An efficient demethylation of aromatic methyl ethers with HCl in water

Supporting information

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1 General considerations

Unless stated otherwise, all solvents and commercially available reagents were used as received. Heptane, used for flash chromatography, was distilled prior to use. Pine wood was bought from a local supplier (Aveve) and grinded to powder. Non-commercial starting materials were prepared as described below. Water was deionized using a EUROTEC L4 reverse osmosis plant. The used water had a conductivity of max. 0.5 µS·cm^{-1}. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III 400 (101 MHz for ^{13}C) Fourier Transform NMR spectrometer at 300 K (unless stated otherwise), using the non or partly deuterated solvent as internal standard (^{1}H: δ 7.26 ppm and ^{13}C{^{1}H}: δ 77.16 ppm for $CDCl_3$; ^{1}H: δ 2.50 ppm and ^{13}C{^{1}H}: δ 39.52 ppm for DMSO-d_6). Chemical shifts (δ) are reported in ppm; coupling constants (*J*) are reported in Hz; splitting patterns are assigned s = singlet, d = doublet, t = triplet, q = quartet, quint = quint, sext = sextet, sept = septet, b = broad signal, m = multiplet or combinations thereof. ^{13}C NMR spectra were recorded with complete proton decoupling. ^{1}H NMR Yields were determined by addition of a known amount of an internal standard and dissolving everything in a suitable deuterated solvent, followed by ^{1}H NMR analysis. Gas chromatography-mass spectrometry (GC-MS) samples were prepared by dissolving 0.1-5 mg of the compound in acetone or acetonitrile and further diluted to a concentration of 10^{-4}-10^{-6} M. 3 µL of the samples were injected. The apparatus used was an Agilent Technologies 7890 A GC System coupled to an Agilent Technologies 5975 C inert MSD with triple-axis detector. As column an Optima 725820.30 30 m × 250 µm × 0.25 µm was selected. Carrier gas was helium. For enantiopurity determination using liquid-chromatography-mass spectrometry (LC-MS), samples were prepared by dissolving 2-4 mg of the compound in hexane/EtOH (80:20) and further diluted to a concentration of 10^{-3}-10^{-4} M. From these samples 20 µL were injected and analyzed via a Kontron HPLC autosampler 465 equipped with a Kontron HPLC pump 522, Chiralpak column, Waters Photo Diode Array detector and Jasco X-LC 3195CD system. High resolution mass spectrometry (HRMS) samples were prepared by dissolving 0.1-5 mg of the compound in MeOH/H_2O-containing 0.1% formic acid and further diluted to a concentration of 10^{-5}-10^{-6} M for positive ion mode and by dissolving 0.1-5 mg of the compound in MeCN/H_2O and further diluted to a concentration of 10^{-4}-10^{-5} M for negative ion mode. 10 µL of each sample was injected using the CapLC system (Waters) and electrosprayed using a standard electrospray source. Samples were injected with an interval of 3 minutes. Positive and/or negative ion mode accurate mass spectra were acquired using a Q-TOF II instrument (Waters). The MS was calibrated prior to use with a 0.1% H_3PO_4 solution. The spectra were lock mass corrected using the known mass of the nearest H_3PO_4 cluster or nearest known background ion. In positive ion mode, analytes were detected as protonated molecule or as a sodium adduct. In negative ion mode, analytes were detected as deprotonated molecule. All measured masses are within a difference of 5 ppm compared to the calculated mass unless specified otherwise. Thin layer chromatography (TLC) was performed using an organic solvent as mobile phase and silica coated on an aluminum plate (Machery-Nagel Precoated TLC sheets Alugram® SIL G/UV$_{254}$) as stationary phase. Compounds were detected by irradiation with UV light (254 nm and 366 nm). Melting points (m.p.) (uncorrected) were measured on a Büchi Melting Point B-545 apparatus. Chromatographic purification of products was performed by using an automated flash chromatography BiotageTM or Combiflash® system eluting with a flow rate of 30 mL·min^{-1}, otherwise indicated, utilizing commercially available Grace^{TM} GraceResolv^{TM} Silica Flash Cartridges or Büchi Flash Pure Reversed Phase C18 Cartridges. Centrifugation was performed using an Eppendorf Centrifuge 5702 at 4000 rpm for 1 h, unless stated otherwise.

2 High pressure equipment

2.1 Description of the reactors

A Parr® 4625 Pressure Vessel (600 mL internal volume) and a Parr® 4596 Micro Stirred Reactor (25 mL internal volume) were used. The latter was connected to a Parr® 4848 control unit, which enables to control the heating and read the internal pressure.

Experiments in the Parr® 4625 Pressure Vessel (600 mL internal volume) were typically performed in 4 mL glass vials (Wheaton®) containing a magnetic stirring bar. The loaded vials were sealed with a plastic cap (*Wheaton® 13-425 cap, phenolic*) equipped with a septum (*Wheaton® 13 mm septum, PTFE/white rubber*), through which a syringe needle (*Sterican® 0.55 × 25 mm 24G×1*) was sting, and placed in a home-made aluminum alloy plate (which can contain up to 7 vials), which was then placed in a glass beaker (*Parr® glass liner 762HC3*) (Figure S1(a)). The beaker was placed in the Parr® 4625 reactor (Figure S1(b)). The autoclave was sealed (Figure S1(b)), using a torque wrench set at 27 Nm, purged (10 bar, 3 times) and pressurized with the indicated gas (pressure was measured by a classical pressure gauge). Then, the autoclave was heated in an IHP® band heater under magnetic stirring (Figure S1(d)). When the reaction was stirred during the indicated time at the indicated temperature, the autoclave was cooled down to room temperature in air or in an ice bath and subsequently, the gas was released and the reactor was opened.

Large scale experiments were performed in the glass beaker from Figure S1(a) as reaction vessel, without using the metal insert. This beaker was placed in the Parr® 4625 Pressure Vessel (Figure S1(b)). The reactor was closed, pressurized and heated as described before.

(a) *(b)* *(c)* *(d)*

Figure S1. *Set-up for screening: running multiple reactions at the same time.*

(a) Reactions are run in 4 mL glass vials, which are sealed with a cap and a septum. A syringe needle sting through the septum enables gas to enter the vial, which provides the reaction mixtures (inside the glass vials) of the same atmosphere as applied in the reactor (outside the glass vials).

(b) The Parr® 4625 Pressure Vessel (600 mL internal volume).

(c) The closed Parr® 4625 reactor equipped with a pressure gauge, gas inlet, gas outlet and rupture disk.

(d) The complete set-up in which the reactor is placed in the heating mantle on a magnetic stirring plate. Heating is controlled by the heating mantle (IHP® ceramic band heater).

Experiments in the Parr® 4596 Micro Stirred Reactor (25 mL internal volume) were typically performed in 4 mL vials (*vide supra*), which were placed in a homemade stainless steel insert (Figure S2). Samples were prepared as described for the 600 mL reactor. The autoclave was managed similarly to the 600 mL reactor, with as difference that to seal the reactor no torque wrench was used but a normal wrench.

(a) (b) (c)

Figure S2. *Set-up for running screening reactions.*

(a) Reactions are run in 4 mL glass vials, which are sealed with a cap and a septum. A syringe needle sting through the septum enables gas to enter the vial, which provides the reaction mixtures (inside the glass vials) of the same atmosphere as applied in the reactor (outside the glass vials). The small gap next to the vial enables to measure the temperature of the insert.

(b) The Parr® 4596 Micro Stirred Reactor vessel (25 mL internal volume).

(c) The complete set-up in which the reactor is placed on a magnetic stirring plate. The Parr® 4596 Micro Stirred Reactor vessel is equipped with pressure gauge, gas inlet, gas outlet and rupture disk. A thermocouple is connected to the Parr® 4848 control unit in order to read the inside temperature (vide infra). This control unit itself is connected to the heating mantle, enabling regulation of heating rate.

2.2 Temperature control

The **Parr® 4596** reactor (25 mL internal volume) is connected to a **Parr® 4848 control unit** (Figure S3), which enables us to set the heating rate and regulate the temperature inside the reactor (for our specific set-up, i.e. a 4 mL glass vial in a home-made aluminum insert (see Figure S2(a)), the thermocouple fits in the small gap in the insert). This means that the temperature which is shown on the screen is the actual temperature of the reaction mixture, measured by a thermocouple connected to this control unit.

The IHP Ceramic ring heating mantle, which is used for heating of the **Parr® 4625 reactor** (600 mL internal volume) itself is connected to a similar control unit for heat regulation. In this case the temperature of the mantle is regulated rather than the temperature inside the reactor. Therefore, by placing a temperature sticker (*Thermax® Irreversible Temperature Recording Strips*) in the reactor (i.e. on the metal insert), it is possible to learn more about the heat transfer through the reactor wall and the actual temperature of the reaction mixture. It was found that to achieve a reaction temperature of 235 °C (Figure S4), it was necessary to heat the mantle to 260 °C. In this manuscript and SI, the temperature of the insert is always reported. For experiments in the Parr® 4625 reactor, this is the corrected temperature by using those stickers, while for the Parr® 4596 reactor, this is the temperature measured by the thermocouple.

Figure S3. *A Parr® 4848 control unit. The left screen indicates the desired (green) and actual (red) temperature (in °C) inside the reactor. The middle screen indicates the desired (green) and actual (red) stirring rate (in rpm) of the mechanical overhead stirrer, which is not used in this project. The right screen indicates the actual (red) and maximal allowed (green) pressure (in bar) before the system stops working.*

(a) *(b)*

Figure S4. *(a) A used temperature sticker, showing that the reaction media reached a temperature between 232 and 241 °C. (b) The heating system that was used for heating the Parr® 4625 reactor (IHP® Ceramic Ring Heating Mantle) (Figure S1(d)).*

3 *O*-Dealkylation

3.1 General procedures

3.1.1 Screening experiments in the Parr® 4625 reactor

General procedure A

A 4 mL (or 20 mL if the reaction volume was higher than 3 mL) glass vial was charged with a magnetic stirring bar, the desired substrate (in the amount as reported), acidic catalyst and additional H_2O. The vial was closed using a black cap and septum and a needle was pierced through the septum. The vial was placed in the metal insert, together with other vials which could be run at the same time (when reaction time, atmosphere and temperature allowed it). The insert was placed in the glass beaker and the beaker was placed in the 600 mL reactor. The reactor was closed properly (in a criss-cross pattern, using a torque wrench which was set at 27 Nm, as requested by Parr®). The reactor was three times filled with 10 bar of the desired gas and released (while stirring magnetically), in order to flush. Subsequently, the reactor was filled with the desired gas (while stirring magnetically) to the desired pressure and the gas inlet line was closed and disconnected. The reactor was placed in the heating mantle and when the desired temperature was obtained (temperature heating mantle), counting of the reported reaction time started. After that time, the reactor was taken out of the heating mantle and cooled down to r.t., first in the air and when a safe temperature was reached (around 170 °C) further in an ice bath. Subsequently, the gas was released (while stirring magnetically), the reactor was opened and samples were taken out. To the crude sample were added an exact amount of internal standard and acetone (around 1-2 mL for 4 mL vials and around 10 mL for 20 mL vials) and the sample was stirred magnetically until homogenization. Subsequently, part of the solution was evaporated under reduced pressure. The residue was dissolved in a suitable deuterated solvent and measured with ^1H NMR spectroscopy. The yield for remaining substrate, formed product and other compounds was calculated versus the internal standard. Identity of the peaks on which the integration was performed was based on reference spectra in the same solvent. The experimental error on our data has been determined and the error related to the ^1H NMR yields was found to be +/- 5%.

3.1.2 Screening experiments in the Parr® 4596 reactor

General procedure B

A 4 mL glass vial was charged with a magnetic stirring bar, the desired substrate (in the amount as reported), acidic catalyst and additional H_2O. The vial was closed using a black cap and septum. A needle was pierced through the septum. The vial was placed in the metal insert, which was then placed in the 25 mL reactor. The reactor was closed properly (in a criss-cross pattern, as tight as possible). The reactor was three times filled with 10 bar of the desired gas and released (while stirring magnetically), in order to flush. Subsequently, the reactor was filled with the desired gas (while stirring magnetically) to the desired pressure and the gas inlet line was disconnected. The reactor was placed in the heating mantle, heating was started and when the desired temperature was obtained (temperature in the reactor), counting of the reported reaction time started. After that time, the reactor was taken out of the heating mantle and cooled down to r.t. in an ice bath. Subsequently, the gas was released (while stirring magnetically), the reactor was opened and samples were taken out. To the crude sample were added an exact amount of internal standard and acetone (around 1-2 mL) and the sample was stirred magnetically until homogenization. Subsequently, part of the solution was evaporated under reduced pressure. The residue was dissolved in a suitable deuterated solvent and measured with ^1H NMR spectroscopy. The yield for remaining substrate, formed product and other compounds was calculated versus the internal standard. Identity of the peaks on which the integration was performed was based on reference spectra in the same solvent. The experimental error on our data has been determined and the error related to the ^1H NMR yields was found to be +/- 5%.

3.1.3 General procedure for experiments with isolation of the product

General procedure C
Reaction mixtures were prepared as described in General Procedure A or B and placed in the selected reactor. The reactor was closed, flushed, pressurized and heated as described. After the required reaction time, the reactor was cooled to r.t., depressurized and opened. The reaction mixture was transferred to a separatory funnel, NaCl (s) was added and the product was extracted with EtOAc. The combined organic layers were washed with brine and evaporated under reduced pressure.

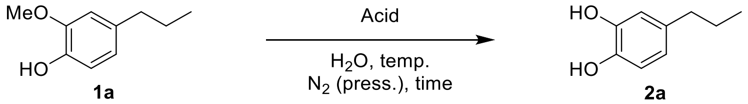
General procedure D
Reaction mixtures were prepared as described in General Procedure A or B and placed in the selected reactor. The reactor was closed, flushed, pressurized and heated as described. After the required reaction time, the reactor was cooled to r.t., depressurized and opened. The reaction mixture was transferred to a separatory funnel, NaCl (s) was added and the product was extracted with EtOAc. The combined organic layers were treated with $NaHCO_3$ (aq., sat.). Subsequently, the aqueous layer was slowly neutralized with HCl (aq., 1 M) and extracted with EtOAc, after which the organic phase was evaporated under reduced pressure.

3.2 Reaction optimization

In preliminary research, we reported the *O*- and *C*-dealkylation of ferulic acid (**11**) to catechol (**2i**) in the presence of catalytic HCl in hot pressurized water. The formation of a benzylic alcohol upon Michael addition of H_2O to **11** was found to be crucial for the given conversion.[1] 4-Propylguaiacol (**1a**), not able to form a benzylic alcohol under the given conditions, only *O*-demethylated with the formation of 4-propylcatechol (**2a**) in 97% yield. However, these conditions were obtained through optimization of the *O*- and *C*-dealkylation of ferulic acid (**11**). Given the different nature of the side chain in 4-propylguaiacol (**1a**), it is expected that for selective *O*-demethylation of this compound, optimal conditions can be identified with improved Green Metrics also allowing scale-up.

We started from the initial reaction conditions (0.13 M, 50 mol% HCl, 250°C, initial N_2 pressure 50 bar, 3 h) reported for ferulic acid.[1] On 4-propylguaiacol (**1a**) these delivered 4-propylcatechol (**2a**) in 97% yield (Table S1, Entry 1). First, we looked if the substrate concentration could be increased, therefore leading to less solvent use, which will be beneficial for the green credentials of the reaction (see Section 4.3 of this SI). Gratifyingly, this was the case for concentrations up to 1.00 M (Table S1, Entries 1-6), since NMR yields for 4-propylcatechol (**2a**) higher than 90% were obtained in all cases. When pushing the substrate concentration further the yield decreased significantly from 92% at 1.0 M to 64% at 2.0 M (Entries 6-8). This is due to tar formation via unselective reactions clearly observed visually. At higher substrate concentration the crude product obtained after evaporation of volatiles became darker and more difficult to solidify, while the pure product is a(n) (off-) white solid. At 2.0 M, deposition of small black particles at the glass vial was also observed after 3 h. Interestingly, when the reaction time was reduced to 1 h at this concentration again 91% yield was obtained, pointing to an instability of reaction product (Entry 9). Despite the good result obtained in this reaction, it was decided to continue this optimization further at 1.00 M. This should prevent issues regarding solubility and subsequent decomposition of other organic molecules in the scheduled scope study.

Table S1. *Optimization of the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): substrate concentration.*

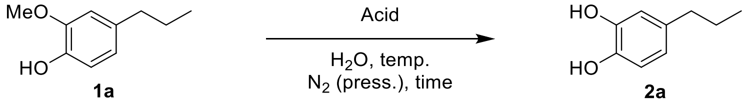


Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Temp. (°C)	Press. (bar)	Time (h)	NMR Yield (%) [a]	
							1a	2a
1	MBAL-380, JBO-1658	0.13	HCl (50)	250	50	3	0	99 (97 [c])
2	MBAL-405	0.20	HCl (50)	250	50	3	0	100
3	MBAL-310	0.35	HCl (50)	250	50	3	0	98
4	MBAL-406	0.50	HCl (50)	250	50	3	0	97
5	MBAL-407	0.75	HCl (50)	250	50	3	0	93
6	MBAL-408	1.00	HCl (50)	250	50	3	0	92
7	MBAL-409	1.50	HCl (50)	250	50	3	0	84
8	MBAL-410	2.00	HCl (50)	250	50	3	0	64 [b]
9	JBO-643	2.00	HCl (50)	250	50	1	0	91 (91 [c])

Experiments were performed according to General Procedure B in 3 mL H_2O. [a] ^{1}H NMR Yield determined with dimethyl sulfone as internal standard. [b] Tar formation. [c] Yield of isolated product (General Procedure C).

Next to increasing substrate concentration, altering the amount of catalyst, i.e. HCl, was studied. Therefore, the amount of HCl present was varied from 100% to 10%. These loadings were performed at different substrate concentrations (i.e. 0.13, 0.35, 0.50, 0.75, 1.00 and 1.50 M) (Table S2). For all considered substrate concentrations, it was observed that no full conversion was obtained when using 10 mol% HCl (Entries 1, 5, 9, 13, 17 and 20). At 0.13 M **1a**, there was even no full conversion with 20 mol%, in contrast with all other substrate concentrations (Entry 2), while for 0.35, 0.50 and 0.75 M **1a**, no significant difference in yield was observed between 20 and 50 mol% HCl (Entries 6-7, 10-11, 14-15, 18-19 and 22-23), while increasing HCl loading to 100 mol% clearly had a deteriorating effect on the yield and the mass balance in combination with higher substrate concentrations (Entries 16, 20 and 24). This was even the case with 50 mol% at 1.00 and 1.50 M **1a** (Entries 19 and 23). From this Table S2, , it can be concluded that the best result was obtained when using 0.50 M **1a** and 20 mol% HCl (Entry 10). This loading is beneficial for the green credentials of the methodology when compared with the initial conditions reported (Table S1, Entry 1).

Table S2. *Optimization of the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): concentration and HCl loading.*

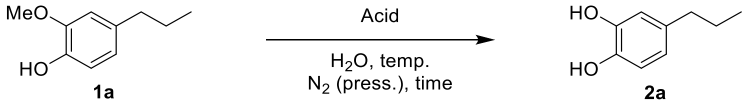


Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Temp. (°C)	Press. (bar)	Time (h)	NMR Yield (%) [a]	
							1a	2a
1	MBAL-412	0.13	HCl (10)	250	50	3	53	49
2	MBAL-379	0.13	HCl (20)	250	50	3	13	86
3	MBAL-380	0.13	HCl (50)	250	50	3	0	99
4	MBAL-413	0.13	HCl (100)	250	50	3	0	103
5	MBAL-308	0.35	HCl (10)	250	50	3	8	91
6	MBAL-309	0.35	HCl (20)	250	50	3	0	98
7	MBAL-310	0.35	HCl (50)	250	50	3	0	99
8	MBAL-414	0.35	HCl (100)	250	50	3	0	93
9	MBAL-415	0.50	HCl (10)	250	50	3	5	90
10	JBO-496, MBAL-441	0.50	HCl (20)	250	50	3	0	100 (97 [b])
11	MBAL-406	0.50	HCl (50)	250	50	3	0	97
12	MBAL-416	0.50	HCl (100)	250	50	3	0	97
13	MBAL-417	0.75	HCl (10)	250	50	3	2	98
14	MBAL-442	0.75	HCl (20)	250	50	3	0	98
15	MBAL-407	0.75	HCl (50)	250	50	3	0	93
16	MBAL-418	0.75	HCl (100)	250	50	3	0	84 [c]
17	MBAL-419	1.00	HCl (10)	250	50	3	3	97
18	MBAL-338, 382	1.00	HCl (20)	250	50	3	0	95
19	MBAL-409	1.00	HCl (50)	250	50	3	0	84 [c]
20	MBAL-420	1.00	HCl (100)	250	50	3	0	66 [c]
21	MBAL-421	1.50	HCl (10)	250	50	3	5	93
22	MBAL-422	1.50	HCl (20)	250	50	3	< 1	95
23	MBAL-409	1.50	HCl (50)	250	50	3	0	84 [c]
24	MBAL-423	1.50	HCl (100)	250	50	3	0	39 [c]

Experiments were performed according to General Procedure B in 3 mL H_2O. [a] ^1H NMR Yield determined with dimethyl sulfone as internal standard. [b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. [c] Tar formation.

Up to now, only HCl was considered as acidic catalyst. Since Chapter 2 showed that also other strong acids might be useful for this reaction,[1] an acid screening was subsequently performed, (Table S3). From a blank experiment revealved that addition of a suitable catalyst is required for this reaction (Entry 1), since no conversion was observed in neutral water. The optimal reaction conditions of Table S2 (Entry 10) were used as reference (Entry 3). Full conversion was not achieved using another Brønsted Acid (Entries 2-10). When analyzing the obtained results, we found a directly proportional relation between conversion and acid strength (Figure S5), where only triflic acid deviates (Entry 2). It was found that HCl could be successfully replaced by Lewis acid $FeCl_3$ leading to quantitative conversion (Entry 11), presumably by in situ HCl generation, while no reaction took place upon addition of CuCl2 (Entry 12). This route was not explored further, due to the more material intensive work-up when a metal is present in the reaction mixture.

Table S3. *Optimization of the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): acid screening.*



Entry	ELN code	Conc. 1a (M)	Acid (mol%)	pK_a [a]	Temp. (°C)	Press. (bar)	Time (h)	NMR Yield (%) [b]	
								1a	2a
1	JBO-799, MBAL-377	0.50	-	-	250	50	3	100	0
2	JBO-1476	0.50	TfOH (20)	-15	250	50	3	25	75
3	JBO-496, MBAL-441	0.50	HCl (20)	-8	250	50	3	0	100 (97 [c])
4	JBO-414, MBAL-311	0.50	H_2SO_4 (20)	-3	250	50	3	6	94
5	JBO-435	0.50	MsOH (20)	-1.9	250	50	3	6	94
6	JBO-388	0.50	H_3PO_4 (20)	2.15	250	50	3	70	30
7	JBO-452	0.50	4-NO_2PhCOOH (20)	3.41	250	50	3	89	11
8	JBO-451	0.50	PhCOOH (20)	4.20	250	50	3	97	3
9	JBO-372	0.50	HOAc (20)	4.76	250	50	3	100	0
10	JBO-371	0.50	H_3BO_3 (20)	9.25	250	50	3	> 99	< 1 [d]
11	JBO-382	0.50	$FeCl_3$ (20)	N/A	250	50	3	0	100
12	JBO-381	0.50	$CuCl_2$ (20)	N/A	250	50	3	> 99	< 1 [d]

Experiments were performed according to General Procedure B in 3 mL H_2O. [a] pK_a of the used acid. For polyprotic acids, the pK_a of the first dissociation is mentioned. [b] ^{1}H NMR Yield determined with dimethyl sulfone as internal standard. [c] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. [d] Reaction product was observed via MS analysis of the crude mixture.

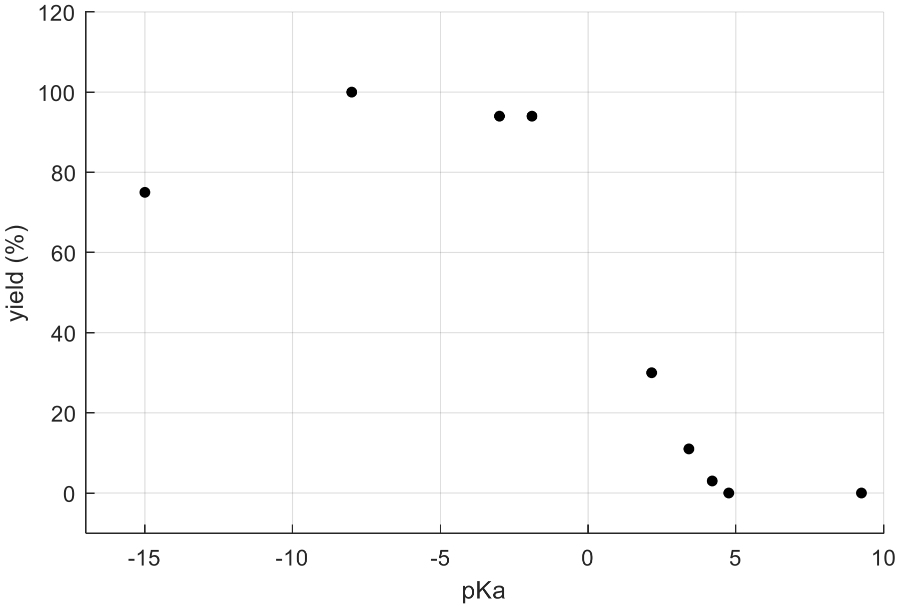


Figure S5. *O-demethylation of propylguaiacol (**1a**) to propylcatechol (**2a**) as function of the pK$_a$ of the used Brønsted Acid.*

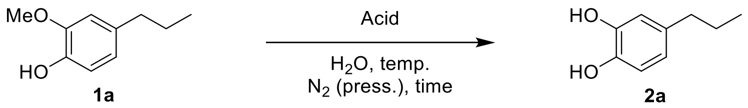
Considering of 20 mol% H_2SO_4 nearly delivered full conversion (Table S3, Entry 4), the effect of increasing the acid loading to 60 mol% and even a stoichiometric amount was investigated (Table S4).). Despite the increased acid loading, full conversion was not achieved as traces of substrate were still detected in the NMR analysis (Entries 3-5). Additionally, these new conditions revealed a loss of mass balance, in contrast with the result obtained by applying 100 mol% HCl (Entries 2 and 5). We found that when extending the reaction time to 6 h with 20 mol% H_2SO_4 gave full conversion and delivered the desired product in 97% yield (Entry 6). Also with the other H_2SO_4 loadings, full conversion of the starting material was observed after 6 h, though the desired product was obtained in significantly lower yield with lower mass balances (Entries 7-8), which was not the case when using HCl under the same conditions (Entries 8 and 9).

In a next stage, a temperature study was performed (Table S5). Increasing the temperature from 250 °C to 275 °C had no impact on the reaction outcome pointing to thermal stability of substrate and product (Entries 4 and 5). Lowering the temperature to 225 °C led to incomplete conversion (77%) (Entry 3). At 200 °C conversion decreased to only 3% (Entry 2). At 185 °C, substrate **1a** could be completely recovered (Entry 1). For comparison, applying Abu-Omar's conditions, based on 500 mol% HBr under reflux (Entry 6),[2] delivered a quantitative yield of **2a** after 20 h. When replacing this stronger acid by HCl, only 30% **2a** was obtained (Entry 7), leaving 56% **1a**.

An evaluation regarding the required reaction time was subsequently performed (Table S6). With reaction time, we mean the actual residence time of the reaction at the given temperature, not incorporating the time required for heating and cooling the set-up. We observed that already after 1 h more than 80% of the substrate was converted (Entry 1) and nearly quantitative conversion was achieved after 2 h (Entry 2). Therefore, a reaction time of 3 h was still considered to be optimal (Entry 3). By doubling the reaction time to 6 h 100% NMR and 95% isolated yield of the desired product was still achieved. This proves that this compound is relatively stable under the given reaction conditions

(Entry 4). 6 h at half the HCl loading still led to full conversion since only traces of the substrate remained (Entry 6). With this HCl loading 5% substrate remained after 3 h (Entry 5).

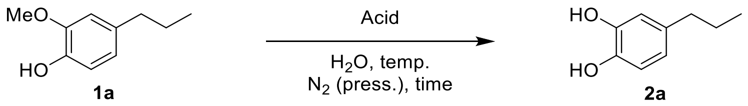
Table S4. *Optimization of the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): replacing HCl by H_2SO_4.*



Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Temp. (°C)	Press. (bar)	Time (h)	NMR Yield (%) [a]	
							1a	**2a**
1	JBO-496, MBAL-441	0.50	HCl (20)	250	50	3	0	100 (97 [b])
2	MBAL-416	0.50	HCl (100)	250	50	3	0	97
3	JBO-414, MBAL-463	0.50	H_2SO_4 (20)	250	50	3	6	94
4	MBAL-464	0.50	H_2SO_4 (60)	250	50	3	< 1	86
5	JBO-1421, MBAL-465	0.50	H_2SO_4 (100)	250	50	3	< 1	89
6	MBAL-460	0.50	H_2SO_4 (20)	250	50	6	0	97
7	MBAL-461	0.50	H_2SO_4 (60)	250	50	6	0	81 [c]
8	MBAL-462	0.50	H_2SO_4 (100)	250	50	6	0	26 [c]
9	MBAL550	0.50	HCl (100)	250	50	6	0	91

Experiments were performed according to General Procedure B in 3 mL H_2O. [a] ^1H NMR Yield determined with dimethyl sulfone as internal standard. [b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. [c] Tar formation.

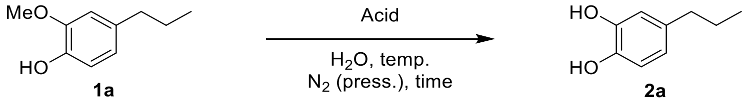
Table S5. *Optimization of the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): screening of reaction temperature.*



Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Temp. (°C)	Press. (bar)	Time (h)	NMR Yield (%) [a]	
							1a	**2a**
1	MBAL-439	0.50	HCl (20)	185	50	3	100	0
2	MBAL-444	0.50	HCl (20)	200	50	3	97	3
3	MBAL-357	0.50	HCl (20)	225	50	3	23	77
4	JBO-496, MBAL-441	0.50	HCl (20)	250	50	3	0	100 (97 [b])
5	MBAL-388	0.50	HCl (20)	275	50	3	0	100
6	BL-12	1.46 [c]	HBr (500)	115	1	20	0	99
7	JBO-598	2.40 [c]	HCl (500)	115	1	20	56	30

Experiments were performed according to General Procedure B in 3 mL H_2O. [a] ^1H NMR Yield determined with dimethyl sulfone as internal standard. [b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. [c] The reported concentractions are obtained after dissolving substrate **1a** in the required amount of conc. HBr or HCl to deliver the reported acid loading.

