**	**Settings**
Sodium hydride equivalents	NaH	mg	Quantitative	Controlled	2.5–7.5
Allyl Bromide equivalents	All	mL	Quantitative	Controlled	1.5–3.0
Residence time	Res	Min	Quantitative	Controlled	10-20
Cycling	Cyc	time	Quantitative	Controlled	3-9

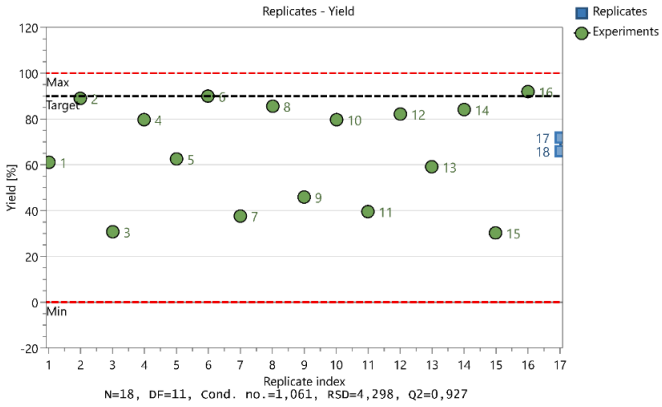


Figure 10: Representation of replicate plot that demonstrates the variation between results within the experimental limits

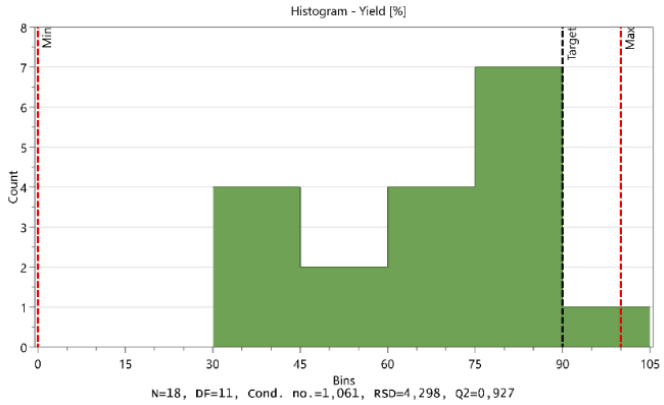


Figure 11: Representation of a histogram that displays a normal distribution curve

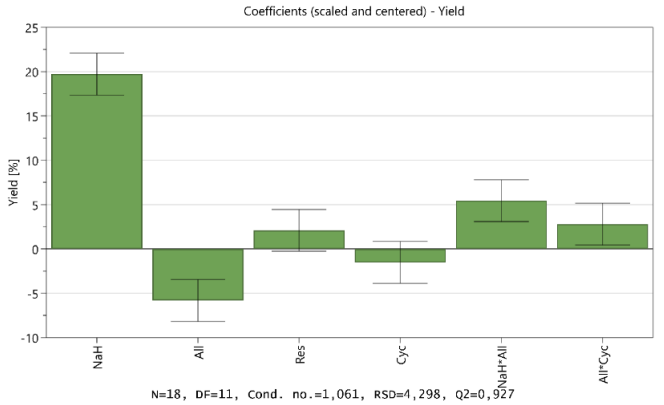


Figure 12: Representation of a coefficient plot illustrating important terms and their interactions

The non-significant terms were:

Term	The interaction between
NaH* Res	sodium hydride and residence times
NaH*Cyc	sodium hydride and cycling of reaction
All*Res	equivalents of allyl bromide and residence time
Res*Cyc	residence time and cycling.

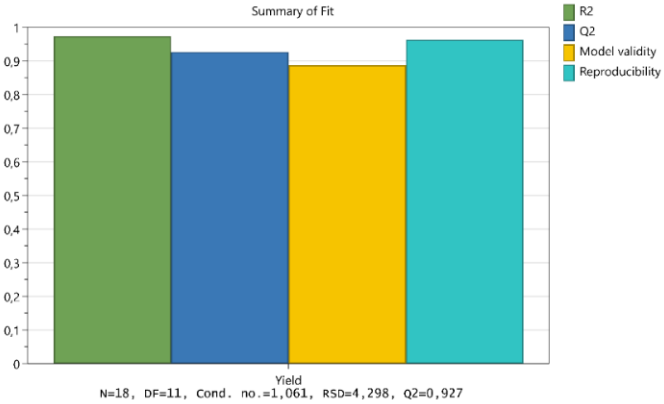


Figure 13: Representation of a summary of fit plot demonstrating the reliability and validity of the model

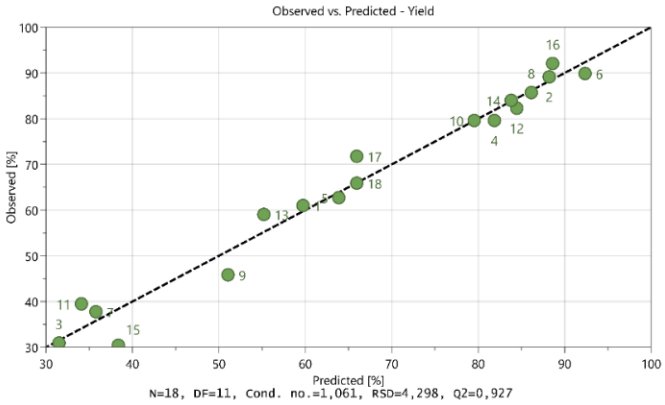


Figure 14: Representation of the observed vs. predicted plot for the results based on a line of best fit

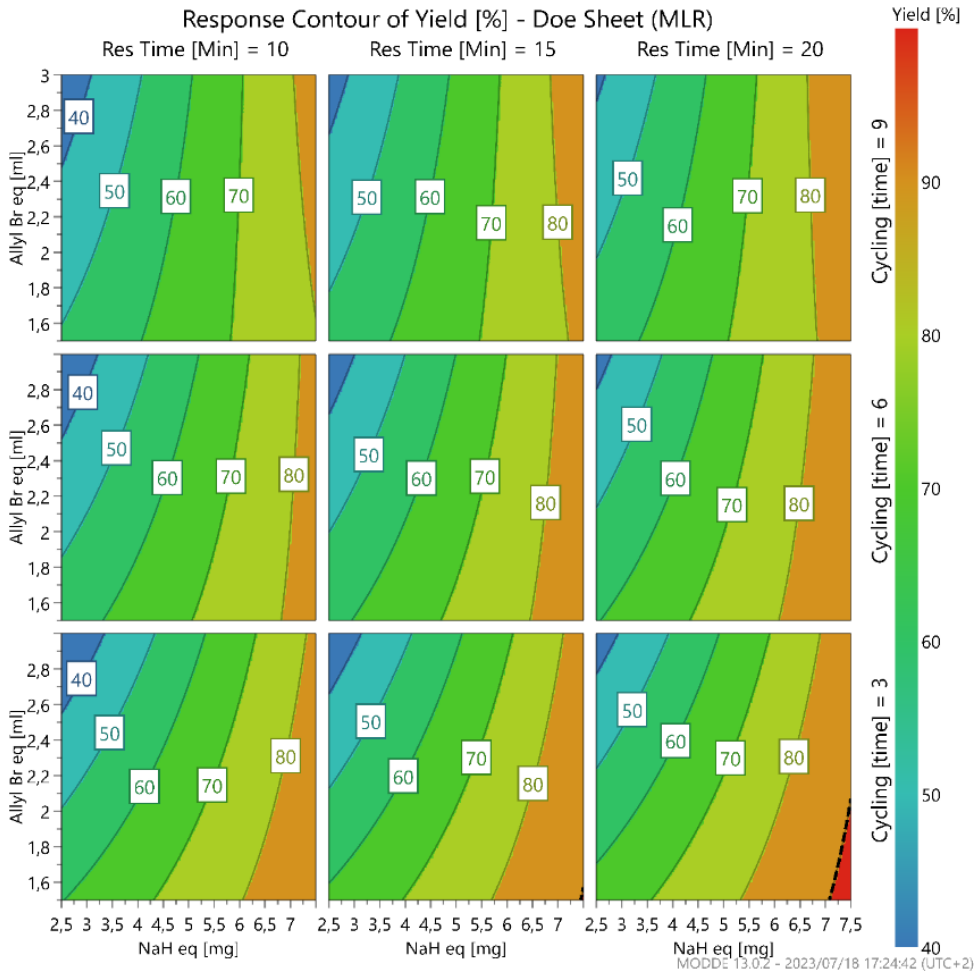


Figure 15: Representation of a 3-D contour plot illustrating the optimal area for achieving high product conversions

Table 7: Follow-up flow screens for the second allylation

Entry No	Reaction scale (g)	NaH equiv.	Allyl Bromide Equiv.	Residence Time (min)	Flow rate (ml/min)	Recycling	LC Conversion (%)
1	0.256	7.5	2.04	20	0.50	3	91.57
2	0.256	7.3	1.76	20	0.50	3	83.57

2.6 Ring closing metathesis design of experiment data

Table 8: Ring-closing metathesis screening approach-DoE Design-Full Factorial Screening

Screening approach-DoE Design-Full Factorial Screening					
Name	**Abbreviation**	**Units**	**Type**	**Use**	**Settings**
Solvent	Sol		Qualitative	Controlled	EtOAc; Toluene
Catalyst	Cat		Qualitative	Controlled	GII; HGII
Temperature	Temp	°C	Quantitative	Controlled	60-90
Residence time	Res	min	Quantitative	Controlled	15-45
Catalyst Loading	Cat	mol%	Quantitative	Constant	3

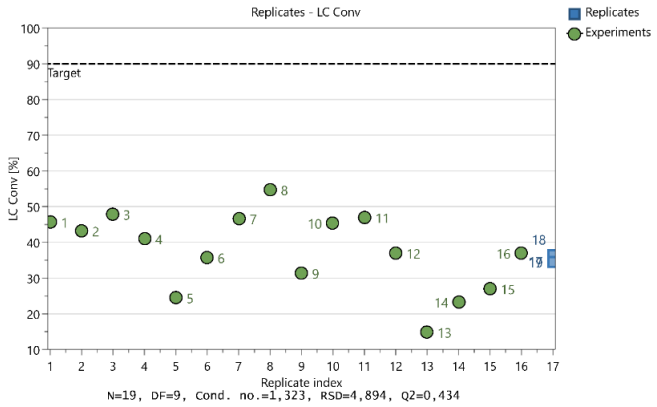


Figure 16: Representation of replicate plot that demonstrates the variation between results within the experimental limit for the RCM step

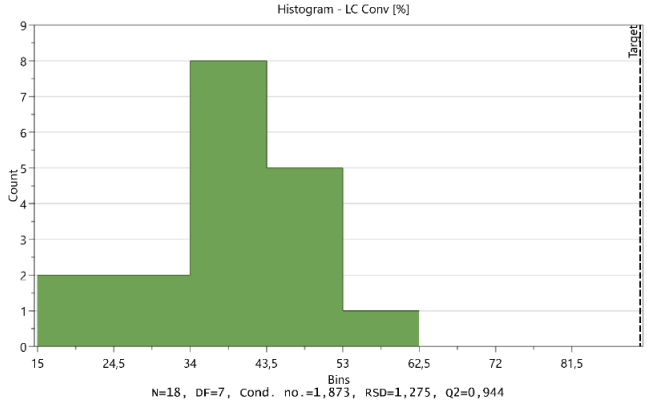


Figure 17: Representation of a histogram that displays a normal distribution curve

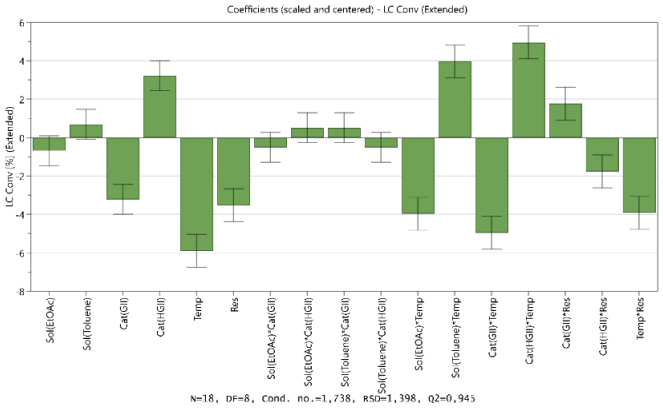


Figure 18: Representation of a coefficient plot illustrating important terms and their interactions for the RCM step

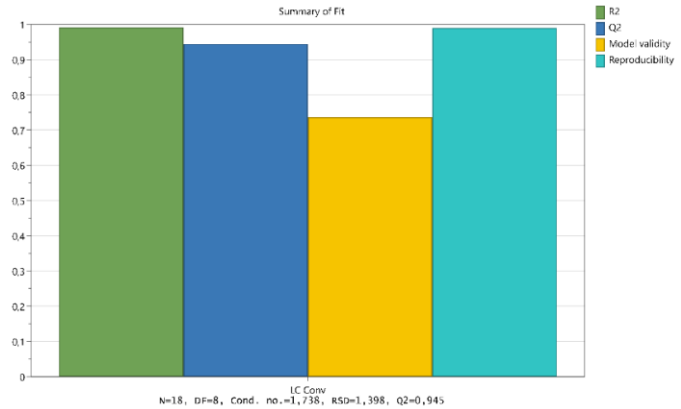


Figure 19: Representation of a summary of fit plot demonstrating the reliability and validity of the model for the RCM step

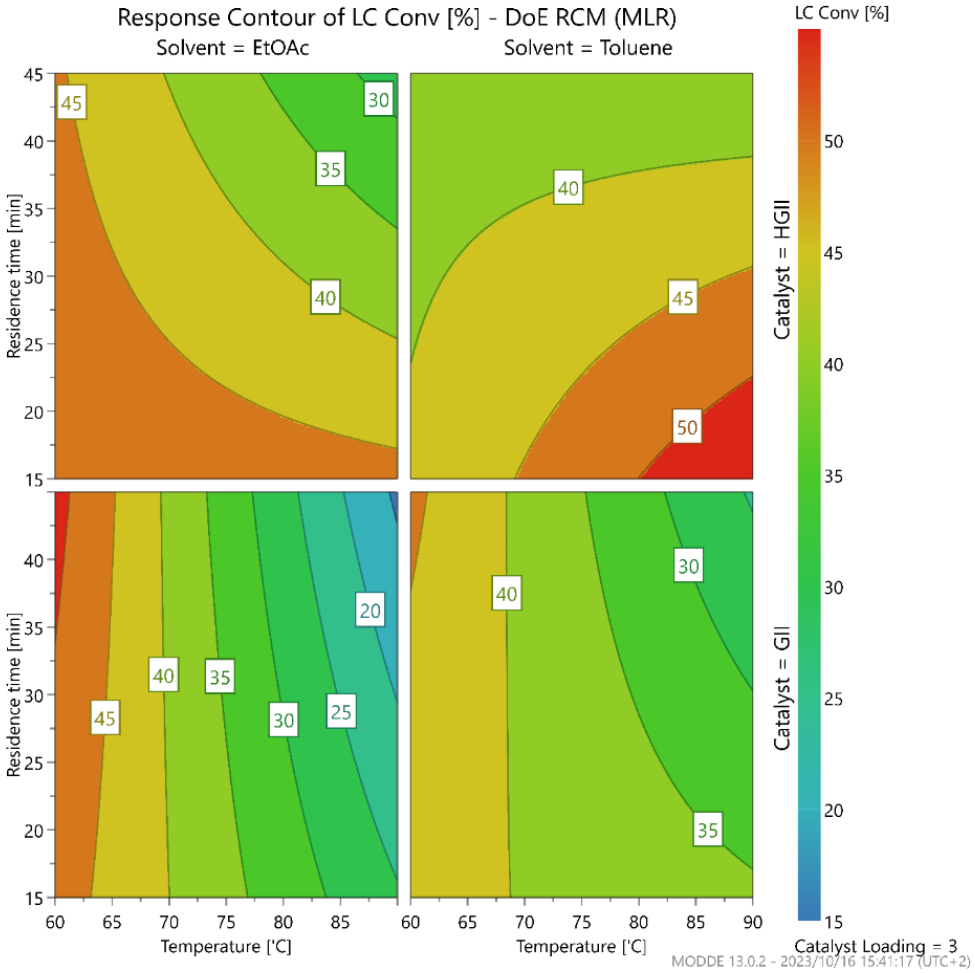
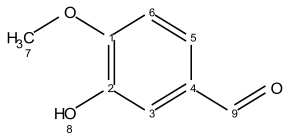


Figure 20: Representation of a 3-D contour plot illustrating the optimal area for achieving high product conversions

3. Synthesis experimental

3.1 Isovanillin (Start Material)



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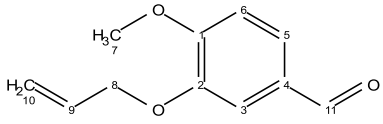
Rf = 0.20 (25% ethyl acetate/hexane); **^{1}H NMR (400 MHz, Chloroform-d)** δ 9.82 (s, 1H, H_{-9}), 7.41 (m, 2H, H_3 and H_5), 6.96 (d, J = 8.7 Hz, 1H, H_6), 5.92 (s, 1H, H_8), 3.97 (s, 3H, H_7), 2.97 ($DMSO_2$, internal standard); **IR V_{max}/cm^{-1}** 3184 (O-H stretch), 2843 (C-H stretch), 1668 (C=O stretch), 1574, 1508, 1243 (C-H bend), 1113 (C-O stretch), 825, 581.

3.2 Phenolic allylation:



4

3.2.1 Batch method using potassium carbonate

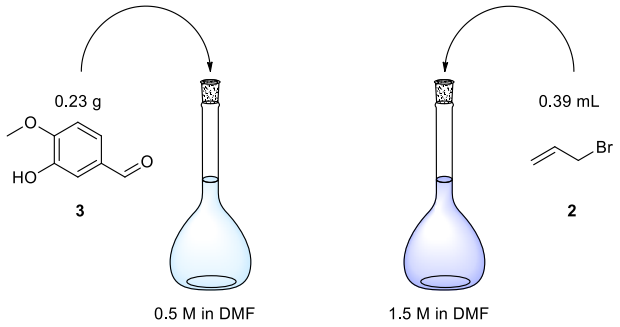
Isovanillin **3** (10.05 g, 66.07 mmol, 1.0 equiv.), and allyl bromide **2** (11.45 mL, 132.31 mmol, 2.0 equiv.) were added to a stirring solution of potassium carbonate (22.80 g, 164.94 mmol, 2.5 equiv.) in dimethylformamide (0.50 M, 132.00 mL). The reaction was heated to 60 °C and stirred for 20 hours under argon, then cooled to room temperature and filtered through a celite pad. The residue was then extracted with aqueous sodium hydroxide (3.00 M, 30 mL) and dichloromethane (3 × 30 mL). The organic layers were combined and dried with sodium sulphate, filtered and concentrated *in vacuo* to obtain 3-(allyloxy)-4-methoxybenzaldehyde **4**, as a dark yellow oil (10.43 g, 82 %). **Rf** = 0.53 (25% ethyl acetate/hexane); **^{1}H NMR (300 MHz, Chloroform-d)** δ 9.70 (s, 1H, H_{11}), 7.37 – 7.23 (m, 2H, H_5, H_3), 6.85 (d, J = 8.2 Hz, 1H, H_6), 6.06 – 5.86 (ddt, *J* = 20.90, 14.22, 14.22 Hz, 1H, H_9), 5.31 (dd, *J* = 17.3, 1.6 Hz, 1H, H_{10b}), 5.18 (dd, *J* = 10.5, 1.4 Hz, 1H, H_{10a}), 4.52 (dt, *J* = 5.4, 1.5 Hz, 2H, H_8), 3.81 (s, 3H, H_7). **^{13}C NMR (101 MHz, Chloroform-d)** δ 190.60 (C_{11}), 154.59 (C_1), 148.24 (C_2), 132.36 (C_9), 129.72 (C_4), 126.54 (C_5), 118.21 (C_{10}), 110.64 ($C_{3/6}$)*, 110.52 ($C_{3/6}$)*, 69.40 (C_8), 55.88 (C_7); **IR V_{max}/cm^{-1}** 2936 (C-H stretch), 2839 (C-H stretch), 1682 (C=O stretch), 1586, 1508, 1433 (C-H bend), 1261, 1127, 1012 (C-O stretch), 806, 636.; **HRMS m/z (ES+)** 193.1040 **[M+H]$^{+}$** ($C_{11}H_{12}O_3$ requires 192.211 g.mol^{-1}). * Signals indistinguishable.

3.2.2 Batch method using potassium hydroxide solution

Potassium hydroxide (0.28 g, 4.99 mmol, 1.5 equiv.) was added to methanol: water (0.40 M, 8.21 mL, 70:30) and allowed to stir for 5 minutes. Isovanillin **3** (0.50 g, 3.23 mmol, 1.0 equiv.) and allyl bromide **2** (0.53 mL, 6.12 mmol,1.85 equiv.) was added to the solution and heated to 70 °C for 20 hours. After 20 hours the reaction was cooled to room temperature the solvent was removed *in vacuo*, and the residue was then extracted with aqueous sodium hydroxide (3.00 M, 30 mL) and dichloromethane (3 × 30 mL). The organic layers were combined and dried with sodium sulphate, filtered and concentrated *in vacuo* to obtain 3-(allyloxy)-4-methoxybenzaldehyde **4** as a dark yellow oil (0.49 g, 78 %).

3.2.3 Flow method using potassium carbonate

a. Preparation of stock solution using potassium carbonate



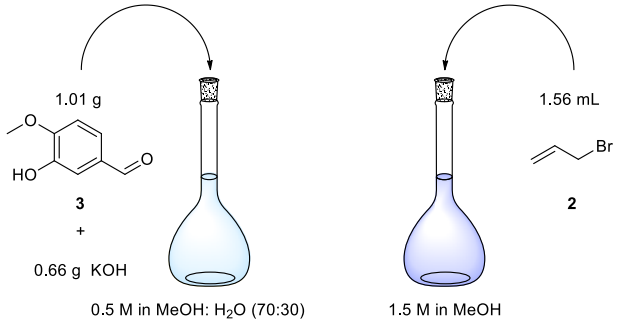
A 0.50 M stock solution of isovanillin **3** was prepared by the dissolution of **3** (0.23 g, 1.50 mmol, 1.0 equiv.) in dimethylformamide to a total volume of 3 mL and a 1.5 M stock solution of allyl bromide **2** was prepared by dissolution of **2** (0.39 mL, 4.50 mmol, 3.0 equiv.) in dimethylformamide to a total volume of 3 mL.

b. Uniqsis^{TM} binary pump reactor setup

Stock solutions were prepared as described above. The Uniqsis^{TM} binary pump reactor was plumbed with two Uniqsis^{TM} 10 mm columns and a 8 bar BPR (Scheme 2). The two columns were packed with crushed potassium carbonate (6.40 g, 46.34 mmol, 3.0 equiv.) and their volumes were determined as 3.20 mL and 3.59 mL respectively. A total flow rate of 0.227 mL.min^{-1} was used to introduce 1.56 mL of each stock from the stock reservoir into the flow system. Dimethylformamide was used as a pushing solvent. The solutions were combined at the T-piece mixer and pumped through the packed columns held at 100 °C (T_R = 30 min). The solutions were collected, and solvent was removed and processed according to batch method to obtain 3-(allyloxy)-4-methoxybenzaldehyde **4** as a dark yellow oil (92 % from LC conversion).

3.2.4 Flow method using potassium hydroxide

a. Preparation of stock solution using potassium hydroxide

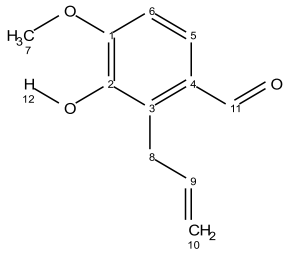


A 0.50 M stock solution of isovanillin **3** was prepared by dissolution of **3** (1.01 g, 6.64 mmol, 1.0 equiv.) and potassium hydroxide (0.66 g, 11.76 mmol, 1.8 equiv.) in methanol:water (13.14 mL of 70:30). A 1.00 M stock solution of allyl bromide **2** was prepared by dissolution of **2** (1.56 mL, 18.03 mmol, 2.0 equiv.) in methanol (16.40 mL).

b. Uniqsis™ binary pump reactor setup and description

Stock solutions were prepared as described above. The Uniqsis™ binary pump reactor was used with a 25.00 mL (1.5 mm inner diameter) coil (Scheme 2). A total flow rate of 1.67 mL.min^{-1} was used to introduce 13.14 mL of each stock from the stock reservoir into the flow system. methanol:water (70:30) was used as a pushing solvent. The solutions were combined at the T-piece mixer and pumped through a static mixer at room temperature and a coil reactor held at 80 °C (T_R = 15 min) with an 8-bar BPR. The solutions were collected, and HPLC analysis was performed before solvent was removed processed according to batch method to obtain 3-(allyloxy)-4-methoxybenzaldehyde **4** as a dark yellow oil (1.12 g, 88%).

3.3 Claisen Rearrangement:



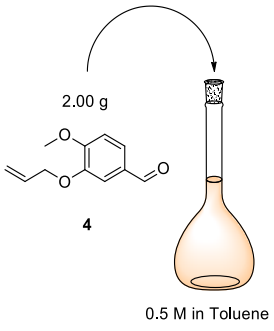
5

3.3.1 Batch method

3-(Allyloxy)-4-methoxybenzaldehyde **4** (2.02 g, 10.51 mmol, 1.0 equiv.) was dissolved in toluene (0.25 M, 42.00 mL) and was allowed to reflux for 72 hours at 120 °C. After 72 hours the reaction was cooled to room temperature the solvent was removed *in vacuo* to obtain 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** as a dark brown oil (6.9 % by qNMR analysis).