***Table S6.** Optimization of the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): screening of reaction time.*



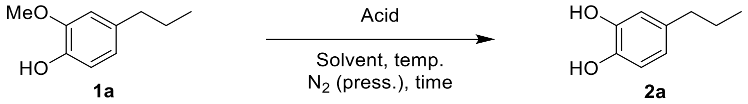
Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Temp. (°C)	Press. (bar)	Time (h)	NMR Yield (%) [a]	
							1a	**2a**
1	MBAL-340	0.50	HCl (20)	250	50	1	17	83
2	MBAL-362	0.50	HCl (20)	250	50	2	4	96
3	JBO-496, MBAL-441	0.50	HCl (20)	250	50	3	0	100 (97 [b])
4	MBAL-449	0.50	HCl (20)	250	50	6	0	100
5	MBAL-415	0.50	HCl (10)	250	50	3	5	90
6	MBAL-466	0.50	HCl (10)	250	50	6	< 1	99

Experiments were performed according to General Procedure B in 3 mL H_2O. [a] ^1H NMR Yield determined with dimethyl sulfone as internal standard. [b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture.

In a final stage of this optimization, the influence of the addition of co-solvents was investigated, given the limited solubility of most organic molecules in water (Table S7). Both EtOH and MeOH were selected because of their miscibility with water and their classification as recommended solvent.[3] In these experiments, a 100 mol% HCl loading was used since it delivered the same result as with 20 mol% when running the reaction in pure water (Entries 1-2), and in this way tackle a possible decrease in reaction rate because of the co-solvents. For both of the selected alcohols, an increase in reaction volume taken by this solvent had a negative impact on the yield for the desired product. For both, the decrease in yield is proportional to the amount of organic solvent added, leading to 0% of the desired product when running the reaction in pure alcohol (Entries 3-8 and 9-14). Furthermore, the increase in alcohol content negatively influenced the selectivity of the performed experiment. A noteworthy difference between EtOH and MeOH was observed, since when using the latter, a significant yield of the desired product **2a** with good mass balance is obtained even with 50% MeOH, opening opportunities for application of our methodology on (larger) less water soluble organic molecules.

Based on the results from this optimization, the conditions reported in Table S8 can be considered as "optimal" for the *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**). With these conditions in hand, a substrate scope was performed.

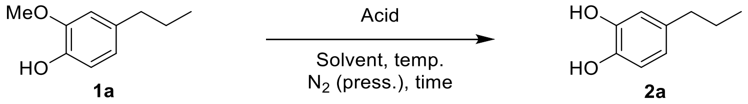
Table S7. *Optimization of the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): solvent screening.*



Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Solvent	Temp. (°C)	Press. (bar)	Time (h)	NMR Yield (%) [a]	
								1a	2a
1	JBO-496 MBAL-441	0.50	HCl (20)	H_2O	250	50	3	0	100 (97 [b])
2	MBAL-416	0.50	HCl (100)	H_2O	250	50	3	0	97
3	MBAL-352	0.50	HCl (100)	H_2O / EtOH (90:10) [c]	250	50	3	< 1	78
4	MBAL-353	0.50	HCl (100)	H_2O / EtOH (75:25) [c]	250	50	3	3	69
5	MBAL-352	0.50	HCl (100)	H_2O / EtOH (50:50) [c]	250	50	3	11	65
6	MBAL-351	0.50	HCl (100)	H_2O / EtOH (25:75) [c]	250	50	3	48	30
7	MBAL-350	0.50	HCl (100)	H_2O / EtOH (10:90) [c]	250	50	3	97	6
8	MBAL-349 MBAL-368	0.50	HCl (100)	EtOH [c]	250	50	3	61	0
9	MBAL-367	0.50	HCl (100)	H_2O / MeOH (90:10)	250	50	3	4	85
10	MBAL-366	0.50	HCl (100)	H_2O / MeOH (75:25)	250	50	3	7	87
11	JBO-442 MBAL-365	0.50	HCl (100)	H_2O / MeOH (50:50)	250	50	3	19	72
12	MBAL-446	0.50	HCl (100)	H_2O / MeOH (25:75)	250	50	3	58	2
13	MBAL-447	0.50	HCl (100)	H_2O / MeOH (10:90)	250	50	3	38	0
14	MBAL-448	0.50	HCl (100)	MeOH [d]	250	50	3	16	0

Experiments were performed according to General Procedure B in 3 mL H_2O. [a] ^{1}H NMR Yield determined with dimethyl sulfone as internal standard. [b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. [c] Commercial HCl in EtOH (1.25 M) was used, diluted with MeOH or EtOH or a mixture thereof. [d] Conc. HCl (aq.) was used, the amount of water present in the reaction medium is thus negligible.

Table S8. *O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**): optimal conditions.*



Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Solvent	Temp. (°C)	Press. (bar)	Time (h)	Yield [a] (%)
1	JBO-496, MBAL-441	0.50	HCl (20)	H_2O	250	50	3	97
2	MBAL-560	0.50	HCl (20)	H_2O	275	50	3	92
3	MBAL-549	0.50	HCl (10)	H_2O	250	50	6	95
4	MBAL-551	0.50	H_2SO_4 (20)	H_2O	250	50	6	97

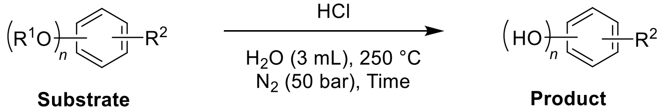
Experiments were performed according to General Procedure C in 3 mL H_2O. Experiments were repeated 5 times and combined for work-up. [a] Yield of isolated product.

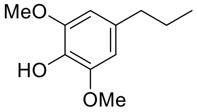
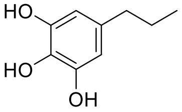
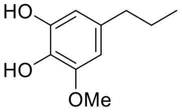
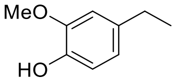
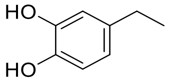
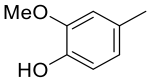
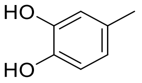
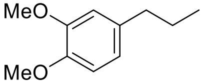
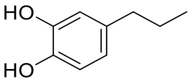
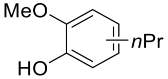
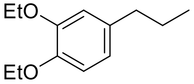
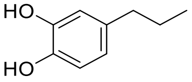
3.3 Reaction scope

3.3.1 Overview

In Table S9, an overview is given of all substrates mentioned in the Manuscript and their corresponding products. Each time, the conditions called "optimal" for the *O*-demethylation of 4-propylguaiacol (**1a**) were applied, as reported in Table S9, Entry 1: Substrate concentration: 0.50 M, HCl loading: 20 mol%, Reaction temperature: 250 °C, Reaction time: 3 h, Pressure at r.t.: 50 bar N_2). If required, a small optimization to improve conversion and yield was performed for every specific substrate, as shown underneath.

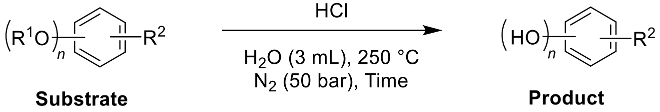
Table S9. *O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.*

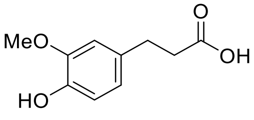
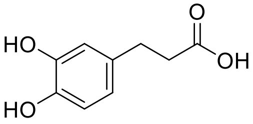
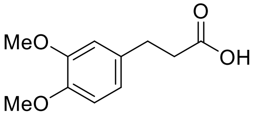
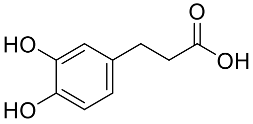
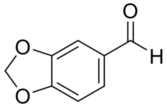
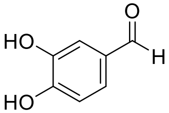
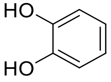


ELN Code	Substrate	Conc (M)	HCl (mol%)	Time (h)	Product 1		Product 2		Substr. left (%) [a]
					Structure	Yield (%) [a]	Structure	Yield (%) [a]	
JBO-510 MBAL-456	 **1b**	0.50	20	3	 **2b**	72	 **1x**	8	3
MBAL-564		0.50	20	6		70		< 1	6
MBAL-554		0.50	40	4		37		0	4
MBAL-500 MBAL-839		0.33	20	3		87 (74 [b, c])		< 1	3
MBAL-763	 **1c**	0.50	20	3	 **2c**	87			7
MBAL-775 MBAL-776		0.50	20	6		90 (90 [b])			0
MBAL-487 MBAL-494	 **1d**	0.50	20	3	 **2d**	99 (99 [b])			0
MBAL-635	 **1e**	0.50	20	3	 **2a**	92	 **1a** (4-*n*Pr) **1v** (5-*n*Pr)	**1a**: 4 **1v**: 4	0
MBAL-646 MBAL-660		0.50	20	6		96 (91 [b])		0	0
MBAL-726	 **1f**	0.50	20	3	 **2a**	35			27
MBAL-647 MBAL-659		0.50	20	6		97 (91 [b])			0

[a] ^{1}H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); [b] Yield of isolated product (General Procedure C); [c] Additionally, recrystallization from toluene.

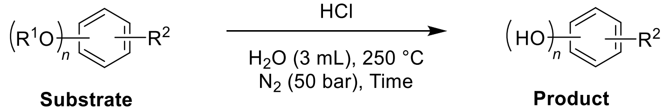
Table S9 (continued). *O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.*

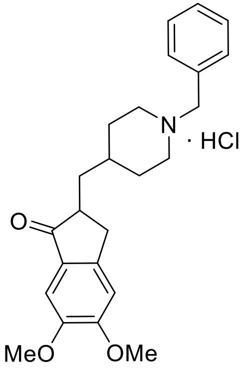
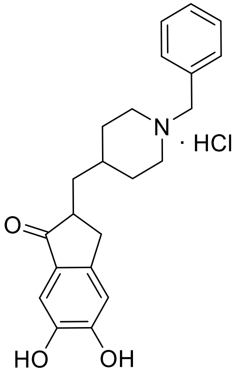
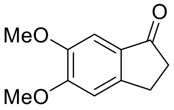
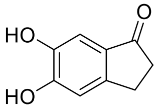
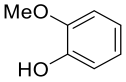
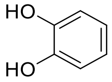


ELN Code	Substrate	Conc (M)	HCl (mol%)	Time (h)	Product 1		Product 2		Substr. left (%) [a]
					Structure	Yield (%) [a]	Structure	Yield (%) [a]	
MBAL-451	 **1g**	0.50	20	3	 **2e**	93			3
MBAL-614		0.50	20	4		96			2
MBAL-687 MBAL-699		0.50	20	6		90 (85 [d])			0
MBAL-504	 **1h**	0.50	20	3	 **2e**	87			4
MBAL-688 MBAL-700		0.50	20	6		91 (86 [d])			0
MBAL-484	 **1i**	0.50	20	3	 **2f**	12	 **2i**	8	0
MBAL-491		0.33	20	3		17		8	0
MBAL-502		0.13	20	3		47		0	0
MBAL-511		0.13	20	1		61		0	0
MBAL-543 MBAL-709		0.13	-	1		58 (62 [b])		0	0

[a] ^1H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); [b] Yield of isolated product (General Procedure C); [d] Yield of isolated product (General Procedure D).

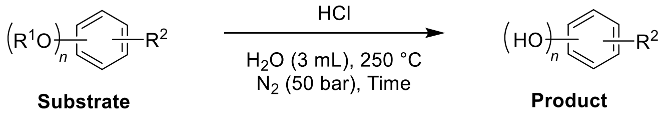
Table S9 (continued). *O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.*

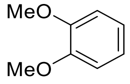
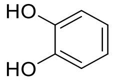
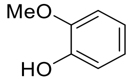
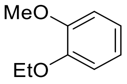
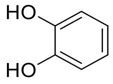
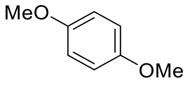
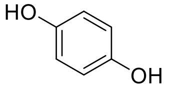
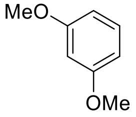
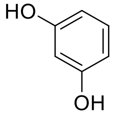
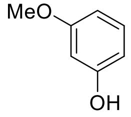
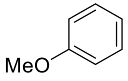
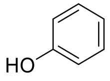
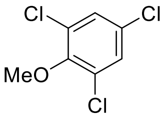
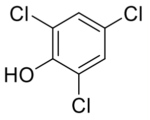


ELN Code	Substrate	Conc (M)	HCl (mol%)	Time (h)	Product 1		Product 2		Substr. left (%) [a]
					Structure	Yield (%) [a]	Structure	Yield (%) [a]	
MBAL-695	 **1j**	0.13	20	3	 **2g**	14			31
MBAL-705		0.13	20	6		36			11
MBAL-710 (MBAL-782)		0.13	40	6		57 (42 [b])			<1
MBAL-723		0.13	40	10		59			<1
MBAL-724		0.13	60	12		65			<1
MBAL-725		0.13	100	12		60			<1
MBAL-505	 **1k**	0.50	20	3	 **2h**	34			<1
MBAL-627		0.50	20	6		22			<1
MBAL-592		0.13	20	3		12			44
MBAL-628		0.13	20	6		53			11
MBAL-639 MBAL-698		0.13	40	6		83 (79 [b])			<1
MBAL-428 SA-024	 **1l**	0.50	20	3	 **2i**	95 (97 [b])			0

[a] ^{1}H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); [b] Yield of isolated product (General Procedure C).

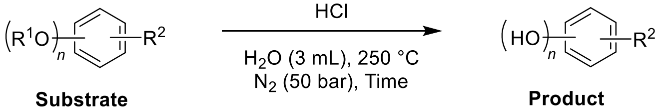
Table S9 (continued). *O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.*

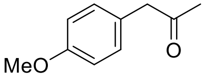
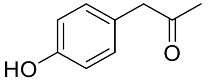
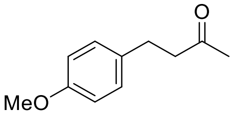
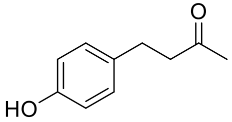
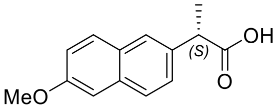
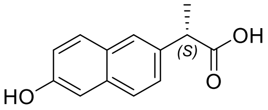
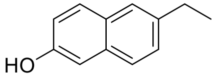


ELN Code	Substrate	Conc (M)	HCl (mol%)	Time (h)	Product 1		Product 2		Substr. left (%) [a]
					Structure	Yield (%) [a]	Structure	Yield (%) [a]	
MBAL-453 MBAL-457		0.50	20	3		97		2	0
MBAL-472	**1m**	0.50	20	4	**2i**	86 (89 [b])	**1l**	<1	0
MBAL-480 MBAL-493	 **1n**	0.50	20	3	 **2i**	98 (98 [b])			0
MBAL-492 MBAL-497	 **1o**	0.50	20	3	 **2j**	98 (98 [b])			
MBAL-452 JBO-325		0.50	20	3		83		4	0
MBAL-503 MBAL-518	**1p**	0.33	20	3	**2k**	94 (92 [b])	**1w**	0	0
SA-097		0.50	20	3		55			11
SA-101 SA-107	**1q**	0.50	100	3	**2l**	72 (62 [b])			< 1
MBAL-622		0.50	20	3		63			25
MBAL-629 MBAL-640	**1r**	0.50	20	6	**2m**	99 (95 [b])			0

[a] ^{1}H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); [b] Yield of isolated product (General Procedure C).

Table S9 (continued). *O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.*

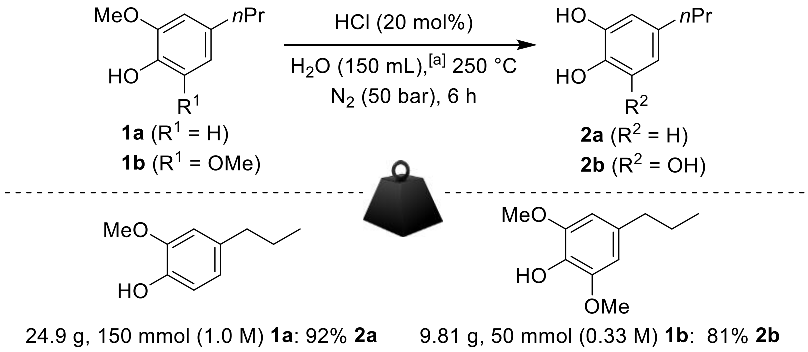


ELN Code	Substrate	Conc (M)	HCl (mol%)	Time (h)	Product 1 Structure	Product 1 Yield (%) [a]	Product 2 Structure	Product 2 Yield (%) [a]	Substr. left (%) [a]
MBAL-526	 **1s**	0.50	20	3	 **2n**	92			3
MBAL-552 MBAL-613		0.50	20	4		88 (80 [b])			0
MBAL-625 MBAL-634	 **1t**	0.50	20	3	 **2o**	90 (94 [b])			0
MBAL-572	 **1u**	0.50	20	3	 **2p**	56	 **2r**	53	0
MBAL-573		0.13	20	3		71		70	0
MBAL-640		0.13	20	1		96		10	0
MBAL-631		0.13	10	1		97		11	0
MBAL-665 [e] MBAL-668 [e]		0.13	20	3		100 (98 [b])		0	0

[a] ^{1}H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); [b] Yield of isolated product (General Procedure C); [e] Temperature = 200 °C.

3.3.2 Bench scale-up on two selected examples

The scalability of the developed *O*-demethylation protocol to multigram quantities was studied (Scheme S1) on 4-propylguaiacol (**1a**) and 4-propylsyringol (**1b**), which can be obtained from wood biorefinery, were selected for this study.[4-7] The maximum scale was determined by the volume the reactor could be loaded with (150 mL) and the maximum applicable concentration for the selected substrate. Gratifyingly, *O*-demethylation of 9.81 grams **1b** at 0.33 M gave 6.69 grams **2b** (81%). With 4-propylguaiacol (**1a**) a higher concentration can be used and 24.9 grams **1a** at 1 M gave 21.1 grams **2a** (92%). These scale-up experiments can be performed without alterations of the reaction conditions at small scale, only the reaction time needed to be extended because of the larger volume to be heated.



Scheme S1. *Bench scale-up examples.* O-*demethylation of 4-propylguaiacol (**1a**) and 4-propylsyringol (**1b**).* [a] *The volume of 150 mL was selected based on the employed 600 mL reactor with 375 mL glass insert (see Figure S1).*

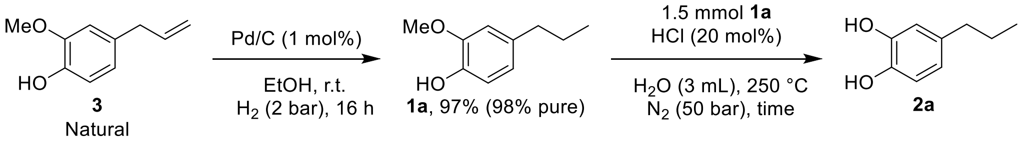
3.3.3 *O*-Demethylation of 4-propylguaiacol obtained from natural feedstock

The developed conditions were applied on two samples of 4-propylguaiacol (**1a**) obtained from natural feedstocks, i.e. eugenol (**3**) from *Eugenia* and lignin oil from pine wood. Methods for obtaining **1a** are described in Section 5.3.1 of this SI.

3.3.3.1 O-Demethylation of 4-propylguaiacol obtained from natural eugenol

Application of the optimal reaction conditions for the conversion of commercial 4-propylguaiacol (**1a**) into 4-propylcatechol on the same substrate **1a,** obtained upon hydrogenation of natural eugenol (**3**) from Merck (see Section 5.3.1.1), was insufficient as only 76% conversion **1a** was obtained after 3 h (Table S10, Entry 1). When doubling the reaction time to 6 h (Entry 2), **2a** was isolated with a yield of 96%, with work-up only involving extraction and filtration.

Table S10. *O-Demethylation of renewable 4-propylguaiacol (**1a**) obtained via hydrogenation of natural eugenol (**3**).*



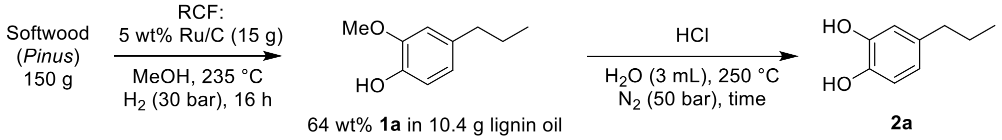
Entry	ELN Code	Scale 1a (mmol)	Conc. 1a (M)	Time (h)	No. of repetitions [a]	Yield 2a [b] (%)
1	MBAL-778	1.5	0.50	3	5	70 [c]
2	MBAL-781	1.5	0.50	6	4	96

Experiments were performed according to General Procedure C. [a] Samples were combined for work-up. [b] Yield of isolated product. [c] A mixture of 70% **2a** and 22% remaining **1a** was obtained.

3.3.3.2 O-Demethylation of 4-propylguaiacol obtained from lignin

Softwood-derived (*Pinus*) lignin oil (**1a**), obtained by Reductive Catalytic Fractionation (RCF) described in Section 5.3.1.2, was selected as second natural resource of 4-propylguaiacol (**1a**). Similarly to **1a** obtained by hydrogenation of natural eugenol (**3**), a reaction time of 6 h was required to obtain full conversion of the lignin oil (Table S11, Entries 1-2). The desired product **2a** could be successfully isolated with a yield of 77%, with the work-up involving only extraction and filtration (Entry 3).

Table S11. *O-Demethylation of 4-propylguaiacol (**1a**) obtained upon Reductive Catalytic Fractionation (RCF) of Pine wood.*



Entry	ELN Code	Scale oil (mg)	Amount 1a in oil (mmol) [a]	Conc. 1a (M)	HCl (mmol)	Time (h)	Yield (%) [b]	
							1a	2a
1	MBAL-797	352	1.35	0.50	0.30	3	19	70
2	MBAL-800	352	1.35	0.50	0.30	6	0	80
3	MBAL-813	390	1.50	0.50	0.30	6	0	79 (77[c])

Experiments were performed according to General Procedure C. [a] Determined via ^{1}H NMR analysis using 1,3,5-trimethoxybenzene or 2-MeTHF as int. std. [b] ^{1}H NMR Yield determined with 1,3,5-trimethoxybenzene or 2-MeTHF as int. std. [c] Yield of isolated product.

4 Evaluation of the green credentials for the developed *O*-demethylation methodology

4.1 Introduction

In order to evaluate the *greenness* of the developed approach for the *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**), this reaction was evaluated using the CHEM21 Green Metrics Toolkit (Section 4.3).[8] Assessment of the so-called *green metrics* is a relative concept. Therefore, the same analysis was performed for other methods, retrieved from literature, involving the same conversion. These methods are briefly described in Section 4.4. This way, we were able to compare our newly developed method with existing methods with respect to greenness.

For this paper, we specifically looked at green chemistry aspects when developing the *O*-demethylation method by reducing the amount of solvents used, and by carefully selecting the solvents used during reaction and work-up (no problematic or hazardous according to the CHEM21 Solvent Selection Guide)[3] in order to maximize greenness. We are aware of the fact that literature procedures are often not written keeping aspects of green chemistry in mind. Moreover, exact amounts of solvents used for extraction as well as other auxiliary materials for purification (e.g. celite for filtration, amount of silicagel used for column chromatography) are simply not specified. In order to have a fair comparison, we therefore look into the *PMI Reactants, Reagents and Catalysts* (PMI RRC), which only takes into account reactants, reagents and catalysts and does not consider the used solvents and work-up methods. This parameter gives a good impression on the green potential of the used chemistry. Considering at discovery level small scales are applied, typically low concentrations are chosen for reactions. While there is in most cases no reason these reactions cannot be executed at a higher concentration, it will negatively influence the *PMI Reaction* (PMI Rxn) involving Reactants, Reagents, Catalysts and Solvent. PMI RRC, excluding reaction solvent, is therefore a fairer and safer way to look at the reaction than *PMI Reaction* (PMI Rxn) at the discovery stage.

4.2 The CHEM21 Green Metrics Toolkit

The CHEM21 Green Metrics Toolkit is split into four *passes* with increasing complexity.[8] The two lowest levels, the so-called *zero pass* and *first pass*, are used for laboratory research (discovery phase), whereas the *second pass* and *third pass* are meant to be used at pilot and industrial scale. This toolkit consists of two major parts: *quantitative* and *qualitative* parameters. For assessing the first category, different calculations are performed after which the obtained values for different methods are compared, while for the latter different parameters are measured with a color code flag (green for *preferred*, yellow for *acceptable* and red for *undesirable*). A user friendly Microsoft Excel spreadsheet is available free of charge and was used in this paper for the assessment of the *greenness* of the different reactions.[9]

Before starting the analysis, the different chemicals used in the reaction need to be classified as either reactant, reagent, catalyst or solvent. The definitions for solvent and catalyst are obvious. A reactant is defined as a compound which contains at least one atom which is built in in the product, while a reagent is only consumed during the reaction without being incorporated in the product.

4.2.1 Quantitative parameters

For every evaluated reaction, the *yield* of the desired product is reported. This parameter can already give a first impression of how the reaction is behaving. When combined with *conversion*, a value for *selectivity* can be obtained. A reaction with high yield and high selectivity is desirable. These parameters are calculated using the following equations:

$$\text{Yield (\%)} = \frac{\text{moles of product}}{\text{moles of limiting reactant}} \times 100\%$$

$$\text{Conversion (\%)} = 100\% - \left(\frac{\text{mass of limiting reactant}}{\text{initial mass of limiting reactant}}\right) \times 100\%$$

$$\text{Selectivity (\%)} = \frac{\text{Yield}}{\text{Conversion}} \times 100\%$$

Next to the parameters presented above, *Atom Economy* (AE) and *Reaction Mass Efficiency* (RME) are often used by organic chemists to get a first view of the efficiency of the reaction. AE is measured by the number of the atoms in the reactants which appear in the final product and therefore, molecular weights are incorporated in the formula. An important remark about AE is that it does not incorporate used excesses of reactants and is a purely theoretical parameter of interest in the retrosynthesis phase. For this reason, RME is also defined incorporating the stoichiometry of the reaction. Important to mention is that both do not incorporate reagents or catalysts. The following formulas are used:

$$\text{AE (\%)} = \frac{\text{MW}_{\text{product}}}{\sum \text{MW}_{\text{reactants}}} \times 100\% \qquad \text{RME (\%)} = \frac{\text{m}_{\text{product}}}{\sum \text{m}_{\text{reactants}}} \times 100\%$$

The most complete mass-based metric is the *Process Mass Intensity* (PMI), which takes into account all mass-based inputs: yield, stoichiometry, solvents, reagents and work-up. It is defined as “mass of all chemicals used in a reaction divided by the mass of the isolated product”, therefore it is expressed on a mass/mass ($g{\cdot}g^{-1}$) basis:

$$\begin{aligned} \text{PMI } (\text{g} \cdot \text{g}^{-1}) &= \frac{\sum \text{mass of all materials used in a process step}}{\text{mass of the isolated product}} \\ &= \frac{\text{m}_{\text{reactants}} + \text{m}_{\text{reagents}} + \text{m}_{\text{catalysts}} + \text{m}_{\text{reaction solvent}} + \text{m}_{\text{work-up chemicals}} + \text{m}_{\text{work-up solvents}}}{\text{m}_{\text{product}}} \end{aligned}$$

PMI is easier to follow if this parameter is split into three categories: *PMI Reactants, Reagents and Catalysts* (PMI RRC), which only takes into account reactants, reagents and catalysts; *PMI Reaction* (PMI Rxn), which additionally also contains reaction solvent; and *PMI Work-up* (PMI WU), in which only the work-up (both auxiliary materials for purification and solvents) of a certain reaction is considered. As already stated earlier, the latter sub category is of less relevance for discovery research.

$$\text{PMI RRC } (\mathrm{g \cdot g^{-1}}) = \frac{\mathrm{m_{reactants} + m_{reagents} + m_{catalysts}}}{\mathrm{m_{product}}}$$

$$\text{PMI Rxn } (\mathrm{g \cdot g^{-1}}) = \frac{\mathrm{m_{reactants} + m_{reagents} + m_{catalysts} + m_{reaction\ solvent}}}{\mathrm{m_{product}}}$$

$$\text{PMI WU } (\mathrm{g \cdot g^{-1}}) = \frac{\mathrm{m_{work\text{-}up\ chemicals} + m_{work\text{-}up\ solvents}}}{\mathrm{m_{product}}}$$

Recently, a new quantitative metric was developed, when a co-product useful in another process is produced in the reaction and therefore not to be considered as waste.[10] This is labelled Feedstock Intensity (FI) and is calculated similarly to PMI. The difference between PMI and $\mathrm{PMI_{FI}}$ is the mass of the produced co-product which is integrated in the denominator of the formula. When a step produces no useful co-product it is waste, $\mathrm{PMI_{FI}}$ is then equal to PMI.

$$\begin{aligned}\mathrm{PMI_{FI}}\ (\mathrm{g \cdot g^{-1}}) &= \frac{\sum \text{mass of all materials used in a process step}}{\text{mass of the isolated products}}\\ &= \frac{\mathrm{m_{reactants} + m_{reagents} + m_{catalysts} + m_{reaction\ solvent} + m_{work\text{-}up\ chemical} + m_{work\text{-}up\ solvents}}}{\mathrm{m_{product} + m_{co\text{-}product}}}\end{aligned}$$

$\mathrm{PMI_{FI}}$ can also be split up in different categories:

$$\mathrm{PMI_{FI}}\ \text{RRC } (\mathrm{g \cdot g^{-1}}) = \frac{\mathrm{m_{reactants} + m_{reagents} + m_{catalysts}}}{\mathrm{m_{product} + m_{co\text{-}product}}}$$

$$\mathrm{PMI_{FI}}\ \text{Rxn } (\mathrm{g \cdot g^{-1}}) = \frac{\mathrm{m_{reactants} + m_{reagents} + m_{catalysts} + m_{reaction\ solvent}}}{\mathrm{m_{product} + m_{co\text{-}product}}}$$

$$\mathrm{PMI_{FI}}\ \text{WU } (\mathrm{g \cdot g^{-1}}) = \frac{\mathrm{m_{work\text{-}up\ chemicals} + m_{work\text{-}up\ solvents}}}{\mathrm{m_{product} + m_{co\text{-}product}}}$$

Similarly, formulas for AE and RME can also be adapted with inclusion of the formed useful co-product:

$$\mathrm{AE_{FI}}\ (\%) = \frac{\mathrm{MW_{product} + MW_{co\text{-}product}}}{\sum \mathrm{MW_{reactants}}} \times 100\%$$

$$\mathrm{RME_{FI}}\ (\%) = \frac{\mathrm{m_{product} + m_{co\text{-}product}}}{\sum \mathrm{m_{reactants}}} \times 100\%$$

A second quantitative parameter including the mass of all used materials, and therefore related to PMI, is the E-factor,[11] quantifying the amount of generated waste to produce a certain mass of the desired product:

$$\begin{aligned}\text{E-factor } (\mathrm{g \cdot g^{-1}}) &= \frac{\text{mass of generated waste}}{\text{mass of the isolated product}}\\ &= \frac{\mathrm{m_{reactants} + m_{reagents} + m_{catalysts} + m_{reaction\ solvent} + m_{work\text{-}up\ chemical} + m_{work\text{-}up\ solvents} - m_{product}}}{\mathrm{m_{product}}}\\ &= \text{PMI } (\mathrm{g \cdot g^{-1}}) - 1\end{aligned}$$

4.2.2 Qualitative parameters

The second part of the CHEM21 Green Metrics Toolkit consists of a series of parameters for which the score is obtained by giving a colored flag. When for a certain item a green flag is scored, it means that the reaction is behaving well, while a red flag leads to the opposite conclusion. Intermediate scores are made visible by scoring a yellow flag which stands for “acceptable, but with some issues”. Whenever possible further optimization should be considered in such case. In Table S12, a brief overview is given on how the flags are determined for each item (except solvents).