3.3.2 Flow method

a. Preparation of stock solution



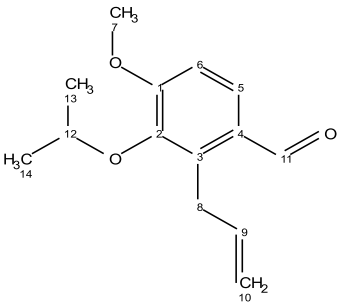
A 1.00 M stock solution of 3-(allyloxy)-4-methoxybenzaldehyde **4** was prepared by dissolution of **4** (2.00 g, 10.04 mmol, 1.0 equiv.) in toluene to a total volume of 10 mL.

b. Uniqsis™ binary pump reactor setup and description

Stock solutions were prepared as described above. The Uniqsis™ binary pump reactor was used with a 20.00 mL (1.0 mm inner diameter) stainless steel coil and a 2.00 mL (1.0 mm inner diameter) stainless steel cooling coil (Scheme 3). A total flow rate of 0.67 mL.min^{-1} was used to introduce 20.0 mL of the stock solution from the stock

reservoir into the flow system. Toluene was used as a pushing solvent. The solution was pumped through a stainless-steel coil reactor held at 240 °C (T_R = 30 min) and a cooling coil held at 0 °C with an 20-bar BPR. The solution was collected, and the solvent was removed *in vacuo* to remove the toluene to obtain 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** as a dark brown oil (1.99 g, 99 %) **Rf** = 0.44 (25% ethyl acetate/hexane) **^{1}H NMR (300 MHz, Chloroform-d)** δ 10.05 (s, 1H, H_{11}), 7.43 (d, J = 8.5 Hz, 1H, H_5), 6.87 (d, J = 8.5 Hz, 1H, H_6), 6.12 – 5.98 (ddt, J= 17.13, 16.08, 12.07 Hz, 1H, H_9), 5.90 (br s, 1H, H_{12}), 5.01 (dd, *J* = 6.2, 1.7 Hz, 1H, H_{10b}), 5.00 – 4.90 (dd, 1H, H_{10a}), 3.96 (s, 3H, H_7), 3.87 (dt, J = 6.0, 1.7 Hz, 2H, H_8). **^{13}C NMR (101 MHz, Chloroform-d)** δ 191.64 (C=O, C_{11}), 150.94 (C_1), 143.88 (C_2), 136.32 (C_9), 128.21 ($C_{3/4}$)*, 127.61 ($C_{3/4}$)*, 125.55 (C_5), 115.37 (C_{10}), 108.19 (C_6), 56.15 (C_7), 28.44 (C_8); **IR V_{max}/cm^{-1}** 3354 (O-H stretch), 2849 (C-H stretch), 1671 (C=O stretch), 1584, 1277(C-H bend), 1241, 1192, 1078 (C-O stretch), 790; **HRMS m/z (ES+)** 193.1040 **[M+H]$^+$** ($C_{11}H_{12}O_3$ requires 192.211 g.mol^{-1}). * Signals indistinguishable

3.4 ***Iso*-propyl protection:**



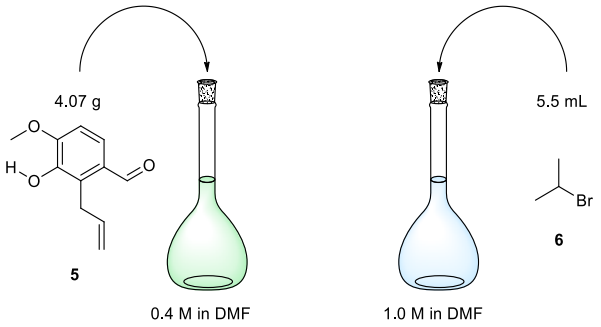
7

3.4.1 Batch method using potassium carbonate

2-Allyl-3-hydroxy-4-methoxybenzaldehyde **5** (9.02 g, 46.94 mmol, 1.0 equiv.) was added to a stirring solution of potassium carbonate (16.21 g, 117.29 mmol, 2.5 equiv.) and 2-bromopropane **6** (11.01 mL, 117.27 mmol, 2.5 equiv.) in dimethylformamide (0.50 M, 94.00 mL). The solution was stirred for 20 hours under argon atmosphere at 60 °C. After 20 hours the reaction was cooled to room temperature was filtered through a celite pad. The solvent was removed under a flow of compressed air, and the residue was then extracted with aqueous sodium hydroxide (3.00 M, 30 mL) and dichloromethane (3 × 30 mL). The organic layers were combined and dried with sodium sulphate, filtered and concentrated *in vacuo* to obtain 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**, as a light brown oil (8.59 g, 78 %). **Rf** = 0.67 (25% ethyl acetate/hexane); **^{1}H NMR (300 MHz, Chloroform-d)** δ 10.06 (s, 1H, H_{11}), 7.62 (d, *J* = 8.6 Hz, 1H, H_5), 6.89 (d, *J* = 8.6 Hz, 1H, H_6), 5.99 (ddt, *J* = 17.2, 10.2, 5.7 Hz, 1H, H_9), 5.00 (dd, *J* = 10.2, 1.7 Hz, 1H, H_{10b}), 4.89 (dd, *J* = 17.2, 1.8 Hz 1H, H_{10a}), 4.49 (sept, J = 6.2 Hz, 1H, H_{12}), 3.90 (s, 3H, H_7), 3.87 (dt, J = 5.7, 1.9 Hz, 2H, H_8), 1.27 (d, J = 6.2 Hz, 6H, H_{13}, H_{14}).**^{13}C NMR (101 MHz, Chloroform-d)** δ 191.06 (C_{11}), 157.60 (C_1), 144.94 (C_2), 137.14 (C_9), 136.36 (C_3), 128.14 (C_4), 128.02 (C_5), 115.57 (C_{10}), 109.67 (C_6), 74.90 (C_{12}), 55.68 (C_7), 29.00 (C_8), 22.53 (C_{13}, C_{14}); **IR V_{max}/cm^{-1}** 2975, 2846, 2723 (C-H stretch), 1684 (C=O stretch), 1581, 1440 (C-H bend), 1275, 1077 (C-O stretch), 912, 808; **HRMS m/z (ES+)** 235.1351 **[M+H]$^+$** ($C_{14}H_{18}O_3$ requires 234.29 g.mol^{-1}).

3.4.2 Flow method using potassium carbonate

a. Preparation of stock solution using potassium carbonate



A 0.40 M stock solution of 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** was prepared by the dissolution of **5** (4.07 g, 21.17 mmol, 1.0 equiv.) in dimethylformamide to a total volume of 50 mL, and a 1.00 M stock solution of 2-bromopropane **6** was prepared by dissolution of **6** (5.50 mL, 58.53 mmol, 2.5 equiv.) in dimethylformamide to a total volume of 50 mL.

b. Uniqsis^{TM} binary pump reactor setup and description

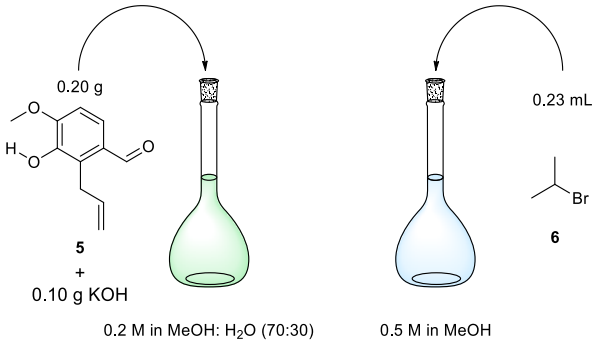
Stock solutions were prepared as described above. The Uniqsis^{TM} binary pump reactor was used with two Uniqsis^{TM} 10 mm columns and an 8 bar BPR (Scheme 4). The two columns were packed with crushed potassium carbonate (8.09 g, 58.52 mmol, 2.5 equiv.) and their total volume was determined to be 8.72 mL. A total flow rate of 0.436 mL.min^{-1} was used to introduce 56.00 mL of each stock from the stock reservoir into the flow system. Dimethylformamide was used as a pushing solvent. The solutions were combined at the T-piece mixer and pumped through the packed columns held at 80 °C (T_R = 20 min).The solutions were collected, and solvent was removed and processed according to batch method to obtain 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7** as a light brown oil (4.37 g, 88%).

3.4.3 Batch method using potassium hydroxide

Potassium hydroxide (0.22 g, 3.92 mmol, 1.5 equiv.) was added to methanol: water (0.20 M, 13.00 mL, 70:30) and allowed to stir for 5 minutes. 2-Allyl-3-hydroxy-4-methoxybenzaldehyde **5** (0.50 g, 2.60 mmol, 1.0 equiv.) and 2-bromopropane **6** (0.42 mL, 4.77 mmol, 1.85 equiv.) was added to the solution and heated to 70 °C for 20 hours. After 20 hours the reaction was cooled to room temperature the solvent was removed *in vacuo*, and the residue was then extracted with aqueous sodium hydroxide (3.00 M, 30 mL) and dichloromethane (3 × 30 mL). The organic layers were combined and dried with sodium sulphate, filtered and concentrated *in vacuo* to obtain 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**, as a light brown oil (0.37 g, 60 %). **Rf** = 0.67 (25% ethyl acetate/hexane)

3.4.4 Flow method using potassium hydroxide

a. Preparation of stock solution using potassium hydroxide

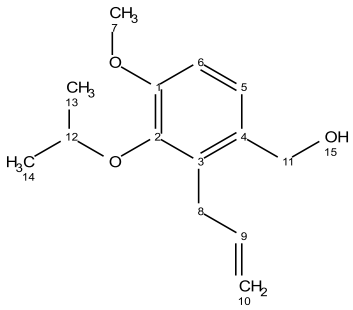


A 0.20 M stock solution of 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** was prepared by dissolution of **5** (0.20 g, 1.00 mmol, 1.0 equiv.) and potassium hydroxide (0.10 g, 1.80 mmol, 1.8 equiv.) in methanol:water (5.00 mL of 70:30). A 0.50 M stock solution of 2-bromopropane **6** was prepared by dissolution of **6** (0.23 mL, 2.50 mmol, 2.50 equiv.) in methanol (5.00 mL).

b. UniqsisTM binary pump reactor setup and description

Stock solutions were prepared as described above. The Uniqsis^{TM} binary pump reactor was used with a 25.00 mL (1.5 mm inner diameter) coil. A total flow rate of 1.25 mL.min^{-1} was used to introduce 5.00 mL of each stock from the stock reservoir into the flow system. Methanol:water (70:30) was used as a pushing solvent. The solutions were combined at the T-piece mixer and pumped through a static mixer at room temperature and a coil reactor held at 120 °C (T_R = 25 min) with an 8-bar BPR. The solutions was collected, and HPLC analysis was performed before solvent was removed processed according to batch method to obtain 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**as a light brown oil (69 %).

3.5 <u>Aldehyde Reduction:</u>



8

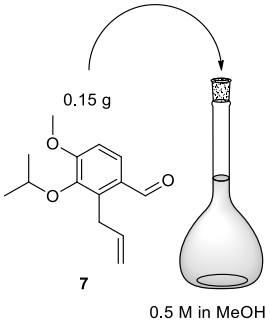
3.5.1 Batch method using sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al, 60% in toluene)

Red-Al (60% in toluene, 15.62 mL, 73.85 mmol, 2.5 equiv.) was added dropwise to a stirring solution of 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7** (4.50 g, 19.21 mmol, 1.0 equiv.) in toluene (0.15 M, 128.00 mL) under argon at 15-20 °C. The solution was left for 20 hours under inert conditions while stirring. The reaction was quenched by adding 10% aqueous sodium hydroxide while stirring for 30 minutes. The solvent was removed *in vacuo*, and the

residue was then extracted with water (30 mL) and dichloromethane (3 × 30 mL). The organic layers were combined and dried with magnesium sulphate, filtered and concentrated *in vacuo* to obtain (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** as a dark yellow oil (3.47 g, 76 %). The method was repeated using the same conditions while varying the reducing agent and solvent. **Rf** = 0.46 (25% ethyl acetate/hexane); **^{1}H NMR (300 MHz, Chloroform-d)** δ 7.03 (d, J = 8.4 Hz, 1H, H_5), 6.75 (d, J = 8.4 Hz, 1H, H_6), 5.95 (ddt, J = 17.1, 10.2, 5.8 Hz, 1H, H_9), 5.02 – 4.95 (dd, 1H, H_{10b}), 4.88 (dd, J=1.9 hz, 1H, H_{10a}), 4.55 (br s, 2H, H_{11}), 4.48 (sept, J = 6.2 Hz, 1H, H_{12}), 3.80 (s, 3H, H_7), 3.53 (dt, J = 5.9, 1.8 Hz, 2H, H_8), 2.22 (br s, 1H, H_{15}), 1.25 (d, J = 6.2 Hz, 6H, H_{14} & H_{13}).**^{13}C NMR (75 MHz, Chloroform-d)** δ 152.39 (C_1), 144.96 (C_2), 137.58 (C_9), 132.41 ($C_{3/4}$)*, 132.12 ($C_{3/4}$)*, 123.76 (C_5), 114.98 (C_{10}), 109.98 (C_6), 74.61, (C_{12}), 62.91 (C_{11}), 55.63, (C_7), 30.54 (C_8), 22.64 (C_{14} & C_{13}); **IR V_{max}/cm^{-1}** 3380 (O-H stretch), 2973, 2934 (C-H stretch), 1601, 1485, 1435(C-H bend), 1267, 1081 (C-O stretch), 985, 911, 803; **HRMS m/z (ES+)** 219.1538 **[M-OH]$^{+}$** ($C_{14}H_{20}O_3$ requires 236.31 g.mol^{-1}).* Signals indistinguishable.

3.5.2 Flow method using polymer supported sodium borohydride

a. Preparation of stock solution



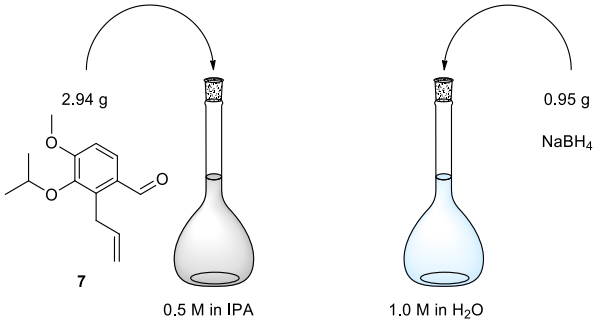
Stock solution of 0.50 M of 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7** was prepared by dissolution of **7** (0.15 g, 0.63 mmol, 1.0 equiv.) in methanol (1.25 mL).

b. Uniqsis^{TM} binary pump reactor setup and description

Stock solutions were prepared as described above. The Uniqsis^{TM} binary pump reactor was used with one Uniqsis^{TM} 10 mm column and an 8 bar BPR (Scheme 2 ESI). The column was packed with polymer supported sodium borohydride and its volumes was determined to be 4.00 mL. A total flow rate of 0.089 mL.min^{-1} was used to introduce 1.28 mL of stock from the stock reservoir into the flow system. Methanol was used as a pushing solvent. The solutions were pumped through the packed column held at room temperature (T_R = 45 min).The solution was collected and HPLC analysis was performed before the solvent was removed *in vacuo* and processed according to batch method to obtain (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** as a dark yellow oil (0.11 g, 68 %).

3.5.3 Flow method using sodium borohydride solution

a. Preparation of stock solution

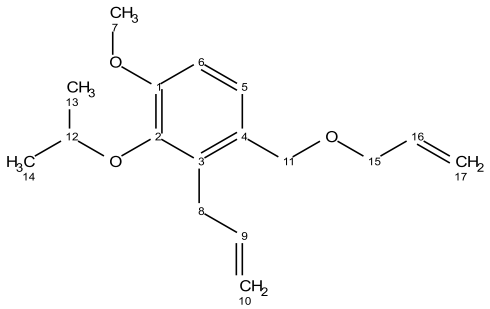


Stock solution of 0.50 M of 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7** was prepared by dissolution of **7** (2.94 g, 12.53 mmol, 1.0 equiv.) in IPA to a total volume of 25 mL and stock solution of 1.0 M of $NaBH_4$ was prepared by dissolution of $NaBH_4$ (0.95 g, 25.06 mmol, 2.0 equiv.) in water to a total volume of 25 mL.

b. Vapourtec™ peristaltic pump reactor setup and description

Stock solutions were prepared as described above. The Vapourtec™ easy-MedChem E-series peristaltic pump reactor was used with a 3 bar BPR (Scheme 5). A total flow rate of 1.25 mL.min^{-1} was used to introduce 25.00 mL of each stock from the stock reservoir into the flow system. IPA was used as a pushing solvent. The solutions were combined at the T-piece mixer and pumped through a 0.50 mL static mixer at room temperature and a coil reactor held at room temperature (T_R = 20 min).The solution was collected in 5.00 mL saturated $NaHCO_3$ and water and HPLC analysis was performed before solvent was removed *in vacuo* and processed according to batch method to obtain(2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** as a dark yellow oil (2.53 g, 85 %).

3.6 Second Allylation:



9

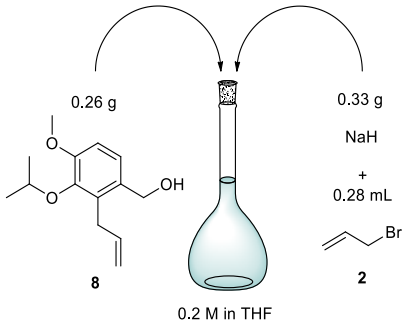
3.6.1 Batch Procedure

(2-Allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** (1.70 g, 7.21 mol, 1.0 equiv.) was added to a solution of sodium hydride pre-washed with hexane to remove mineral oil (0.72 g, 30.03 mmol, 2.5 equiv., 60% dispersion in mineral oil) and tetrahydrofuran (0.15 M, 50.00 mL) under argon atmosphere. Allyl bromide **2** (1.56 mL, 18.02 mmol, 2.5 equiv.) was added dropwise to the reaction mixture at 15-20 °C and left to reflux for 20 hours while stirring. The reaction was quenched with 10% sodium hydroxide while continuously stirring for 30 minutes. The solvent was removed *in vacuo* and the residue was then extracted with water (30 mL) and dichloromethane (3 × 30 mL). The organic layers were combined and dried with magnesium sulphate, filtered and concentrated *in vacuo* to obtain 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** as a light yellow oil (1.69 g, 85%). **Rf** = 0.88 (25% ethyl acetate/hexane); **^{1}H NMR (300 MHz, Chloroform-d)** δ 7.03 (d, J = 8.3 Hz, 1H, H_5), 6.74 (d, J = 8.4 Hz, 1H, H_6), 5.94 (ddt, *J* = 12.80, 8.56, 5.86 Hz, 1H, H_9), 5.91 (ddt, J = 9.86, 7.53, 6.30 Hz, 1H, H_{16}), 5.35 – 5.23 (dd, 1H, H_{17b}), 5.28 (dd, *J* = 17.2, 1.7 Hz, 1H, H_{17a}), 5.18 (dd, *J* = 10.2, 1.4 Hz, 1H, H_{10a}), 4.96 (dd, *J* = 9.2 Hz, 1H, H_{10b}), 4.58 –

4.38 (sept, 1H, H_{12}), 4.44 (s, 2H, H_{11}), 3.99 (dt, J = 5.7, 1.4 Hz, 2H, H_{15}), 3.80 (s, 3H, H_7), 3.54 (dt, J = 6.0, 1.8 Hz, 2H, H_8), 1.26 (d, J = 6.2 Hz, 6H, H_{13} & H_{14}).**^{13}C NMR (75 MHz, Chloroform-d)** δ 152.54 (C_1), 145.10 (C_2), 136.91 (C_9), 134.97 (C_{16}), 132.83 (C_3), 129.57 (C_4), 124.42 (C_5), 116.94 (C_{17}), 114.77 (C_{10}), 109.70 (C_6), 74.43 (C_{12}), 71.06 (C_{11}), 70.08 (C_{15}), 55.54 (C_7), 30.63 (C_8), 22.62 (C_{14} & C_{13}); **IR V_{max}/cm^{-1}** 2971 (C-H stretch), 2927, 2855, 1486, 1437 (C-H bend), 1270, 1080 (C-O stretch), 913, 803; **HRMS m/z (ES+)** 276.1749 **[M+H]$^+$** ($C_{17}H_{24}O_3$ requires 276.3739 g.mol^{-1}).

3.6.2 Flow method

a. Preparation of stock solution

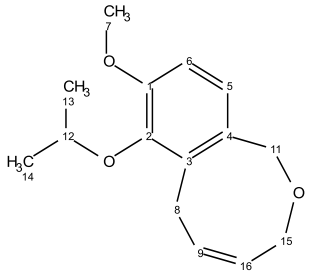


Stock solution of 0.2 M of (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** was prepared by dissolution of **8** (0.26 g, 1.10 mmol, 1.0 equiv.), sodium hydride (0.33 g, 13.57 mmol, 7.5 equiv., 60% dispersion in mineral oil) and allyl bromide **2** (0.28 mL, 3.26 mmol, 3.0 equiv.) in tetrahydrofuran to a total volume of 5.5 mL with continuous stirring under nitrogen atmosphere.

b. Vaportec peristaltic reactor setup and description

Stock solutions were prepared as described above. The Vapourtec^{TM} easy-MedChem E-series peristaltic pump reactor was used with 1.5 mm inner diameter tubing for the sodium hydride slurry and using a 10.00 mL coil reactor. One of the peristaltic pumps was used as a BPR and the pressure was adjusted to 10 bar (Scheme 6). The reactor was purged with dried tetrahydrofuran. A total flow rate of 0.50 mL.min^{-1} was used to introduce 5.43 mL of stock from the stock reservoir into the flow system. Tetrahydrofuran was used as a pushing solvent. The solutions were mixed at the static mixer at room temperature and was pumped through a coil reactor held at 100 °C (T_R = 20 min).The solution was collected in the reagent reservoir and were allowed to cycle through the reaction path for the required number of cycles before collection into 2.00 mL water. HPLC analysis was performed before solvent was removed *in vacuo* and processed according to batch method to obtain 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** as a light yellow oil (0.21 g, 69%).

3.7 <u>Ring closing metathesis:</u>



1

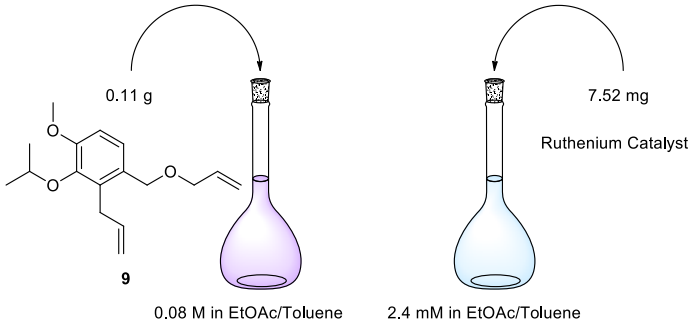
3.7.1 Batch Procedure

To a solution of 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** (0.28 g, 1.00 mmol, 1.0 equiv.) in degassed toluene (0.012 M, 83.00 mL) was added Grubbs II catalyst (0.042 g, 0.050 mmol, 0.05 equiv.) and the reaction was stirred at 60 °C under an argon atmosphere for 2 hours. The solution was cooled, and the solvent was removed *in vacuo*. The reaction mixture was purified via column chromatography (10 % ethyl acetate/Hexane)

to obtain a clear oil of (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1** as a colorless oil (0.012g, 46 %) **Rf** = 0.70 (10% ethyl acetate/hexane); **^{1}H NMR (300 MHz, Chloroform-d)** δ 6.82 (d, J = 8.3 Hz, 1H, H_5), 6.71 (d, J = 8.3 Hz, 1H, H_6), 6.03 – 5.87 (m, 1H, H_9), 5.68 – 5.61 (dt, J = 10.5, 5.1 Hz, 1H, H_{16}), 4.80 (s, 2H, H_{11}), 4.42 (sept, J = 6.2 Hz, 1H, H_{12}), 4.15 (d, J = 5.0 Hz, 2H, H_{15}), 3.82 (s, 3H, H_7), 3.74 (d, J = 7.2 Hz, 2H, H_8), 1.29 (d, J = 6.1 Hz, 6H, H_{13} & H_{14}) ; **^{13}C NMR (75 MHz, Chloroform-d)** δ 152.80 (C_1), 144.34 (C_2), 133.59 (C_3), 131.72 (C_4), 130.07 (C_9)*, 127.91 (C_{16})*, 123.69 (C_5), 109.51 (C_6), 74.81 (C_{12}), 72.18 (C_{11}), 66.27 (C_{15}), 55.75 (C_7), 29.71 (C_8), 22.58 (C_{14} & C_{13}); **HRMS m/z (ES+)** 249.14 **$[M+H]^+$** ($C_{15}H_{20}O_3$ requires 248.14 g.mol^{-1}). * Signals indistinguishable.