Table S12. *Brief overview of the different qualitative parameters to be considered in a green metrics analysis at First Pass.*

Item	Green flag	Yellow flag	Red flag
	🟩	🟨	🟥
Catalyst / Enzyme use	Reaction uses a catalyst or enzyme or no additional reagent was used	Use of stoichiometric quantities of reagents	Use of reagents in excess
Catalyst / Enzyme recovery	Recovery	No recovery	-
Critical elements	Supply remaining for more than 500 years	Supply remaining for 50 to 500 years	Supply remaining for less than 50 years
Energy (part 1)	Reaction temperature between 0 and 70 °C	Reaction run between -20 to 0 °C or 70 to 140 °C	Reaction run below -20 °C or above 140 °C
Energy (part 2)	Reaction run 5 °C or more below the solvent’s boiling point	-	Reaction run at reflux
Batch / Flow	Flow	Batch	-
Work-up	Quenching, Filtration, Centrifugation, Crystallization, Low temperature distillation / evaporation / sublimation	Solvent exchange, quenching into aqueous solvent	Chromatography, ion exchange, high temperature multiple recrystallization
Health and Safety	-	H205, H220, H224, H241, H301, H311, H331, H341, H351, H361, H371, H373, H401, H412	H200, H201, H202, H203, H230, H240, H250, H300, H310, H330, H340, H350, H360, H370, H372, H400, H410, H411, H420

For solvent use, one can make use of the open access CHEM21 Solvent Selection Guide.[3] In Table S13, the most common solvents are listed together with the flag they score. When a solvent is not in this list, the Solvent Guide explains which properties of the solvent should be considered when classifying the solvent in a specific category. These parameters are physical properties (e.g. boiling and flash points, ignition temperature), peroxability, resistivity, H statements and REACH registration.

Table S13. *CHEM21 solvent selection guide of classical solvents.*[3]

Green flag **"Recommended"**	🟩	water, methanol (MeOH), ethanol (EtOH), isopropanol (^{i}PrOH), 1-butanol (^{n}BuOH), *tert*-butanol (^{t}BuOH), ethylene glycol, acetone, methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), ethyl acetate (EtOAc), isopropyl acetate (^{i}PrOAc), *n*-butyl acetate (^{n}BuOAc), anisole, isobutanol, isoamyl alcohol, isobutyl acetate, isoamyl acetate, glycol diacetate, *tert*-amyl methyl ether (TAME), dimethyl carbonate
Yellow flag **"Problematic"**	🟨	benzyl alcohol, cyclohexanone, methyl acetate, tetrahydrofuran (THF), 2-methyl tetrahydrofuran (2-MeTHF), heptane, cyclohexane, methylcyclohexane, toluene, xylene, chlorobenzene, acetonitrile, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), dimethyl sulfoxide (DMSO), formic acid, acetic acid, acetic anhydride, 1,3-propanediol, glycerol, diethyl succinate, cyclopentyl methyl ether (CPME), ethyl *tert*-butyl ether (ETBE), D-limonene, turpentine, *p*-cymene, ethylene carbonate, propylene carbonate, cyrene, ethyl lactate, lactic acid
Red flag **"Hazardous"**	🟥	di-isopropyl ether, methyl *tert*-butyl ether (MTBE), 1,4-dioxane, dimethoxyethane (DME), pentane, hexane, dichloromethane (DCM), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc), *N*-methyl-2-pyrrolidone (NMP), sulfolane, methoxy-ethanol, pyridine, triethylamine, trimethylamine
Dark red flag **"Highly hazardous"**	🟥	diethyl ether (Et_2O), benzene, chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), dichloroethane (DCE), nitromethane, hexamethylphosphoramide (HMPA), carbon disulfide (CS_2)

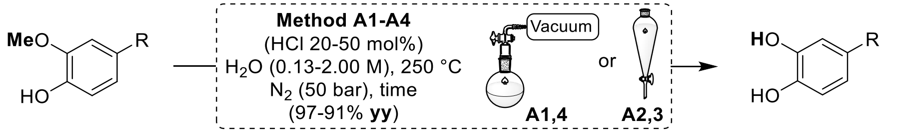
4.3 Application of the CHEM21 Green Metrics Toolkit on the developed demethylation strategy

In the Manuscript, the Green Metrics analysis for Methods A1-3 has been reported. These methods describe the demethylation of 4-propylguaiacol [Method A1: 0.50 M **1a** and 20 mol% HCl (Table S14, Entry 2); Method A2: 1.0 M **1a** and 20 mol% HCl (Table S14, Entry 3); Method A3: 2.0 M **1a** and 50 mol% HCl (Table S14, Entry 4)] and guaiacol [Method A3: 2.0 M **1a** and 50 mol% HCl (Table S14, Entry 6)]. Furthermore, we also applied the Green Metrics Analysis for the demethylation of 4-propylguaiacol under the earlier reported conditions not specifically designed for this process [Method A4: 0.13 M **1a** and 50 mol% HCl (Table S14, Entry 1)],[1] and for demethylation of guaiacol under the conditions reported in the Scope Section of the Manuscript [Method A1: 0.50 M **1a** and 20 mol% HCl (Table S14, Entry 5)].

From the results in Table S14 can be derived that, despite the high yield for Method A4 (Entry 1), a PMI of 52 g·g^{-1} was obtained. The work-up of this Method did not require any material, as it consisted of removing volatiles via freeze-drying, and therefore its PMI is completely attributable to the reaction itself. The difference between PMI Rxn and PMI RRC, 50.6 g·g^{-1}, shows that the solvent use is the biggest material sink (more than 97% of the required input is attributed to the solvent). After the reaction optimization, Method A1 (Entry 2) revealed to be optimal , involving an increased substrate concentration and decreased HCl loading. Both modifications had a beneficial impact on the greenness of the reaction, since from the original PMI Rxn less than 30% was left (15 g·g^{-1}) and PMI RRC decreased slightly to 1.3 $g\cdot g^{-1}$, leading to a total PMI of 15 $g\cdot g^{-1}$. By applying a further increase in substrate concentration to 1.0 M or 2.0 M (Methods A2-3, Entries 3-4), however with increased HCl loading (50 mol%) and decreased reaction time (1 h) for the latter, the desired product was obtained in good selectivity. Despite the decrease in yield to 91%, PMI decreased even further to 11 $g\cdot g^{-1}$. In this case, work-up, based on extraction with EtOAc, was required in order to remove the formed impurities since freeze drying was not possible. Therefore, PMI WU is not equal to zero. Overall, PMI Rxn (including the reaction solvent, which is H_2O) could be reduced to 5.0 $g\cdot g^{-1}$.

For the demethylation of guaiacol (**1l**) to catechol (**2i**), similar conclusions could be drawn (Methods A1,3, Entries 5 and 6, respectively). Again, performing the reaction at a higher substrate concentration (2.0 M) and HCl loading (50 mol%) led to a 25% decrease in PMI. Because of the lower molecular weight of catechol (**2i**) compared to 4-propylcatechol (**2a**), PMI values are slightly higher in this case. For this specific conversion, the new conditions did not affect the yield. When looking at the qualitative metrics (Table S15), it can be seen that for this method mainly green flags are obtained. Only for energy consumption, a red flag is scored because of the high reaction temperature. One needs to realize that this is a very basic analysis of energy consumption, suitable for first pass green metrics, and does not reflect the final energy use, which is simply not possible at the discovery level as e.g. reaction times are not minimized, no heat recovery, etc. In development projects using this new method, a more in-depth study should be performed. The required extraction in the work-up when working at higher substrate concentration (Methods A2-3), brings a yellow flag there, in contrast with the obtained green flag in the cases when freeze drying was sufficient to deliver pure reaction product.

Table S14. *Quantitative metrics for the demethylation of (4-propyl)guaiacol (**1a** and **1l**) to (4-propyl)catechol (**2a** and **2i**) under acidic catalysis.*



1a (R = *n*Pr)
1l (R = H)

2a (R = *n*Pr)
2i (R = H)

Entry	Method [a] [ELN Code]	Substrate	R	Time (h)	Conc. (M)	HCl (mol%)	Yield (%)	AE (%)	RME (%)	PMI (g·g^{-1})	PMI RRC [b] (g·g^{-1})	PMI Rxn [b] (g·g^{-1})	PMI WU [b] (g·g^{-1})	E-factor (g·g^{-1})
1	**A4** [JBO-1658]	**1a**	*n*Pr	3	0.13	50	97	83	80	52	1.4	52	0	51
2	**A1** [JBO-496]	**1a**	*n*Pr	3	0.50	20	97	83	80	15	1.3	15	0	14
3	**A2** [MBAL-766]	**1a**	*n*Pr	3	1.00	20	96	83	79	20	1.3	8.0	12	19
4	**A3** [JBO-643]	**1a**	*n*Pr	1	2.00	50	91	83	75	11	1.5	5.0	6.4	10
5	**A1** [SA-024]	**1l**	H	3	0.50	20	96	77	75	20	1.4	20	0	19
6	**A3** [MBAL-467]	**1l**	H	1	2.00	50	93	77	72	15	1.6	6.3	8.7	14

[a] Experimental procedures are reported in Section 5.1 of this SI. The required N_2 gas to provide the pressurized atmosphere was not incorporated in the calculations since it is dependent on the volume of the reaction vessel and it would not affect the results significantly. [b] RRC: Reactants, Reagents, Catalysts. Rxn: Reaction. WU: Work-up.

Table S15. *Qualitative Appraisal of Solvent Use, Inherent Hazards of Used Chemicals, Catalyst or Reagent Use, Energy and Work-up Methods for the demethylation of (4-propyl)guaiacol (**1a** and **1l**) to (4-propyl)catechol (**2a** and **2i**) under acidic catalysis.*

Method [ELN Code] and Substrate	Solvent Rxn	Flag	Solvent WU	Flag	Critical elements [a]	Flag	Health and Safety [a, b]	Flag	Reagent use	Flag	Energy	Flag	Work-up	Flag
A4 [JBO-1658] **(1a)** **A1** [JBO-496] **(1a)** **A1** [SA-024] **(1l)**	H_2O	🟩	-	🟩	-	🟩	-	🟩	Catalyst	🟩	250 °C	🟥	Freeze drying	🟩
A2 [MBAL-766] **(1a)** **A3** [JBO-643] **(1a)** **A3** [MBAL-467] **(1l)**	H_2O	🟩	EtOAc	🟩	-	🟩	-	🟩	Catalyst	🟩	250 °C	🟥	Extraction	🟨

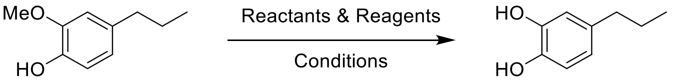
[a] When a yellow or red flag is not applicable, this column is left blank. [b] 4-propylguaiacol (**1a**), is toxic in contact with skin (H311). Also catechol (**2i**) has this property and has a long term toxicity issue (H341), which all lead to a yellow flag for “Health & Safety”. However, these are the starting material or product for the different approaches and therefore not included.

4.4 Selection of reference *O*-demethylation methods for Green Metrics analysis

4.4.1 Literature reports for the synthesis of 4-propylcatechol from 4-propylguaiacol

In order to select suitable literature examples, a SciFinder® search was performed containing 4-propylguaiacol (**1a**) as reactant and 4-propylcatechol (**2a**) as product. The methods reported in Table S16 were retrieved from this search. Methods B and F2 were repeated in our lab, since either no complete work-up was provided in literature (Method B) or the experiment was performed on a very small scale (Method F1). Full experimental procedures can be found in Sections 5.2.1 and 5.2.2.

Table S16. *Literature reports for the O-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**).*



1a **2a**

Method	Scale (mmol)	Reactants & Reagents	Conditions	Work-up	Yield [a] (%)	Ref.
B [MBAL-810]	3.00	Nb_2O_5 (25 mol%)	H_2O (0.30 M) 300 °C, 3 h N_2 (65 bar)	Centrifugation Extraction with EtOAc	79	12
C1	100	HBr (4.9 equiv.)	H_2O (2.4 M) 115 °C, 19 h	NaCl for saturation Extraction with Et_2O	94	2
C2	200	HBr (5.0 equiv.)	H_2O (2.4 M) 115 °C, 16 h	Dilution with MTBE Washing with brine and $NaHCO_3$	97	13
D	5.00	AlI_3 (1.1 equiv.) DMSO (1.1 equiv.)	MeCN (0.13 M) 80 °C, overnight	Quenching with HCl Extraction with EtOAc Washing with $Na_2S_2O_3$	96	14
E	0.70	SIBX (2.1 equiv.) [c]	THF (0.05 M) r.t., 12 h	Dilution with H_2O Extraction with CH_2Cl_2 Washing with aq. Solutions	89	15
F1	0.23	BBr_3 (1.1 equiv.)	CH_2Cl_2 (0.35 M) -78 °C, 1 h	Quenching with H_2O Extraction with CH_2Cl_2 Column chromatography	86	16
F2 [BL-10]	10.0	BBr_3 (1.1 equiv.)	CH_2Cl_2 (0.67 M) -94 °C, 1 h	Quenching with H_2O NaCl (s) until saturation Extraction with CH_2Cl_2	92	17
A3 [JBO-643]	10.0	HCl (0.2 equiv.)	H_2O (2.0 M) 250 °C, 3 h N_2 (50 bar)	Salting out with NaCl Extraction with EtOAc	91	-

[a] Yield of isolated product, unless stated otherwise. [b] 3% starting material was left. [c] SIBX: stabilized formulation of 2-iodoxobenzoic acid (IBX), i.e. a mixture of benzoic acid (22%), isophthalic acid (29%) and 2-iodoxobenzoic acid (49%).

4.4.2 Other classical *O*-demethylation procedures for Green Metrics analysis

Classical *O*-demethylating agents such as TMSI and $AlCl_3$ described for *O*-demethylation of guaiacol (**1l**) and analogues, are not reported on 4-propylguaiacol (**1a**). For these methods, we applied the reaction conditions as retrieved from literature for demethylation of guaiacol derivatives on **1a**.The amount of the reagents and/or the reaction temperature was increased if insufficient conversion of substrate **1a** was observed (optimization data and procedures are reported in Section 5.2 of this SI). Also, work-up was performed as originally described and material intensive column chromatography was only considered if *greener* purification methods did not deliver the desired product **2a** with sufficient purity. In Table S17, the different methods are summarized. Experimental procedures can be found in Sections 5.2.3-5.2.8.

O-demethylation with TMSI was reported on guaiacol.[17] With 1.1 equiv. of this reagent no full conversion was obtained on 4-propylguaiacol (**1a**) (Method G1). 2.0 equiv. were required to achieve this (Method G2). Unfortunately, the crude mixture did not show sufficient purity of the reaction product, making an additional purification via column chromatography required. This step could also be replaced by filtration through a layer of silica (Method G3), though decreasing the yield from 89% to 74%.

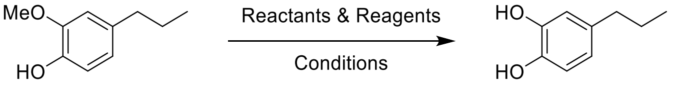
The described *O*-demethylation of guaiacol (**1l**) involving Al powder, I_2 and DMSO could be applied for demethylation of 4-propylguaiacol (**1a**),[18] even without using DMSO (Method H), providing 4-propylcatechol (**2a**) with a yield of 86%.

Demethylation of 4-propylguaiacol (**1a**) with $AlCl_3$,[19, 20] in combination with either NaI or Me_2S was achieved in 63% or 67% yield respectively (Methods I1 and I2), applying conditions reported for demethylation of veratrole or eugenol. However, in both cases full conversion was not observed, even with an excess of the reagents. Therefore, chromatographic separation of product **2a** and substrate **1a** was required, both leading to partial recovery of the starting material.

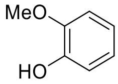
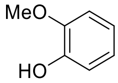
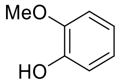
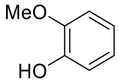
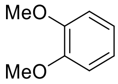
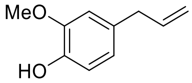
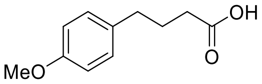
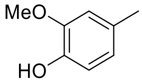
A pilot-scale demethylation of 4-methoxyphenylbutyric acid, involving an excess of molten Py·HCl,[21] was successfully applied on **1a** providing 84% **2a** (Method J).

As last method, LiBr and HBr in excess, described for the demethylation of 4-methylguaiacol (**1d**),[22] was employed on **1a**, leading to **2a** in 82% yield (Method K).

Table S17. *O-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) by applying literature methodologies reported for the same reaction on related guaiacol derivatives.*



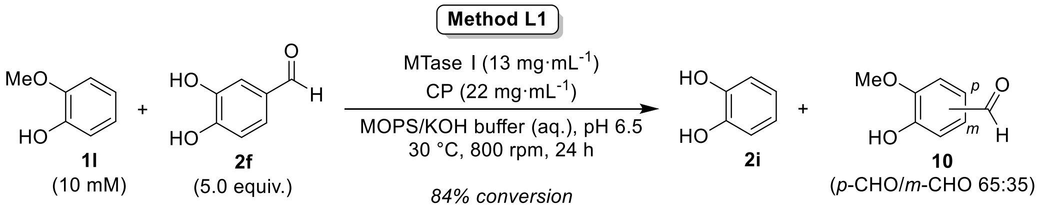
1a **2a**

Method **[ELN Code]**	**Scale (mmol)**	**Reactants & Reagents**	**Conditions**	**Work-up**	**Yield [a] (%)**	**Ref. [b]**	**Literature subtrate**
G1 [BL-20]	10.0	TMSI (1.1 equiv.)	$CHCl_3$ (1.0 M) r.t., 70 h	Quenching with MeOH Extraction with $CHCl_3$ Washing with brine Column chromatography	54 [c]	17	
G2 [BL-32]	10.0	TMSI (2.0 equiv.)	$CHCl_3$ (1.0 M) r.t., 70 h	Quenching with MeOH Extraction with $CHCl_3$ Washing with brine Column chromatography	74	17	
G3 [BL-22]	10.0	TMSI (2.0 equiv.)	$CHCl_3$ (1.0 M) r.t., 70 h	Quenching with MeOH Extraction with $CHCl_3$ Washing with brine Filtration over silica	89	17	
H [JBO-GM-119]	10.0	Al (4.3 equiv.) I_2 (1.7 equiv.)	MeCN (0.12 M) 80 °C, 18 h	Quenching with HCl Extraction with EtOAc Washing with aq. solutions Column chromatography	87	18	
I1 [BL-47]	10.0	$AlCl_3$ (2.0 equiv.) NaI (2.0 equiv.)	EtOAc (1.0 M) 70 °C, 3 h	Quenching with $Na_2S_2O_3$ (aq.) Extraction with EtOAc Column chromatography	63 [d]	19	
I2 [BL-44]	10.0	$AlCl_3$ (4.0 equiv.) Me_2S (4.0 equiv.)	$CHCl_3$ (1.0 M) 70 °C, 3 h	Quenching with $Na_2S_2O_3$ (aq.) Extraction with $CHCl_3$ Column chromatography	67 [e]	20	
J [MBAL-642]	10.0	Py·HCl (4.0 equiv.)	Neat 195 °C, 1 h	Quenching with HCl (aq.) Extraction with MTBE Washing with HCl	84	21	
K [MBAL-795]	0.60	LiBr (117 equiv.) HBr (14.7 equiv.)	H_2O (0.15 M) reflux, 18 h	Diluting with brine Extraction with EtOAc Re-dissolving in MTBE Filtration over celite	82	22	

[a] Yield of isolated product. [b] The experimental procedure, reported in Section 5.2, was based on the given references. [c] The starting material **1a** was recovered for 26%. [d] The starting material **1a** was recovered for 2%. [e] The starting material **1a** was recovered for 20%.

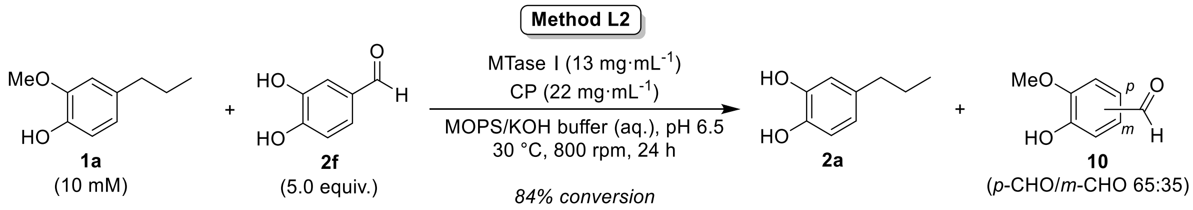
4.4.3 Synthesis of catechol from guaiacol via biocatalysis

The use of enzymes in organic synthesis is emerging. In 2018, Kroutil reported a biocatalytic method based on corrinoid-dependent methyl transferases acting as methyl transferring agent.[23] In the presence of methyl transferase (MTase I), corrinoid protein (CP) and the required buffer, guaiacol (**1l**) was demethylated to catechol (**2i**), while at the same time methyl acceptor protocatechualdehyde (5. equiv.) was converted in a mixture of vanillin and isovanillin (**10**) (Scheme S2, Method L1). Unfortunately, the conversion for this specific reaction was only determined by means of HPLC-UV and the yield for the isolated products was not reported. Work-up involved addition of HPLC solvent (MeCN:H_2O) and removal of proteins via centrifugation. Considering multiple organic compounds are present in the crude mixture, purification via column chromatography may be expected for obtaining pure product **2i**, as the authors for example describe for the isolation of (iso)ferulic acid, obtained upon methylation of caffeic acid and simultaneous demethylation of syringol.[23]



Scheme S2. *Biocatalytic conversion of guaiacol (**1l**) and protocatechualdehyde (**2f**) in catechol (**2i**) and vanillins **10** by MTase I and CP, as described by Kroutil.*[23]

As we did not have access to these enzymes, we could unfortunately not perform this experiment on 4-propylguaiacol (**1a**) directly. Therefore, a theoretical simulation was performed, assuming the reaction on **1a** would occur with the same efficiency as reported on **1l** (Method L2, Scheme S3). We recently disclosed that in this way a reliable quantitative metrics can be obtained when no data are available for a synthetic method on a specific substrate.[24]



Scheme S3. *Biocatalytic conversion of 4-propylguaiacol (**1a**) and protocatechualdehyde (**2f**) in 4-propylcatecholcatechol (**2a**) and vanillins **10** by MTase I and CP, simulated based on data described by Kroutil with **1l** and **2f**.*[23]

4.5 Comparison of the Green Metrics for classical versus new method

4.5.1 General remarks

For green metrics calculations, all experimental details (e.g. the exact amount of all chemicals involved) need to be gathered to obtain a meaningful analysis. Unfortunately, literature routes are often concise in description and some data are lacking in the experimental procedures with respect to work-up. Therefore, if not indicated in the experimental procedure, the following assumptions were made:

- Solvent filtration / extraction: 5 mL for 1 mmol limiting reactant
- Filtration over celite: 2 g for 1 mmol limiting reactant
- Drying over $MgSO_4$ / Na_2SO_4: 1 g for 1 mmol limiting reactant
- Flash chromatography: 100 mL solvent (heptane / EtOAc 80:20) and 8 g SiO_2 for 1 mmol limiting reactant

Often, the selected reactions were quenched with aq. solution(s). If this was the case, the quenching agent, delivering a proton to the product, was fully considered as reactant. If no quenching agent was used, H_2O itself was assumed to be the quenching agent. Then the theoretically required 1.0 equiv. was considered as reactant and the remaining amount was considered as work-up solvent.

A reagent amount higher than 1.0 equiv. is an excess, leading to a red flag. This definition should better be nuanced as a very small excess cannot be distinguished from a large excess applying the original qualitative metrics. Therefore, in this manuscript, the use of 1.0-1.5 equiv. of a certain reagent is given a yellow flag and amounts higher than 1.5 equiv. a red one. Consequently, considering reagent use, yellow flags will be obtained for the Methods D, F1, F2 and G1, while this would be a red flag when using the definition reported in the original metrics. Important to mention is that the use of reactants is not incorporated in this flag. Excess of reactants (as well as reagents) will always be reflected when looking at the quantitative metrics, i.e. PMI.

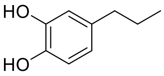
4.5.2 Demethylation of 4-propylguaiacol to 4-propylcatechol

In the manuscript, a comparison of *greenness* is described for the different methods allowing *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**). Complete Excel sheets for all methods considered are reported in Section 7.[9] For Method L2 (MTase), the results are based on simulated rather than experimental data, keeping all other parameters constant (*vide supra*, Section 4.4.3).

5 Experimental procedures

5.1 Products of *O*-demethylation

4-Propylbenzene-1,2-diol (2a) [JBO-296, JBO-496]



The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (**1a**, 166 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.2 mmol, 0.2 equiv.) and H_2O (1.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 97% yield (735 mg, 4.83 mmol). The obtained spectroscopic data are in accordance with literature.[2]
Off-white solid, m.p.: 58 °C (lit.: 58-59 °C),[25] R_f = 0.29 in heptanes/EtOAc (75:25). ^1H NMR (400 MHz, DMSO-d_6): δ 8.56 (bs, 2H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.40 (dd, *J* = 7.9, 1.8 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.50 (sext, *J* = 7.5 Hz, 2H), 0.85 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.9 (C), 143.1 (C), 132.9 (C), 118.9 (CH), 115.7 (CH), 115.4 (CH), 36.7 (CH_2), 24.3 (CH_2), 13.6 (CH_3) ppm. HRMS (ESI) for $C_9H_{13}O_2$ $[M+H]^+$ calcd. 153.0910, found 153.0916.

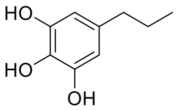
Remark [MBAL-766] - Reaction at substrate concentration of 1.0 M: This compound **2a** could also be synthesized using 2-methoxy-4-propylphenol (**1a**, 332 mg, 2.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.40 mL, 0.40 mmol, 0.2 equiv.) as reagent. Reaction time was 3 h, keeping other factors constant as in the previous example. The experiment was repeated 5 times and samples were combined for work-up, delivering the desired product **2a** in 96% yield (1.46 g, 9.59 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Remark [JBO-643] - Reaction at substrate concentration of 2.0 M: This compound **2a** could also be synthesized using 2-methoxy-4-propylphenol (**1a**, 666 mg, 4.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.0 mmol, 0.5 equiv.) as reagent. The experiment was repeated 5 times and samples were combined for work-up. Reaction time was 1 h, keeping other factors constant as in the previous example, delivering the desired product **2a** in 91% yield (2.77 g, 18.2 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Remark [JBO-1658] - Reaction at substrate concentration of 0.13 M: This compound **2a** could also be synthesized using 2-methoxy-4-propylphenol (**1a**, 66 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.20 mmol, 0.5 equiv.) as reagent. Reaction time was 3 h, keeping other factors constant as in the previous example. The experiment was repeated 5 times and samples were combined for work-up, delivering the desired product **2a** in 97% yield (295 mg, 1.95 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Remark [MBAL-734] – Large scale synthesis of 2a (1.0 M): The glass insert (beaker shown in Figure S1(a), without metal insert containing vials) for the Parr® 4625 reactor, equipped with magnetic stirring bar, was loaded with 2-methoxy-4-propylphenol (**1a**, 24.93 g, 150 mmol, 1.0 equiv.), HCl (aq., 1 M, 30.0 mL, 30.0 mmol, 0.2 equiv.) and H_2O (120 mL). The beaker was placed in the Parr® 4625 reactor, which was then closed properly, flushed with N_2 (3 × 10 bar) and filled with N_2 gas (50 bar). The mixture in the reactor was heated to 250 °C and stirred for 6 h. Subsequently, the reactor was cooled to r.t., the pressure was released and the reactor was opened. The reaction mixture was transferred to a separatory funnel, NaCl (s, 20 g) was added, the product was extracted with EtOAc (300 mL), and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, evaporated under reduced pressure and freeze-dried. Pure 4-propylcatechol (**2a**) was obtained in 92% yield (21.06 g, 138 mmol).

5-Propylbenzene-1,2,3-triol (2b) [MBAL-839]



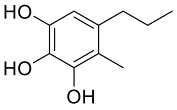
The reaction was performed using General procedure C, using 2,6-dimethoxy-4-propylphenol (**1b**, 196 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.2 mmol, 0.2 equiv.) and H_2O (2.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 8 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Subsequently, the crude mixture was recrystallized from toluene. Pure 5-propylbenzene-1,2,3-triol (**2b**) was obtained in 74% yield (376 mg, 2.24 mmol). There are no spectroscopic data available in literature.

Grey powder, m.p.: 75 °C (lit.: 78 °C), R_f = 0.37 in heptanes / EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (bs, 2H), 7.83 (bs, 1H), 6.08 (s, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 1.48 (sext, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 145.9 (C), 132.2 (C), 130.7 (C), 107.0 (CH), 37.0 (CH_2), 24.1 (CH_2), 13.6 (CH_3) ppm.

Remark [MBAL-653] – Reaction at higher concentration 1b:

The reaction was performed using General procedure C, using 2,6-dimethoxy-4-propylphenol (**1b**, 294 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The product was purified by an automated reversed phase flash chromatography system using a H_2O/MeCN gradient (Cartridge: 12 g C18-SiO_2, flow rate: 20 mL·min^{-1}, eluent: 10% MeCN in H_2O, 30 min; 10% MeCN in H_2O to 40% MeCN in H_2O, 25 min; 40% MeCN in H_2O, 3 min; 40% MeCN in H_2O to 50% MeCN in H_2O, 7 min; 50% MeCN in H_2O, 3 min; 50% MeCN in H_2O to 60% MeCN in H_2O, 3 min; 60% MeCN in H_2O to 100% MeCN, 3 min; 100% MeCN, 10 min). Pure 4-methyl-5-propylbenzene-1,2,3-triol (**2q**) was obtained in 22% yield (184 mg, 1.01 mmol). Furthermore, 5-propylbenzene-1,2,3-triol (**2b**) was obtained in 44% yield (332 mg, 1.97 mmol). There are no spectroscopic data available in literature.