3.7.2 Flow procedure

a. Preparation of stock solution



Stock solution of 0.08 M of 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** was prepared by dissolution of **9** (0.11 g, 0.4 mmol, 1.0 equiv.) in toluene/ethyl acetate to a total volume of 5 mL and a 2.4 mM stock solution of catalysts (3 mol %) in toluene/ethyl acetate to a total volume of 5 mL.

b. Uniqsis^{TM} binary pump reactor setup and description

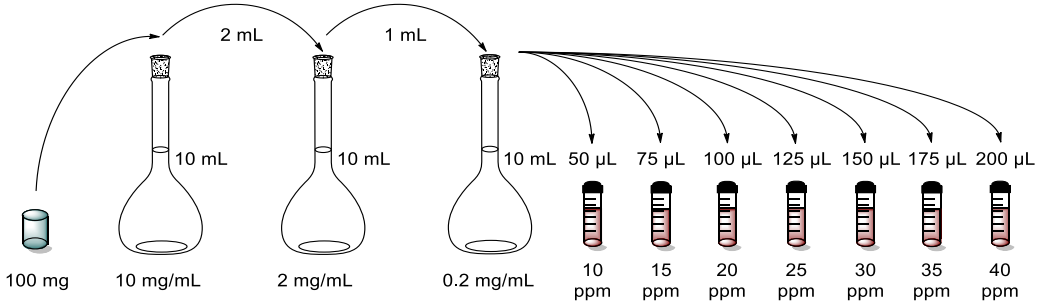
Stock solutions were prepared as described above. The Uniqsis^{TM} binary pump reactor was used with 2.00 mL sample loops. A total flow rate of 0.44 – 1.33 mL.min^{-1} was used to inject 2.00 mL of each stock from the sample loops into the flow system. Toluene/ethyl acetate was used as a pushing solvent. The solutions were pumped through a 20.00 mL glass mixing chip reactor held between 60 - 90 °C (T_R = 15 - 45 min) using a 4 bar BPR (Scheme 7).The solution was collected in the reagent reservoir and HPLC analysis was performed before solvent was removed *in vacuo* and processed according to batch method to obtain (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1** as a colorless oil.

Analysis of compound 4, 5, 7, 8, 9 and 1 corresponded with literature results obtained van Otterlo and co-workers.[1]

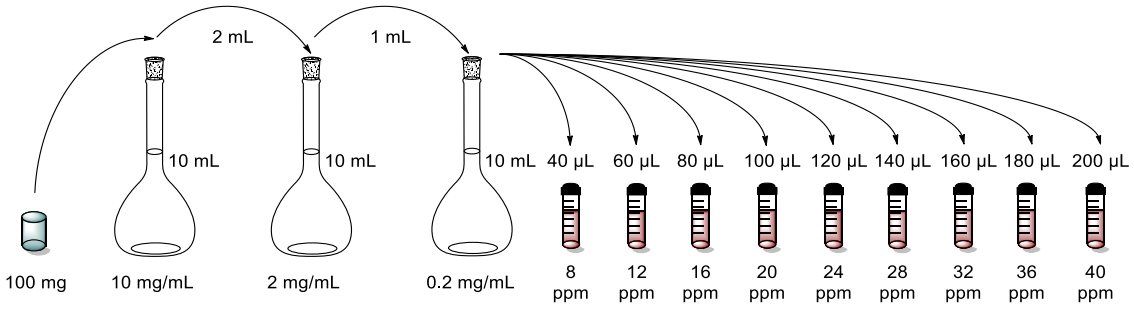
4. HPLC Method Information

4.1 General procedure for preparing concentrations for standard curve

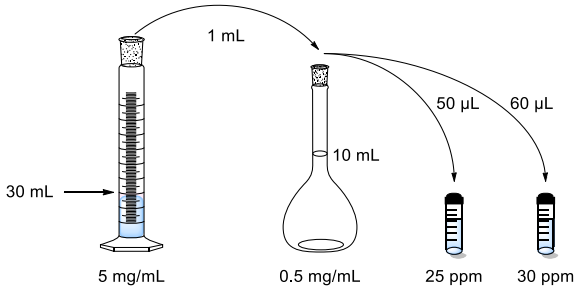
Method 1: Purified compound **X** (100 mg) was weighed and dissolved in 10mL acetonitrile (10 mg.mL^{-1}). From this 2 mL was diluted to 10 mL (2 mg.mL^{-1}). A 0.2 mg.mL^{-1} stock was prepared by adding 1mL of the 2 mg.mL^{-1} stock solution and diluting to 10 mL. From these stock solutions several concentrations were prepared in triplicate 10 ppm, 15 ppm, 20 ppm, 25 ppm, 30 ppm, 35 ppm and 40 ppm.



Method 2: Purified compound **X** (100 mg) was weighed and dissolved in 10 mL acetonitrile (10 mg.mL-1). From this 2 mL was diluted to 10 mL (2 mg.mL-1). A 0.2 mg.mL-1 stock was prepared by adding 1 mL of the 2 mg.mL-1 stock solution and diluting to 10 mL. From these stock solutions several concentrations were prepared in triplicate 8 ppm, 12 ppm, 16 ppm, 20 ppm, 24 ppm, 28 ppm, 32 ppm, 36 ppm and 40 ppm.



4.2 Example of dilution procedure for experiments



Each reaction was collected and diluted to a volume of 30 mL with acetonitrile, resulting in a concentration of 5 mg.mL^{-1}. From here, 1 mL was diluted with acetonitrile to a concentration of 0.5 mg.mL^{-1} in a 10 mL volumetric flask. To obtain 25 ppm, a dilution factor of 200, a 50 µL aliquot of this solution was added to an LC vial and diluted to 1 mL. In addition, a 60 µL aliquot from this solution was added to an LC vial and diluted to 1 mL to give 30 ppm, which equated to a dilution factor of 167 and was used for validation.

Conversions were obtained by dividing the sample's area by the equation deduced from the standard curve- in this case, for example the allylated product **4**, which was 3.3528. After that, the value was multiplied by the dilution factor, which for 25 ppm was 200. To convert from ppm to $mg.mL^{-1}$, this amount was then divided by 1000. The value is then multiplied by the volume of the collection, in this example 30 mL, to obtain the amount obtained in grams. Finally, the conversion is calculated by dividing the number of grams obtained by the number of grams theoretically expected.

Table 9: Example of descriptions and letters used for calculation of optimization reactions for 3-(allyloxy)-4-methoxybenzaldehyde **4**

Letter	Description
A	Starting material mass (Isovanillin **3**, 95 %)
B	Concentration in 30 mL sample
C	Concentration in 10 mL sample
D	Concentration in 1 mL LC vail sample (50 µL)
E	Dilution factor
F	Area of product
G	Area/ Equation of product
H	G × Dilution factor
I	H / 1000
J	I × Collected volume
K	% Conversion

4.3 HPLC analysis for the phenolic allylation

Table 10: HPLC method information for optimization of 3-(allyloxy)-4-methoxybenzaldehyde **4**

Quat. Pump		
Flow rate	1.00 $mL.min^{-1}$	
Maximum pressure	400 bar	
Stop time	5 minutes	
Oven Temperature	35 °C	
Injection Volume	2.00 uL	
Channel	**Name**	**Percentage (%)**
A	Organic (50 % MeOH/ACN)	60
B	Aqueous 10 mM Phosphate buffer (90 % H_2O/Organic)	40
Signals	**Name**	**Retention time (min)**
260 nm	Isovanillin **3**	1.131
260 nm	3-(allyloxy)-4-methoxybenzaldehyde **4**	1.826
260 nm	Anisole **10** (Internal standard)	2.241

4.3.1 Raw data for standard curve

Table 11: Raw data for triplicates at each concentration for standard curve for 3-(allyloxy)-4-methoxybenzaldehyde **4**

Isovanillin 3				**Product: 3-(Allyloxy)-4-methoxybenzaldehyde 4**			**Anisole 10 (Internal Standard)**		
PPM	**Retention time**	**Area (mAU*S)**	**Average Area**	**Retention time**	**Area (mAU*S)**	**Average Area**	**Retention time**	**Area (mAU*S)**	**Average Area**
10	1.129	63.9542	65.1178	1.828	34.8695	35.0602	2.252	31.3119	30.8464
	1.131	66.9859		1.826	34.7801		2.254	31.0402	
	1.129	64.4133		1.815	35.5309		2.213	30.187	
15	1.128	96.1887	97.2439	1.821	53.9597	54.0119	2.244	30.3435	30.5361

	1.129	96.6802		1.822	53.1735		2.249	30.4251	
	1.129	98.8628		1.812	54.9025		2.211	30.8397	
20	1.128	130.27	130.447	1.819	71.2548	72.0068	2.244	31.2041	30.9331
	1.131	130.545		1.824	71.6022		2.22	30.6329	
	1.133	130.528		1.82	73.1634		2.22	30.9624	
25	1.13	162.174	157.382	1.825	87.0507	88.23	2.249	30.4089	30.3933
	1.132	160.362		1.826	88.4288		2.258	30.5315	
	1.131	149.609		1.816	89.2103		2.218	30.2395	
30	1.129	194.908	192.485	1.823	108.553	108.238	2.25	30.6887	30.7177
	1.129	191.528		1.82	107.895		2.249	30.8783	
	1.13	191.019		1.815	108.266		2.215	30.5861	
35	1.128	223.121	222.839	1.818	120.957	124.936	2.243	30.8532	30.804
	1.13	221.503		1.82	128.003		2.215	30.5713	
	1.131	223.894		1.823	125.848		2.247	30.9874	
40	1.13	257.647	258.546	1.823	143.579	142.37	2.25	30.766	30.7488
	1.13	254		1.82	142.599		2.213	31.1933	
	1.159	263.991		1.92	140.933		2.349	30.2872	

4.3.2 Standard curve Graph

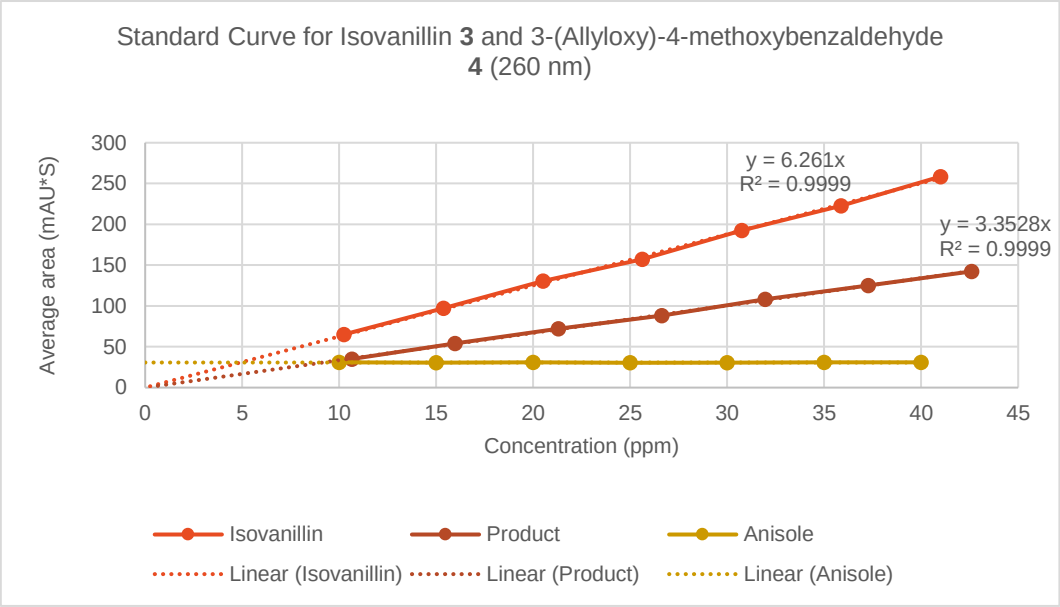


Figure 21: Standard curve for Isovanillin **3** and 3-(allyloxy)-4-methoxybenzaldehyde **4** at 260 nm

4.3.3 Example HPLC Chromatograms

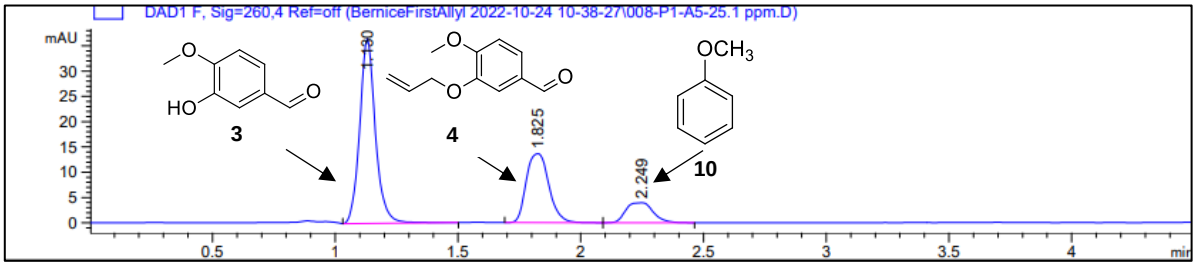


Figure 22: Chromatogram for standard curve at 260 nm at 25 ppm for isovanillin **3** (1.130 min), 3-(allyloxy)-4-methoxybenzaldehyde **4** (1.825 min), and Anisole **10** (2.249 min)

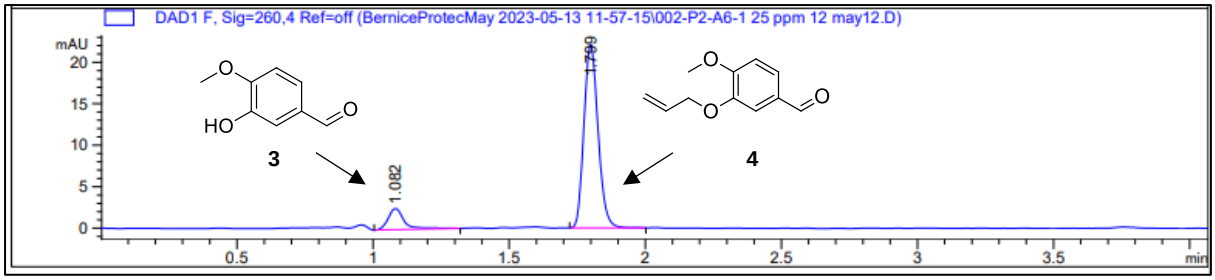


Figure 23: Chromatogram of large-scale allylation reaction using potassium hydroxide at 25 ppm

4.3.4 Experiment calculations

Table 12: Calculations for experiments conducted for allylation using potassium carbonate

Exp No	A	B	C	D	E	F	G	H	I	J	K
1	124.8	5.26	0.53	26.28	200	69.26	20.66	4131.26	4.13	123.94	78.61
2	124.8	5.26	0.53	26.28	200	61.75	18.42	3683.23	3.68	110.50	70.09
3	124.9	5.26	0.53	26.30	200	78.50	23.41	4682.81	4.68	140.48	89.03
4	124.7	5.25	0.53	26.26	200	77.35	23.07	4614.26	4.61	138.43	87.87
5	124.7	5.25	0.53	26.26	200	80.79	24.10	4819.06	4.82	144.57	91.77
6	124.9	5.26	0.53	26.30	200	78.63	23.45	4690.58	4.69	140.72	89.18

Table 13: Calculations for experiments conducted for allylation using potassium hydroxide

Exp No	A	B	C	D	E	F	G	H	I	J	K
1	159.6	5.04	0.50	25.20	200	57.41	17.12	3424.61	3.42	136.98	67.95
2	159.6	5.04	0.50	25.20	200	63.78	19.02	3804.31	3.80	152.17	75.49
3	159.5	5.04	0.50	25.19	200	65.87	19.65	3929.32	3.93	157.17	77.99
4	159.5	5.04	0.50	25.19	200	66.22	19.75	3949.91	3.95	158.00	78.40
5	159.5	5.04	0.50	25.19	200	64.61	19.27	3854.25	3.85	154.17	76.50
6	161.6	5.10	0.51	25.52	200	65.77	19.62	3923.48	3.92	156.94	76.88
7	161.6	5.10	0.51	25.52	200	68.72	20.50	4099.49	4.10	163.98	80.33
8	161.6	5.10	0.51	25.52	200	67.85	20.24	4047.25	4.05	161.89	79.31
9	161.6	5.10	0.51	25.52	200	66.14	19.73	3945.32	3.95	157.81	77.31
10	160.5	5.07	0.51	25.34	200	66.38	19.80	3959.61	3.96	158.38	78.12
11	160.5	5.07	0.51	25.34	200	68.06	20.30	4059.68	4.06	162.39	80.09

4.4 HPLC analysis for the Claisen rearrangement and Iso-propyl protection

Table 14: HPLC method information for optimization of 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** and 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**

Quat. Pump		
Flow rate	1.00 mL.min^{-1}	
Maximum pressure	400 bar	
Stop time	6 minutes	
Oven Temperature	35 °C	
Injection Volume	2.00 uL	
Channel	**Name**	**Percentage (%)**
A	Organic (50 % MeOH/ACN)	60
B	Aqueous 10 mM Phosphate buffer (90 % H_2O/Organic)	40

Signals	Name	Retention time (min)
220 nm	2-allyl-3-hydroxy-4-methoxybenzaldehyde **5**	1.437
220 nm	2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**	3.029
220 nm	Anisole **10** (Internal standard)	1.851

4.4.1 Raw data for standard curve

Table 15: Raw data for triplicates at each concentration for standard curve for 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** and 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**

	2-allyl-3-hydroxy-4-methoxybenzaldehyde 5			2-allyl-3-isopropoxy-4-methoxybenzaldehyde 7			Anisole 10 (Internal Standard)		
PPM	Retention time	Area (mAU*S)	Average Area	Retention time	Area (mAU*S)	Average Area	Retention time	Area (mAU*S)	Average Area
8	1,446	68,944	67,025	3,055	40,73	40,334	1,861	211,000	214,187
	1,438	65,666		3,02	40,60		1,85	214,077	
	1,437	66,464		3,012	39,68		1,847	214,298	
12	1,44	91,894	90,510	3,043	58,93	59,330	1,854	213,575	215,887
	1,437	89,273		3,035	59,26		1,853	216,687	
	1,435	90,364		3,01	59,79		1,846	217,399	
16	1,436	114,964	114,220	3,033	80,55	80,011	1,852	215,671	215,455
	1,435	113,704		3,034	79,94		1,852	215,915	
	1,433	113,992		3,016	79,54		1,847	214,780	
20	1,432	141,040	140,193	3,025	99,34	99,901	1,846	216,117	215,823
	1,436	139,718		3,026	101,86		1,849	215,769	
	1,435	139,823		3,032	98,51		1,851	215,584	
24	1,438	165,021	165,015	3,052	120,95	119,848	1,857	216,641	216,529
	1,435	164,330		3,014	119,67		1,848	216,268	
	1,434	165,695		3,011	118,92		1,846	216,678	
28	1,451	191,351	189,840	3,077	142,94	141,019	1,874	217,995	218,399
	1,442	189,808		3,047	140,93		1,862	218,000	
	1,439	188,361		3,017	139,18		1,85	219,202	
32	1,435	213,910	213,997	3,05	161,21	161,386	1,853	215,586	216,365
	1,4444	213,340		3,059	160,55		1,861	216,204	
	1,439	214,740		3,025	162,40		1,853	217,307	
36	1,434	239,197	238,919	3,015	178,00	179,342	1,848	215,717	216,387
	1,431	237,377		3,006	178,97		1,843	215,548	
	1,431	240,184		3,006	181,06		1,844	217,897	
40	1,431	262,151	262,544	3,008	200,25	197,853	1,844	217,452	216,846
	1,44	262,695		3,037	196,67		1,854	216,015	
	1,432	262,785		3,009	196,64		1,845	217,071	

4.4.2 Standard curve graph

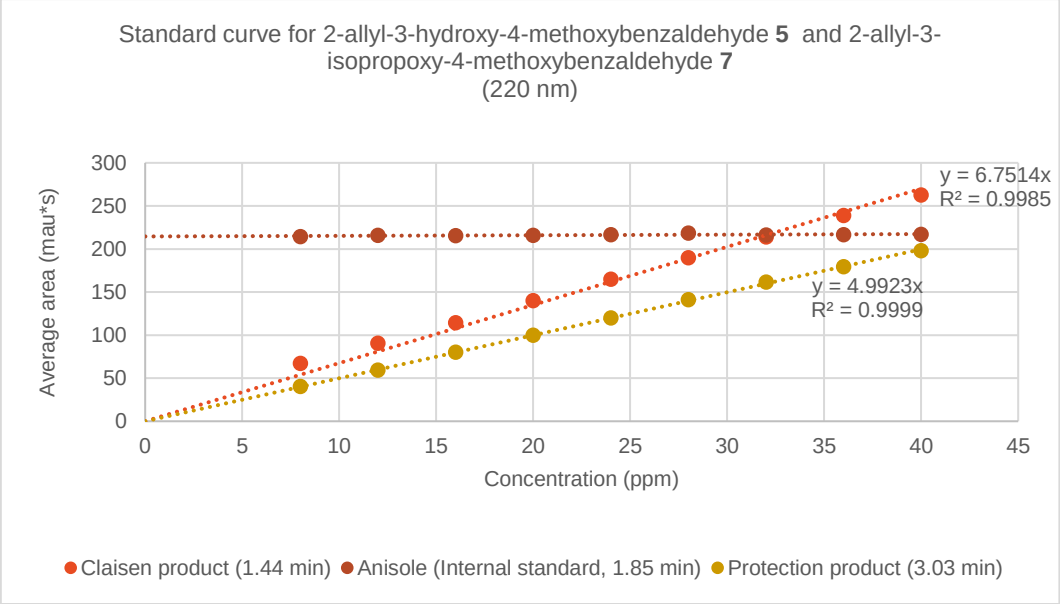


Figure 24: Standard curve for 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** and 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7** at 220 nm

4.4.3 Example HPLC Chromatograms

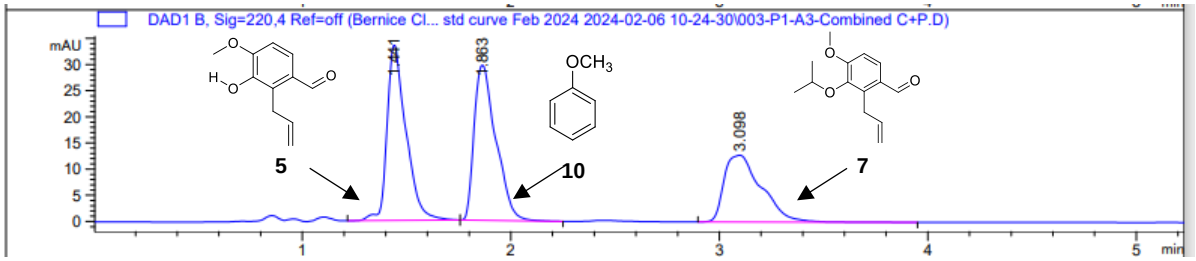


Figure 25: Chromatogram for standard curve at 220 nm at 30 ppm 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5** (1.437 min) and 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7** (3.029 min) and Anisole **10** (1.851 min)

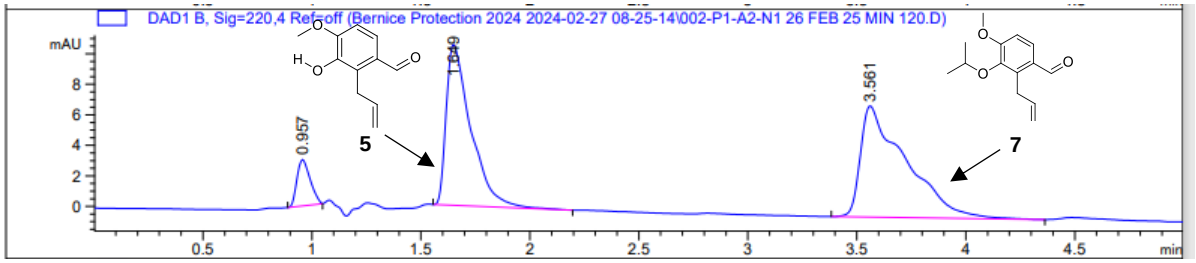


Figure 26: Chromatogram protection reaction (entry 8) using potassium hydroxide solution at 25 ppm

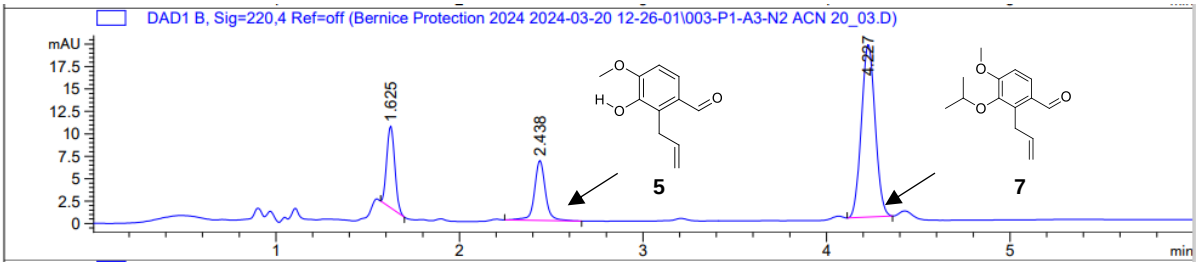


Figure 27: Chromatogram protection reaction (entry 29) using potassium hydroxide solution at 25 ppm

4.4.4 Experiment calculations

Table 16: Calculations for experiments conducted for reduction using polymer supported sodium borohydride

Exp No	A	B	C	D	E	F	G	H	I	J	K
1	165.05	5.03	0.50	25.15	200	55.21	11.06	2211.72	2.21	88.47	43.97
2	165.05	5.03	0.50	25.15	200	45.84	9.18	1836.39	1.84	73.46	36.51
3	165.10	5.03	0.50	25.16	200	30.63	6.14	1227.13	1.23	49.09	24.39
4	165.10	5.03	0.50	25.16	200	31.75	6.36	1272.10	1.27	50.88	25.28
5	165.10	5.03	0.50	25.16	200	29.80	5.97	1193.76	1.19	47.75	23.73
6	165.10	5.03	0.50	25.16	200	23.01	4.61	921.82	0.92	36.87	18.32
7	165.10	5.03	0.50	25.16	200	12.86	2.58	515.09	0.52	20.60	10.24
8	201.90	6.15	0.62	30.76	200	105.25	21.08	4216.50	4.22	168.66	68.53
9	193.90	5.91	0.59	29.54	200	95.40	19.11	3821.98	3.82	152.88	64.68
10	191.00	5.82	0.58	29.10	200	92.34	18.50	3699.28	3.70	147.97	63.56
11	192.80	5.88	0.59	29.38	200	90.54	18.14	3627.37	3.63	145.09	61.74
12	194.80	5.28	0.53	26.38	200	77.99	15.62	3124.42	3.12	140.60	59.21
13	198.10	5.37	0.54	26.83	200	79.06	15.84	3167.17	3.17	142.52	59.02
14	380.60	11.60	1.16	57.99	200	170.37	34.13	6825.48	6.83	273.02	58.85
15	194.40	5.27	0.53	26.33	200	75.99	15.22	3044.33	3.04	136.99	57.81
16	105.10	3.20	0.64	32.03	100	88.01	17.63	1763.00	1.76	70.52	55.05
17	198.30	6.04	0.60	30.21	200	80.54	16.13	3226.49	3.23	129.06	53.39
18	191.80	5.84	0.58	29.22	200	75.19	15.06	3012.15	3.01	120.49	51.54
19	101.90	3.11	0.62	31.05	100	79.59	15.94	1594.27	1.59	63.77	51.34
20	194.00	5.91	0.59	29.56	200	72.82	14.59	2917.23	2.92	116.69	49.35
21	194.80	5.94	0.59	29.68	200	69.84	13.99	2797.73	2.80	111.91	47.13
22	193.80	5.91	0.59	29.53	200	82.07	16.44	3288.05	3.29	131.52	55.68
23	192.80	5.88	0.59	29.38	200	71.31	14.28	2856.75	2.86	114.27	48.62
24	77.04	2.35	0.47	23.48	100	52.20	10.46	1045.56	1.05	41.82	44.54
25	77.04	2.35	0.47	23.48	100	68.57	13.73	1373.49	1.37	54.94	58.51
26	80.50	4.91	0.49	24.53	200	41.58	8.33	1665.96	1.67	33.32	33.96
27	80.50	4.91	0.49	24.53	200	61.42	12.30	2460.75	2.46	49.22	50.16
28	39.12	2.38	0.48	23.84	100	47.34	9.48	948.34	0.95	18.97	39.78
29	77.04	2.35	0.47	23.48	100	100.84	20.20	2019.82	2.02	80.79	86.04
30	77.68	2.37	0.47	23.67	100	89.43	17.91	1791.27	1.79	71.65	75.67
31	39.12	2.38	0.48	23.84	100	48.88	9.79	979.19	0.98	19.58	41.07

4.5 HPLC analysis for the aldehyde reduction

Table 17: HPLC method information for optimization of (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**

Quat. Pump	
Flow rate	1.00 mL.min^{-1}

Maximum pressure	400 bar	
Stop time	7 minutes	
Oven Temperature	35 °C	
Injection Volume	2.00 uL	
Channel	**Name**	**Percentage (%)**
A	Organic (50 % MeOH/ACN)	60
B	Aqueous 10 mM Phosphate buffer (90 % H_2O/Organic)	40
Signals	**Name**	**Retention time (min)**
210 nm	2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**	4.454
210 nm	(2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**	2.794
210 nm	Anisole **10** (Internal standard)	2.302

4.5.1 Raw data for standard curve

Table 18: Raw data for triplicates at each concentration for standard curve for (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**

	(2-allyl-3-isopropoxy-4-methoxyphenyl)methanol 8			**Anisole 10 (Internal standard)**		
PPM	**Retention time**	**Area (mAU*S)**	**Average Area**	**Retention time**	**Area (mAU*S)**	**Average Area**
8	2.822	118.062	117.7746	2.299	195.744	191.73
	2.826	111.586		2.302	189.702	
	2.832	127.538		2.305	195.774	
	2.835	113.912		2.306	185.699	
12	2.843	172.908	172.703	2.311	191.802	193.446
	2.878	170.603		2.33	191.496	
	2.83	179.118		2.306	198.772	
	2.823	168.183		2.3	191.712	
16	2.829	229.446	230.5423	2.304	192.057	193.357
	2.842	227.327		2.312	191.403	
	2.826	228.725		2.301	192.919	
	2.834	236.672		2.309	197.048	
20	2.84	289.051	289.4722	2.311	194.098	194.054
	2.848	288.881		2.316	194.485	
	2.819	288.1		2.298	190.899	
	2.83	291.857		2.305	196.733	
24	2.832	355.547	349.9926	2.304	192.497	194.63
	2.827	346.697		2.303	192.944	
	2.838	347.143		2.309	195.284	
	2.835	350.584		2.308	197.794	
28	2.818	402.65	402.2017	2.297	194.774	197.717
	2.812	403.336		2.294	202.473	
	2.833	401.947		2.304	194.95	
	2.815	400.873		2.295	198.672	
32	2.832	458.862	462.5346	2.307	194.602	196.914
	2.827	462.118		2.302	196.909	
	2.83	466.624		2.307	199.232	
36	2.833	523.034	520.9403	2.309	195.356	197.17

	2.826	518.316		2.303	197.018	
	2.83	520.916		2.306	196.264	
	2.825	521.495		2.301	200.043	
40	2.833	574.388	577.4676	2.308	199.295	195.59
	2.834	574.03		2.307	192.807	
	2.833	583.572		2.307	195.194	
	2.837	577.881		2.309	195.064	

4.5.2 Standard curve graph

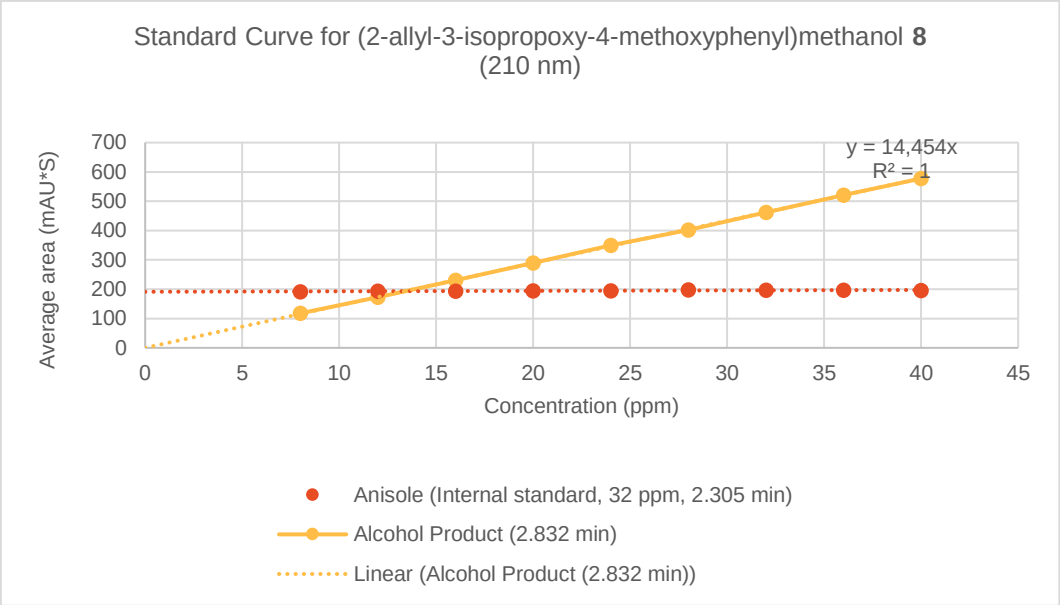


Figure 28: Standard curve for (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** at 210 nm

4.5.3 Example HPLC Chromatograms

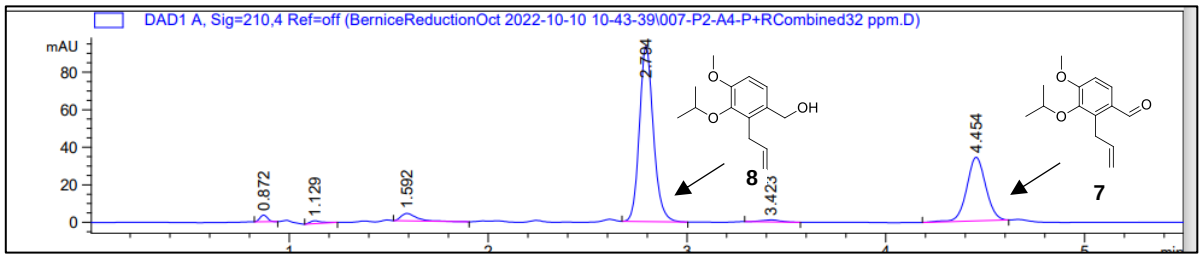


Figure 29: Chromatogram for standard curve at 210 nm at 32 ppm for (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** (2.794 min) and 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7** (4.454 min)

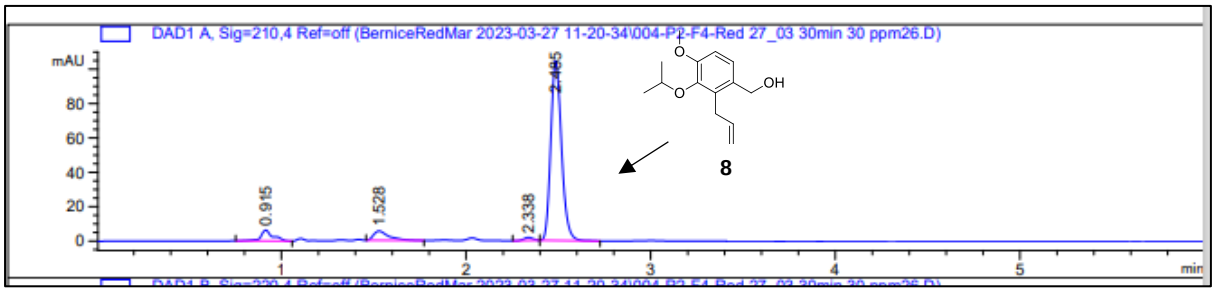


Figure 30: Chromatogram reduction reaction (entry 8) using sodium borohydride solution at 30 ppm

4.5.4 Experiment calculations

Table 19: Calculations for experiments conducted for reduction using polymer supported sodium borohydride

Exp No	A	B	C	D	E	F	G	H	I	J	K
1	148.6	5.00	0.50	24.98	200	213.95	14.80	2960.49	2.96	88.81	59.77
2	148.3	4.99	0.50	24.93	200	248.18	17.17	3434.12	3.43	103.02	69.47
3	148.4	4.99	0.50	24.95	200	160.66	11.12	2223.08	2.22	66.69	44.94
4	148.6	5.00	0.50	24.98	200	243.51	16.85	3369.39	3.37	101.08	68.02
5	148.7	5.00	0.50	25.00	200	227.05	15.71	3141.68	3.14	94.25	63.38
6	148.2	4.98	0.50	24.91	200	287.05	19.86	3971.91	3.97	119.16	80.40
7	148.3	4.99	0.50	24.93	200	311.70	21.56	4312.94	4.31	129.39	87.25

Table 20: Calculations for experiments conducted for reduction using sodium borohydride solution

Exp No	A	B	C	D	E	F	G	H	I	J	K
1	150.9	5.07	0.51	25.37	203	358.13	24.78	5028.17	5.03	125.70	82.59
2	150.9	5.07	0.51	25.37	203	345.89	23.93	4856.29	4.86	121.41	79.77
3	150.9	5.07	0.51	25.37	203	380.30	26.31	5339.40	5.34	133.48	87.70
4	150.9	5.07	0.51	25.37	203	392.27	27.14	5507.39	5.51	137.68	90.46
5	148.7	5.00	0.50	24.99	200	362.39	25.07	5012.52	5.01	125.31	83.57
6	149.9	5.04	0.50	25.20	202	343.37	23.76	4788.43	4.79	119.71	79.19
7	149.9	5.04	0.50	25.20	202	353.64	24.47	4931.69	4.93	123.29	81.56
8	148.7	5.00	0.50	24.99	200	402.00	27.81	5560.38	5.56	139.01	92.71
9	148.7	5.00	0.50	24.99	200	362.39	25.07	5012.52	5.01	125.31	83.57
10	148.7	4.99	0.50	24.97	200	346.34	23.96	4786.15	4.79	124.44	83.07
11	149.9	5.04	0.50	25.20	202	343.37	23.76	4788.43	4.79	119.71	79.19

4.6 HPLC analysis for the second allylation

Table 21: HPLC method information for optimization of 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**

Quat. Pump		
Flow rate	1.00 $mL.min^{-1}$	
Maximum pressure	400 bar	
Stop time	15 minutes	
Oven Temperature	35 °C	
Injection Volume	2.00 uL	
Channel	**Name**	**Percentage (%)**
A	Organic (50 % MeOH/ACN)	60
B	Aqueous 10 mM Phosphate buffer (90 % H_2O/Organic)	40
Signals	**Name**	**Retention time (min)**
210 nm	2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **23**	2.842
210 nm	2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**	12.635
210 nm	Anisole **10** (Internal standard)	2.312

4.6.1 Raw data for standard curve

Table 22: Raw data for triplicates at each concentration for standard curve for 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**

	2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene 9			Anisole 10 (Internal standard)		
PPM	Retention time	Area (mAU*S)	Average Area	Retention time	Area (mAU*S)	Average Area
8	12.498	108.301	112.633	2.299	195.744	191.73
	12.529	113.333		2.302	189.702	
	12.543	116.618		2.305	195.774	
	12.516	112.281		2.306	185.699	
12	12.564	170.909	160.798	2.311	191.802	193.446
	12.887	156.423		2.33	191.496	
	12.528	170.925		2.306	198.772	
	12.501	144.934		2.3	191.712	
16	12.488	214.966	209.593	2.304	192.057	193.357
	12.635	186.987		2.312	191.403	
	12.464	203.858		2.301	192.919	
	12.527	232.56		2.309	197.048	
20	12.54	256.135	268.122	2.311	194.098	194.054
	12.631	284.768		2.316	194.485	
	12.475	267.461		2.298	190.899	
	12.531	264.125		2.305	196.733	
24	12.514	305.583	308.535	2.304	192.497	194.63
	12.601	316.829		2.303	192.944	
	12.537	312.303		2.309	195.284	
	12.524	299.424		2.308	197.794	
28	12.51	357.065	360.322	2.297	194.774	197.717
	12.548	370.957		2.294	202.473	
	12.384	359.945		2.304	194.95	
	12.502	353.322		2.295	198.672	
32	12.531	412.432	413.423	2.307	194.602	196.914
	12.467	410.094		2.302	196.909	
	12.54	417.744		2.307	199.232	
36	12.58	464.48	475.525	2.309	195.356	197.17
	12.468	472.772		2.303	197.018	
	12.48	472.633		2.306	196.264	
	12.513	492.213		2.301	200.043	
40	12.478	514.906	525.35	2.308	199.295	195.59
	12.531	538.272		2.307	192.807	
	12.504	509.217		2.307	195.194	
	12.476	539.004		2.309	195.064	

4.6.2 Standard curve graph

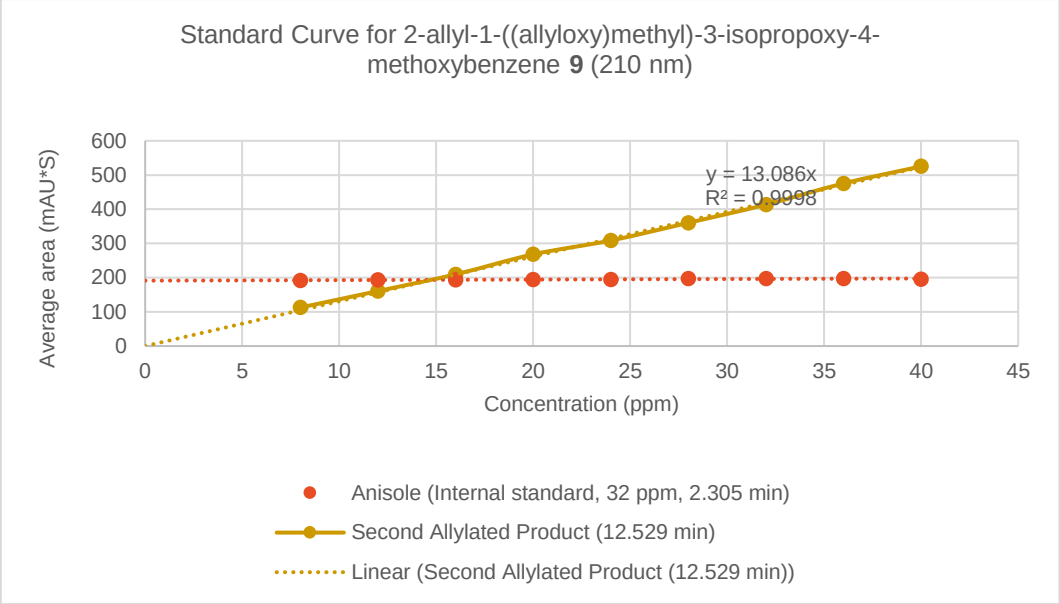


Figure 31: Standard curve for 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** at 210 nm

4.6.3 Example HPLC Chromatogram

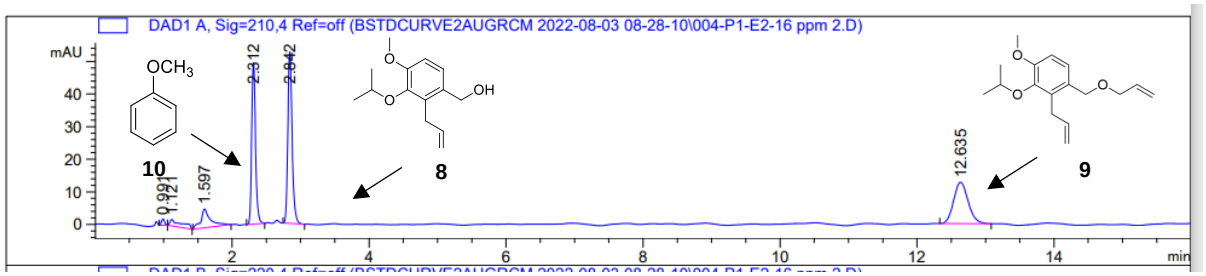


Figure 32: Chromatogram for standard curve at 210 nm at 16 ppm for 2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8** (2.842 min), 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** (12.365 min), and Anisole **10** (2.312 min)

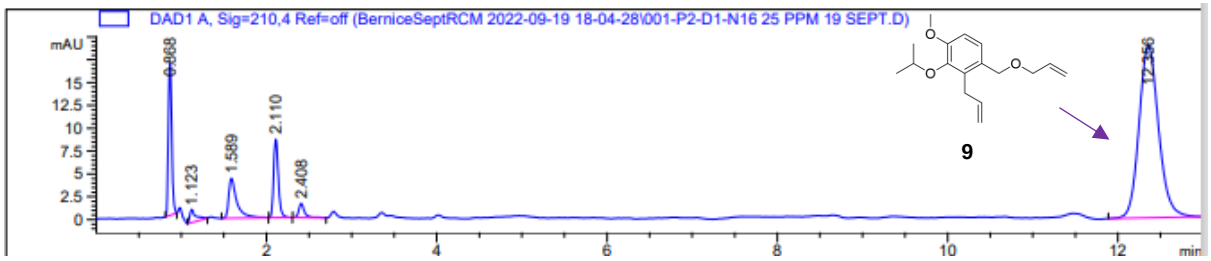


Figure 33: Chromatogram of 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** (entry 16) at 25 ppm

4.6.4 Experiment calculations

Table 23: Calculations for experiments conducted for 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**

Exp No	A	B	C	D	E	F	G	H	I	J	K
1	255.7	4.98	0.50	24.92	200	199.64	15.26	3051.16	3.05	183.07	61.22
2	255.2	4.97	0.50	24.87	200	291.65	22.29	4457.42	4.46	267.45	89.61

3	255.8	4.99	0.50	24.93	200	100.75	7.70	1539.86	1.54	92.39	30.88
4	256.4	5.00	0.50	24.99	200	260.77	19.93	3985.54	3.99	239.13	79.75
5	255	4.97	0.50	24.85	200	205.13	15.68	3135.16	3.14	188.11	63.08
6	256.2	4.99	0.50	24.97	200	293.93	22.46	4492.29	4.49	269.54	89.96
7	255.7	4.98	0.50	24.92	200	123.25	9.42	1883.72	1.88	113.02	37.79
8	255.1	4.97	0.50	24.86	200	280.30	21.42	4283.91	4.28	257.03	86.15
9	255.9	4.99	0.50	24.94	200	149.27	11.41	2281.35	2.28	136.88	45.74
10	255.1	4.97	0.50	24.86	200	260.30	19.89	3978.32	3.98	238.70	80.01
11	256.3	5.00	0.50	24.98	200	129.19	9.87	1974.44	1.97	118.47	39.52
12	256.7	5.00	0.50	25.02	200	269.12	20.57	4113.11	4.11	246.79	82.20
13	255.7	4.98	0.50	24.92	200	192.98	14.75	2949.39	2.95	176.96	59.18
14	255.6	4.98	0.50	24.91	200	274.72	20.99	4198.65	4.20	251.92	84.27
15	255.6	4.98	0.50	24.91	200	99.39	7.59	1518.97	1.52	91.14	30.49
16	256.2	4.99	0.50	24.97	200	301.08	23.01	4601.50	4.60	276.09	92.14
17	256.5	4.98	0.50	24.89	200	234.54	17.92	3584.58	3.58	215.07	72.00
18	255.4	4.98	0.50	24.89	200	215.53	16.47	3294.08	3.29	197.64	66.17

4.7 HPLC analysis for the RCM

Table 24: HPLC method information for optimization of (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**

Quat. Pump		
Flow rate	1.00 mL.min^{-1}	
Maximum pressure	400 bar	
Stop time	15 minutes	
Oven Temperature	35 °C	
Injection Volume	2.00 uL	
Channel	**Name**	**Percentage (%)**
A	Organic (50 % MeOH/ACN)	60
B	Aqueous 10 mM Phosphate buffer (90 % H_2O/Organic)	40
Signals	**Name**	**Retention time (min)**
210 nm	2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**	11.407
210 nm	(*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**	4.408
210 nm	Anisole **10** (Internal standard)	2.158

4.7.1 Raw data for standard curve

Table 25: Raw data for triplicates at each concentration for standard curve for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**

	(*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine 1			**Anisole 10 (Internal standard)**		
PPM	**Retention time**	**Area (mAU*S)**	**Average Area**	**Retention time**	**Area (mAU*S)**	**Average Area**
8	4.472	76.00193	76.56762	2.183	243.965	245.689
	4.451	75.96502		2.175	247.224	
	4.466	77.7359		2.18	245.878	
12	4.457	117.3149	115.0638	2.175	248.04	248.023
	4.408	112.7567		2.158	247.604	
	4.409	115.1197		2.159	248.426	

16	4.488	151.5451	152.9026	2.181	247.708	247.674
	4.49	153.7041		2.188	247.149	
	4.493	153.4585		2.19	248.167	
20	4.427	185.8389	188.6931	2.165	250.686	246.954
	4.362	191.0564		2.15	245.378	
	4.36	189.1839		2.15	244.798	
24	4.372	222.6228	227.1958	2.155	250.405	249.683
	4.487	230.6926		2.185	247.385	
	4.473	228.272		2.183	251.26	
28	4.364	264.0697	263.6516	2.154	247.846	247.52
	4.369	261.9721		2.148	244.727	
	4.394	264.913		2.154	249.987	
32	4.398	306.9771	306.9647	2.163	246.263	245.851
	4.389	304.1098		2.158	248.801	
	4.554	309.8073		2.227	242.488	
36	4.401	341.0914	342.8133	2.172	246.392	246.198
	4.378	341.9056		2.153	245.791	
	4.392	345.443		2.161	246.411	
40	4.9	382.4654	382.5757	2.153	246.858	246.397
	4.376	381.9564		2.159	245.278	
	4.376	383.3054		2.159	247.056	

4.7.2 Standard curve graph

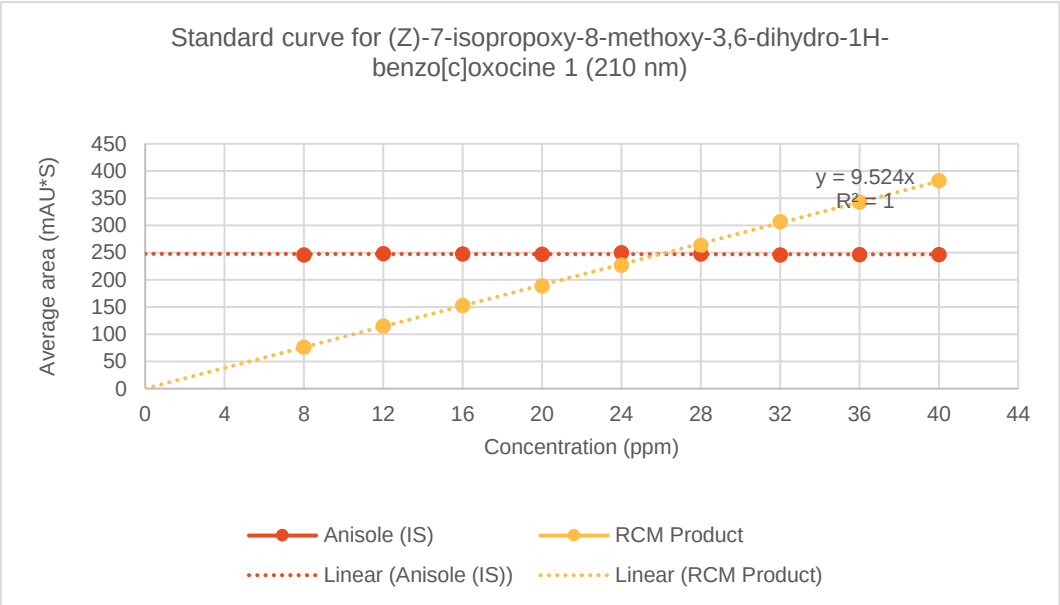


Figure 34: Standard curve for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1** at 210 nm