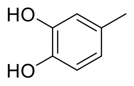
4-Methyl-5-propyl-1,2,3-triol (2q) [MBAL-653]



Grey solid, m.p.: 114-117 °C, R_f = 0.54 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.52 (bs, 1H), 7.87 (bs, 2H), 6.09 (s, 1H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.95 (s, 3H), 1.43 (sext, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.3 (C), 143.0 (C), 130.7 (C), 130.6 (C), 113.0 (C), 107.4 (CH), 34.8 (CH_2), 23.4 (CH_2), 13.9 (CH_3), 11.1 (CH_3) ppm.

Remark [MBAL-735] – Large scale synthesis of 2b: The glass insert (beaker shown in Figure S1(a), without metal insert containing vials) for the Parr® 4625 reactor, equipped with magnetic stirring bar, was loaded with 2,6-dimethoxy-4-propylphenol (**1b**, 9.81 g, 50.0 mmol, 1.0 equiv.), HCl (aq., 1 M, 10.0 mL, 10.0 mmol, 0.2 equiv.) and H_2O (140 mL). The beaker was placed in the Parr® 4625 reactor, which was then closed properly, flushed with N_2 (3 × 10 bar) and filled with N_2 gas (50 bar). The mixture in the reactor was heated to 250 °C and stirred for 6 h. Subsequently, the reactor was cooled to r.t., the pressure was released and the reactor was opened. The reaction mixture was transferred to a separatory funnel, NaCl (s, 20 g) was added, the product was extracted with EtOAc (200 mL), and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, evaporated under reduced pressure and freeze-dried. The obtained purple solid was recrystallized from toluene. Pure 5-propylbenzene-1,2,3-triol (**2b**) was obtained in 80% yield (6.69 g, 39.8 mmol).

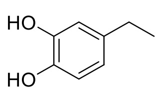
4-Methylbenzene-1,2-diol (2d) [MBAL-494]



The reaction was performed using General Procedure C, using 2-methoxy-4-methylphenol (**1d**, 207 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-methylbenzene-1,2-diol (**2d**) was obtained in 99% yield (551 mg, 4.43 mmol). The obtained spectroscopic data are in accordance with literature.[26]

White solid, m.p.: 65 °C (lit.: 64 °C),[27] R_f = 0.57 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56 (bs, 2H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.39 (dd, *J* = 7.9, 2.0 Hz, 1H), 2.12 (s, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.9 (C), 142.8 (C), 127.8 (C), 119.4 (CH), 116.4 (CH), 115.4 (CH), 20.3 (CH_3) ppm.

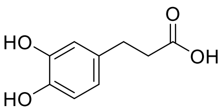
4-Ethylbenzene-1,2-diol (2c) [MBAL-776]



The reaction was performed using General Procedure C, using 4-ethyl-2-methoxyphenol (**1c**, 228 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-ethylbenzene-1,2-diol (**2c**) was obtained in 90% yield (931 mg, 6.74 mmol). The obtained spectroscopic data are in accordance with literature.[28]

Light brown oil, R_f = 0.60 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (bs, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.42 (dd, *J* = 7.9, 2.1 Hz, 1H), 2.42 (q, *J* = 7.6 Hz, 2H), 1.10 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 145.0 (C), 143.0 (C), 134.6 (C), 118.2 (CH), 115.4 (CH), 115.1 (CH), 27.5 (CH_2), 15.9 (CH_3) ppm.

3-(3,4-Dihydroxyphenyl)propanoic acid (2e) [MBAL-699]



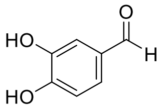
The reaction was performed using General procedure D, using 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (**1g**, 294 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of 50 bar N_2. After cooling down to r.t., the gas was released and the reactor was opened. The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (2 × 10 mL), brine (5.0 mL), $NaHCO_3$ (aq., sat., 10 mL) and HCl (aq., 1 M, 10 mL) and were used. Pure 3-(3,4-dihydroxyphenyl)propanoic acid (**2e**) was obtained in 85% yield (696 mg, 3.82 mmol). The spectroscopic data are in accordance with literature.[29]

Grey solid, m.p.: 136 °C (lit.: 139 °C),[30] R_f = 0.21 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.97 (bs, 1H), 8.65 (bs, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.44 (dd, *J* = 8.0, 2.1

Hz, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 173.8 (C), 145.0 (C), 143.4 (C), 131.7 (C), 118.7 (CH), 115.6 (CH), 115.4 (CH), 35.7 (CH$_2$), 29.8 (CH$_2$) ppm. HRMS (ESI) for $C_9H_{11}O_4$ [M+H]$^+$ calcd. 183.0652, found 183.0649.

Remark [MBAL-700]: This compound **2e** could also be synthesized using using 3-(3,4-dimethoxyphenyl)propanoic acid (**1h**, 315 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) as reagent. Keeping other factors constant as in the previous example delivered the desired product **2e** in 86% yield (705 mg, 3.87 mmol).

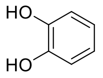
3,4-Dihydroxybenzaldehyde (2f) [MBAL-709]



The reaction was performed using General Procedure C, using 2*H*-1,3-benzodioxole-5-carbaldehyde (**1i**, 60 mg, 0.40 mmol, 1.0 equiv.) as substrate and H_2O (3.0 mL) as reagent. The reaction mixture was heated to 250 °C and stirred for 1 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. Before work-up, all solids were removed by filtration. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 3,4-dihydroxybenzaldehyde (**2f**) was obtained in 62% yield (170 mg, 1.23 mmol). The spectroscopic data are in accordance with literature.[31]

Light grey solid, m.p.: 159 °C (lit.: 155 °C),[31] R_f = 0.27 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.69 (s, 1H), 7.27-7.24 (m, 2H), 6.95-6.93 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 191.0 (CH), 152.2 (C), 145.9 (C), 128.8 (C), 124.3 (CH), 115.6 (CH), 114.5 (CH) ppm.

Benzene-1,2-diol (2i) [JBO-294, SA-024]

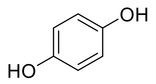


The reaction was performed using General Procedure C, using 2-methoxyphenol (**1l**, 124 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.2 mmol, 0.2 equiv.) and H_2O (1.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-propylbenzene-1,2-diol (**2i**) was obtained in 97% yield (535 mg, 4.86 mmol). The obtained spectroscopic data are in accordance with literature.[32]

Grey solid, m.p.: 104 °C (lit.: 102-103 °C),[32] R_f = 0.29 in heptanes/EtOAc (75:25). ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.90-6.85 (m, 2H), 6.83-6.81 (m, 2H), 5.10 (s, 2H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ 143.7 (C), 121.5 (CH), 115.7 (CH) ppm. HRMS (ESI) for $C_6H_7O_2$ [M+H]$^+$ calcd. 111.0446, found 111.0447.

Remark [MBAL-467]: This compound **2i** could also be synthesized using using 2-methoxyphenol (**1l**, 496 mg, 4.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.0 mmol, 0.5 equiv.) as reagent. Keeping other factors constant as in the previous example, delivering the desired product **2i** in 93% yield (410 mg, 3.73 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Benzene-1,4-diol (2j) [MBAL-497]

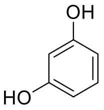


The reaction was performed using General Procedure C, using 1,4-dimethoxybenzene (**1o**, 207 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc

(10 mL) and brine (5.0 mL) were used. Pure benzene-1,4-diol (**2j**) was obtained in 98% yield (488 mg, 4.43 mmol). The obtained spectroscopic data are in accordance with literature.[1, 33]

White solid, m.p.: 169 °C (lit.: 169-171 °C),[1, 33] R_f = 0.61 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 2H), 6.55 (s, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 149.7 (C), 115.6 (CH) ppm.

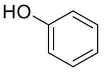
Benzene-1,3-diol (2k) [JBO-325, MBAL-518]



The reaction was performed using General procedure C, using 1,3-dimethoxybenzene (**1p**, 138 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.2 equiv.) and H_2O (2.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure resorcinol (**2k**) was obtained in 92% yield (305 mg, 2.77 mmol). The spectroscopic data are in accordance with literature.[34]

Brown solid, m.p.: 111 °C (lit.: 106-110 °C),[35] R_f = 0.10 in heptanes / EtOAc (75:25). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 2H), 6.90 (t, *J* = 7.8 Hz, 1H), 6.19-6.16 (m, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.4 (C), 129.6 (CH), 106.2 (CH), 102.5 (CH) ppm. HRMS (ESI) for $C_6H_7O_2$ [M+H]$^+$ calcd. 111.0441, found 111.0441.

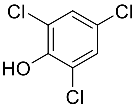
Phenol (2l) [SA-107]



The reaction was performed using General Procedure C, using anisole (**1q**, 108 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 1.0 mL, 1.0 mmol, 1.0 equiv.) and H_2O (1.0 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), MTBE (3 × 10 mL) and brine (5.0 mL) were used. Pure 4-propylbenzene-1,2-diol (**2l**) was obtained in 62% yield (290 mg, 3.10 mmol). The obtained spectroscopic data are in accordance with literature.[36]

White solid, m.p.: 102 °C (lit.: 105 °C),[37] R_f = 0.619 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.21 (m, 2H), 6.95-6.91 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.84-6.81 (m, 2H), 4.87 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6 (C), 129.8 (CH), 121.0 (CH), 115.5 (CH) ppm. EI (+) (m/z (%)): 94 (100), 66 (34), 65 (24).

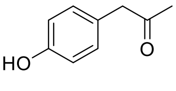
2,4,6-Trichlorophenol (2m) [MBAL-640]



The reaction was performed using General Procedure C, using 1,3,5-trichloro-2-methoxybenzene (**1r**, 317 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N_2 (50 bar). In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 2,4,6-trichlorophenol (**2m**) was obtained in 95% yield (283 mg, 1.43 mmol). The spectroscopic data are in accordance with literature.[38]

Off-white solid, m.p.: 68 °C (lit.: 69-71 °C),[38] R_f = 0.77 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.1 (C), 128.3 (CH), 125.5 (C), 121.8 (C) ppm.

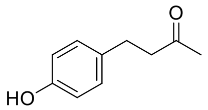
1-(4-Hydroxyphenyl)propan-2-one (2n) [MBAL-613]



The reaction was performed using General Procedure C, using 1-(4-methoxyphenyl)propan-2-one (**1s**, 246 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 4 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 1-(4-hydroxyphenyl)propan-2-one (**2n**) was obtained in 80% yield (539 mg, 3.59 mmol). The spectroscopic data are in accordance with literature.[39]

Pale colorless oil, R_f = 0.43 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (dt, *J* = 8.4, 1.3 Hz, 2H), 6.79 (dt, *J* = 8.4, 1.3 Hz, 2H), 5.62 (bs, 1H), 3.63 (s, 2H), 2.15 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.0 (C), 155.1 (C), 130.7 (CH), 126.2 (C), 115.9 (CH), 50.3 (CH_2), 29.3 (CH_3) ppm. EI (+) (m/z (%)): 150 (1), 107 (100), 77 (15).

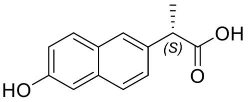
4-(4-Hydroxyphenyl)butan-2-one (2o) [MBAL-634]



The reaction was performed using General Procedure C, using 4-(4-methoxyphenyl)butan-2-one (**1t**, 267 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 2 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-(4-hydroxyphenyl)butan-2-one (**2o**) was obtained in 94% yield (460 mg, 2.80 mmol). The spectroscopic data are in accordance with literature.[40]

Light brown solid, m.p.: 79 °C (lit.: 82-84 °C),[41] R_f = 0.48 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 8.5, 0.9 Hz, 2H), 6.75 (dd, *J* = 8.5, 0.9 Hz, 2H), 4.97 (s, 1H), 2.85-2.81 (m, 2H), 2.74-2.70 (m, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.7 (C), 154.1 (C), 133.2 (C), 129.6 (CH), 115.5 (CH), 45.6 (CH_2), 30.3 (CH_3), 29.1 (CH_2) ppm.

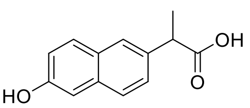
(2*S*)-2-(6-Hydroxynaphthalen-2-yl)propanoic acid (*S*-2p) [MBAL-668]



The reaction was performed using General Procedure C, using (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (**1u**, 100% ee, 92 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.08 mL, 0.08 mmol, 0.2 equiv.) and H_2O (2.92 mL) as reagents. The reaction mixture was heated to 200 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 4 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure (2*S*)-2-(6-hydroxynaphthalen-2-yl)propanoic acid (***S*-2p**) was obtained in 98% yield (340 mg, 1.58 mmol) with 84% ee. The spectroscopic data are in accordance with literature.[42]

White solid, m.p.: 184 °C, R_f = 0.23 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 9.67 (bs, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.64-7.62 (m, 2H), 7.32 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.09-7.05 (m, 2H), 3.76 (q, *J* = 7.1 Hz, 1H), 1.42 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.5 (C), 155.1 (C), 135.3 (C), 133.5 (C), 129.1 (CH), 127.6 (C), 126.1 (CH), 126.1 (CH), 125.5 (CH), 118.8 (CH), 108.4 (CH), 44.6 (CH), 18.4 (CH_3) ppm. HRMS (ESI) for $C_{13}H_{11}O_3$ $[M-H]^-$ calcd. 215.0714, found 215.0723.

In order to proof enantiomeric purity of the obtained product ***S*-2p**, its racemic counterparts was synthesized:

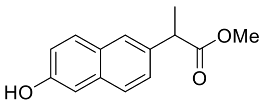


2-(6-Hydroxynaphthalen-2-yl)propanoic acid (*rac*-2p) [MBAL-742]: In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, DL-naproxen (0.50 g, 2.17 mmol) was dissolved in HBr (aq., 48%, 14.19 g, 175 mmol, 81 equiv.) and heated under reflux for 2 h. Subsequently, the mixture was cooled to r.t. and filtered. Solids were washed with ice cold water (10 mL) to afford racemic 2-(6-hydroxynaphthalen-2-yl)propanoic acid (***rac*-2p**) in 81% yield (0.38 g, 1.75 mmol). The obtained spectroscopic data are in accordance with literature.[43]

White solid, m.p.: 185 °C (lit.: 186-188 °C),[44] R_f = 0.23 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.22 (bs, 1H), 9.67 (bs, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.64-7.62 (m, 2H), 7.32 (dd, *J* = 8.6 Hz, 1.8 Hz, 1H), 7.09-7.05 (m, 2H), 3.76 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.5 (C), 155.1 (C), 135.3 (C), 133.5 (C), 129.1 (CH), 127.6 (C), 126.1 (CH), 126.1 (CH), 125.5 (CH), 118.7 (CH), 108.4 (CH), 44.5 (CH), 18.4 (CH_3) ppm.

Subsequently, the obtained carboxylic acids **2p** (both enantiomeric and racemic) were esterified to the corresponding methyl ester **12**, which was later on analyzed with chiral HPLC. The procedure and characterization for the racemic mixture are reported underneath.

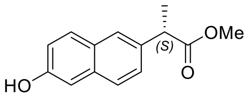
Methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (*rac*-12) [MBAL-815]



In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, 2-(6-hydroxynaphthalen-2-yl)propanoic acid (***rac*-2p**, 0.20 g, 0.93 mmol) was dissolved in MeOH (12 mL) and 2 drops of conc. H_2SO_4 were added. The reaction mixture was stirred for 4 h under reflux and subsequently cooled to r.t., diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (aq., sat., 10 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to afford pure racemic methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (***rac*-12**) in 95% yield (0.20 g, 0.88 mmol) . The spectroscopic data are in accordance with literature.[44]

White solid, m.p.: 90 °C (lit.: 90-92 °C),[44] R_f = 0.65 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.37 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.09-7.06 (m, 2H), 5.87 (bs, 1H), 3.88 (q, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8 (C), 153.8 (C), 135.5 (C), 133.9 (C), 129.7 (CH), 128.9 (C), 127.0 (CH), 126.4 (CH), 126.2 (CH), 118.3 (CH), 109.5 (CH), 52.3 (CH_3), 45.5 (CH), 18.6 (CH_3) ppm.

Methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (*S*-12) [MBAL-814]



In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, 2-(6-hydroxynaphthalen-2-yl)propanoic acid (***rac*-2p**, 0.20 g, 0.93 mmol) was dissolved in MeOH (12 mL) and 2 drops of conc. H_2SO_4 were added. The reaction mixture was stirred for 4 h under reflux and subsequently cooled to r.t., diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (aq., sat., 10 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to afford pure racemic methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (***S*-12**) in 84% yield (0.17 g, 0.78 mmol) with 84% ee. The spectroscopic data are in accordance with literature.[44]

Result of the chiral HPLC analysis:

For the employed substrate **1u**, analysis of enantiopurity was performed on a Chiralpak IB column (4.6 mm × 150 mm, 5 µm) using a Hexane/EtOH/TFA mixture (80:20:0.1%) at a flow rate of 1 mL·min^{-1} at 235 nm (UV and CD analysis), showing enantiopurity of the used substrate (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (***S*-1u**), as shown in Figure S6.

Subsequently, enantiopurity of the esters ***rac*-12** and ***S*-12** was analyzed on a Chiralpak IA column (4.6 mm × 150 mm, 5 µm) using a Hexane/*i*-PrOH mixture (95:5) at a flow rate of 1 mL·min^{-1} at 235 nm (UV and CD analysis). The analysis revealed 84 ee% for ***S*-12**, as shown in Figure S7, while the same analysis of the racemic mixture is reported in Figure S8 as comparison. On the basis of analysis of ***S*-12**, enantiopurity of ***S*-2p** was determined.

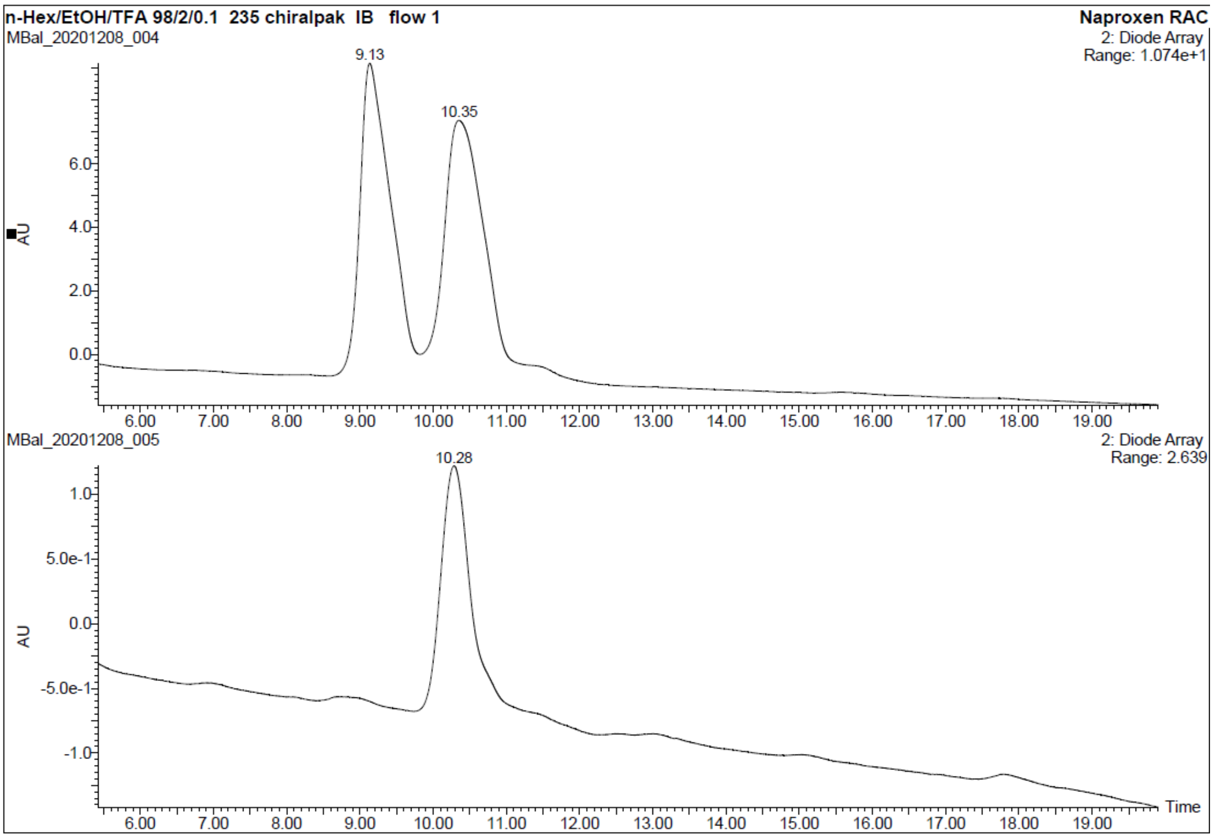


__Figure S6.__ Determination of enantiomeric purity of (2S)-2-(6-methoxynaphthalen-2-yl)propanoic acid (__1u__). Chromatogram from PDA-detector between 200-400 nm. Top: DL-naproxen, Bottom: (2S)-2-(6-methoxynaphthalen-2-yl)propanoic acid (__1u__).

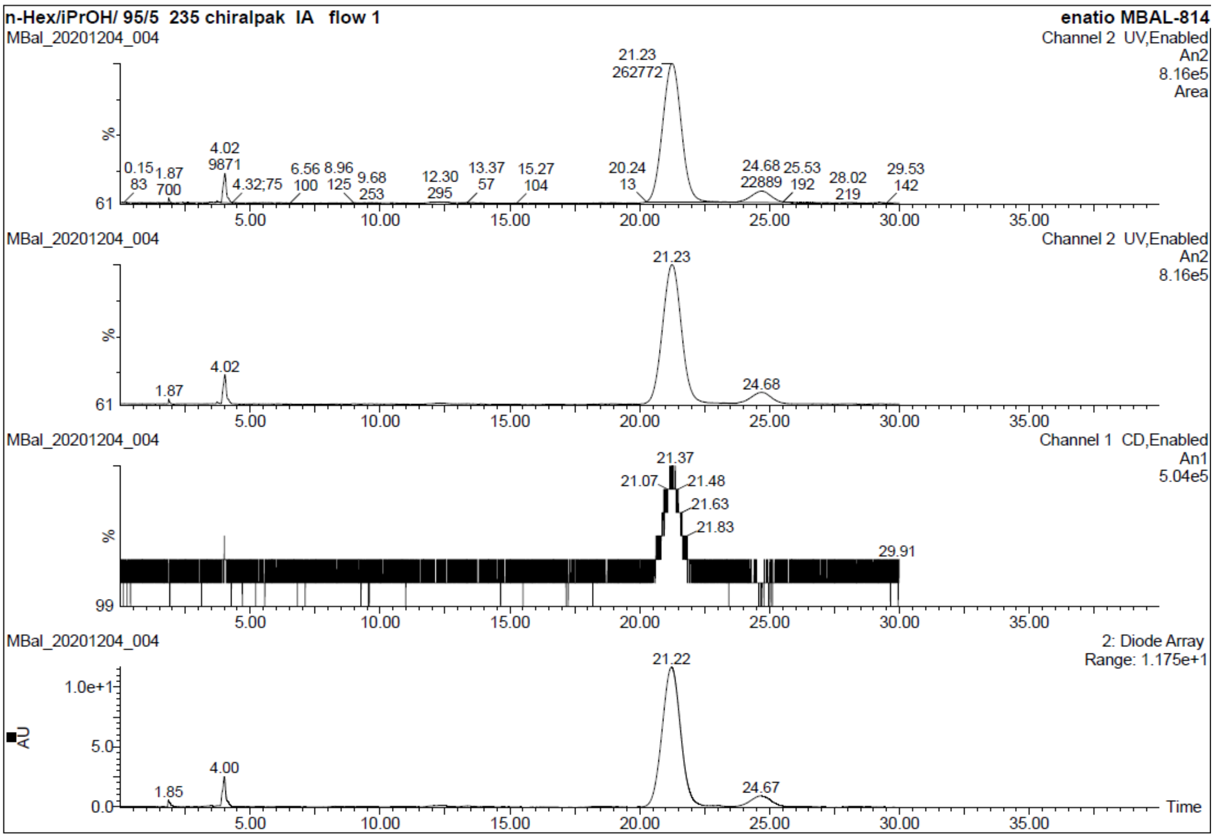


*Figure S7. Determination of enantiomeric purity of **(S)-12**. Chromatograms 1 and 2: UV-trace at 235 nm, Chromatogram 3: CD-trace at 235 nm and Chromatogram 4: PDA-detector between 200-400 nm.*

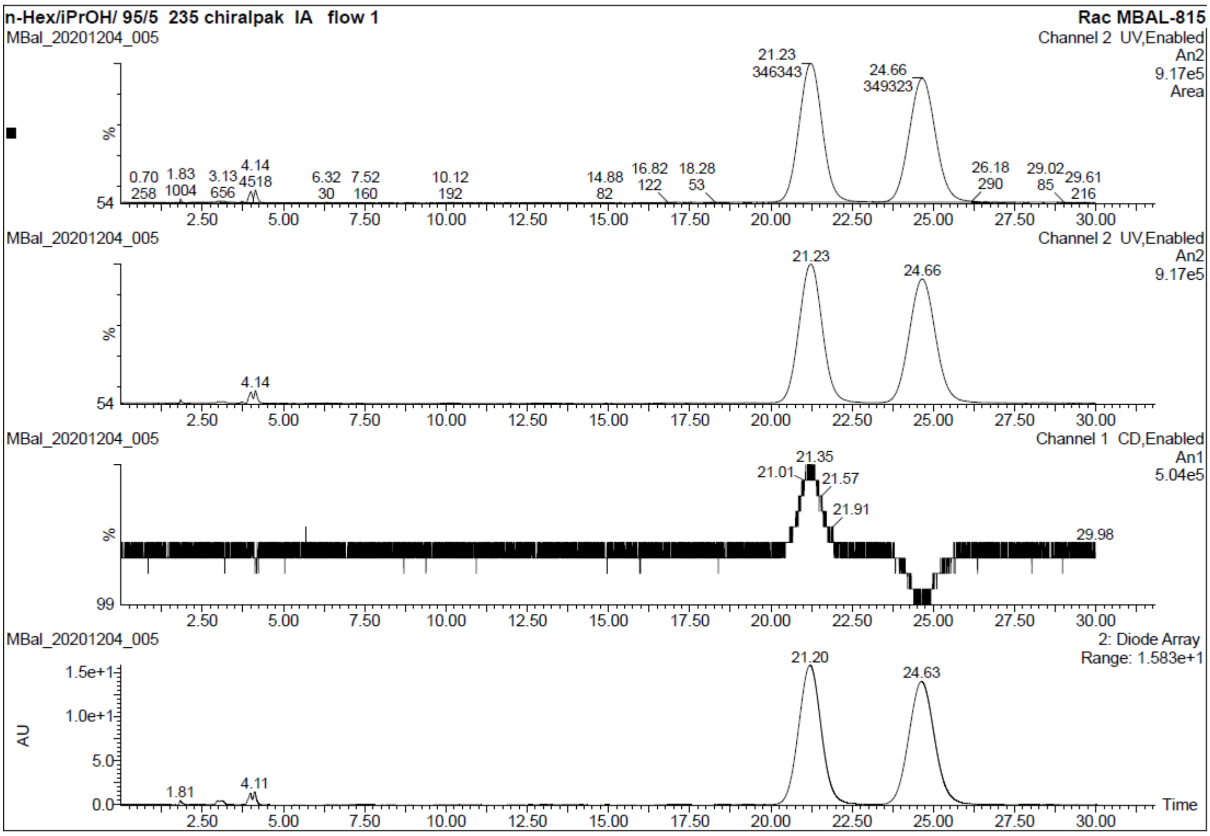
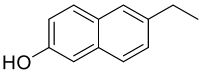


*Figure S8. Determination of enantiomeric purity of **rac-12**. Chromatograms 1 and 2: UV-trace at 235 nm, Chromatogram 3: CD-trace at 235 nm and Chromatogram 4: PDA-detector between 200-400 nm.*

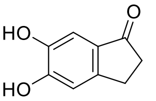
6-Ethylnaphthalen-2-ol (2r) [MBAL-675]



The reaction was performed using General Procedure C, using (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (**1u**, 345 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 4 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The product was purified by an automated flash chromatography system using a heptanes/EtOAc gradient (Cartridge: 12 g SiO_2, flow rate: 20 mL·min^{-1}, eluent: heptanes to 50% EtOAc in heptanes, 60 min). Pure 6-ethylnaphthalen-2-ol (**2r**) was obtained in 61% yield (631 mg, 3.66 mmol). Furthermore, pure (2*S*)-2-(6-hydroxynaphthalen-2-yl)propanoic acid (**2p**) was obtained in 2% yield (22 mg, 0.1 mmol). There are no spectroscopic data (in DMSO-d_6) available in literature.

Grey solid, m.p.: 91 °C (lit.: 96-98 °C),[45] R_f = 0.65 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.54 (bs, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 1H), 7.26 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.07-7.07 (m, 1H), 7.04 (dd, *J* = 8.7, 2.4 Hz, 1H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 154.6 (C), 137.8 (C), 133.0 (C), 128.7 (CH), 127.9 (CH), 127.2 (CH), 126.0 (CH), 125.1 (CH), 118.5 (CH), 108.5 (CH), 28.1 (CH_2), 15.6 (CH_3) ppm. HRMS (ESI) for $C_{12}H_{11}O$ [M-H]$^-$ calcd. 171.0815, found 171.0814.

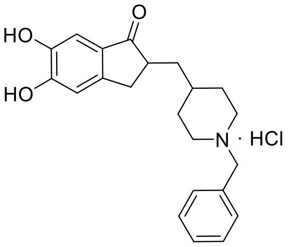
5,6-Dihydroxy-2,3-dihydro-1*H*-inden-1-one (2h) [MBAL-698]



The reaction was performed using General Procedure C, 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (**1k**, 77 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.16 mL, 0.16 mmol, 0.4 equiv.) and H_2O (2.84 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The product was purified by an automated flash chromatography system using a heptanes/EtOAc gradient (Cartridge: 40 g SiO_2, flow rate: 20 mL·min^{-1}, eluent: heptanes to 15% EtOAc in heptanes, 10 min; 15% EtOAc in heptanes to 25% EtOAc in heptanes, 30 min; 25% EtOAc in heptanes, 15 min; 25% EtOAc in heptanes to 40% EtOAc in heptanes, 60 min; 40% EtOAc in heptanes, 55 min). Pure 5,6-dihydroxy-2,3-dihydro-1*H*-inden-1-one (**2h**) was obtained in 79% yield (260 mg, 1.58 mmol). The spectroscopic data are in accordance with literature.[46]

Yellow solid, m.p.: 246 °C, R_f = 0.14 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.66 (bs, 2H), 6.92 (s, 1H), 6.83 (s, 1H), 2.90-2.87 (m, 2H), 2.49-2.47 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 204.2 (C), 153.0 (C), 148.7 (C), 145.6 (C), 128.4 (C), 111.8 (CH), 107.7 (CH), 36.1 (CH_2), 24.6 (CH_2) ppm. HRMS (ESI) for $C_9H_7O_3$ [M-H]$^-$ calcd. 163.0401, found 163.0393.