4.7.3 Example HPLC Chromatograms

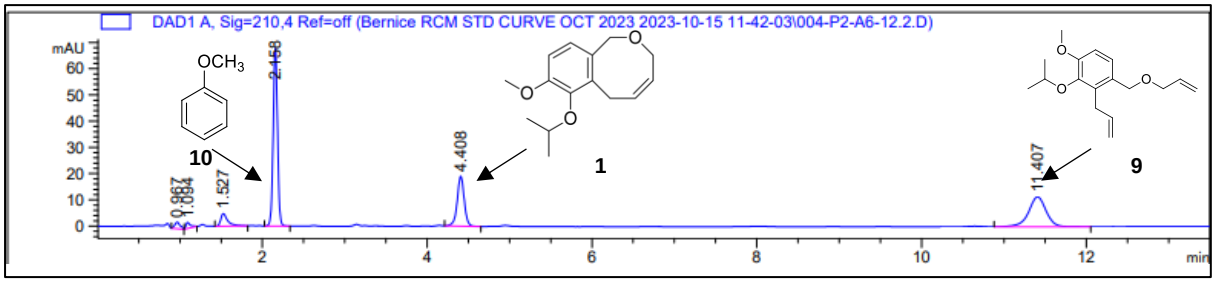


Figure 35: Chromatogram for standard curve at 210 nm at 25 ppm for -allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9** (11.407 min), (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1** (4.408 min), and Anisole **10** (2.158 min)

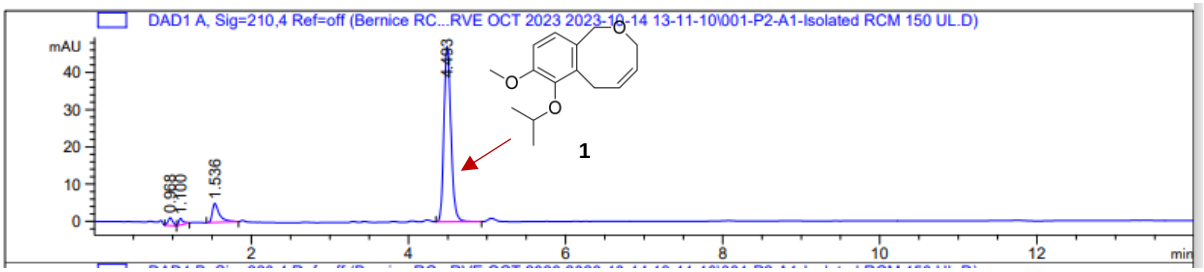


Figure 36: Chromatogram of (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1** (Batch isolated)

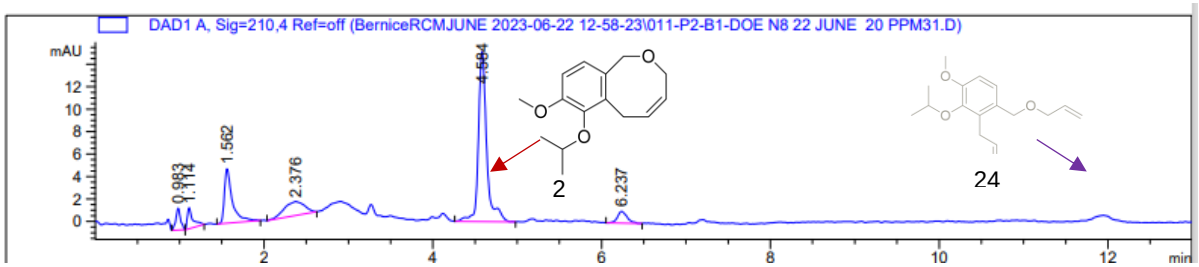


Figure 37: Chromatogram of (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1** (entry 8)

4.7.4 Experiments calculations

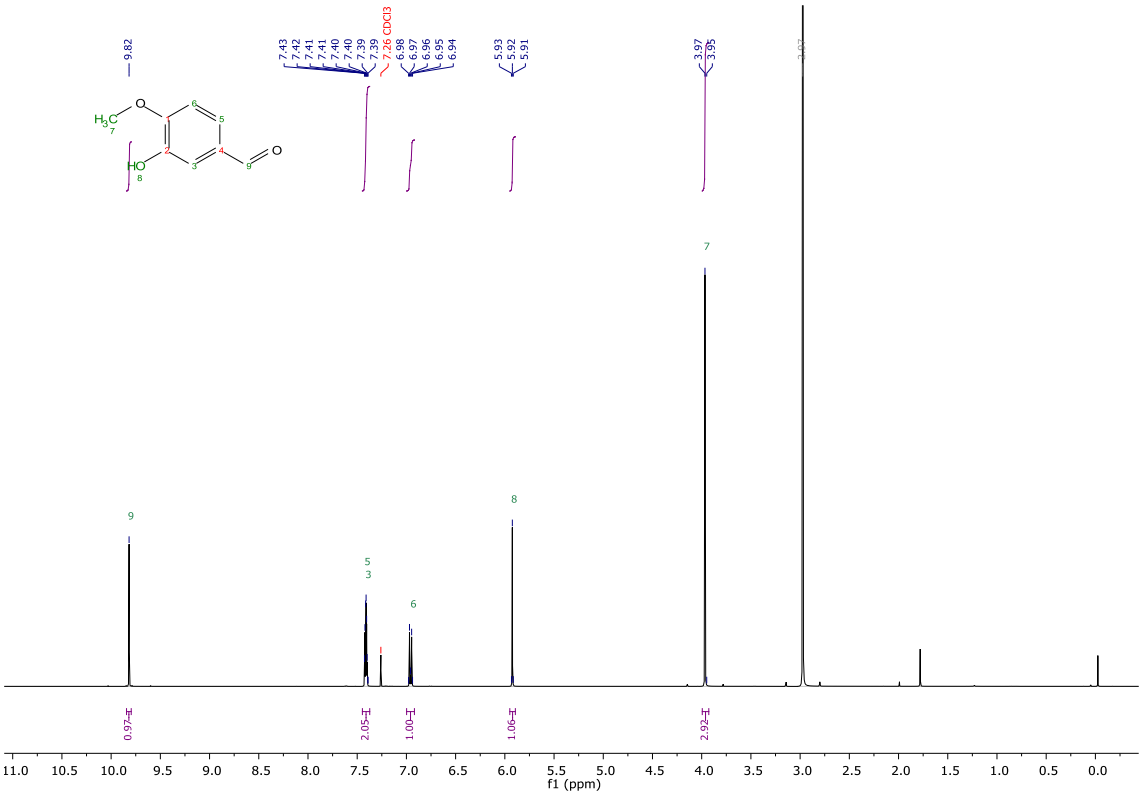
Table 26: Calculations for experiments conducted for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**

Exp No	A	B	C	D	E	F	G	H	I	J	K
1	111.2	2.00	0.20	19.98	100	86.69	9.10	910.21	0.91	18.20	45.55
2	110.5	1.99	0.20	19.86	100	81.83	8.59	859.17	0.86	17.18	43.27
3	110.8	1.99	0.20	19.91	100	91.02	9.56	955.72	0.96	19.11	48.00
4	110.3	1.98	0.20	19.82	100	77.15	8.10	810.11	0.81	16.20	40.87
5	111.5	2.00	0.20	20.04	100	47.14	4.95	494.96	0.49	9.90	24.70
6	110.8	1.99	0.20	19.91	100	67.98	7.14	713.80	0.71	14.28	35.85
7	110.7	1.99	0.20	19.89	100	88.08	9.25	924.80	0.92	18.50	46.49
8	111.2	2.00	0.20	19.98	100	104.19	10.94	1093.99	1.09	21.88	54.75
9	111.2	2.00	0.20	19.98	100	59.45	6.24	624.22	0.62	12.48	43.28
10	110.5	1.99	0.20	19.86	100	85.80	9.01	900.89	0.90	18.02	45.37
11	110.8	1.99	0.20	19.91	100	54.15	5.69	568.56	0.57	11.37	28.56
12	110.3	1.98	0.20	19.82	100	69.81	7.33	732.96	0.73	14.66	36.98
13	111.5	2.00	0.20	20.04	100	28.66	3.01	300.93	0.30	6.02	15.02

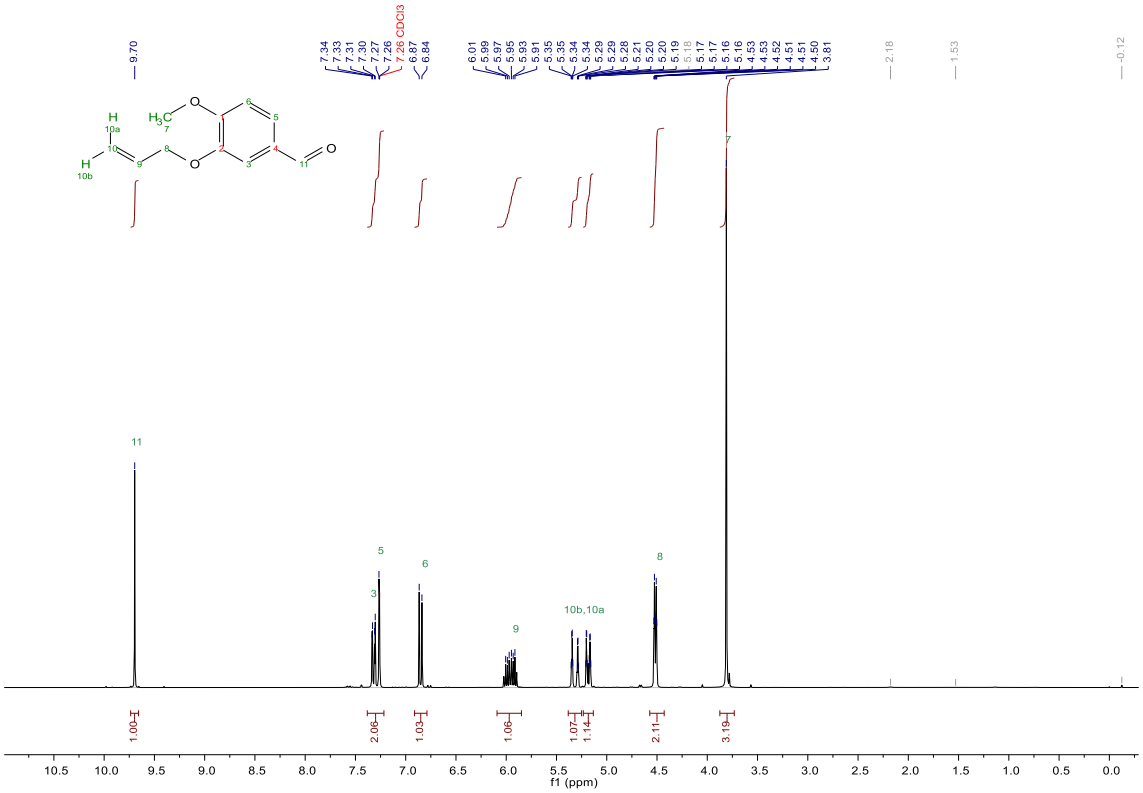
14	110.8	1.99	0.20	19.91	100	44.40	4.66	466.22	0.47	9.32	23.42
15	110.7	1.99	0.20	19.89	100	50.98	5.35	535.33	0.54	10.71	26.91
16	111.2	2.00	0.20	19.98	100	70.44	7.40	739.58	0.74	14.79	37.01
17	111.4	2.00	0.20	20.02	100	66.09	6.94	693.91	0.69	13.88	34.66
18	111.4	2.00	0.20	20.02	100	69.15	7.26	726.10	0.73	14.52	36.27
19	111.4	2.00	0.20	20.02	100	65.49	6.88	687.63	0.69	13.75	34.35

5. Characterization data

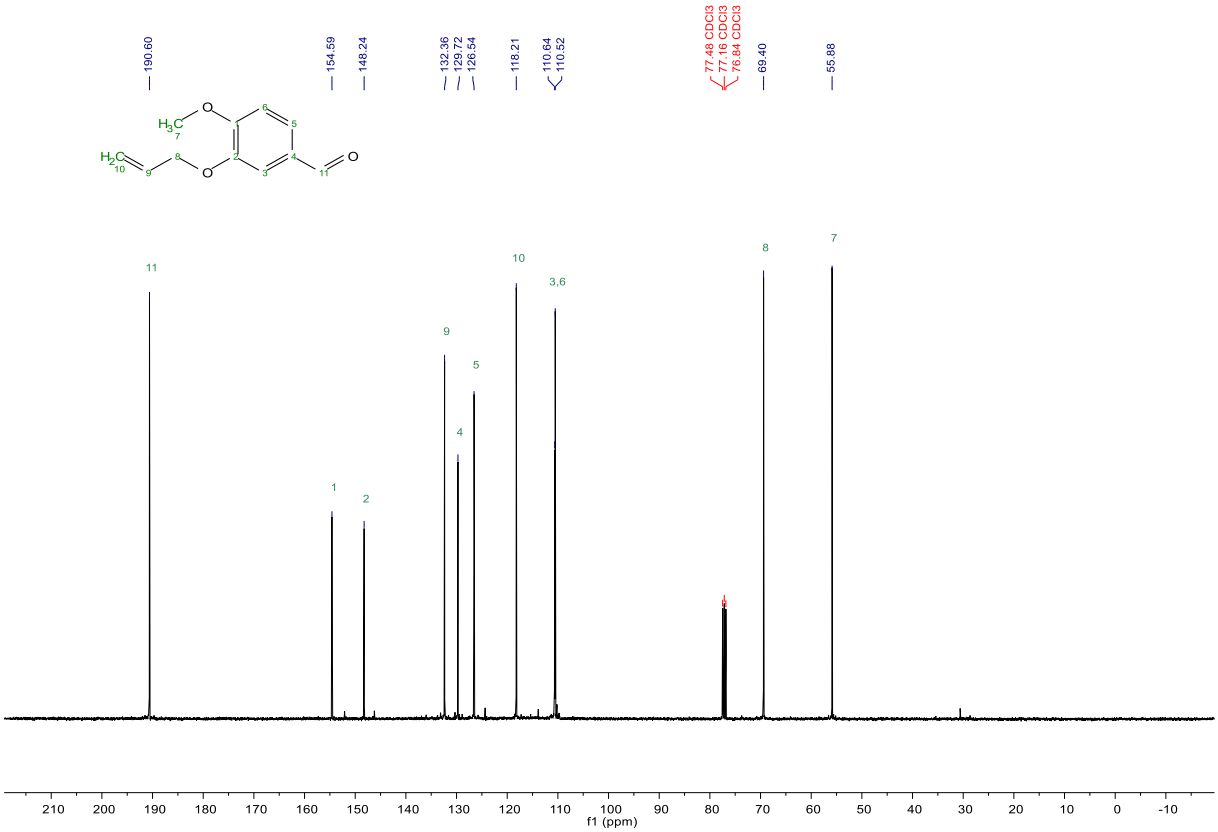
5.1 Nuclear magnetic resonance spectra



NMR 1: ^{1}H spectrum for Isovanillin **3** using internal standard $DMSO_2$

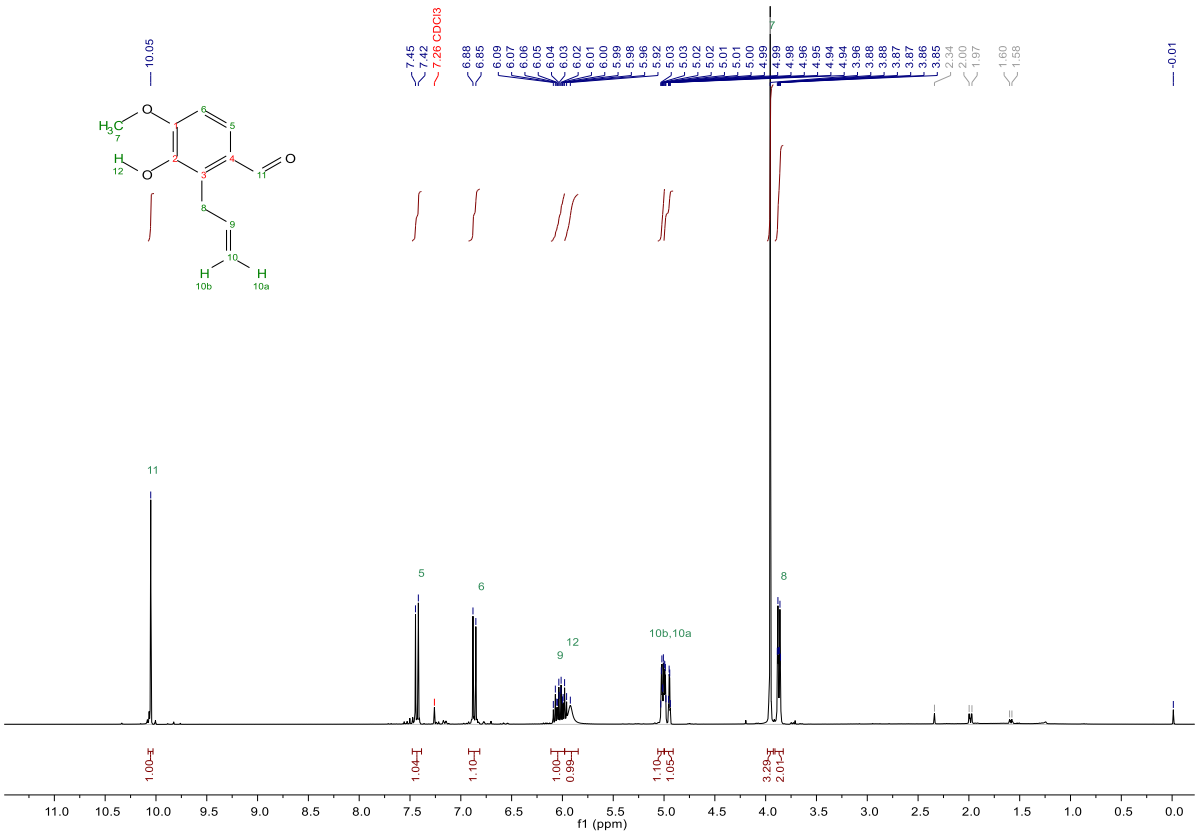


NMR 2: ^{1}H spectrum for 3-(allyloxy)-4-methoxybenzaldehyde **4**

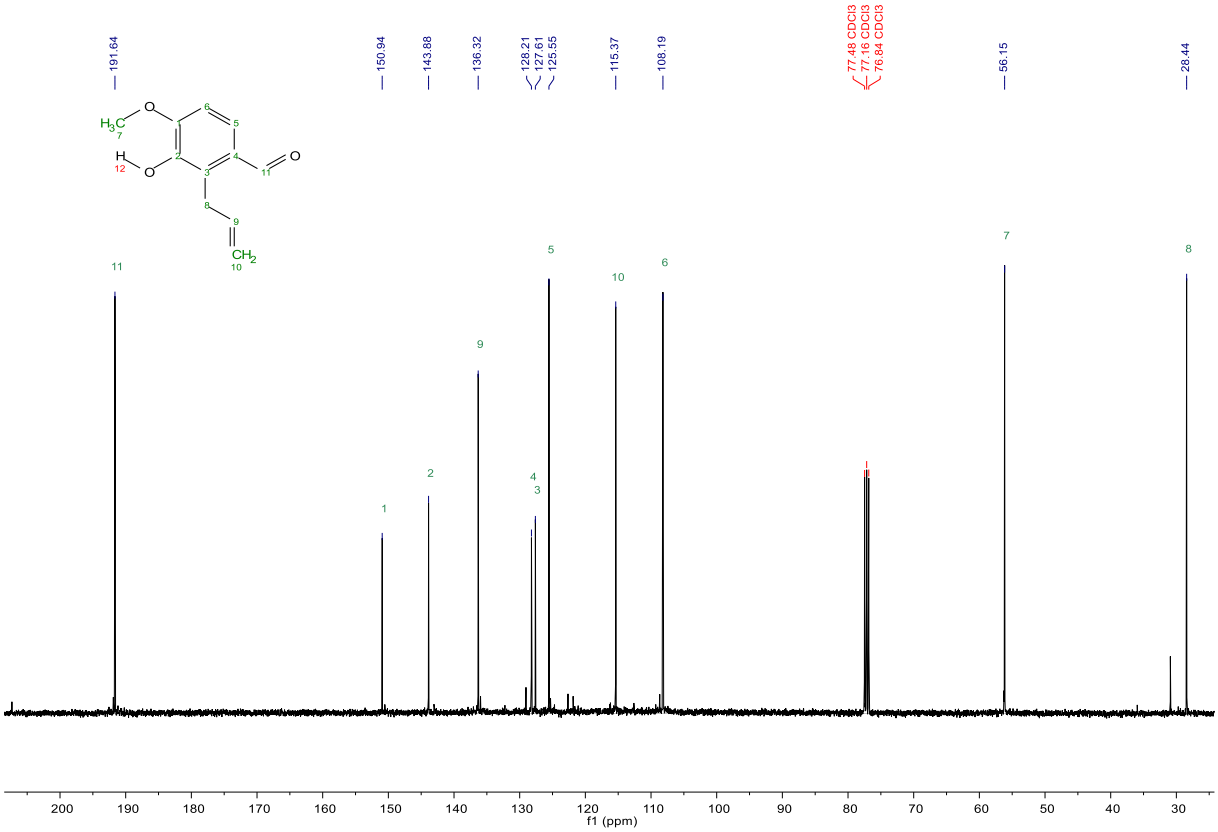


NMR 3: ^{13}C spectrum for 3-(allyloxy)-4-methoxybenzaldehyde **4**

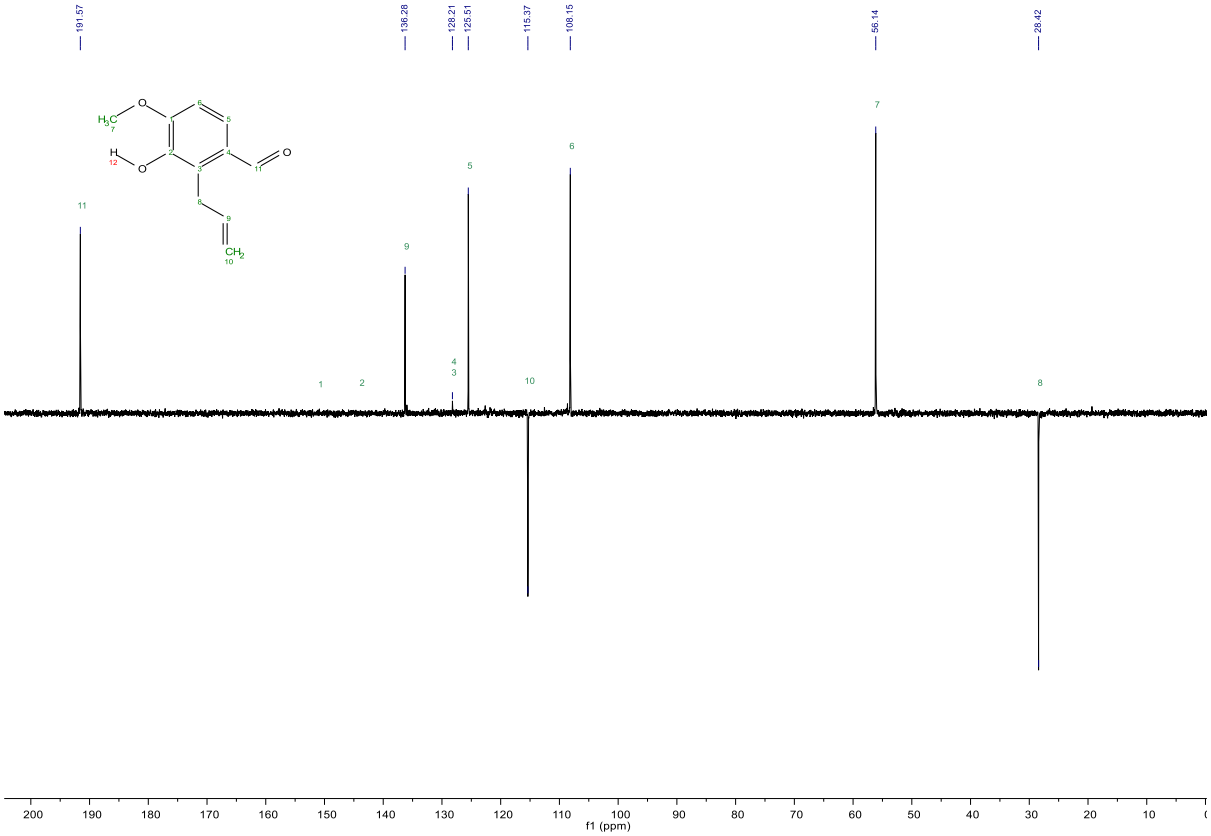
NMR 4: DEPT 135 spectrum for 3-(allyloxy)-4-methoxybenzaldehyde **4**



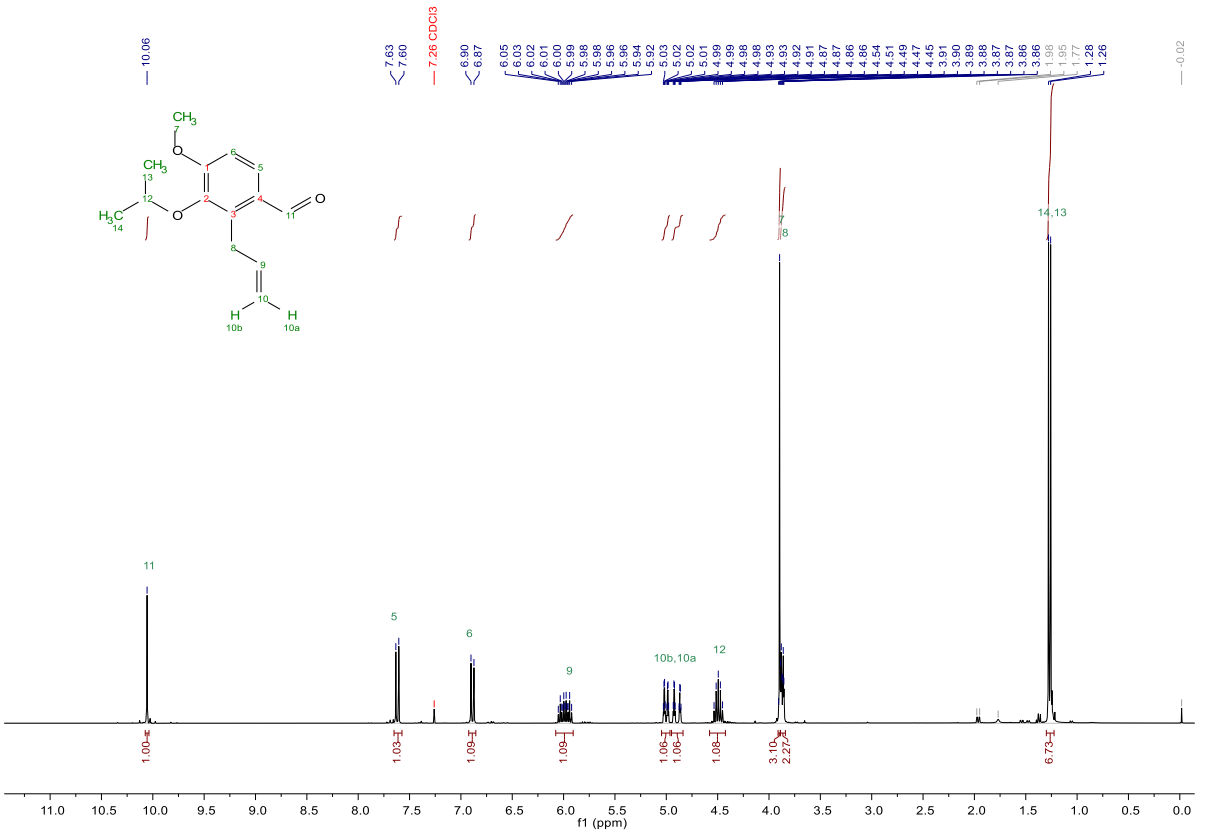
NMR 5: ^{1}H spectrum for 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5**



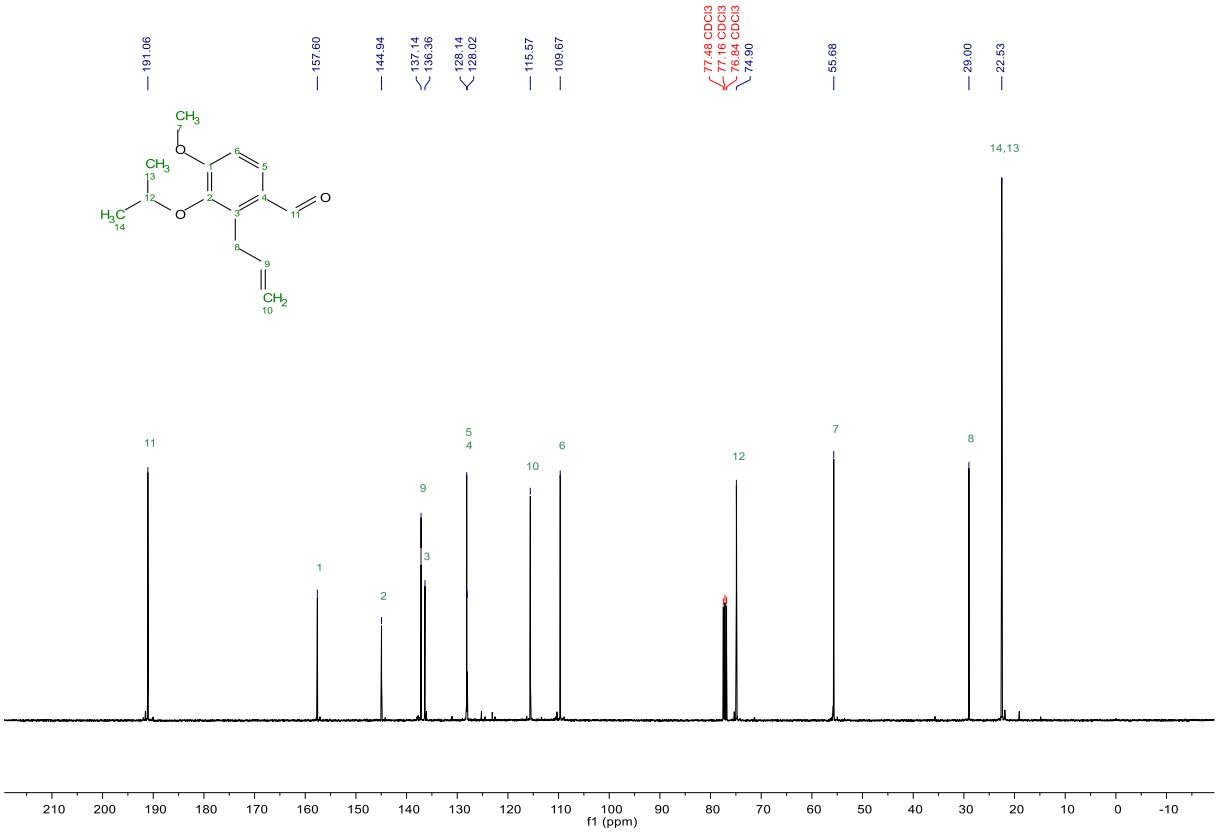
NMR 6: ^{13}C spectrum for 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5**



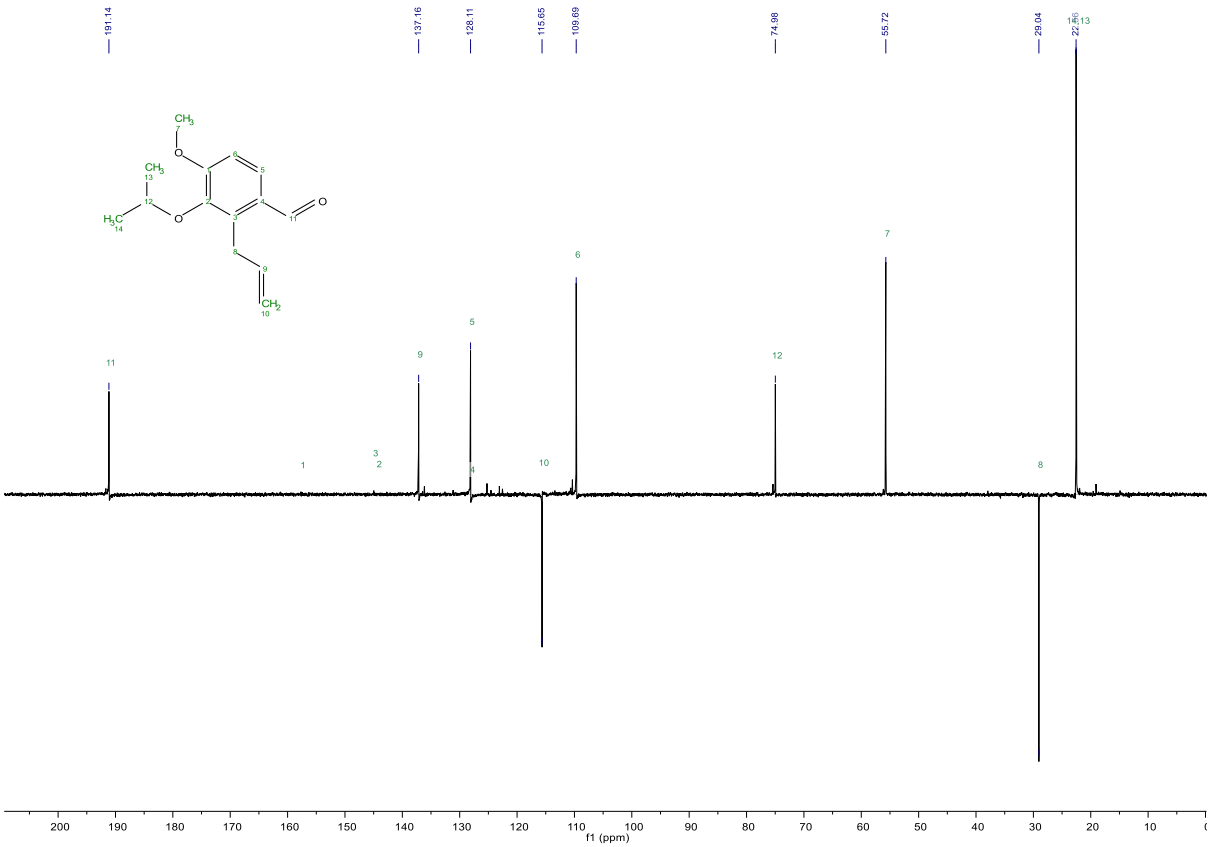
NMR 7: DEPT 135 spectrum for 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5**



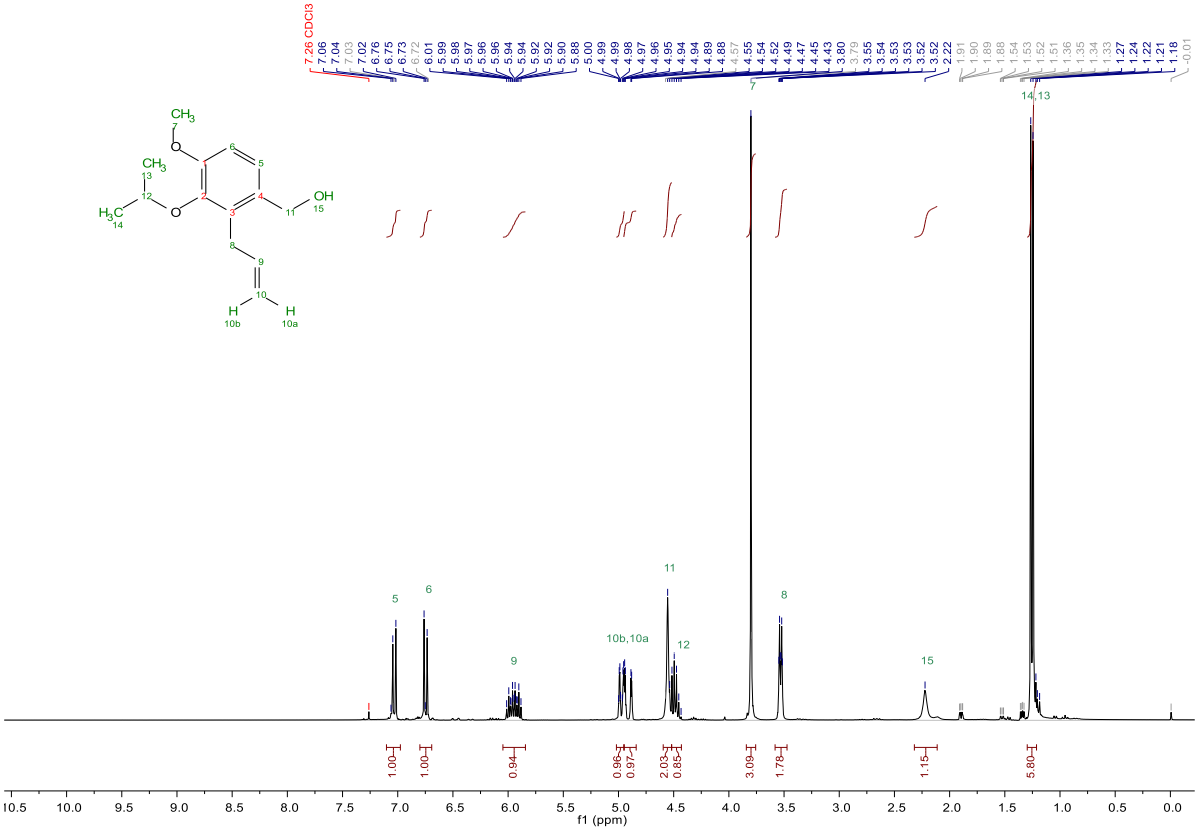
NMR 8: ^{1}H spectrum for 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**



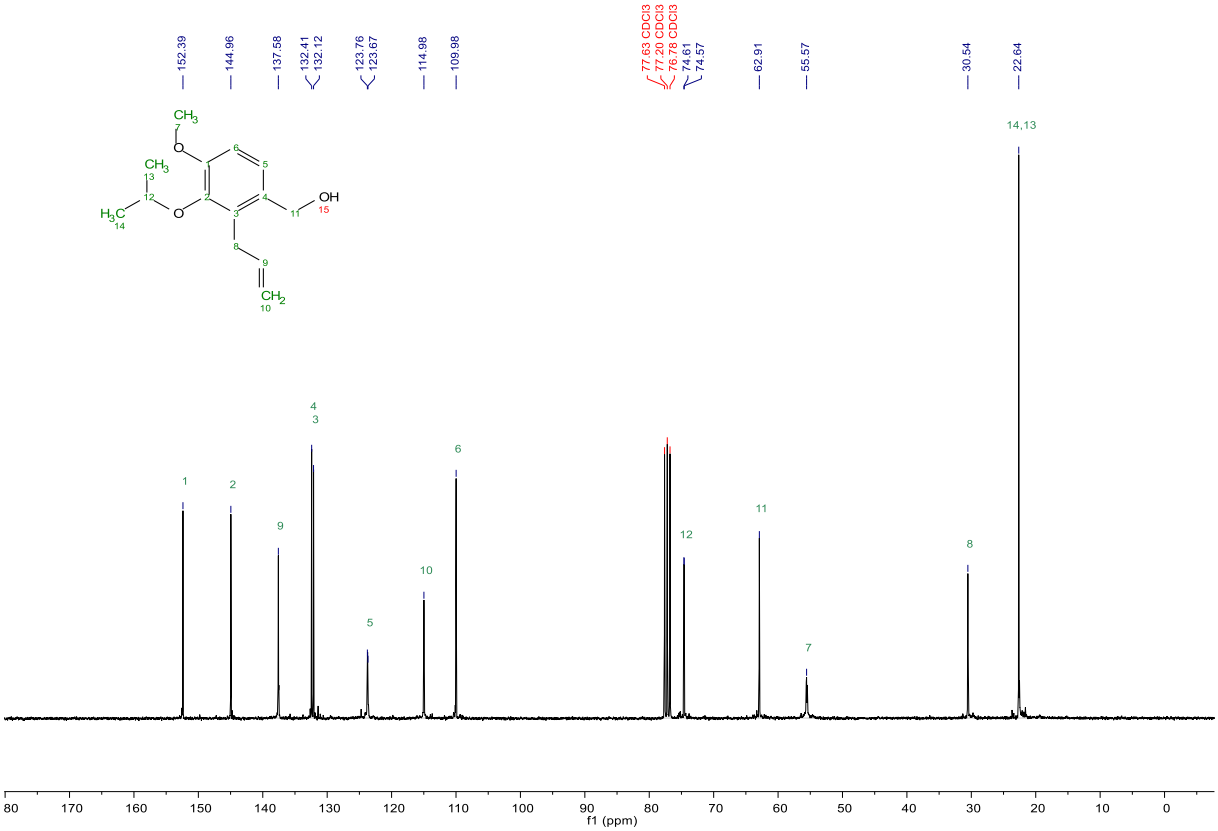
NMR 9: ^{13}C spectrum for 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**



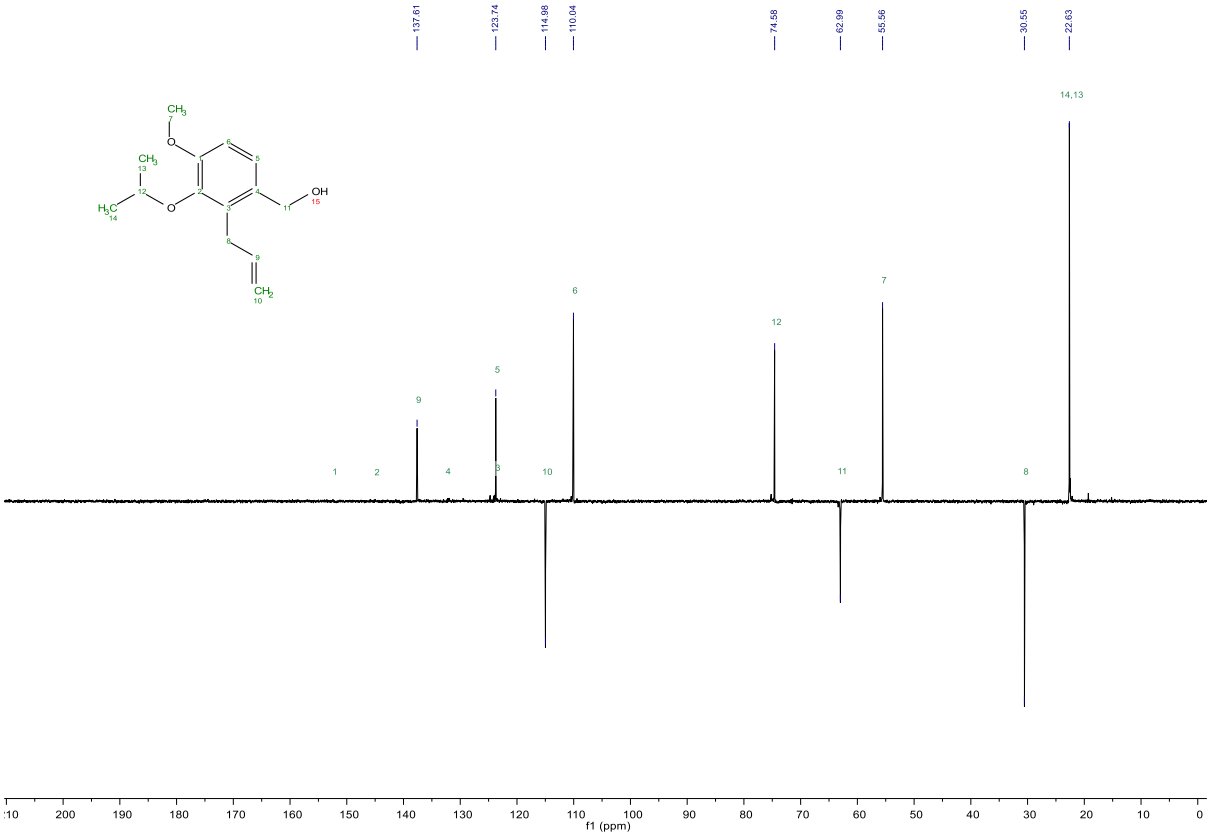
NMR 10: DEPT 135 spectrum for 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**



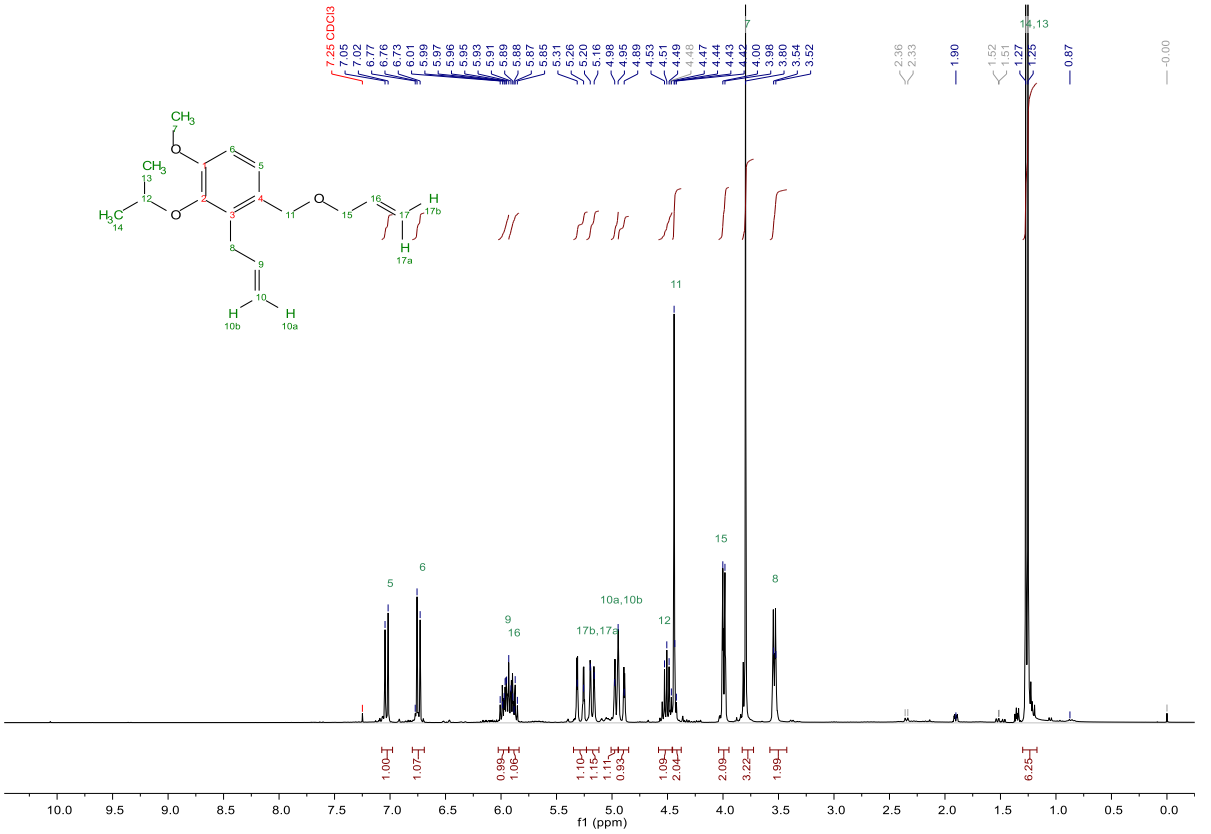
NMR 11: ^{1}H spectrum for (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**



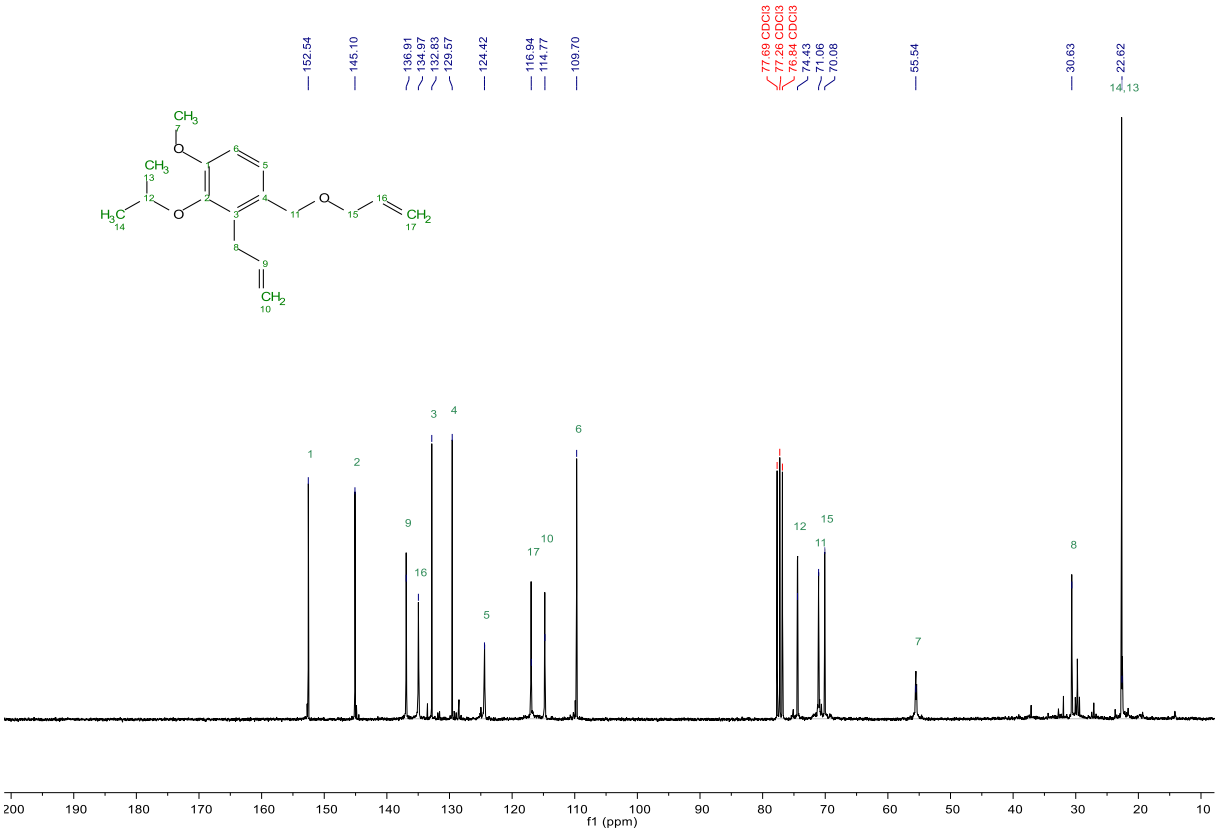
NMR 12: ^{13}C spectrum for (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**