2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dihydroxy-2,3-dihydro-1*H*-inden-1-one hydrochloride (2g) [MBAL-782]



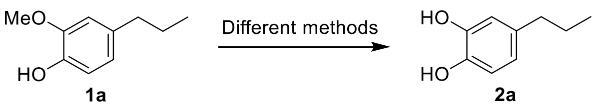
The reaction was performed using General Procedure C, donepezil hydrochloride (**1j**, 166 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.16 mL, 0.16 mmol, 0.4 equiv.) and H_2O (2.84 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, the crude mixture was extracted with *n*BuOH (3 × 15 mL), after which the solvent was partially evaporated under reduced pressure and purified through a SiO_2 cartridge

(+/- 2 cm diameter, 10 cm length) using *n*BuOH as mobile phase. Subsequently, the solvent was evaporated and HCl (2 M in Et_2O, 5 mL) was added. Again, solvent was removed under reduced pressure. Pure 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dihydroxy-2,3-dihydro-1*H*-inden-1-one hydrochloride (**2g**) was obtained in 42% yield (195 mg, 0,50 mmol). There are no spectroscopic data available in literature.

Orange oil, R_f = 0.04 in EtOAc. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.14 (bs, 2H), 7.69-7.58 (m, 2H), 7.40-7.39 (m, 3H), 6.95 (s, 1H), 6.87 (s, 1H), 4.21 (d, J = 5.3 Hz, 2H), 3.24-3.20 (m, 2H), 3.10-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.50-2.46 (m, 1H), 1.87-1.83 (m, 2H), 1.75-1.71 (m, 2H), 1.63-1.56 (m, 4H), 1.19-1.18 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 206.2 (C), 153.6 (C), 147.2 (C), 146.0 (C), 131.7 (CH), 130.1 (C), 129.5 (CH), 128.8 (CH), 127.7 (C), 112.0 (CH), 108.3 (CH), 59.0 (CH_2), 51.5 (CH_2), 51.4 (CH_2), 44.6 (CH), 37.7 (CH_2), 32.4 (CH_2), 31.9 (CH), 29.3 (CH_2), 28.2 (CH_2) ppm. HRMS (ESI) for $C_{22}H_{27}NO_3Cl$ $[M+H]^+$ calcd. 352.1907, found 352.1911.

5.2 State of the art *O*-demethylations

The following methods were applied for the *O*-demethylation of 4-propylguaiaol (**1a**) to 4-propylcatechol (**2a**). These are based on methods published in literature for demethylation of similar guaiacol derived substrates. We repeated the method and if necessary, an optimization was performed to improve the conversion and yield. For those methods already reported for the demethylation of **1a** we refer to the corresponding reference. The data reported there were used in the Green Metrics (see Section 7).



5.2.1 Nb_2O_5

Procedure for Nb_2O_5 synthesis: Based on literature data, as published by Wang, Murayama and Ueda.[12, 47] In a 100 mL autoclave with Teflon liner, Ammonium oxalate (0.35 g, 2.82 mmol, 1.0 equiv.) was mixed with deionized H_2O (25 mL) and a solution of niobium oxalate (9.6 g, 15.3 mmol, 5.4 equiv.) in H_2O (61.2 mL). Subsequently, the autoclave was sealed and kept in an oven at 180 °C during 24 h. After cooling to r.t., the contents of the autoclave were centrifuged (5500 rpm, < 8 min), washed with deionized HO (200 mL) and dried at 100 °C for 12 h. The obtained solid was calcined at 400 °C (heating rate of 5 °C·min^{-1}) for 4 h in static air.

Method B [MBAL-810]: Based on literature data, as published by Liu and Wang.[12] The Parr® 4596 reactor (25 mL internal volume) was charged with 2-methoxy-4-propylphenol (**1a**, 0.50 g, 3.01 mmol, 1.0 equiv.), Nb_2O_5 (0.20 g, 0.75 mmol, 0.25 equiv.) and H_2O (10.0 mL). The reactor was closed, flushed with N_2 gas (3 × 10 bar) and filled with N_2 gas (65 bar). Subsequently, stirring (mechanical overhead stirring, 400 rpm) was started and the reactor and its contents were heated to 300 °C. After the temperature reached the desired value, stirring was continued for 3 h at this temperature. Subsequently, the reactor and its contents were cooled to r.t. (using an ice bath), gas was released and the reactor was opened. The crude reaction mixture was extracted with EtOAc (1 × 15 mL, 2 × 5 mL). The combined organic fractions were centrifuged for 30 min at 4500 rpm. The organic solvent was subsequently evaporated under reduced pressure to afford a mixture of 4-propylbenzene-1,2-diol (**2a**, 79%, 0.36 g, 2.37 mmol), 2-methoxy-4-propylphenol (**1a**, 3%, 15 mg, 0.09 mmol) and catechol (**2i**, 5%, 19 mg, 0.17 mmol) as an orange oil. The obtained spectroscopic data are in accordance with those obtained using other demethylation procedures.

5.2.2 BBr$_3$

Based on literature data, as published by Eisenbraun.[17] Further optimization was not required for the *O*-demethylation of 4-propylguaiacol (**1a**).

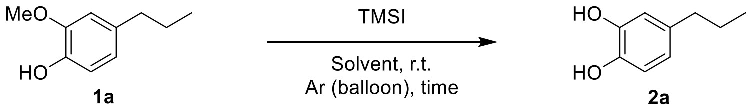
Method F2 [BL-10]: In a flame-dried and argon flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (15 mL). The obtained mixture was cooled to -94 °C and BBr_3 (1.06 mL, 11.0 mmol, 1.1 equiv.) was added dropwise. The cooling bath was removed and the reaction was allowed to reach r.t. The mixture was stirred for 1 h and subsequently, ice cold H_2O (15 mL) was added dropwise. The obtained suspension was stirred for 1 h. NaCl (s) was added until saturation and the crude mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 92% yield (1.40 g, 9.20 mmol). The obtained spectroscopic data are in accordance with those obtained using other demethylation procedures.

5.2.3 TMSI

5.2.3.1 Optimization

Based on the procedure published by Eisenbraun,[17] an optimization was initiated which is reported in Table S18. Combination of substrate **1a** and 1.1 equiv. TMSI led to 88% conversion toward the desired product after 48 h (Entry 1), which could not be improved when prolonging the reaction time to 72 h (Entry 2). Increasing TMSI loading to 2.0 equiv. led to nearly quantitative conversion (Entry 3). Replacing highly hazardous $CHCl_3$ by green alternative EtOAc delivered a complex mixture and a ^1H NMR spectrum not allowing to calculate the yield accurately (Entry 4). With these observations, three procedures were developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.3.2).

Table S18. *O-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) using TMSI.*



Entry	ELN code	TMSI (equiv.)	Solvent	Time (h)	NMR Yield (%) [a]	
					1a	2a
1	BL-35	1.1	$CHCl_3$	48	12	88
2	BL-36	1.1	$CHCl_3$	72	10	90
3	BL-37	2.0	$CHCl_3$	72	3	97
4	BL-07	1.1	EtOAc	48	Complex mixture	

Experiments were performed on a scale of 1.0 mmol **1a** and 1.0 mL solvent. [a] ^1H NMR Yield determined with 1,3,5-trimehoxybenzene as internal standard.

5.2.3.2 Procedures

Method G1 [BL-20]: In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (1.57 mL, 11.0 mmol, 1.1 equiv.) were dissolved in dry $CHCl_3$ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 $mL \cdot min^{-1}$, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 54% yield (0.82 g, 5.36 mmol). Furthermore, 2-methoxy-4-propylphenol (**1a**) was recovered in 26% (0.43 g, 2.56 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

Method G2 [BL-22]: In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry $CHCl_3$ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 $mL \cdot min^{-1}$, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 89% yield (1.35 g, 8.90 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

Method G3 [BL-32]: In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry $CHCl_3$ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated by dissolving the crude material in MTBE (30 mL) and filtering it over a layer of silica. Volatiles were evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 74% yield (1.13 g, 7.41 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

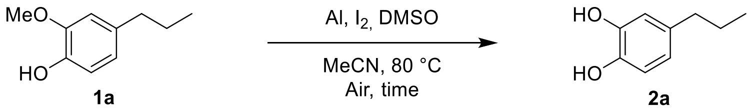
5.2.4 Al and I_2

5.2.4.1 Optimization

Based on the procedure published by Tian and Sang,[18] an optimization was initiated which is reported in Table S19. By applying the literature conditions, no product **2a** was formed, even after 48 h, and substrate **1a** was recovered for 81% (Entry 1). Doubling the Al loading initiated conversion, delivering product **2a** in 62% (Entry 2). We observed that addition of DMSO was not required to convert substrate **1a**. Combination of 4.8 equiv. Al and 1.65 equiv. I_2 delivered desired product in quantitative NMR yield

(Entry 3). With these observations, a procedure was developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.4.2).

Table S19. *O-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) using Al, I_2 and DMSO.*



Entry	ELN code	Al [a] (equiv.)	I_2 (equiv.)	DMSO (equiv.)	Time (h)	NMR Yield (%) [b]	
						1a	**2a**
1	JBO-GM-99	2.2	1.65	2.5	48	81	0
2	JBO-GM-98	4.4	1.65	2.5	18	38	62
3	JBO-GM-105	4.8	1.65	0.0	18	0	> 99

Experiments were performed on a scale of 1.0 mmol **1a** and 6.0 mL MeCN. [a] Al powder was used. [b] ^{1}H NMR Yield determined with 1,3,5-trimehoxybenzene or mesitylene as internal standard.

5.2.4.2 Procedure

Method H [JBO-GM-119]: In a 250 mL roundbottomed flask, equipped with reflux condenser and magnetic stirring bar, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in MeCN (80 mL). Subsequently, Al powder (1.160 g, 43.0 mmol, 4.3 equiv.) was added to the solution and then I_2 (4.188 g, 16.5 mmol, 1.7 equiv.) was added in one portion. The obtained mixture was stirred for 18 h at 80 °C. After cooling to r.t., the mixture was quenched with HCl (aq., 2 M, 5 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with $Na_2S_2O_3$ (aq., sat., 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified with an automatic column chromatography system using a heptanes/EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 mL·min^{-1}, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes, 18 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 86% yield (1.32 g, 8.66 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

5.2.5 $AlCl_3$ and NaI

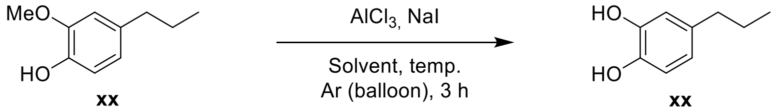
5.2.5.1 Optimization

Based on the procedure, published by Ghiaci,[19] an optimization was initiated which is reported in Table S20. Solventless combination of substrate **1a**, 2.0 equiv. $AlCl_3$ and 2.0 equiv. NaI led to 66% conversion toward the desired product after 3 h at 70 °C (Entry 1). This solventless reaction showed some stirring issues, so we decided to add a solvent. $CHCl_3$ at reflux decreased the yield of **2a** to only 13% (Entry 2). Increasing the temperature to 70 °C in a closed system doubled the yield of **2a** to 26% (Entry 3). Replacing the highly hazardous $CHCl_3$ by the recommended EtOAc delivered the desired product in 71% yield (Entry 4), leaving 29% remaining substrate **1a** . With these observations, a procedure was developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.5.2).

5.2.5.2 Procedure

Method I1 [BL-47]: A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with $AlCl_3$ (2.68 g, 20.0 mmol, 2.0 equiv.) and NaI (3.00 g, 20.0 mmol, 2.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (**1a**, 1.66 g 10.0 mmol, 1.0 equiv.) and dry EtOAc (10 mL) were added through the septum. The septum was removed and the tube was closed. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with $Na_2S_2O_3$ (aq., 5%, 10 mL). The obtained mixture was extracted with EtOAc (3 × 40 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 mL·min^{-1}, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 30 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 63% yield (0.96 g, 6.30 mmol). Furthermore, 2-methoxy-4-propylphenol (**1a**) was recovered in 2% (36 mg, 0.22 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

Table S20. *O-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) using $AlCl_3$ and NaI.*



Entry	ELN code	$AlCl_3$ (equiv.)	NaI (equiv.)	Solvent	Temp. (°C)	NMR Yield (%) [a]	
						1a	2a
1	BL-45	2.0	2.0	-	70	34	66
2	BL-19	2.0	2.0	$CHCl_3$	61	81	13
3	BL-23	2.0	2.0	$CHCl_3$	70	74	26
4	BL-16	2.0	2.0	EtOAc	70	29	71

Experiments were performed on a scale of 1.0 mmol **1a** and 4.0 mL solvent (apart from Entry 1). [a] ^{1}H NMR Yield determined with 1,3,5-trimehoxybenzene as internal standard.

5.2.6 $AlCl_3$ and Me_2S

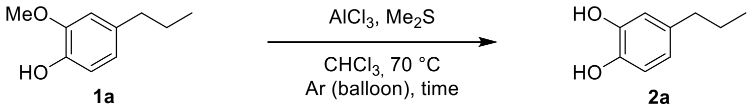
5.2.6.1 Optimization

Based on the procedure, published by Arifin,[20] an optimization was initiated which is reported in Table S21. 64% Product **2a** was obtained by applying 2.0 equiv. of both $AlCl_3$ and Me_2S in $CHCl_3$ after 3 h at 70 °C in a closed vessel (Entry 1). This result could not be significantly improved by doubling reaction time (Entry 2), substrate concentration (Entry 3), Me_2S loading (Entry 4) or $AlCl_3$ and Me_2S loading (Entry 5). With these observations, a procedure was developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.6.2).

5.2.6.2 Procedure

Method I2 [BL-44]: A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with $AlCl_3$ (5.34 g, 40.0 mmol, 4.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.), Me_2S (2.96 mL, 40.0 mmol, 4.0 equiv.) and dry $CHCl_3$ (10 mL) were added through the septum. The septum was removed and the tube was closed. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with $Na_2S_2O_3$ (aq., 5%, 10 mL). The obtained mixture was extracted with $CHCl_3$ (3 × 40 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 mL·min^{-1}, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 30 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 67% yield (1.02 g, 6.70 mmol). 2-Methoxy-4-propylphenol (**1a**) was recovered in 20% (330 mg, 1.99 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

Table S21. *O-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) using $AlCl_3$ and Me_2S.*



Entry	ELN code	Conc. 1a (M)	$AlCl_3$ (equiv.)	Me_2S (equiv.)	Time (h)	NMR Yield (%) [a]	
						1a	**2a**
1	BL-25	0.25	2.0	2.0	3	36	64
2	BL-26	0.25	2.0	2.0	6	39	61
3	BL-28	0.50	2.0	2.0	6	39	61
4	BL-30	0.25	2.0	4.0	3	50	50
5	BL-34	0.25	4.0	4.0	3	32	68

Experiments were performed on a scale of 1.0 mmol **1a** and solvent with volume to reach the given concentration. [a] ^1H NMR Yield determined with 1,3,5-trimehoxybenzene as internal standard.

5.2.7 Py·HCl

Based on literature data, as published by Schmid.[21] Further optimization was not required for the *O*-demethylation of 4-propylguaiacol (**1a**).

Method J [MBAL-642]: A 50 mL two-necked roundbottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1 equiv.) and Py·HCl (4.62 g, 40.0 mmol, 4.0 equiv.). The obtained mixture was stirred for 1 h at 195 °C, after which it was allowed to cool to 90 °C. Subsequently, HCl (aq., 5 M, 2.5 mL, 12.5 mmol, 1.25 equiv.) and H_2O (2.33 mL) were added. Stirring was continued allowing the temperature of the mixture to reach 35 °C. Subsequently, to the crude mixture was added MTBE (5.2 mL). The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 3.5 mL). The combined organic fractions were washed with HCl (aq., 5 M, 0.64 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 84% yield (1.28 g, 8.40 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

5.2.8 LiBr and HBr

Based on literature data, as published by Pan.[21] Further optimization was not required for the *O*-demethylation of 4-propylguaiacol (**1a**).

Method K [MBAL-795]: In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, LiBr (6.10 g, 70.2 mmol, 117 equiv.) was dissolved in H_2O (3.9 mL). When LiBr was completely dissolved, 2-methoxy-4-propylphenol (**1a**, 0.10 g, 0.60 mmol, 1.0 equiv.) and HBr (aq., 48%, 1.50 g, 8.84 mmol, 14.7 equiv.) were added. The mixture was stirred for 18 h under reflux, after which it was cooled to r.t. in ice water. The crude mixture was diluted with brine (10 mL), extracted with EtOAc (3 × 10 mL) and evaporated under reduced pressure. The crude product was re-dissolved in

MTBE (5 mL) and filtered over a plug of Celite. Volatiles were evaporated under reduced pressure, delivering 4-propylbenzene-1,2-diol (**2a**) in 82% yield (75 mg, 0.47 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

5.2.9 Thiols

Based on literature data, as published by Magano.[48] The desired product **2a** was not formed and the substrate **1a** was recovered for 98%.

Procedure [MBAL-708]: An oven dried 100 mL roundbottomed flask, equipped with magnetic stirring bar, septa and N_2 balloon, was charged with 2-(diethylamino)ethane-1-thiol hydrochloride (4.07 g, 24.0 mmol, 2.4 equiv.) and DMF (20 mL). Subsequently, the flask and its contents were cooled in an ice bath and when the temperature was below 5 °C, NaO*t*Bu (4.84 g, 50.4 mmol, 5.0 equiv.) was added. The obtained mixture was stirred for 5 min after which the cooling bath was removed and stirring was continued for 15 min, allowing the mixture to warm to r.t. Subsequently, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) was added and the mixture was stirred for 5 h under reflux. The mixture was cooled to r.t., subsequently placed in an ice bath and HCl (aq., 1 M) dropwise added to decrease the pH to 1. Then H_2O (50 mL) was added. Subsequently, the obtained aqueous mixture was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Pure 2-methoxy-4-propylphenol (**1a**) was obtained in 98% yield (1.64 g, 9.80 mmol). The obtained spectroscopic data are in accordance with those obtained from a commercial sample.

5.2.10 MgI_2

Based on literature data, as published by Zhang and Yao.[49] The substrate **1a** was for 22% converted to the desired product **2a**, leaving the substrate **1a** in 78%, based on ^1H NMR analysis.

Procedure for MgI_2 synthesis [MBAL-758]: An oven dried 50 mL roundbottomed flask, equipped with magnetic stirring bar, septum and Ar balloon, was charged with Mg (powder, 165 mg, 6.80 mmol, 2.0 equiv.) and Et_2O (10 mL). I_2 (863 mg, 3.40 mmol, 1.0 equiv.) was added in portions. The mixture was stirred overnight in the dark under N_2 atmosphere. Subsequently, unreacted Mg was removed by filtration and the solvent was evaporated under reduced pressure, delivering MgI_2 as an orange solid (615 mg, 2.21 mmol, 65%).

Procedure [MBAL-764]: In a 50 mL roundbottomed flask, a solution of MgI_2 (284 mg, 1.02 mmol, 2.0 equiv.) in Et_2O (10 mL) was mixed with a solution of 2-methoxy-4-propylphenol (**1a**, 85 mg, 0.51 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL). The solvents were removed under reduced pressure and the residual solid was heated to 80 °C for 16 h. Subsequently, the reaction mixture was cooled to r.t. and H_2O (20 mL) and $Na_2S_2O_3$ (aq., sat., 20 mL) were added. The resulting mixture was poured into HCl (aq., 5%, 10 mL) and the obtained solution was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with $NaHCO_3$ (aq., sat., 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting crude material was analyzed with ^1H NMR spectroscopy, revealing that **1a** yielded 78% **2a**, while 22% **1a** remained, based on integration of the signals.

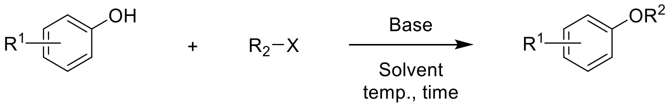
5.2.11 Cu₂O

Based on literature data, as published by Li and Xu.[50] The substrate **1a** was for 34% converted to the desired product **2a**, leaving the substrate **1a** in 60%, based on ^{1}H NMR analysis.

Procedure [JBO-1162]: In a Wheaton® 4 mL Vial, equipped with magnetic stirring bar, 2-methoxy-4-propylphenol (**1a**, 166 mg, 1.00 mmol, 1.0 equiv.) was dissolved in MeOH (2.0 mL). Subsequently, Cu_2O (7.2 mg, 0.05 mmol, 5 mol%) and NaOMe (162 mg, 3.00 mmol, 3.0 equiv.) were added and the vial was placed in the Parr® 4596 reactor. The reactor was closed properly , flushed with N_2 (3 × 10 bar) and filled with N_2 (50 bar). The reactor was heated to 185 °C and the mixture was stirred for 12 h at this temperature. Subsequently, the reactor was cooled to r.t., depressurized and opened. The mixture was acidified to pH 4-5 using HCl (aq.) and extracted with MTBE (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting crude material was analyzed with ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard, revealing that **1a** yielded 34% **2a**, while 60% **1a** remained.

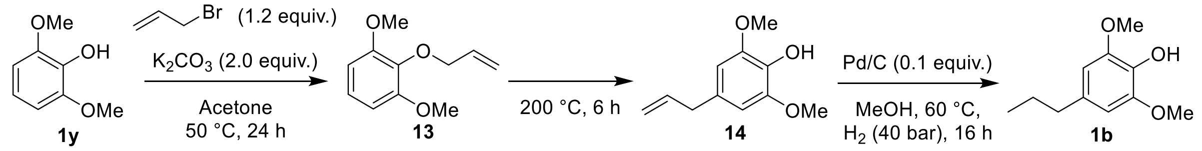
5.3 Synthesis of substrates

General procedure E

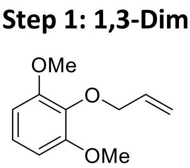


In a roudbottomed flask, equipped with a magnetic stirring bar and a reflux condenser, the appropriate substrate and base were mixed with acetone. The haloalkane (R^2-X) was added and the obtained mixture was stirred for a certain time at a certain temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was diluted with organic solvent and aq. solution. The layers were separated and the aqueous layer was extracted with organic solvent. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product.

Synthesis of 4-propylsyringol



Step 1: 1,3-Dimethoxy-2-[(prop-2-en-1-yl)oxy]benzene (13) [JBO-648]

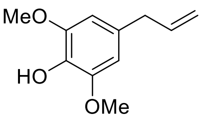


This compound was obtained following General procedure E, 2,6-dimethoxyphenol (**1y**, 3.08 g, 20.0 mmol, 1.0 equiv.) and 3-bromoprop-1-ene (2.07 mL, 24 mmol, 1.2 equiv.) were used as reactants, K_2CO_3 (5.53 g, 40.0 mmol, 2.0 equiv.) as base and acetone (50 mL) as solvent. The work-up was performed using EtOAc (20 mL for dilution and 3 × 20 mL for extraction) and NaOH (1 M, aq., 10 mL). Pure 1,3-dimethoxy-2-[(prop-2-en-1-yl)oxy]benzene (**13**) was obtained in 85% yield (3.28 g, 16.9 mmol). The obtained spectroscopic data are in accordance with literature.[51, 52]

Yellow oil, R_f = 0.45 in heptanes/EtOAc (80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (t, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 6.12 (ddt, *J* = 17.1, 10.5, 6.1 Hz, 1H), 5.31 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.18 (d, *J* =

10.5 Hz, 1H), 4.52 (dt, *J* = 6.1, 1.3 Hz, 2H), 3.85 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9 (C), 137.1 (C), 134.8 (CH), 123.8 (CH), 117.7 (CH_2), 105.5 (CH), 74.3 (CH_2), 56.3 (CH_3) ppm. HRMS (ESI) for $C_{11}H_{15}O_3$ $[M+H]^+$ calcd. 195.1016, found 195.1007.

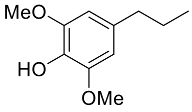
Step 2: 2,6-Dimethoxy-4-(prop-2-en-1-yl)phenol (14) [JBO-649, JBO-654]



A 4 mL glass vial, equipped with a magnetic stirring bar, was filled with 1,3-dimethoxy-2-[(prop-2-en-1-yl)oxy]benzene (**13**, 1.00 g, 5.15 mmol). The vial was closed with a plastic cap and rubber septum and a needle was pierced through the septum. This vial was placed in the Parr® 4596 reactor (in the home made insert) and the reactor was closed. Magnetic stirring was started and the reactor was heated to 200 °C during 6 h. Subsequently, the reactor was opened and cooled to r.t. The crude material was dissolved in MTBE (10 mL), mixed with SiO_2 (1.5 g) and evaporated under reduced pressure. The residue was poured onto a filter and washed with MTBE (10 mL). The filtrate was evaporated under reduced pressure to afford pure 2,6-dimethoxy-4-(prop-2-en-1-yl)phenol (**14**) in 83% yield (0.83 g, 4.25 mmol). The obtained spectroscopic data are in accordance with literature.[52]

Colorless oil, R_f = 0.37 in heptanes/EtOAc (75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (s, 2H), 5.95 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.37 (s, 1H), 5.11-5.06 (m, 2H), 3.87 (s, 6H), 3.32 (d, *J* = 6.7 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.2 (C), 137.7 (CH), 133.2 (C), 131.2 (C), 115.8 (CH_2), 105.4 (CH), 56.4 (CH_3), 40.5 (CH_2) ppm. HRMS (ESI) for $C_{11}H_{15}O_3$ $[M+H]^+$ calcd. 195.1016, found 195.1006.

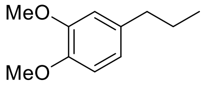
Step 3: 2,6-Dimethoxy-4-propylphenol (1b) [JBO-439, JBO-577]



The glass insert for the 600 mL Parr® reactor was loaded with a stirring bar, 4-allyl-2,6-dimethoxyphenol (**14**, 5.45 g, 28.1 mmol, 1.0 equiv.) and MeOH (100 mL). To this solution, Pd/C (10 m%, 300 mg, 0.3 mmol,1 mol%) was added under an argon flow. The beaker was placed in the Parr® 4625 reactor, which was then closed, flushed with of H_2 (g, 3 × 10 bar) and filled with H_2 gas (40 bar). The mixture in the reactor was heated to 60 °C and stirred for 16 h. Subsequently, the reactor was cooled to r.t., the pressure was released and the reactor was opened. The reaction mixture was filtered over celite (1 cm) and the filtrate was evaporated under reduced pressure to afford pure 2,6-dimethoxy-4-propylphenol (**1b**) in 83% yield (4.52 g, 23.3 mmol). The obtained spectroscopic data are in accordance with literature.[53]

Yellow oil, R_f = 0.29 in heptanes/EtOAc (80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (s, 2H), 5.40 (s, 1H), 3.85 (s, 6H), 2.50 (t, *J* = 7.6 Hz, 2H), 1.61 (sext, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.9 (C), 133.8 (C), 132.8 (C), 105.1 (CH), 56.3 (CH_3), 38.3 (CH_2), 24.8 (CH_2), 13.8 (CH_3) ppm. HRMS (ESI) for $C_{11}H_{17}O_3$ $[M+H]^+$ calcd. 197.1172, found 197.1163. HRMS (ESI) for $C_{11}H_{16}O_3Na$ $[M+Na]^+$ calcd. 219.0992, found 219.0991.

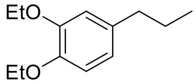
1,2-Dimethoxy-4-propylbenzene (1e) [MS-538, JBO-433]



A 100 mL pressure tube, equipped with magnetic stirring bar, was charged with K_2CO_3 (26 mg, 0.19 mmol, 0.01 equiv.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 18.8 mmol, 1.0 equiv.) and dimethyl carbonate (9.47 mL, 112 mmol, 6.0 equiv.). The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to r.t. The content of the pressure tube was transferred with EtOAc (5 mL) and filtered through cotton wool into a roundbottomed flask, after which the precipitate was further washed with EtOAc (5 mL). The solvent was evaporated in order to afford **1e** in quantitative yield (3.39 g, 18.8 mmol). The obtained spectroscopic data are in accordance with literature.[54]

Pale yellow oil, R_f = 0.79 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, *J* = 8.6 Hz, 1H), 6.73-6.71 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.63 (sext, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9 (C), 147.2 (C), 135.5 (C), 120.3 (CH), 112.0 (CH), 111.3 (CH), 56.0 (CH_3), 55.9 (CH_3), 37.7 (CH_2), 24.8 (CH_2), 13.9 (CH_3) ppm. HRMS (ESI) for $C_{11}H_{17}O_2$ $[M+H]^+$ calcd. 181.1229, found 181.1229.

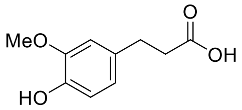
1,2-Diethoxy-4-propylbenzene (1f) [JBO-1375, JBO-1359, EB-558]



A 50 mL roundbottomed flask, equipped with magnetic stirring bar, was charged with 4-propylbenzene-1,2-diol (**2a**, 1.07 g, 7.00 mmol, 1.0 equiv.), K_2CO_3 (3.87 g, 28.0 mmol, 4.0 equiv.) and EtOH (10 mL). EtI (2.25 mL, 28.0 mmol, 4.0 equiv.) was added and the reaction mixture was stirred for 24 h under reflux. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with an aqueous solution of NaOH (1 M, 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure in order to afford 1,2-diethoxy-4-propylbenzene (**1f**) in 99% yield (1.44 g, 6.92 mmol). The obtained spectroscopic data are in accordance with literature.[55]

Brown liquid, R_f = 0.89 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 2.1 Hz, 1H), 6.69 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 4.07 (q, *J* = 7.0 Hz, 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 1.62 (sext, *J* = 7.4 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.43 (t, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8 (C), 147.0 (C), 135.8 (C), 120.7 (CH), 114.5 (CH), 114.1 (CH), 64.9 (CH_2), 64.7 (CH_2), 37.8 (CH_2), 24.8 (CH_2), 15.1 (CH_3), 15.1 (CH_3), 13.9 (CH_3) ppm. HRMS (ESI) for $C_{13}H_{21}O_2$ $[M+H]^+$ calcd. 209.1542, found 209.1544.