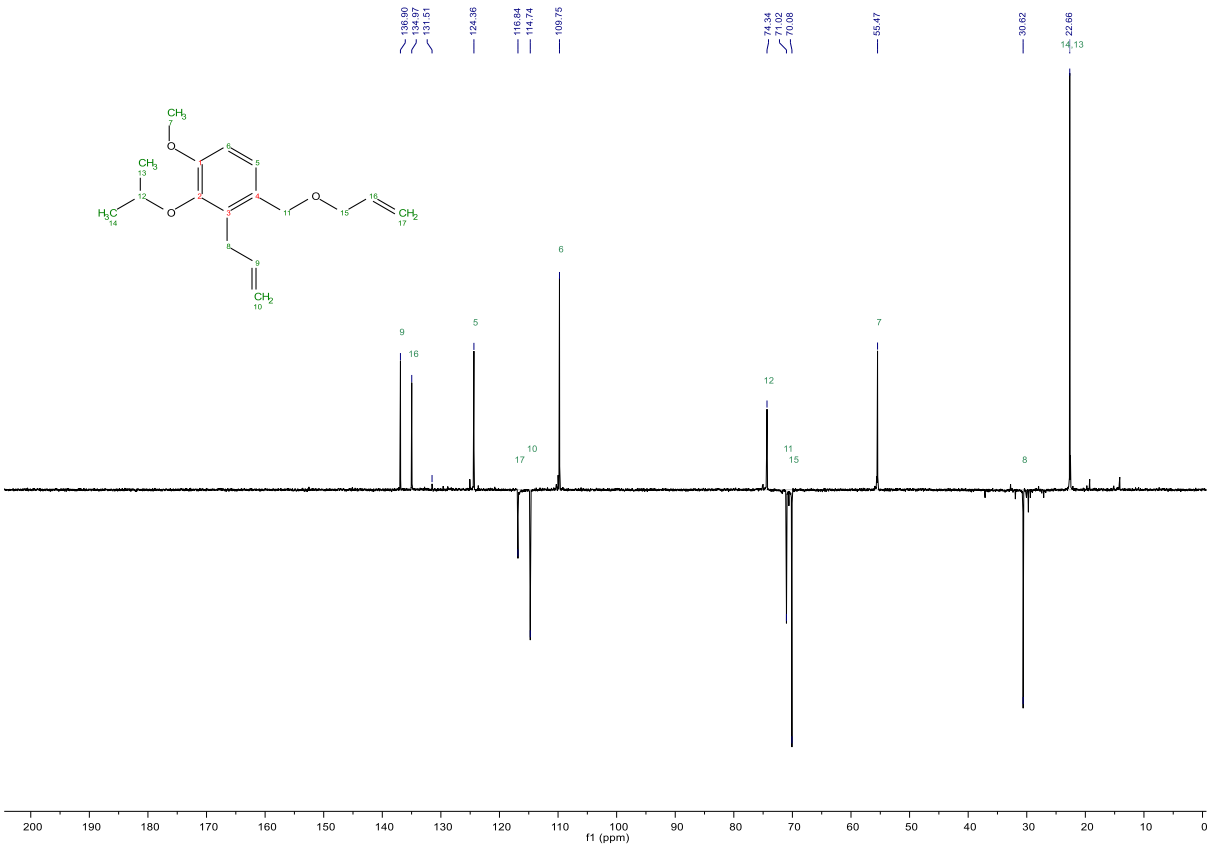
NMR 13: DEPT 135 spectrum for (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**



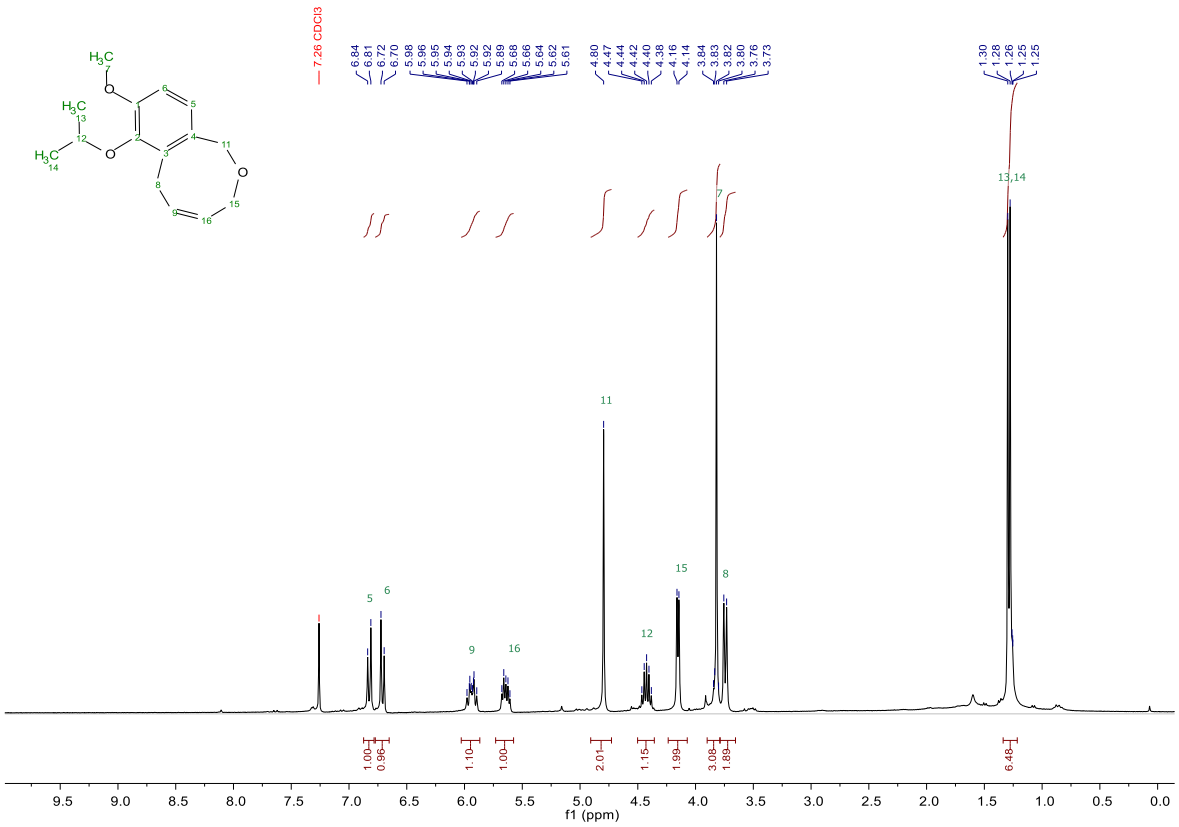
NMR 14: ^{1}H spectrum for 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**



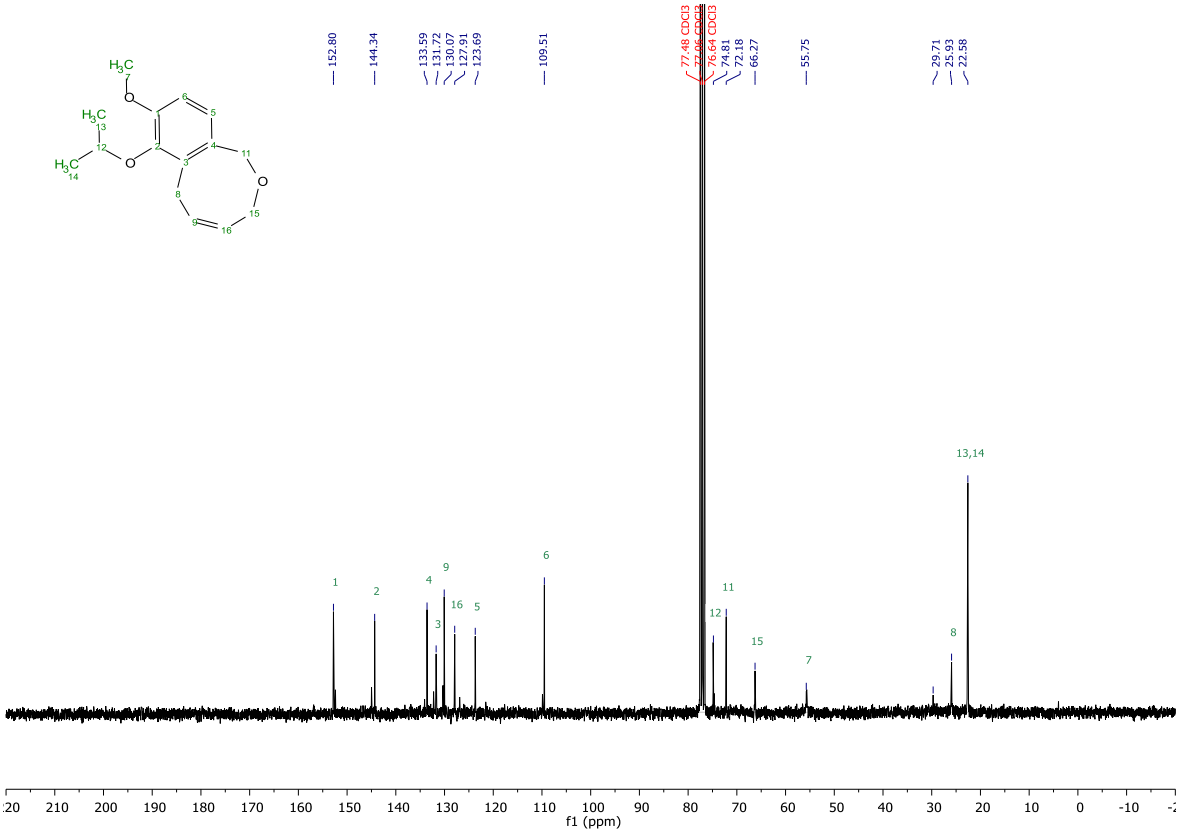
NMR 15: ^{13}C spectrum for 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**



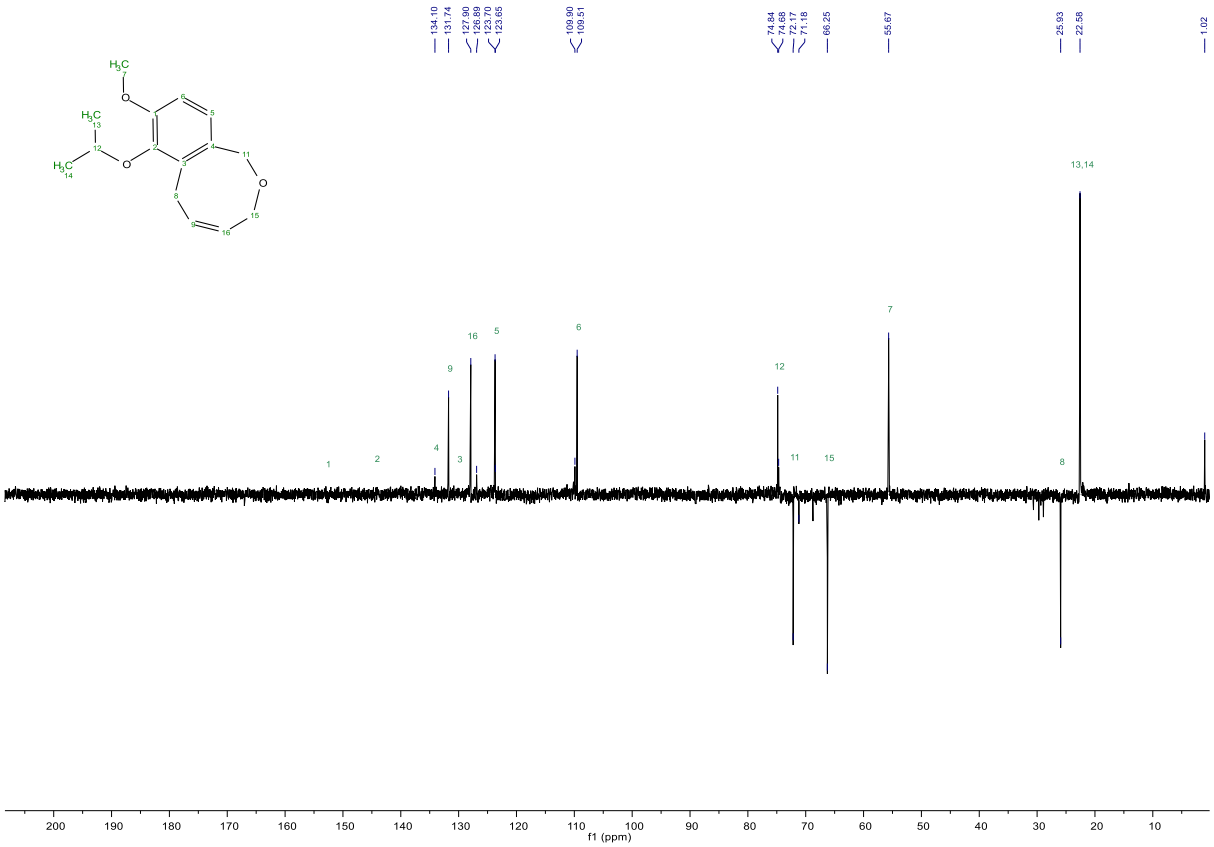
NMR 16: DEPT 135 spectrum for 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**



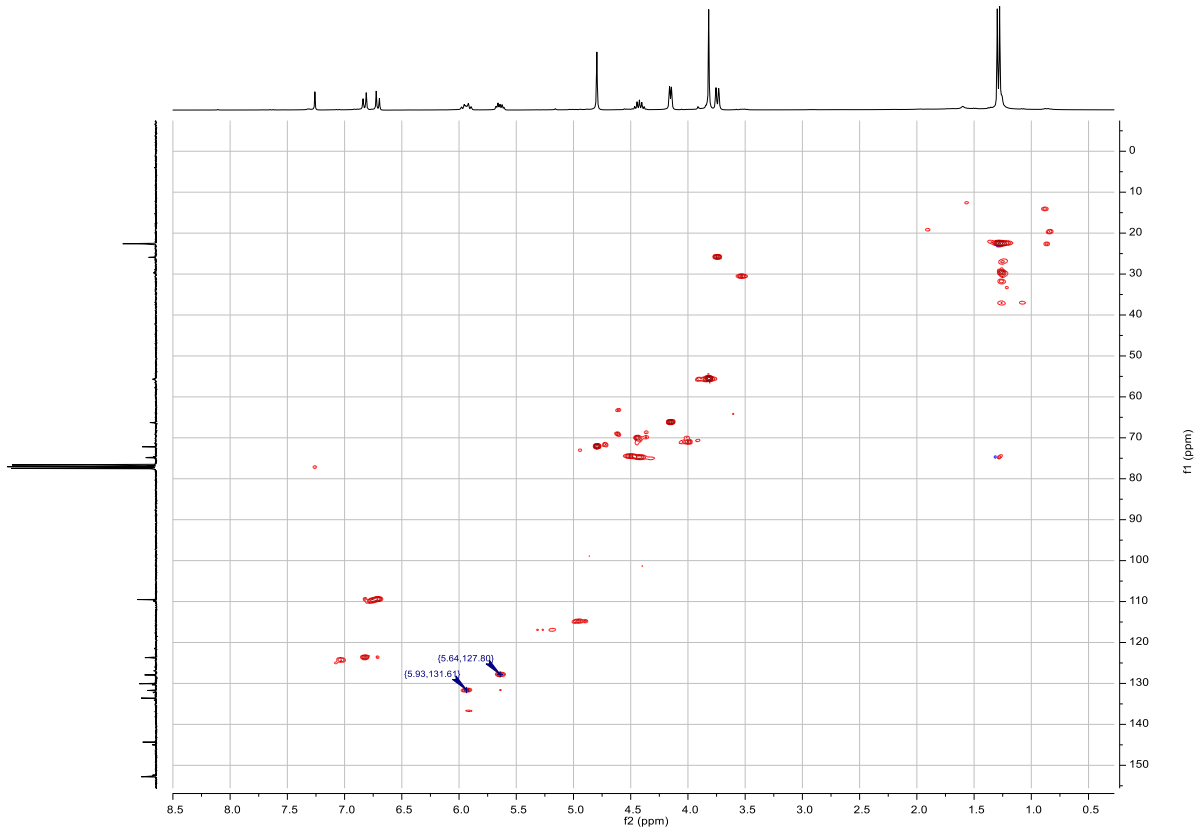
NMR 17: ^{1}H spectrum for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**



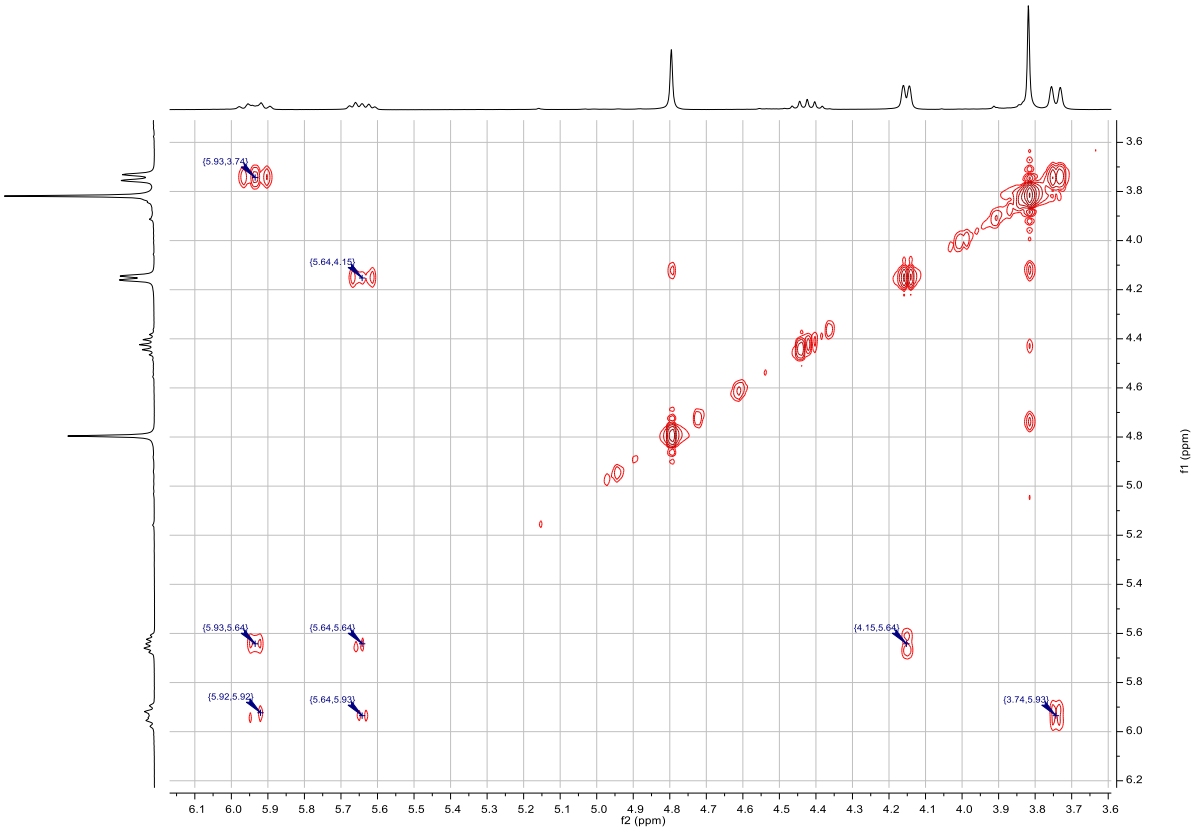
NMR 18: ^{13}C spectrum for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**



NMR 19: DEPT 135 spectrum for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**



NMR 20: HSQCGP spectrum for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**



NMR 21: COSY90 spectrum for (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**

5.2 Fourier transform infrared specta

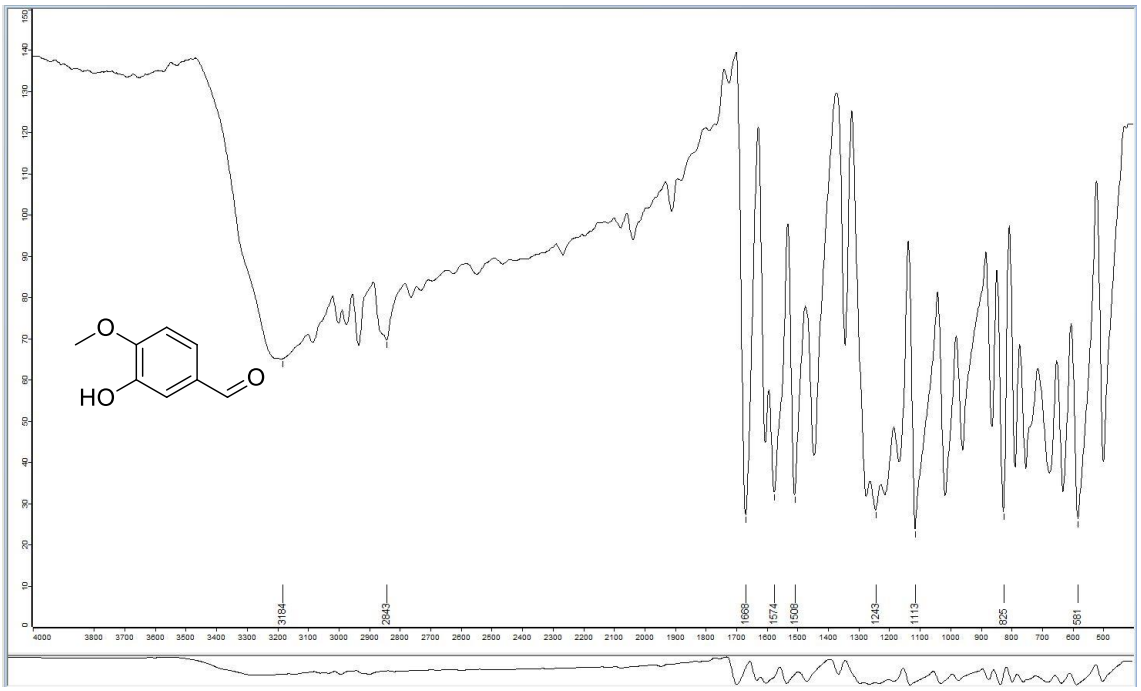


Figure 51: IR spectrum - Isovanillin **3**

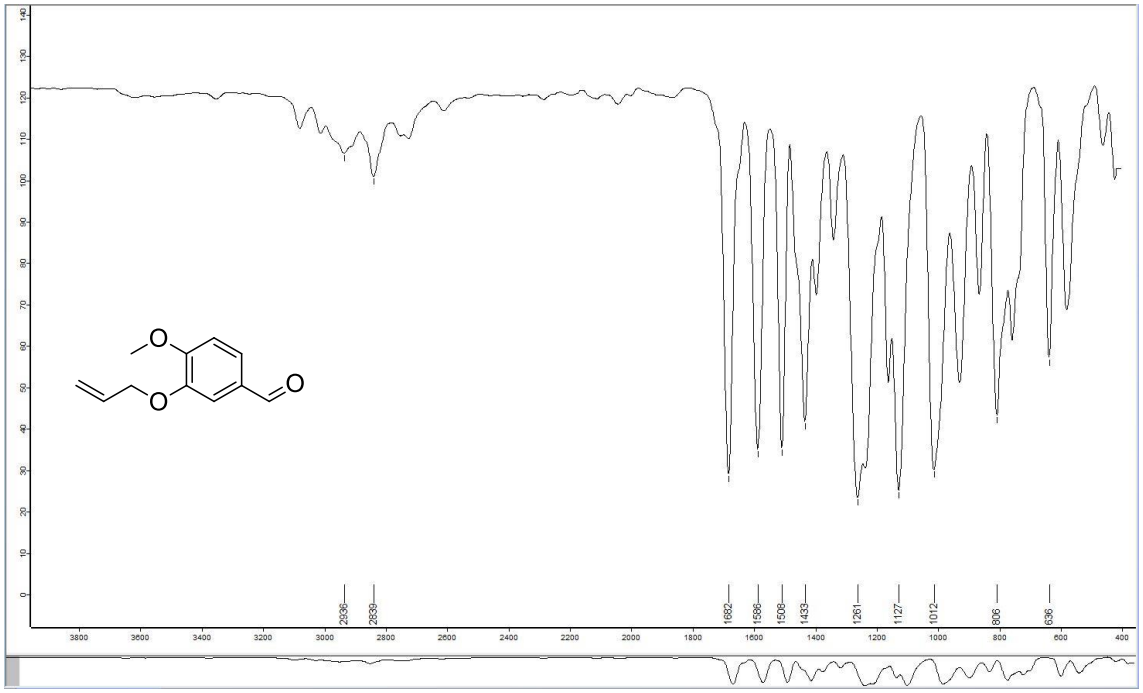


Figure 52: IR spectrum - 3-(allyloxy)-4-methoxybenzaldehyde **4**

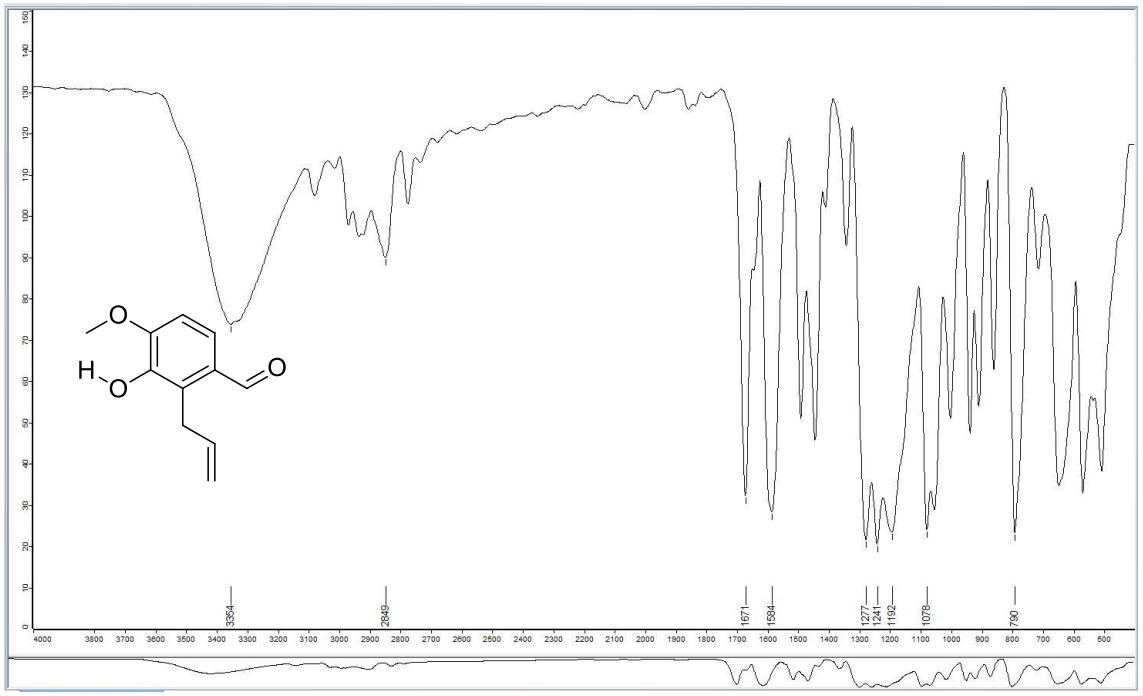


Figure 53: IR spectrum - 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5**