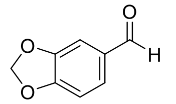
3-(4-Hydroxy-3-methoxyphenyl)propanoic acid (1g) [JBO-GM-126]



In a Parr® hydrogenation bottle (2*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid (**11**, 5.00 g, 25.7 mmol, 1.0 equiv.) was dissolved in MeOH (50 mL). Pd/C (10 m%, 0.50 g, 0.47 mmol, 2 mol%) was added under argon flow and the vessel was placed in a Parr® 3911 Hydrogenation Apparatus. The vessel was flushed with H_2 (3 × 4 bar) and filled with H_2 (4 bar). The vessel was shaken for 1 h at r.t.. Subsequently, the pressure was released and the crude mixture was filtered over Celite. The filter was rinsed with MeOH (50 mL) and the combined filtrates were evaporated under reduced pressure. The obtained residue was mixed with H_2O (33 mL) and NaOH (2.68 g, 6.70 mmol, 2.6 equiv.) was added. The mixture was stirred for 24 h under reflux. Subsequently, the mixture was cooled to r.t., neutralized with HCl (conc.) to neutral pH and extracted with MTBE (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford pure 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (**1g**) in 94% yield (4.75 g, 24.2 mmol). The obtained spectroscopic data are in accordance with literature.[56]

Beige solid, m.p.: 91 °C (lit.: 91 °C),[57] R_f = 0.26 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (bs, 1H), 8.64 (bs, 1H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.59 (dd, *J* = 8.0, 1.8 Hz, 1H), 3.74 (s, 3H), 2.71 (t, *J* = 7.7 Hz, 2H), 2.51-2.46 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 173.9 (C), 147.4 (C), 144.7 (C), 131.7 (C), 120.2 (CH), 115.3 (CH), 112.5 (CH), 55.5 (CH_3), 35.7 (CH_2), 30.0 (CH_2) ppm. HRMS (ESI) for $C_{10}H_{11}O_4$ [M-H]$^-$ calcd. 195.0663, found 195.0667.

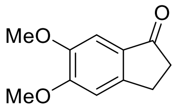
2*H*-1,3-Benzodioxole-5-carbaldehyde (1i) [MBAL-411]



In a 50 mL roundbottemed flask, equipped with magnetic stirring bar, (2*H*-1,3-benzodioxol-5-yl)methanol (**15**, 1.52 g, 10.0 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (20 mL). MnO_2 (8.69 g, 100 mmol, 10 equiv.) was added and the mixture was stirred at r.t. for 20 h. Subsequently, the crude mixture was filtered through Celite and evaporated under reduced pressure. The crude material was purified by an automated flash chromatography system using a heptanes/EtOAc gradient (Cartridge: 40 g SiO_2, flow rate: 30 mL·min^{-1}, eluent: heptanes to 50% EtOAc in heptanes, 60 min). Pure 2*H*-1,3-benzodioxole-5-carbaldehyde (**1i**) was obtained in 85% yield (1.28 g, 8.54 mmol). The obtained spectroscopic data are in accordance with literature.[58]

White solid, m.p.: 35 °C (lit.: 35-37 °C),[59] R_f = 0.73 in heptanes/EtOAc (50:50) ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.41 (d, *J* = 7.9, 1.5 Hz, 1H), 7.33 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.07 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.4 (CH), 153.3 (C), 148.9 (C), 132.1 (C), 128.8 (CH), 108.5 (CH), 107.1 (CH), 102.2 (CH_2) ppm. EI (+) (m/z (%)): 150 (80), 149 (100).

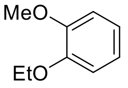
5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-one (1k) [MBAL-495]



In a 20 mL pressure tube 3-(3,4-dimethoxyphenyl)propanoic acid (**1h**, 1.00 g, 4.76 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (10 mL). The tube and its contents were cooled to 0 °C and TfOH (1.47 mL, 16.7 mmol, 3.5 equiv.) was slowly added to the mixture. The tube was sealed and heated to 80°C for 90 min under magnetic stirring. Subsequently, the mixture was cooled to r.t., poured into ice water (50 mL) and stirred for another 20 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were washed with H_2O (25 mL) and $NaHCO_3$ (aq., sat., 20 mL), dried over Na_2SO_4, and evaporated under reduced pressure to afford 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (**1k**) in 96% yield (0.88 g, 4.57 mmol). The obtained spectroscopic data are in accordance with literature.[60]

Pink solid, m.p.: 113 °C (lit.: 113-115 °C),[60] R_f = 0.40 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (s, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.06-3.03 (m, 2H), 2.68-2.65 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.8 (C), 155.6 (C), 150.5 (C), 149.6 (C), 130.1 (C), 107.6 (CH), 104.4 (CH), 56.3 (CH_3), 56.2 (CH_3), 36.7 (CH_2), 25.7 (CH_2) ppm. HRMS (ESI) for $C_{11}H_{13}O_3$ [M+H]$^+$ calcd. 193.0859, found 193.0860.

1-Ethoxy-2-methoxybenzene (1n) [SA-017, JBO-248]



This compound was obtained following General procedure E, using 2-methoxyphenol (**1l**, 1.24 g, 10.0 mmol, 1.0 equiv.) and EtI (0.9 mL, 12.0 mmol, 1.2 equiv.) as reactants, K_2CO_3 (1.67 g, 12 mmol, 1.2 equiv.) as base and acetone (20 mL) as solvent. The mixture was stirred for 24 h under reflux. The work-up was performed using CH_2Cl_2 (3 × 30 mL) and NaOH (aq., 1 M, 10 mL). Pure 1-ethoxy-2-methoxybenzene (**1n**) was obtained in 86% yield (1.20 g, 7.88 mmol). The obtained spectroscopic data are in accordance with literature.[61]

Colorless oil, R_f = 0.79 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94-6.88 (m, 4H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 1.47 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6 (C), 148.5 (C), 121.0 (CH), 120.9 (CH), 113.2 (CH), 111.9 (CH), 64.4 (CH_2), 56.0 (CH_3), 14.9 (CH_3) ppm. HRMS (ESI) for $C_9H_{13}O_2$ $[M+H]^+$ calcd. 153.0916, found 153.0913.

5.3.1 Synthesis of 4-propylguaiacol from natural feedstocks

5.3.1.1 Hydrogenation of natural eugenol

Natural eugenol, obtained from *Eugenia* upon biological extraction and purification,[62] had a purity of 97 wt%, which was determined via ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene (1,3,5-TMB) as internal standard (Figure S9):

- Ratio between **3** and **1,3,5-TMB:** $\text{ratio}_{3/\mathbf{1,3,5-TMB}} = \frac{154.26/1}{100.00/3} = 4.6278$
- The sample contains 16 mg **1,3,5-TMB**, corresponding to 0.0954 mmol
- Leading to $4.6278 \times 0.0954 = 0.4415 \text{ mmol } \mathbf{3} = 72.43 \text{ mg } \mathbf{3}$
- There is 72.43 mg **3** present in 75 mg natural eugenol, corresponding to $\frac{72.43}{75} \times 100\% = 97 \text{ wt\%}$

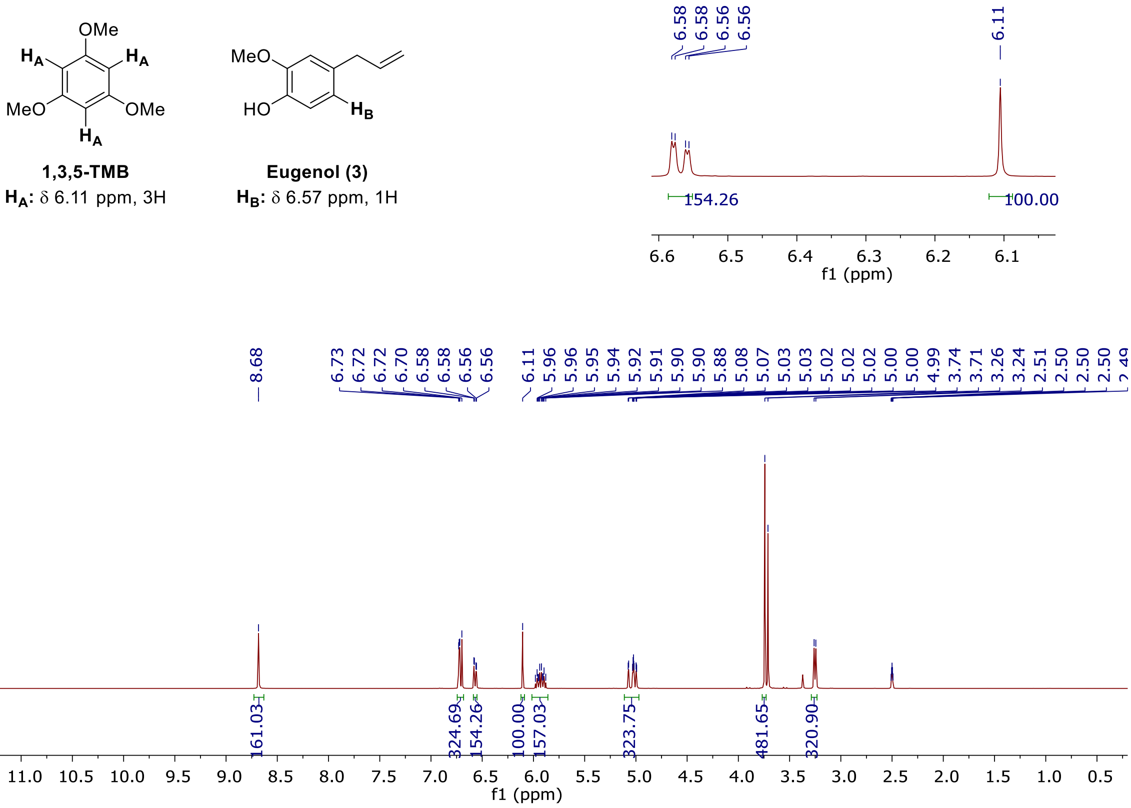
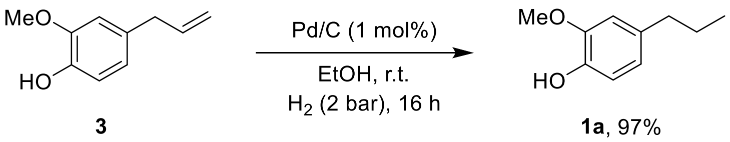
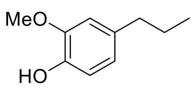


Figure S9. *^{1}H NMR Spectrum of natural eugenol (**3**), revealing 97% purity. Quantification is based on the integration of the assigned signals for **H_A** and **H_B**. Therefore, 75 mg natural feedstock and 16 mg 1,3,5-trimethoxybenzene were dissolved in DMSO-d_6.*

Subsequently, hydrogenation was performed as follows:



2-Methoxy-4-propylphenol (1a) [MBAL-777]



In a Parr® hydrogenation bottle, 4-allyl-2-methoxyphenol (natural eugenol, **3**, 2.00 g, 12.2 mmol, 1.0 equiv.) was dissolved in EtOH (100 mL). Pd/C (10 wt% Pd, 0.13 g, 0.12 mmol, 1 mol%) was added under argon flow and the vessel was placed in a Parr® 3911 Hydrogenation Apparatus. The vessel was flushed with H_2 (3 × 1 bar) and filled with H_2 (2 bar). The vessel was shaken for 16 h at r.t.. Subsequently, the pressure was released and the crude mixture was filtered over Celite. The filter was rinsed with acetone (25 mL), the combined filtrates were evaporated under reduced pressure to afford pure 2-methoxy-4-propylphenol (**1a**) in 97% yield (1.96 g, 11.8 mmol). The obtained spectroscopic data are in accordance with literature and commercial **1a**.[63]

Colorless oil, R_f = 0.76 in heptanes/EtOAc (50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, *J* = 8.1 Hz, 1H), 6.70-6.67 (m, 2H), 5.48 (s, 1H), 3.88 (s, 3H), 2.53 (t, *J* = 7.4 Hz, 2H), 1.63 (sext, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.4 (C), 143.7 (C), 134.8 (C), 121.1 (CH), 114.2 (CH), 111.2 (CH), 56.0 (CH_3), 37.9 (CH_2), 25.0 (CH_2), 13.9 (CH_3) ppm.

5.3.1.2 Reductive catalytic fractionation of softwood lignin

In a Soxhlet set-up, pine wood particles (10 g) were extracted with a boiling mixture of toluene (250 mL) and EtOH (125 mL) during 3 h. This extraction was repeated 15 times and the remaining 'extracted pine wood' was combined and dried. A 2 L autoclave (Parr®) was loaded with the obtained extracted pine wood (150 g), Ru/C (5 wt% Ru, 15 g) and MeOH (800 mL). The autoclave was closed, pressurized with H_2 (30 bar), heated to 235 °C and kept under these conditions for 16 h under stirring (750 rpm). Subsequently, the autoclave and its contents were cooled to r.t., pressure was released and the reaction mixture was filtered and evaporated under reduced pressure. To the residue was added H_2O (220 mL) and the obtained mixture was extracted with EtOAc (200 mL and 2 × 175 mL). The combined organic fractions were evaporated under reduced pressure and to the residue was added heptane (140 mL). The obtained mixture was refluxed for 30 min and cooled to r.t. The solvent was decanted, fresh heptane (140 mL) was added to the residue and the obtained mixture was refluxed for 30 min. After cooling to r.t., the process of decantation and addition of heptane (140 mL) was repeated, followed by refluxing for 2 h and decantation. The three heptane fractions were combined, stored at 5 °C overnight and decanted. The decanted fraction was evaporated under reduced pressure, delivering a lignin oil, rich in 4-propylguaiacol (**1a**) (64 wt%, based on ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as int. std., *vide infra*), corresponding to 18.2% of the original lignin content of the wood.

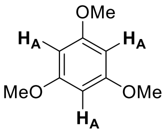
In order to determine the lignin content of the used pine wood, the following procedure was followed, similarly to a previously published method:[64]

Product yields in lignin depolymerisation literature are typically based on the amount of acid insoluble lignin, also called Klason lignin, in the lignocellulose sample. The determination of the Klason lignin content of pine was based on a procedure from Lin & Dence.[65] Triplicate samples of pre-extracted pine wood (1 g each) were transferred to 50 mL beakers after which 15 mL of a 72 wt% H_2SO_4 solution was added. The mixture was left at room temperature for 2 h while being continuously stirred with a magnetic rod. Afterwards the content of each beaker was transferred to a round-bottom-flask which already contained 300 to 400 mL of water. The beakers were rinsed and additional water was added until a H_2SO_4 concentration of 3 wt% was reached. The diluted solution was boiled for 4 h under reflux conditions, to maintain a constant volume and acid concentration. After filtration of the hot solution, a brown lignin precipitate was retained. The precipitate was washed with hot water to remove any leftover acid and the obtained residue was dried at 80 °C overnight. The reported Klason lignin content of 24.6 wt% was determined relative to the oven dried substrate by averaging the measured weight of the residues.

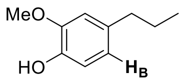
Analysis of the obtained lignin oil:

Upon ^{1}H NMR Analysis using 1,3,5-trimethoxybenzene (1,3,5-TMB) as internal standard (Figure S10), we found that the obtained lignin oil contains 64 wt% 4-propylguaiacol (**1a**):

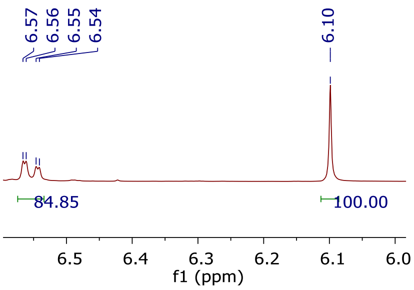
- Ratio between **1a** and **1,3,5-TMB:** $\text{ratio}_{\mathbf{1a}/\mathbf{1,3,5-TMB}} = \frac{84.85/1}{100.00/3} = 2.5455$
- The sample contains 15 mg **1,3,5-TMB**, corresponding to 0.0911 mmol
- Leading to $2.5455 \times 0.0911 = 0.2321 \text{ mmol } \mathbf{1a} = 38.58 \text{ mg } \mathbf{1a}$
- There is 38.58 mg **1a** present in 60 mg lignin oil, corresponding to $\frac{38.58}{60} \times 100\% = 64 \text{ wt\%}$



1,3,5-TMB
H_A: δ 6.10 ppm, 3H



4-Propylguaiacol (1a)
H_B: δ 6.55 ppm, 1H



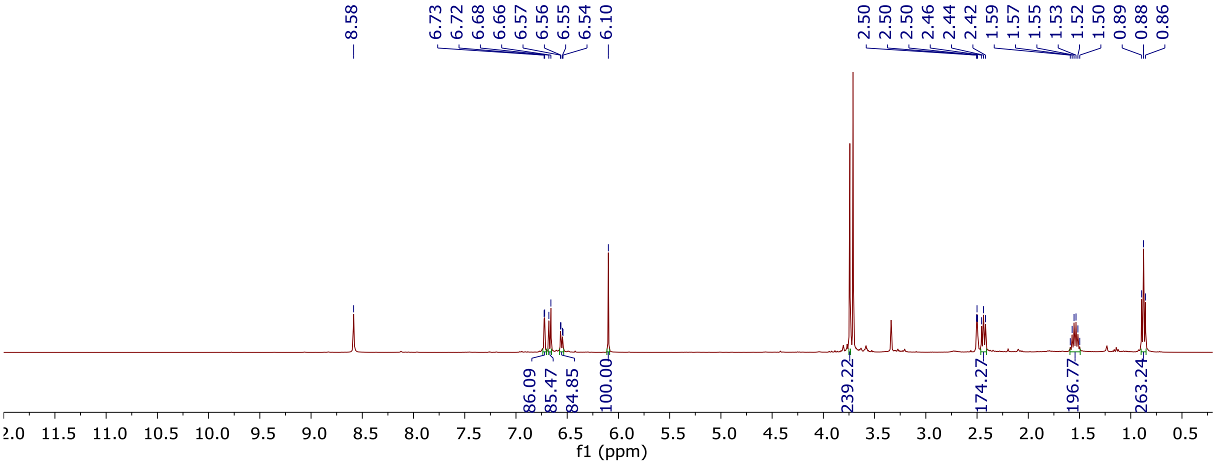


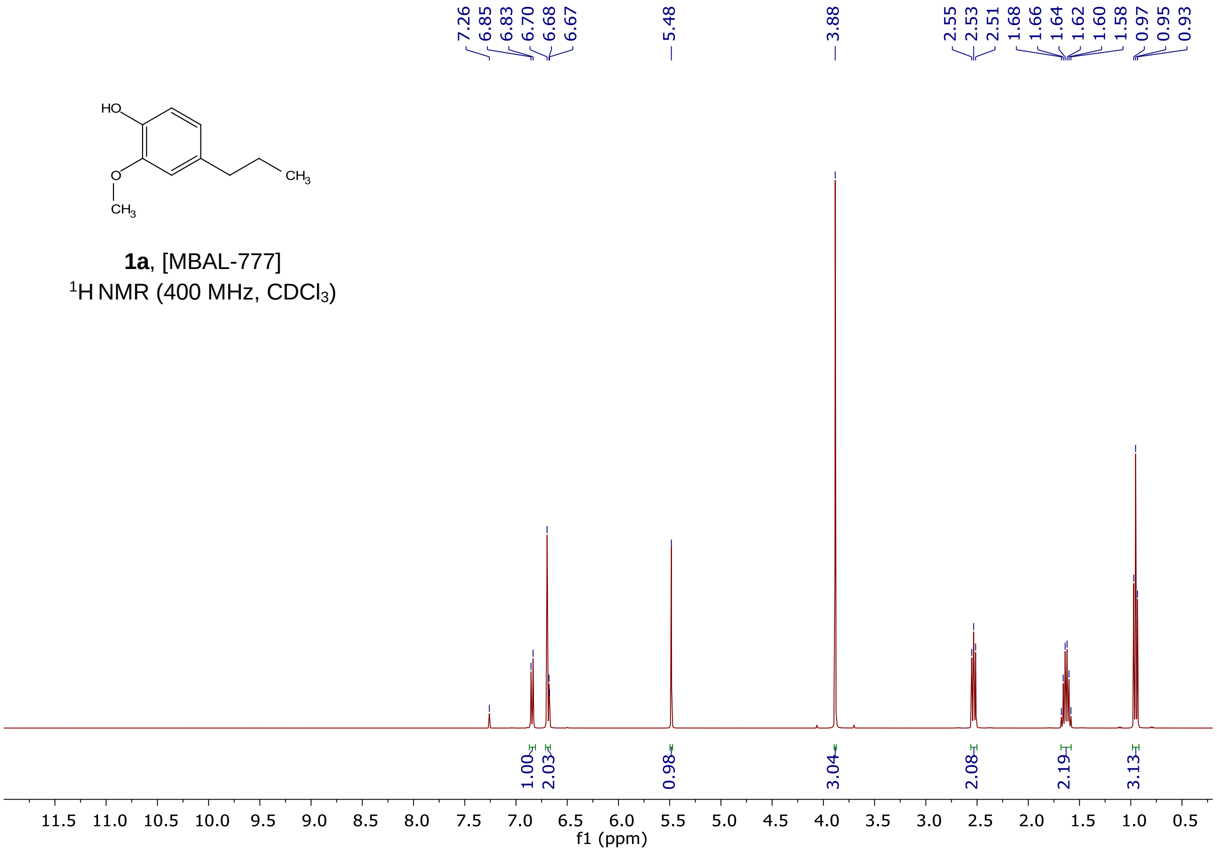
Figure S10. *^{1}H NMR Spectrum of lignin oil, revealing 64 wt%* ***1a****. Quantification is based on the integration of the assigned signals for* ***H_A*** *and* ***H_B****. Therefore, 60 mg oil and 15 mg 1,3,5-trimethoxybenzene were dissolved in DMSO-d$_6$.*

Analysis of the lignin oil using GC-MS showed that **1a** was present next to the following monomers as minor compounds:

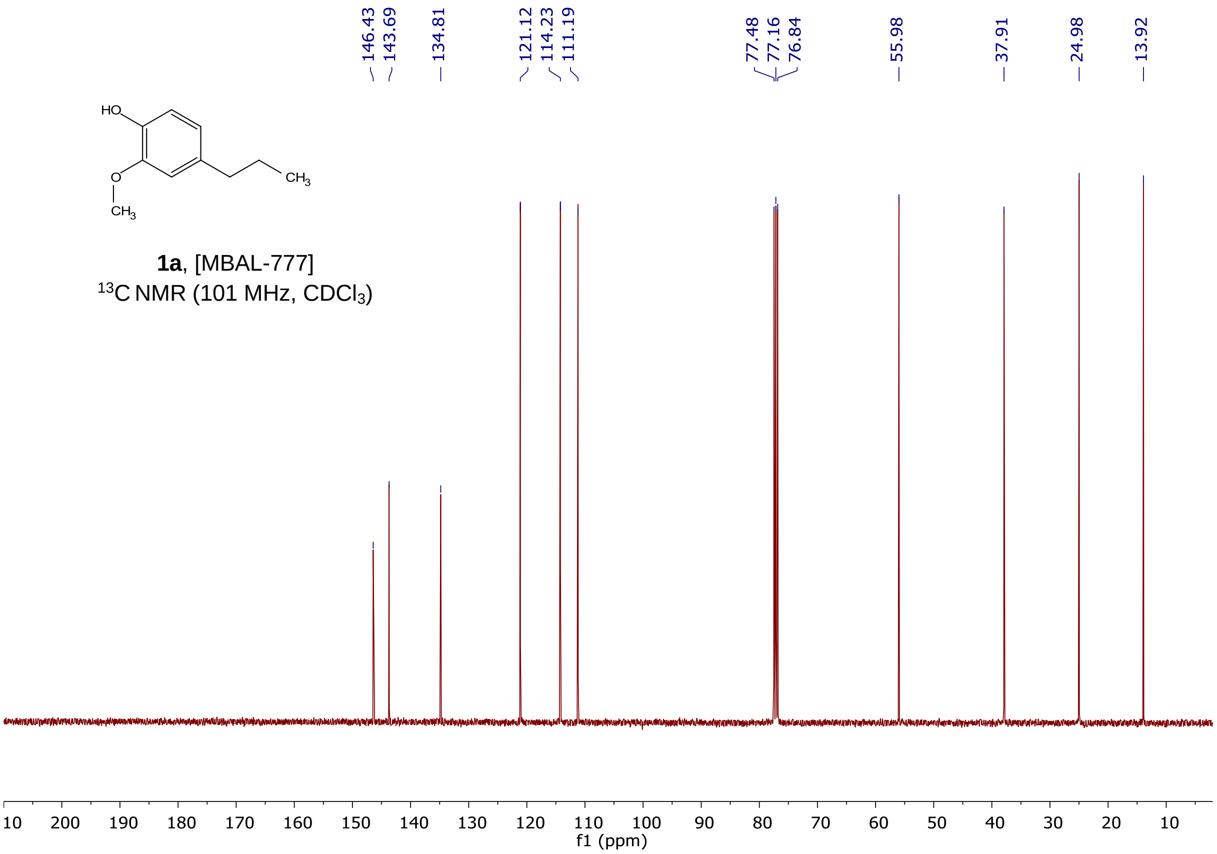
- 4-Ethylguaiacol (2 wt%)
- Isoeugenol (< 1 wt%)
- Methoxylpropanolguaiacol (< 1 wt%)
- Dihydroconiferylalcohol (< 1 wt%)

Also some unidentified dimers were present. All these compounds are minor based on the ^{1}H NMR Spectrum of the lignin oil presented in Figure S10.

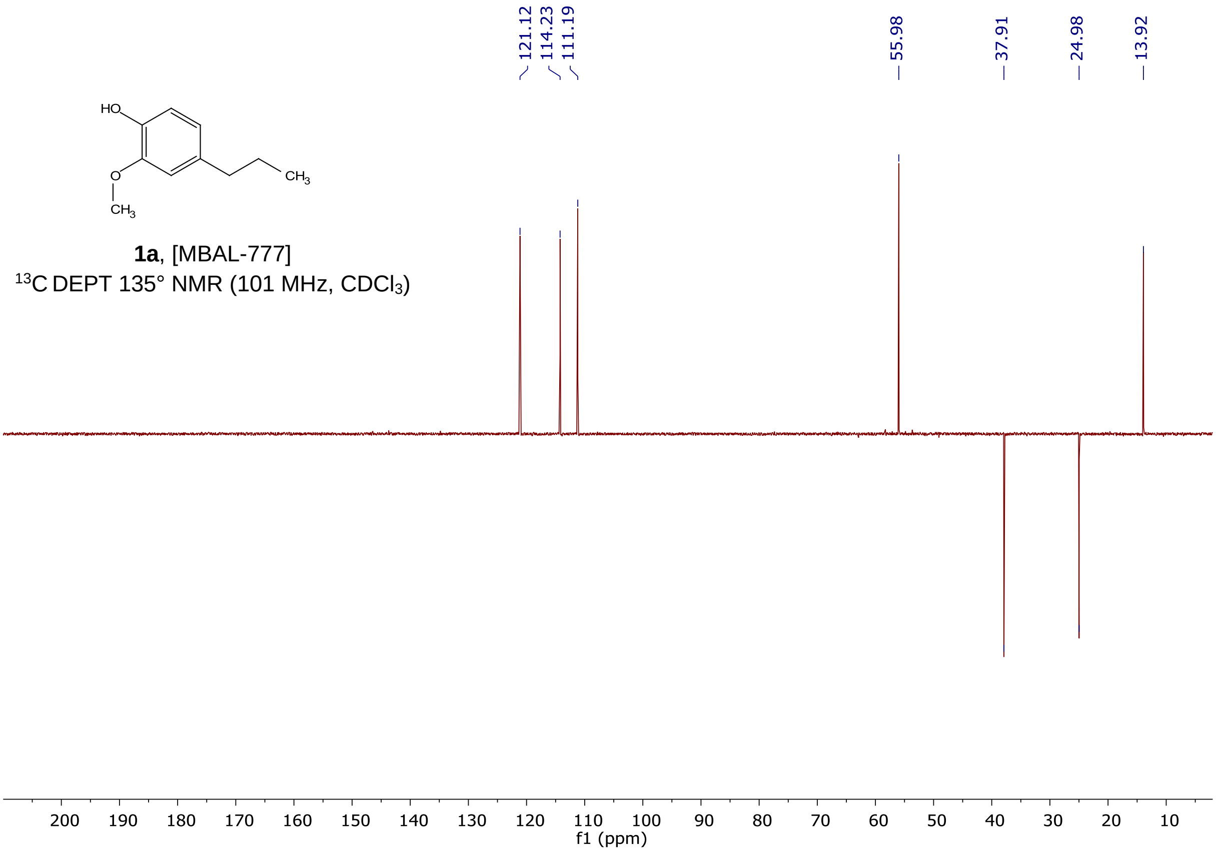
6 NMR spectra of compounds



1a, [MBAL-777]
^{1}H NMR (400 MHz, $CDCl_3$)

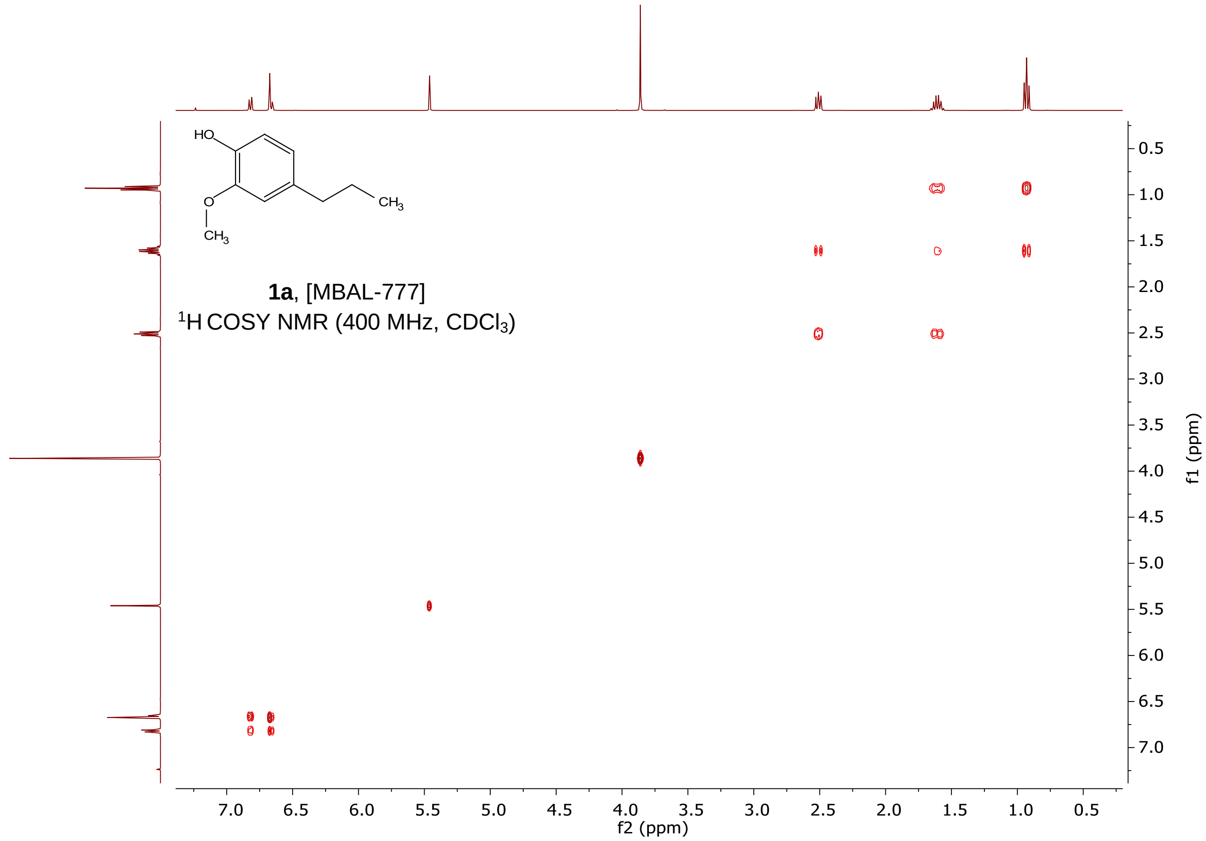


1a, [MBAL-777]
^{13}C NMR (101 MHz, $CDCl_3$)