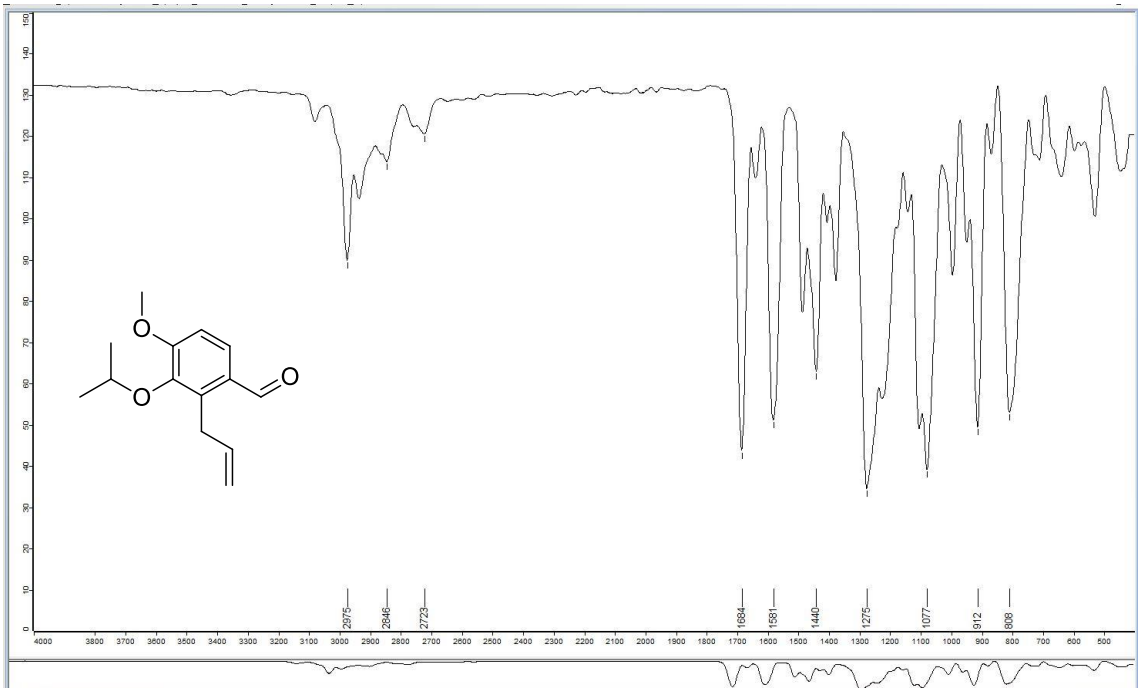


Figure 54: IR spectrum - 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**

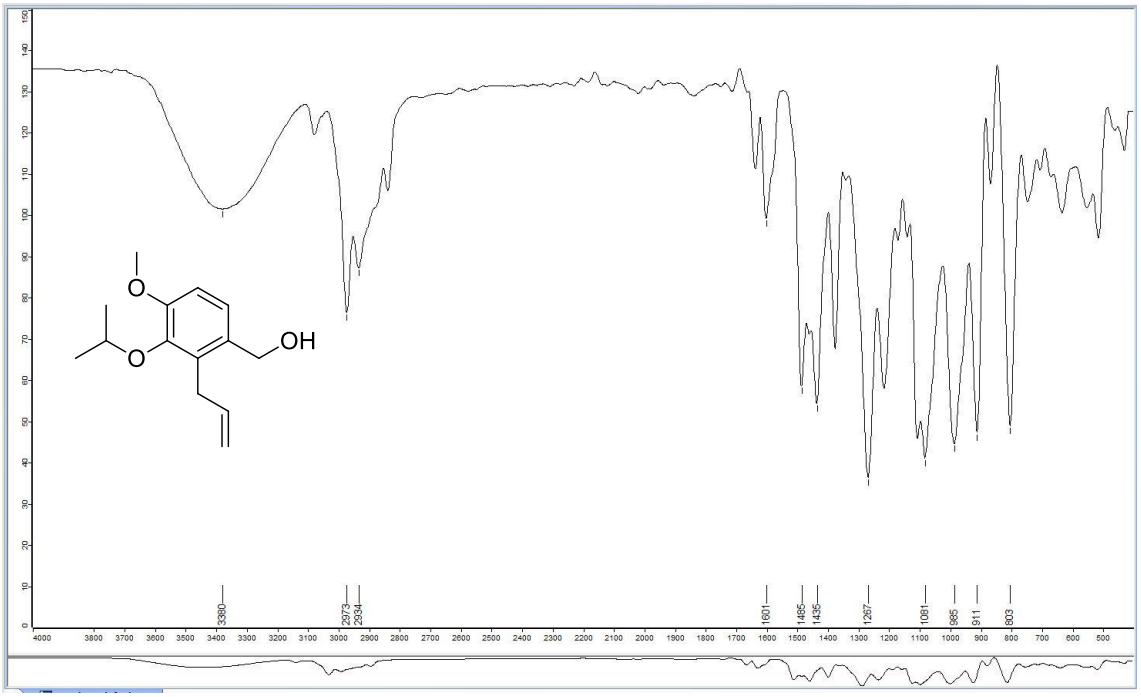


Figure 55: IR spectrum - (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**

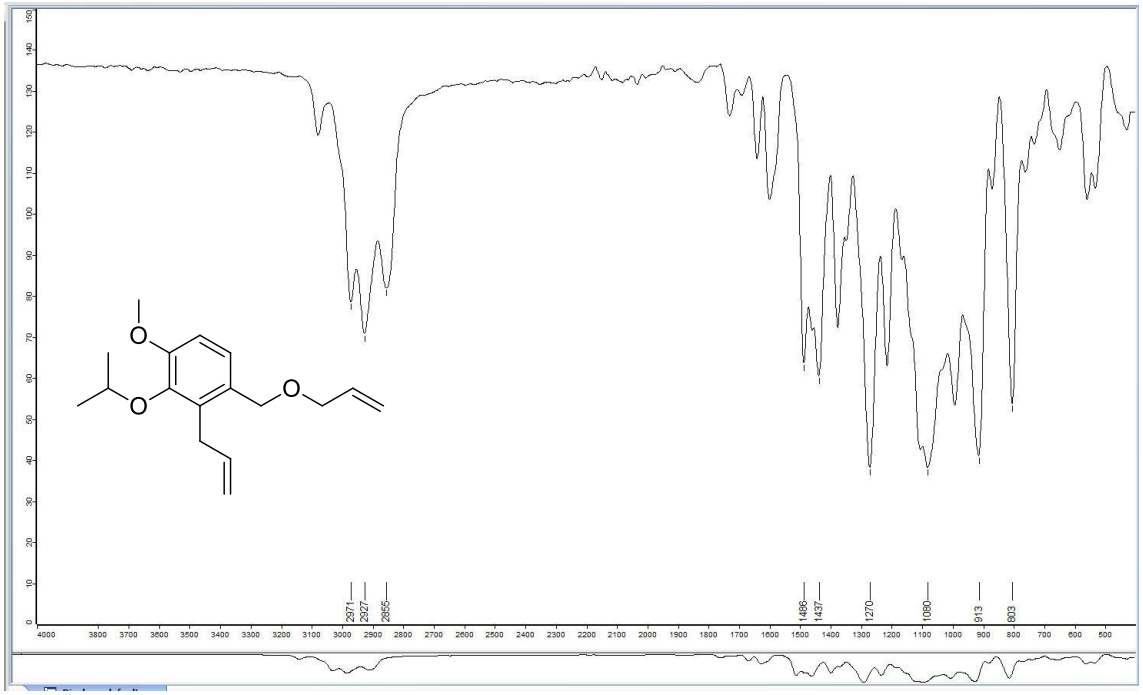


Figure 56: IR spectrum - 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**

5.3 Mass spectrometry spectra

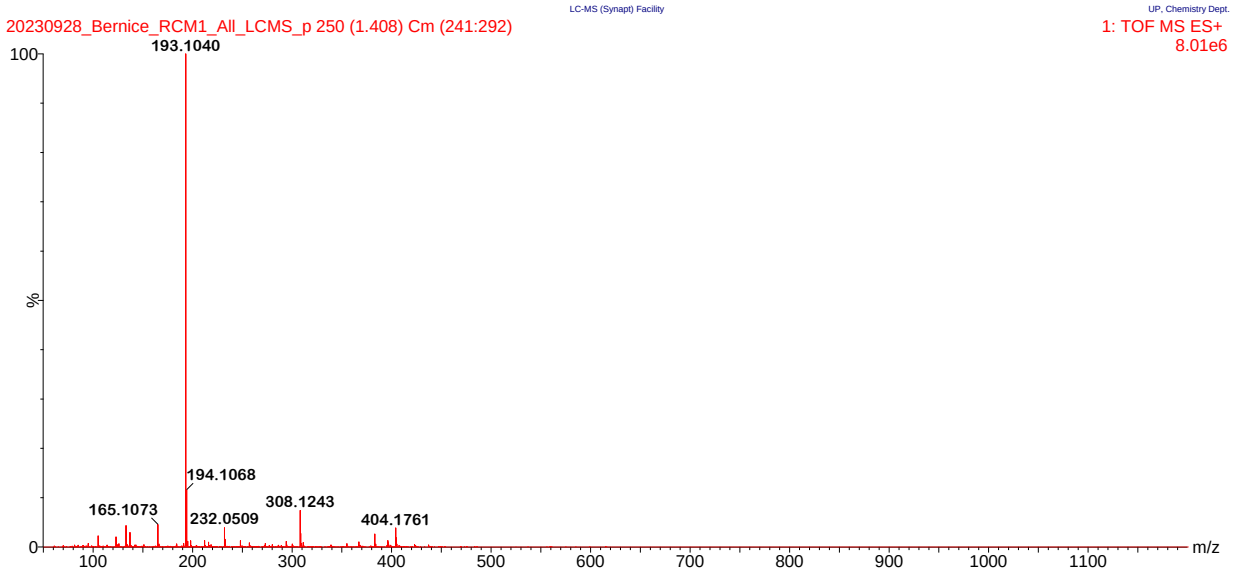


Figure 57: Mass spectrum - 3-(allyloxy)-4-methoxybenzaldehyde **4**

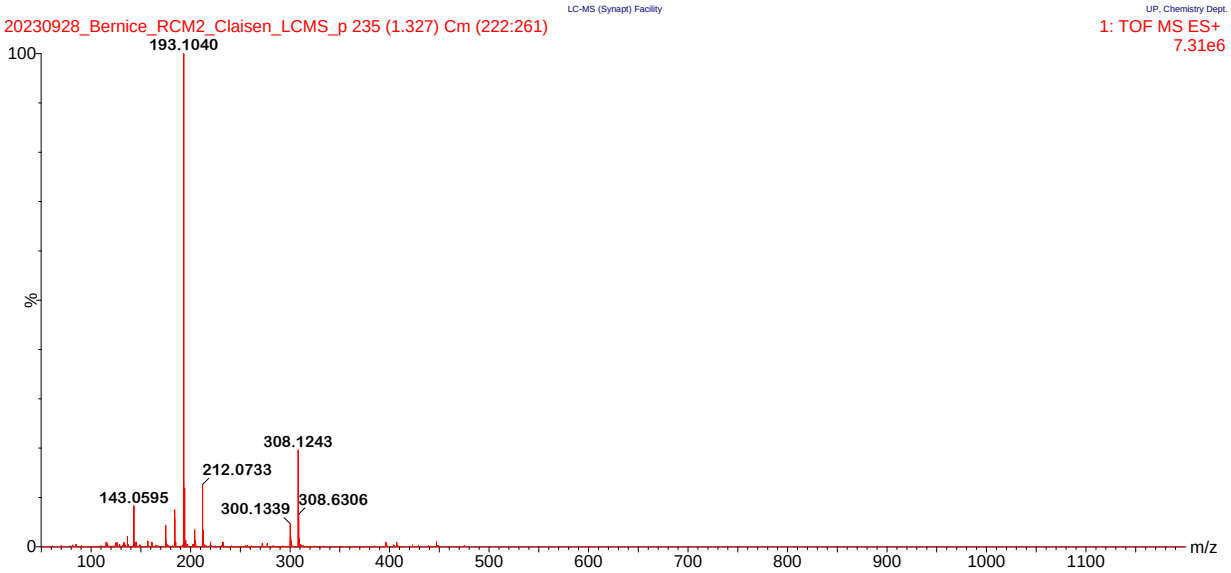


Figure 58: Mass spectrum - 2-allyl-3-hydroxy-4-methoxybenzaldehyde **5**

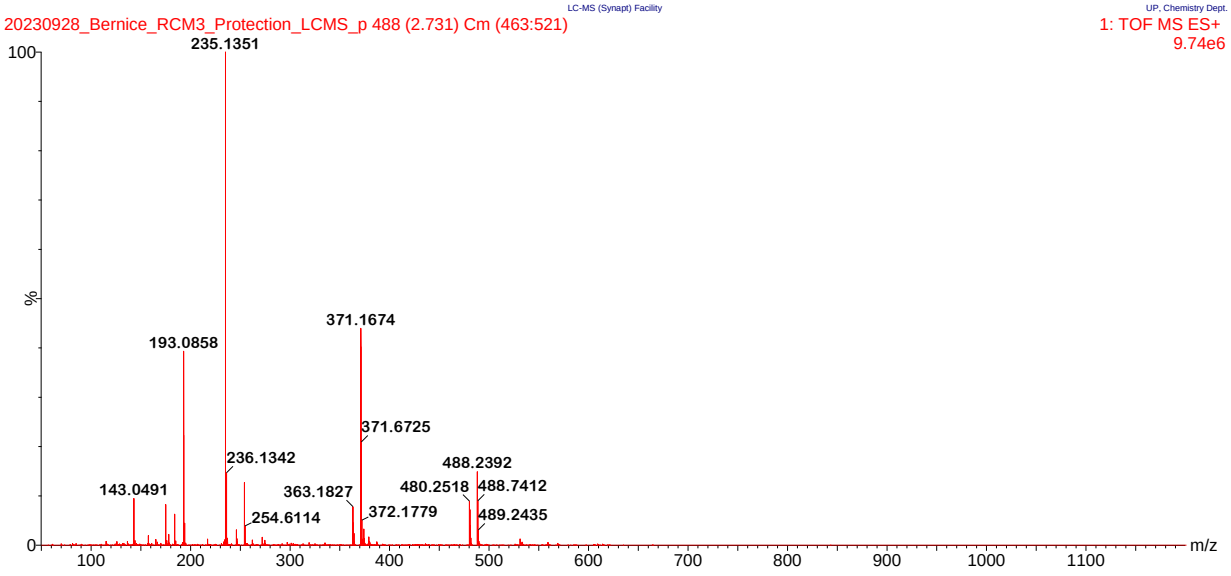


Figure 59: Mass spectrum - 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **7**

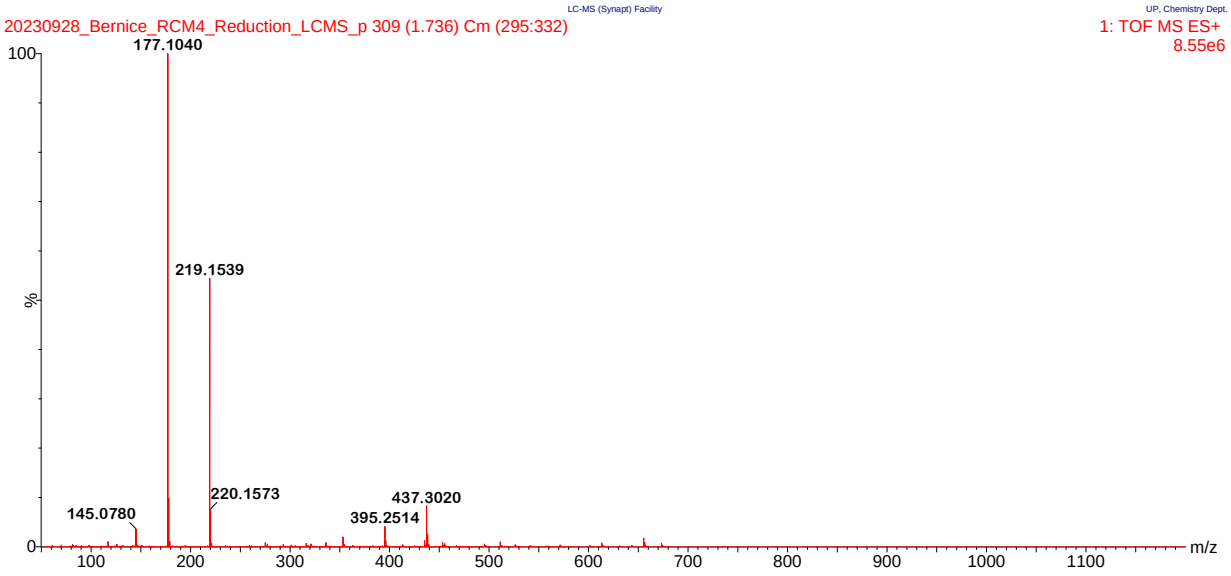


Figure 60: Mass spectrum - (2-allyl-3-isopropoxy-4-methoxyphenyl)methanol **8**

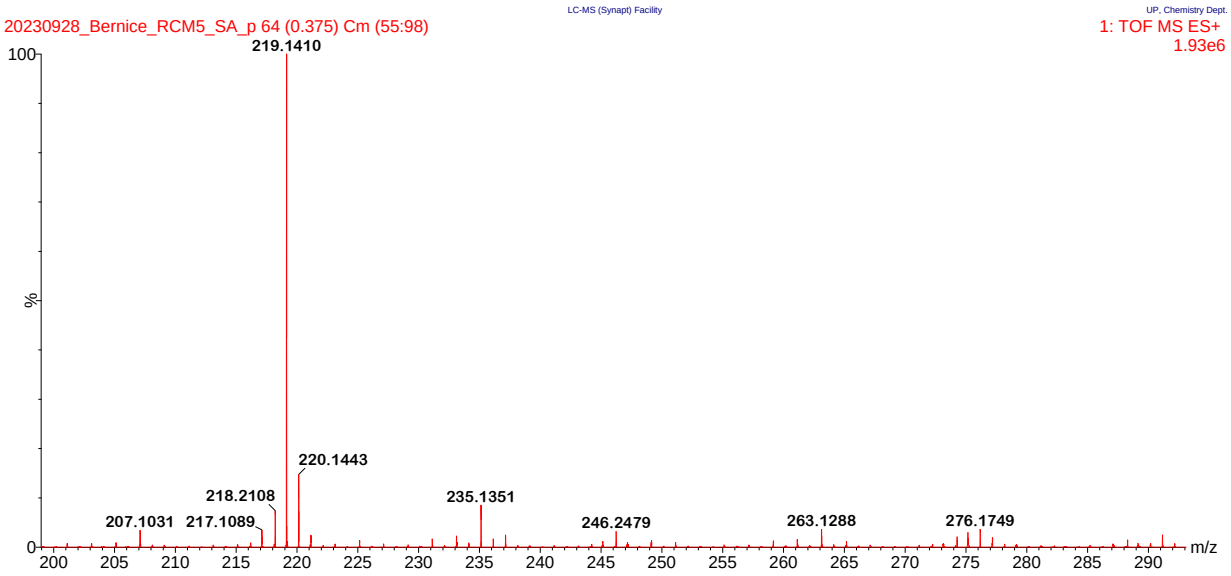


Figure 61: Mass spectrum - 2-allyl-1-((allyloxy)methyl)-3-isopropoxy-4-methoxybenzene **9**

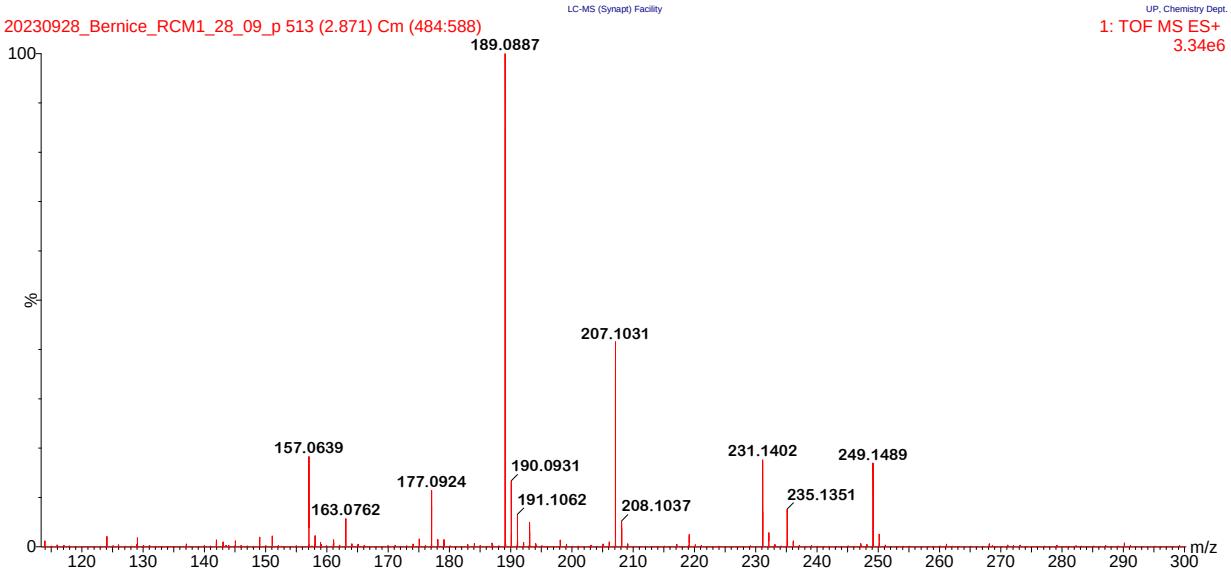


Figure 62: Mass spectrum 1: (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**

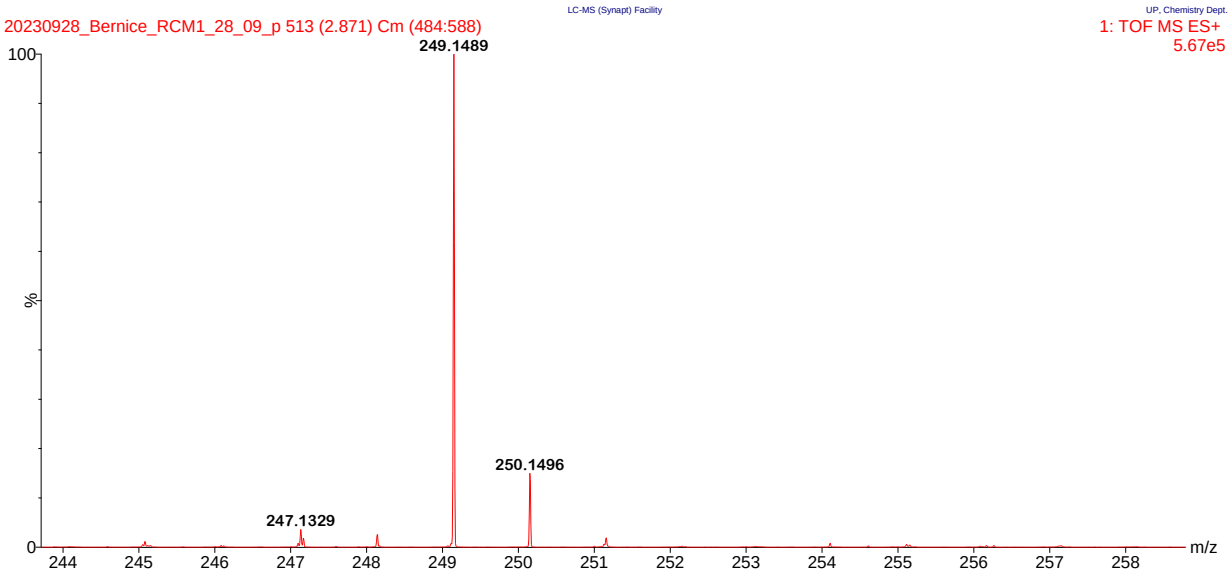


Figure 63: Mass spectrum - (*Z*)-7-isopropoxy-8-methoxy-3,6-dihydro-1*H*-benzo[*c*]oxocine **1**

6. References

1 R. Pathak, J.-L. Panayides, T. D. Jeftic, C. B. De Koning and W. A. L. Van Otterlo, *The Synthesis of 5-, 6-, 7-and 8-Membered Oxygen-containing Benzo-fused Rings using Alkene Isomerization and Ring-closing Metathesis Reactions*, .