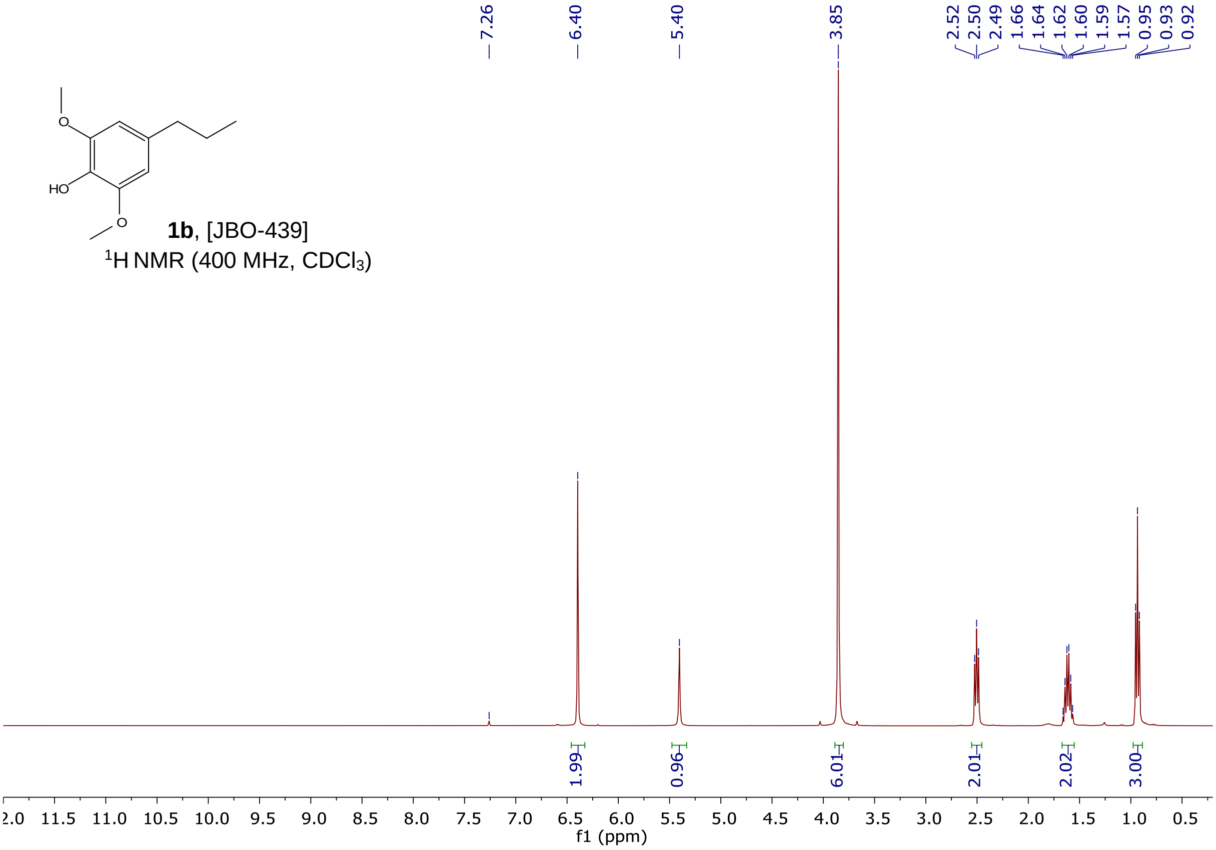
1a, [MBAL-777]

^{13}C DEPT 135° NMR (101 MHz, CDCl$_3$)

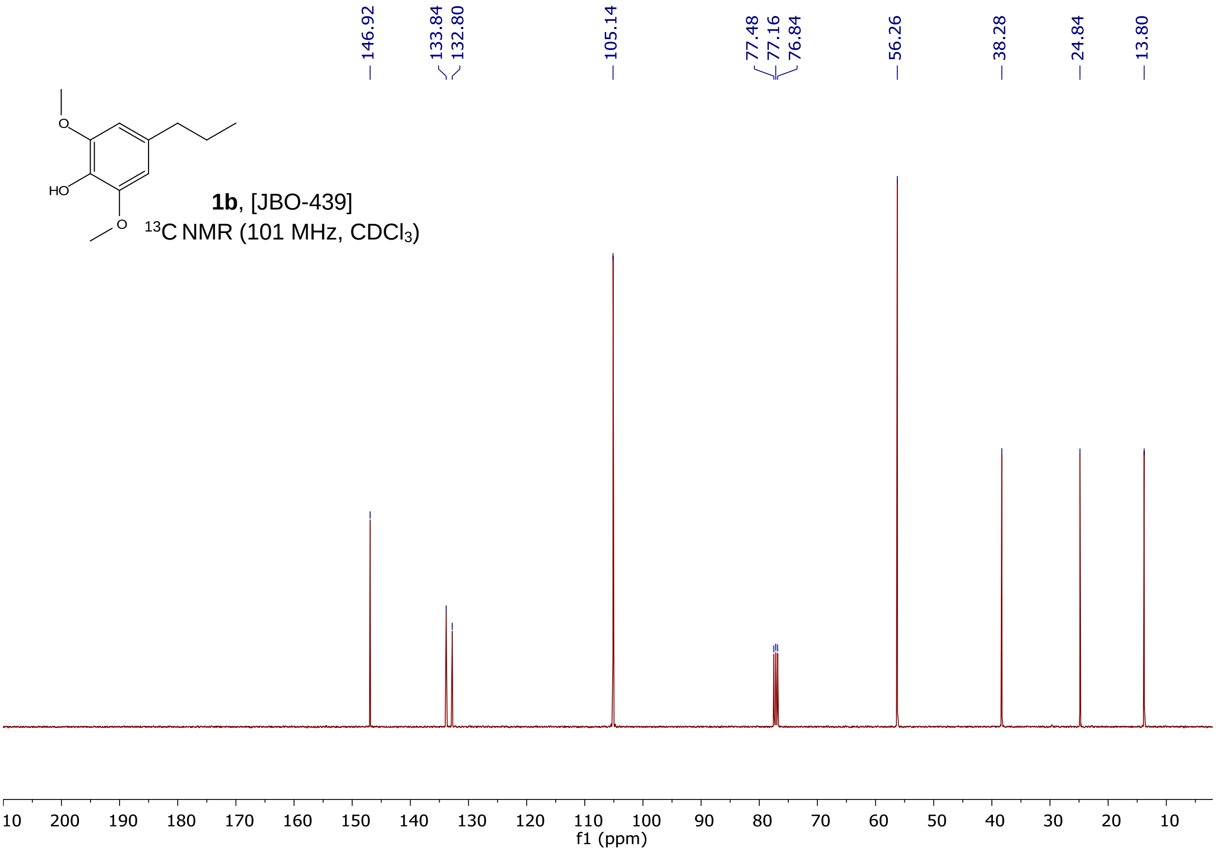


1a, [MBAL-777]

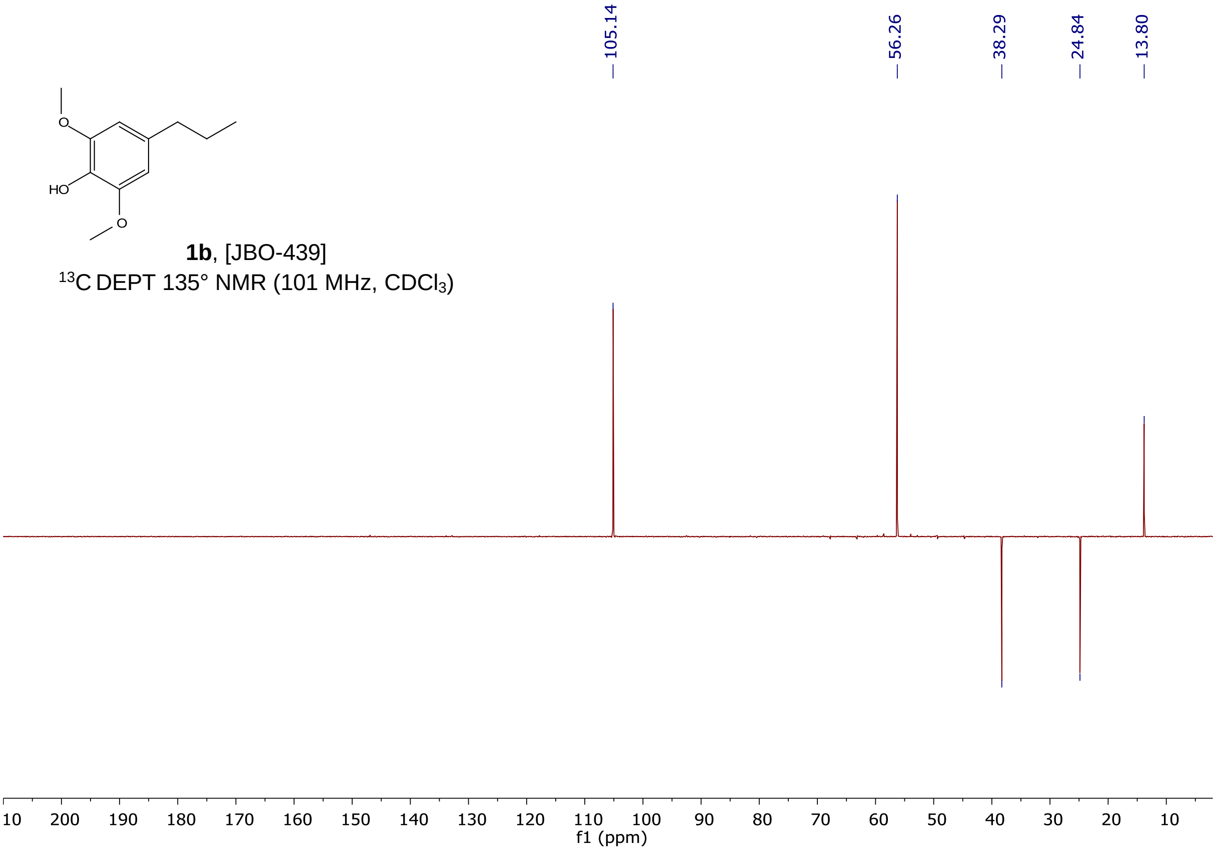
^{1}H COSY NMR (400 MHz, CDCl$_3$)



1b, [JBO-439]
^{1}H NMR (400 MHz, $CDCl_3$)

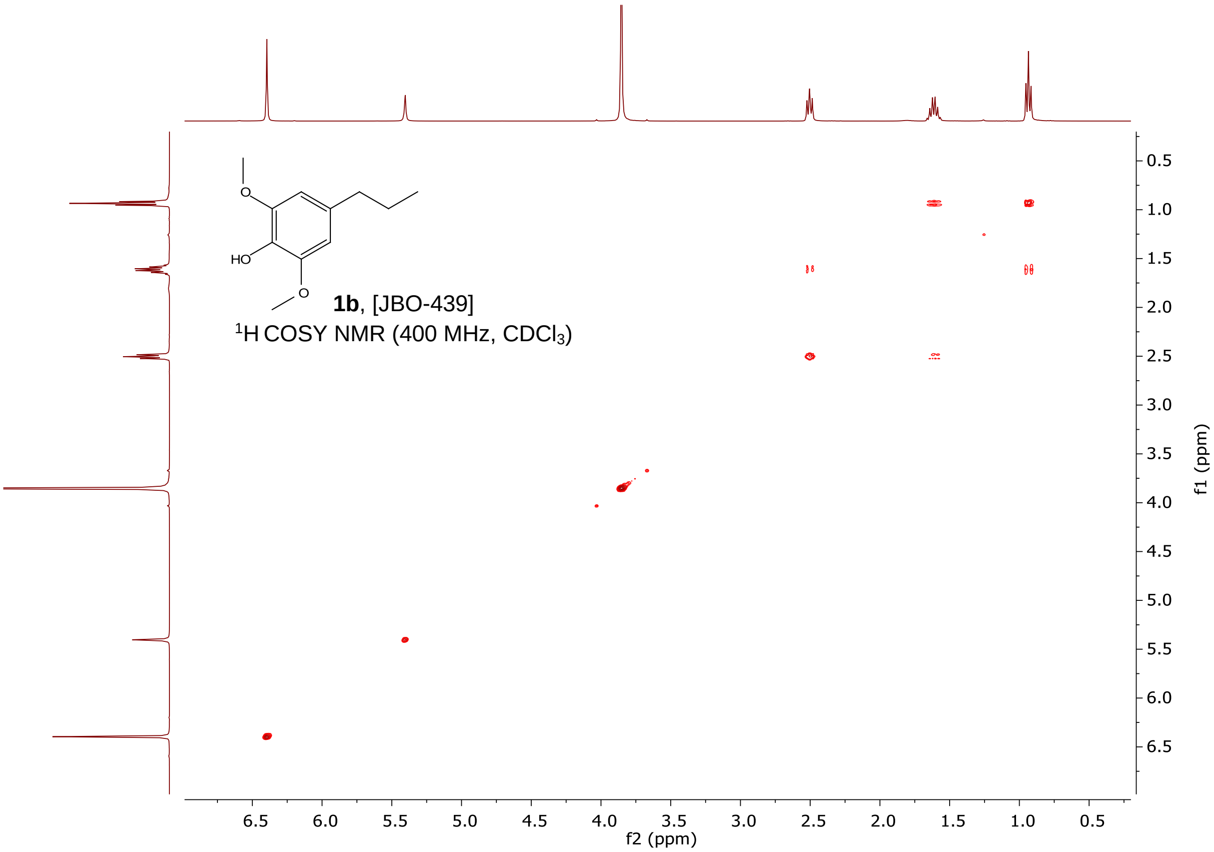


1b, [JBO-439]
^{13}C NMR (101 MHz, $CDCl_3$)



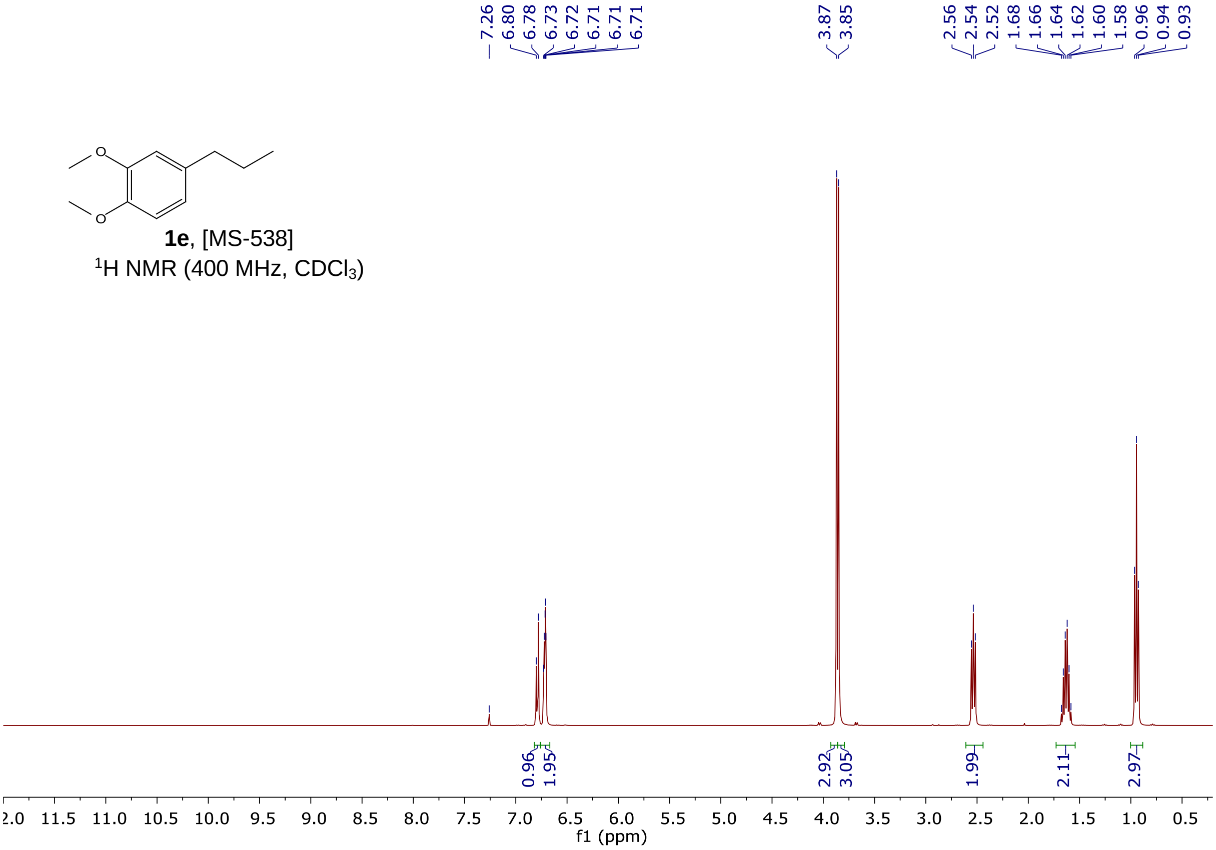
1b, [JBO-439]

^{13}C DEPT 135° NMR (101 MHz, $CDCl_3$)



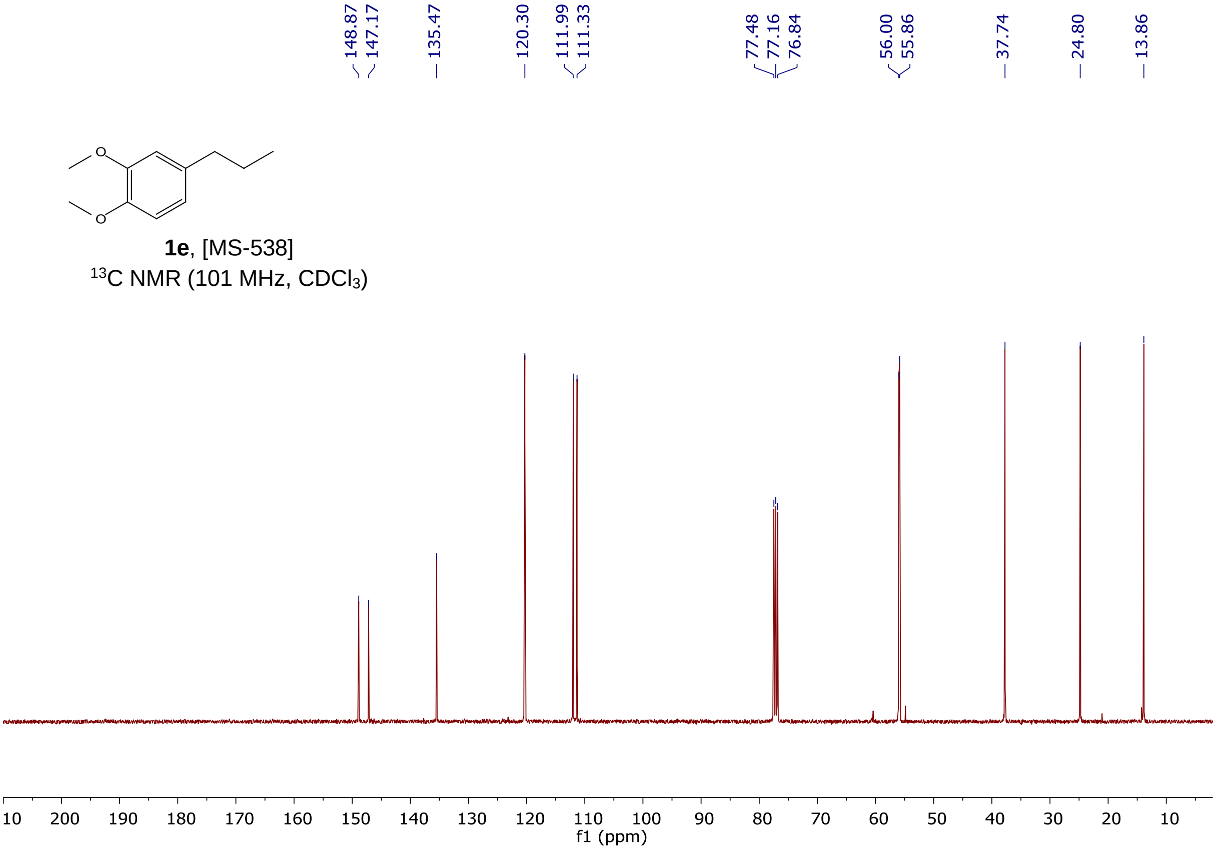
1b, [JBO-439]

^{1}H COSY NMR (400 MHz, $CDCl_3$)



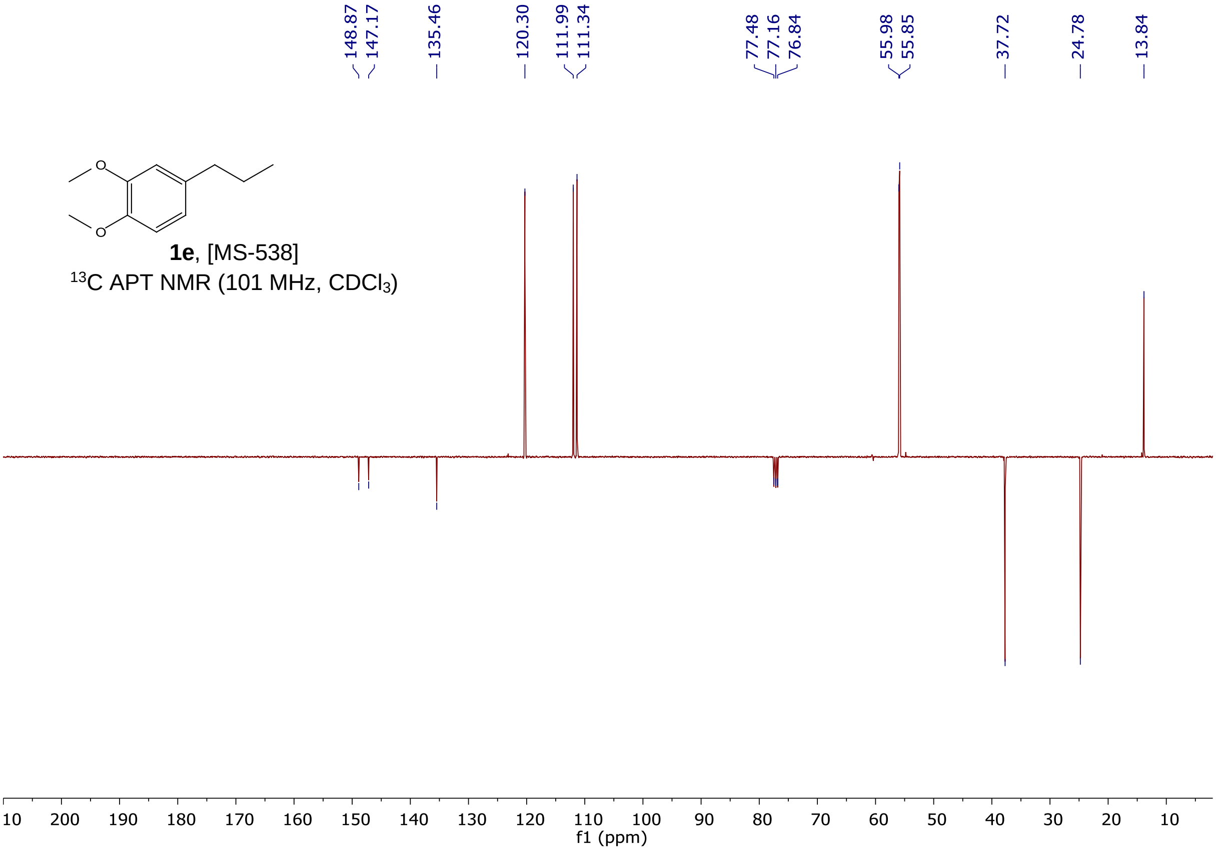
1e, [MS-538]

^{1}H NMR (400 MHz, CDCl$_3$)



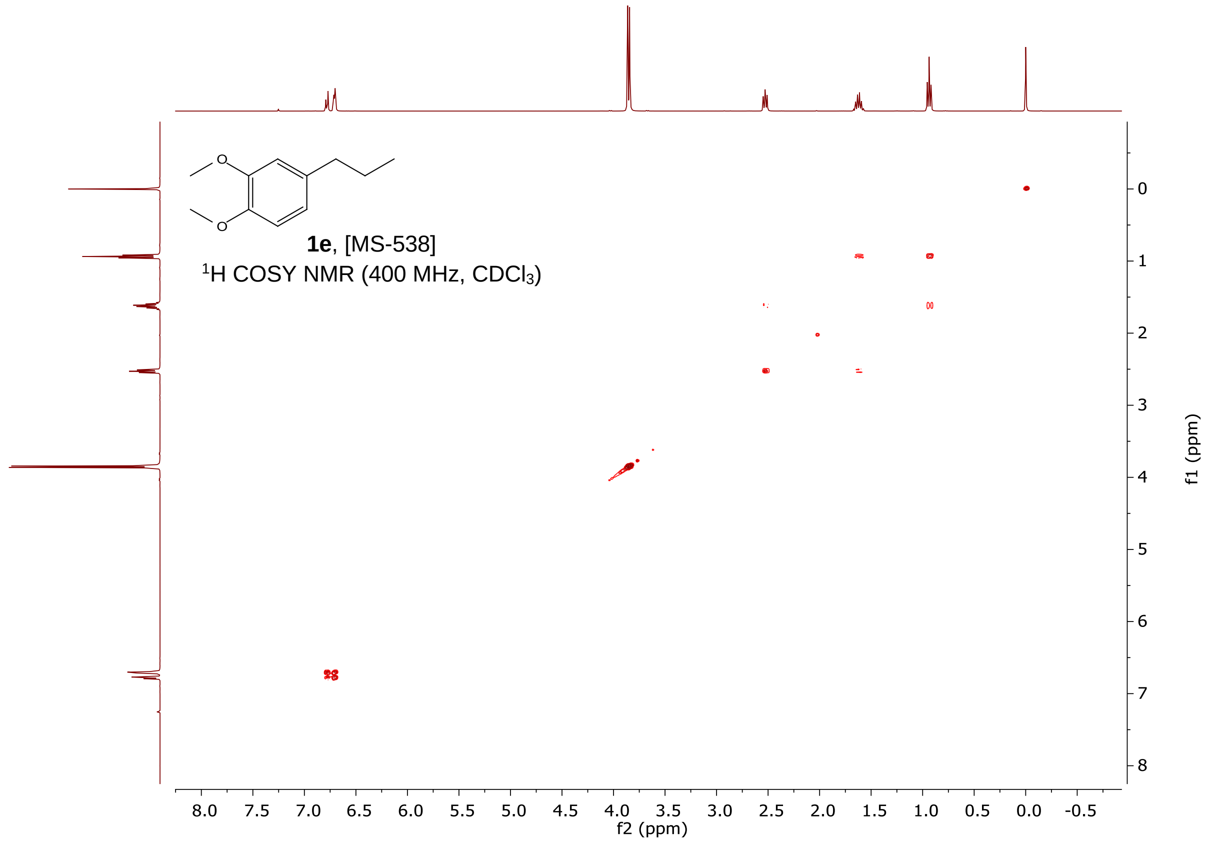
1e, [MS-538]

^{13}C NMR (101 MHz, CDCl$_3$)



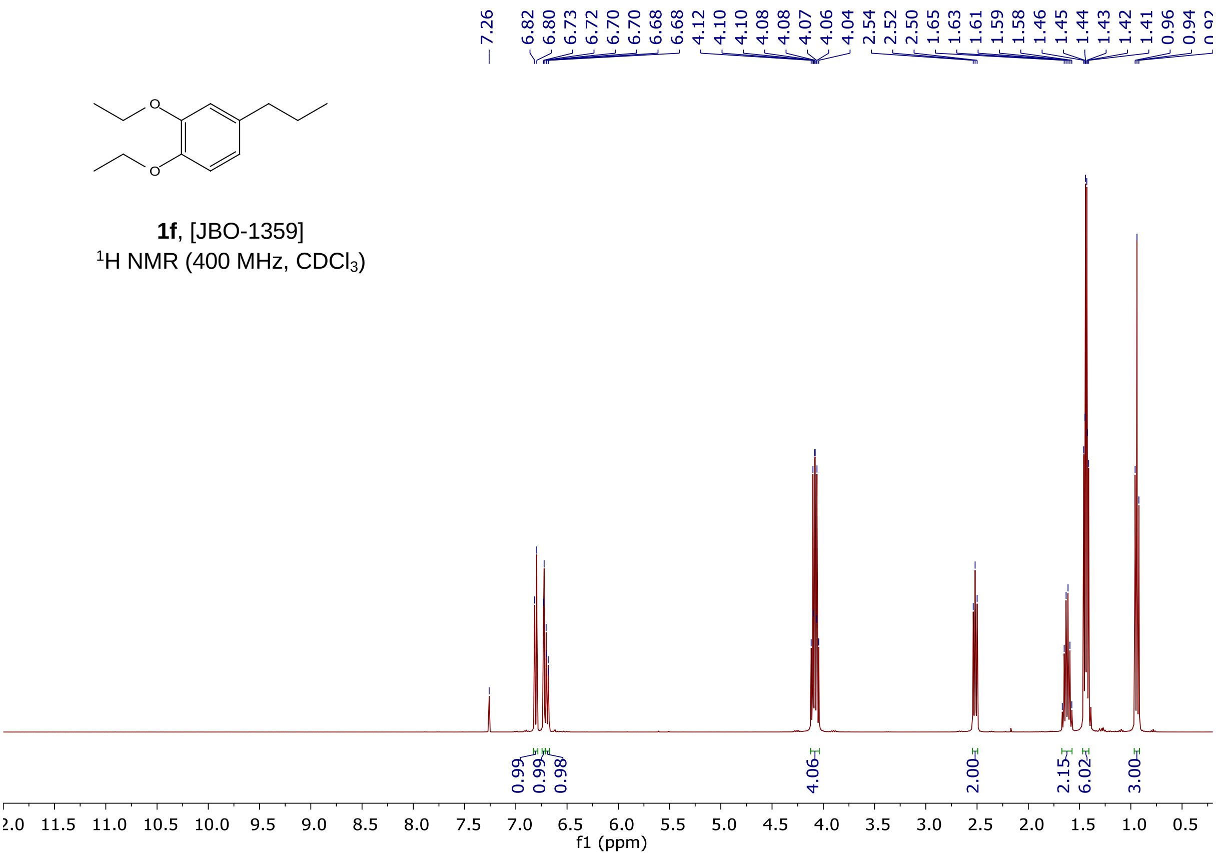
1e, [MS-538]

^{13}C APT NMR (101 MHz, CDCl$_3$)

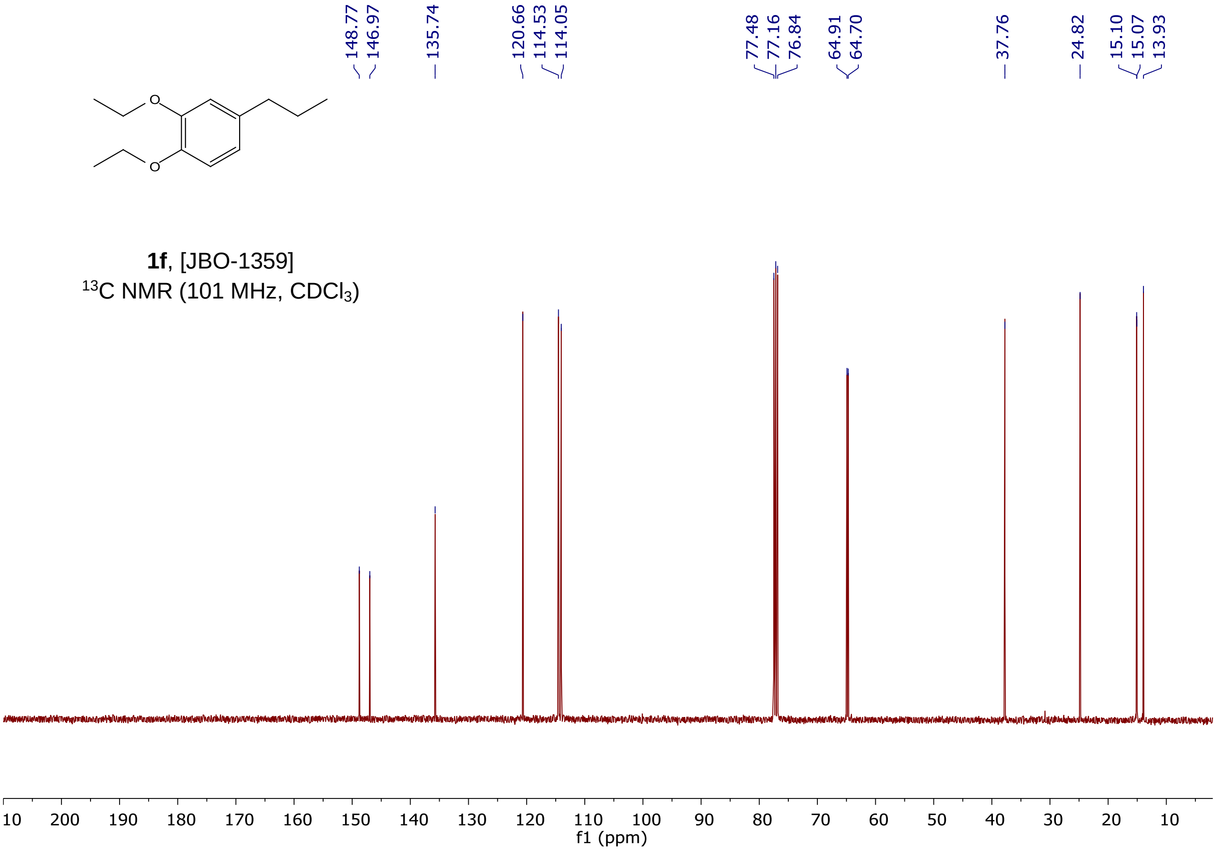


1e, [MS-538]

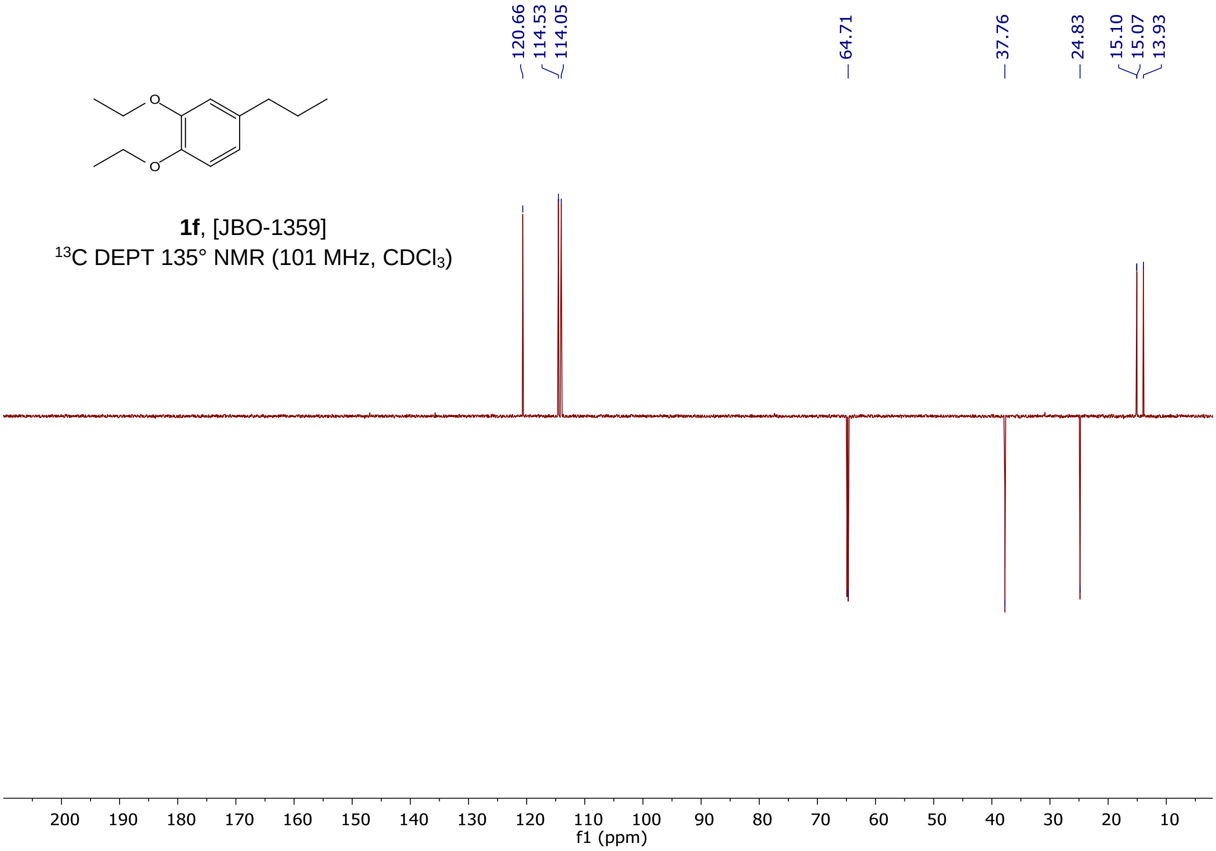
^{1}H COSY NMR (400 MHz, CDCl$_3$)



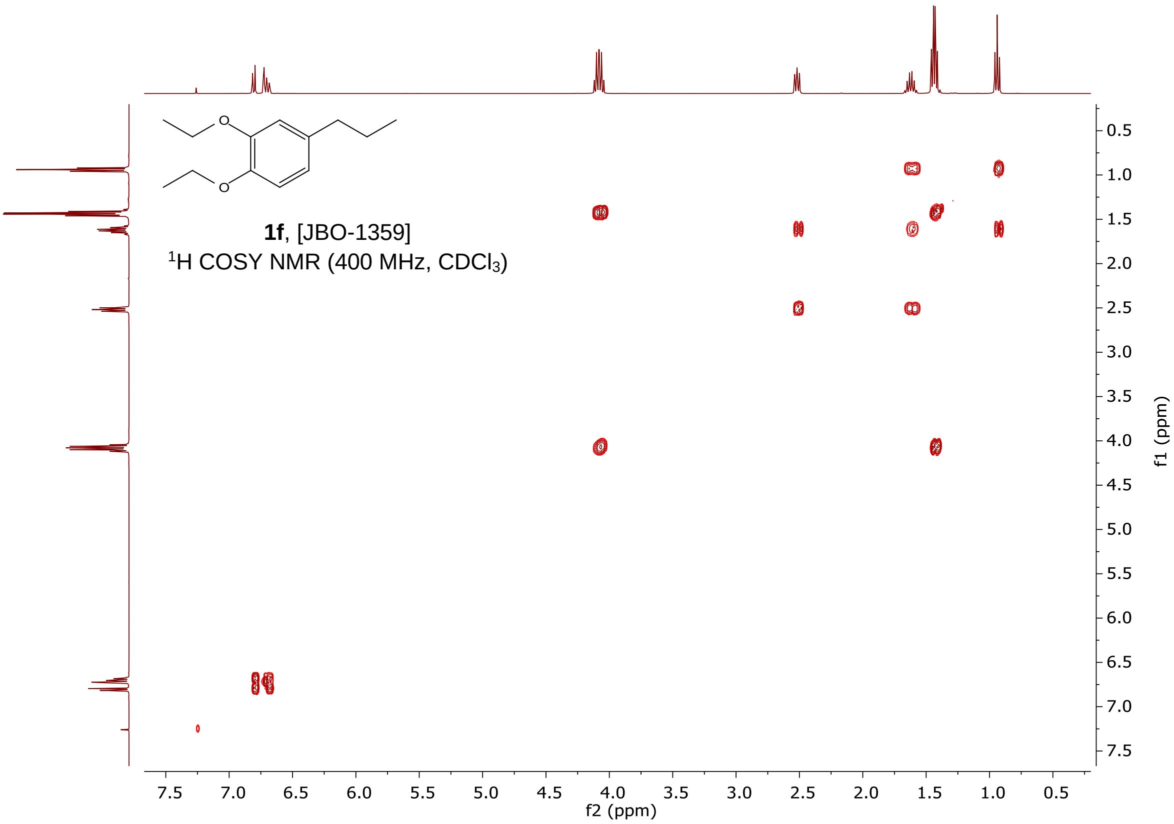
1f, [JBO-1359]
^{1}H NMR (400 MHz, $CDCl_3$)



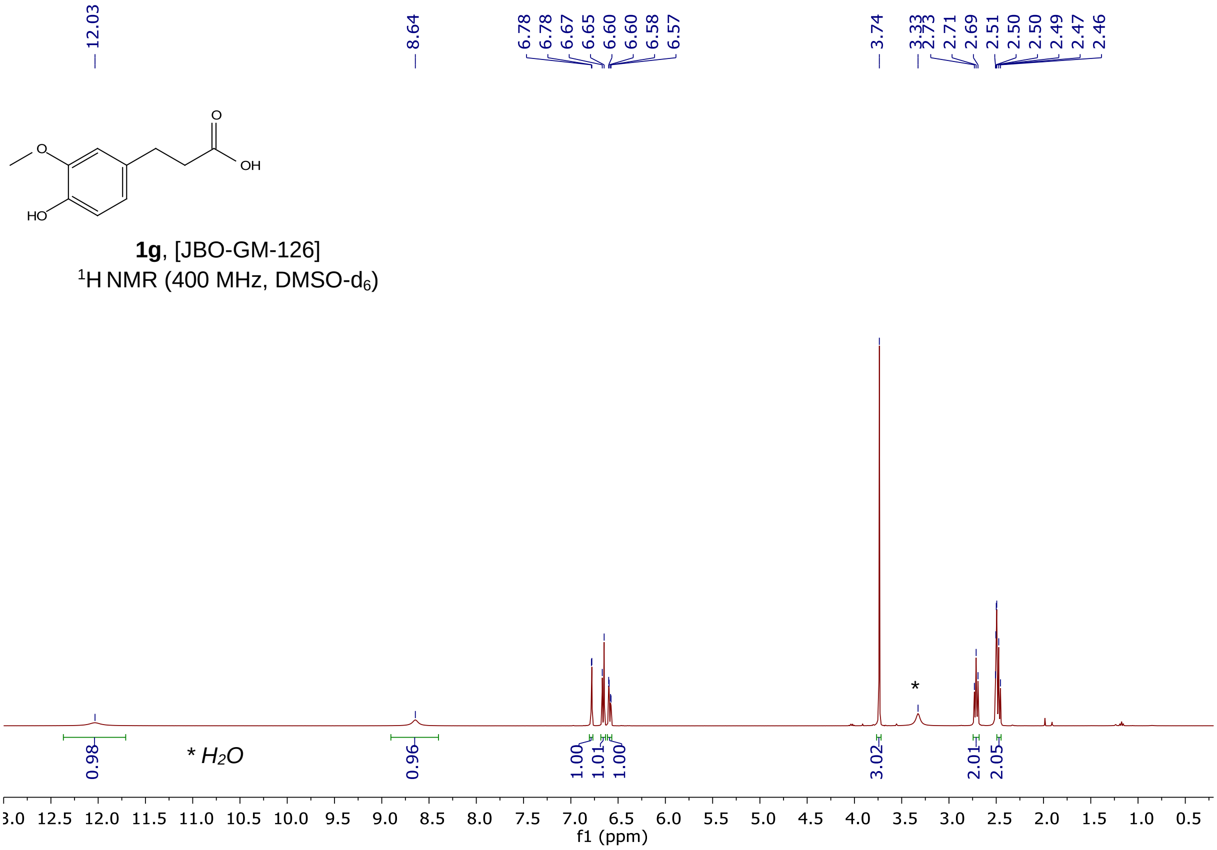
1f, [JBO-1359]
^{13}C NMR (101 MHz, $CDCl_3$)



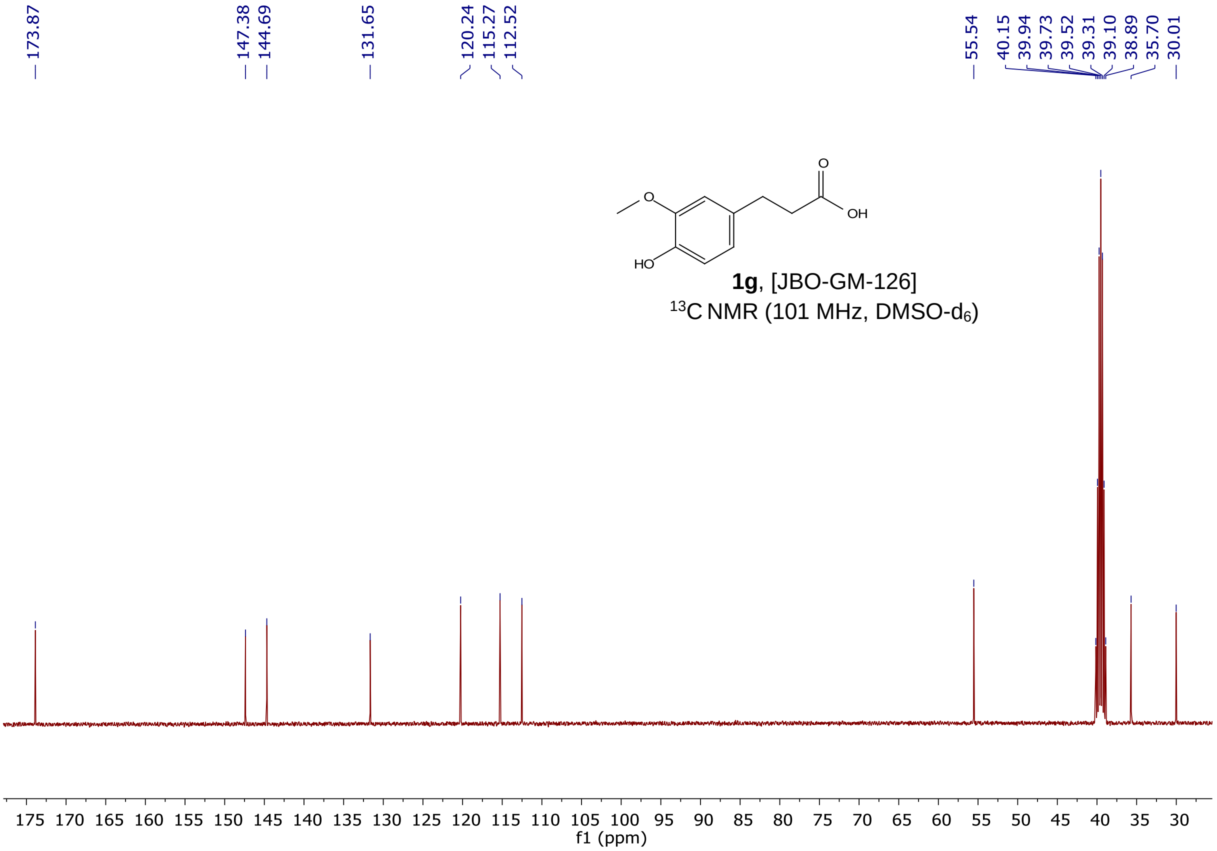
1f, [JBO-1359]
^{13}C DEPT 135° NMR (101 MHz, $CDCl_3$)



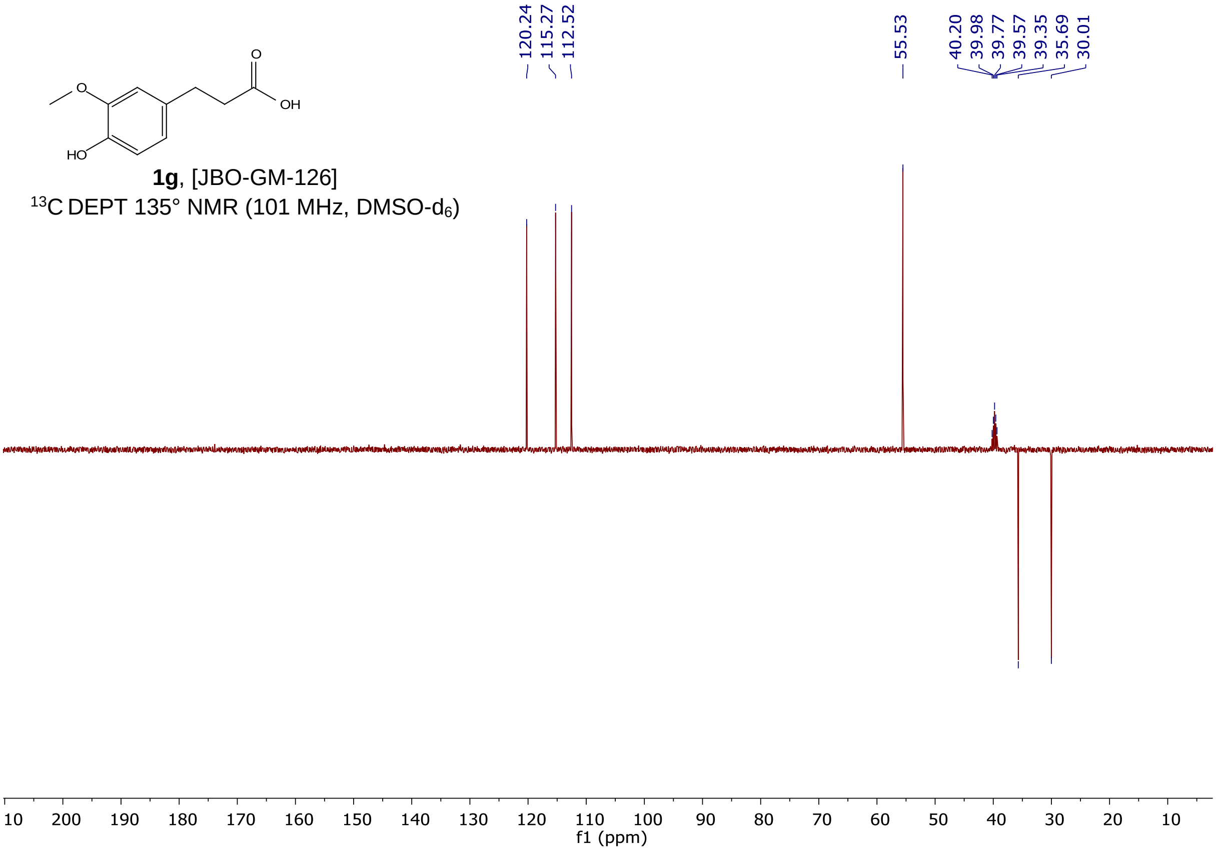
1f, [JBO-1359]
^{1}H COSY NMR (400 MHz, $CDCl_3$)



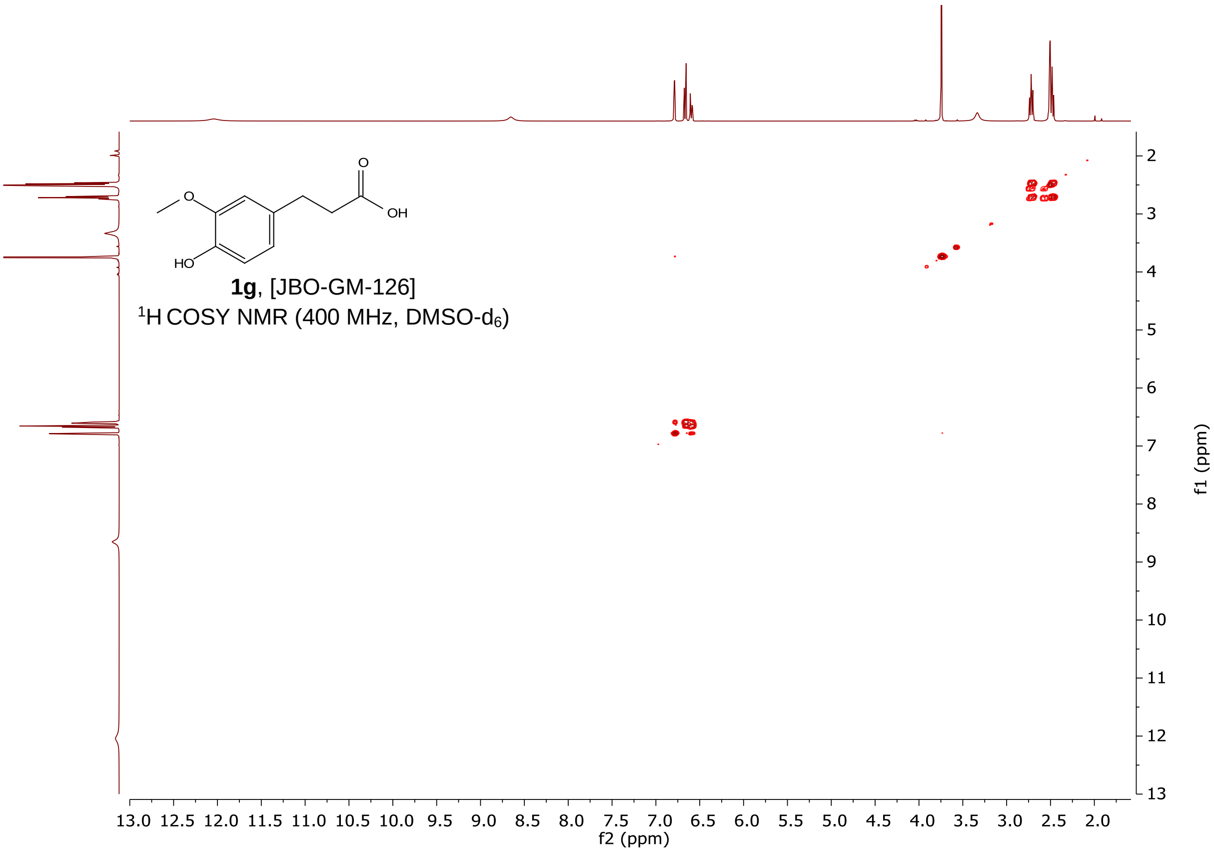
1g, [JBO-GM-126]
^{1}H NMR (400 MHz, DMSO-d_6)



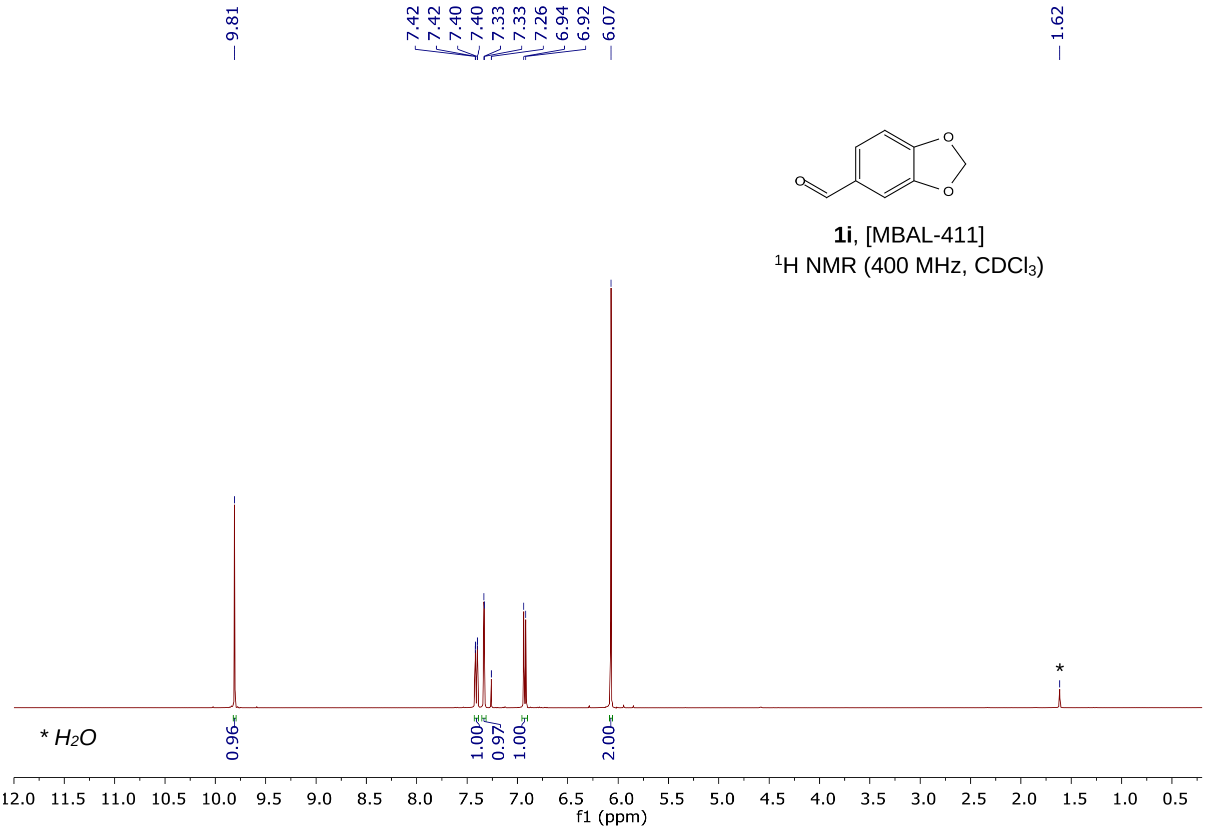
1g, [JBO-GM-126]
^{13}C NMR (101 MHz, DMSO-d_6)



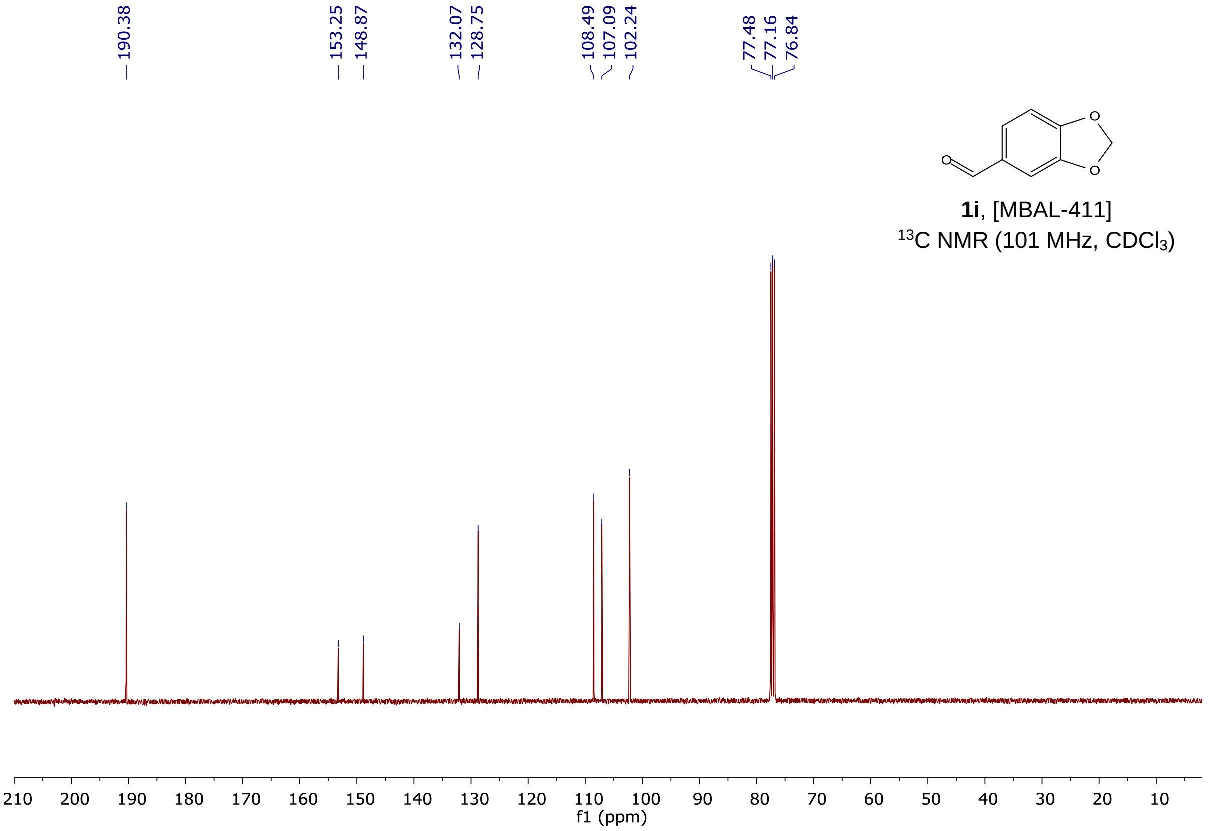
1g, [JBO-GM-126]
^{13}C DEPT 135° NMR (101 MHz, DMSO-d_6)



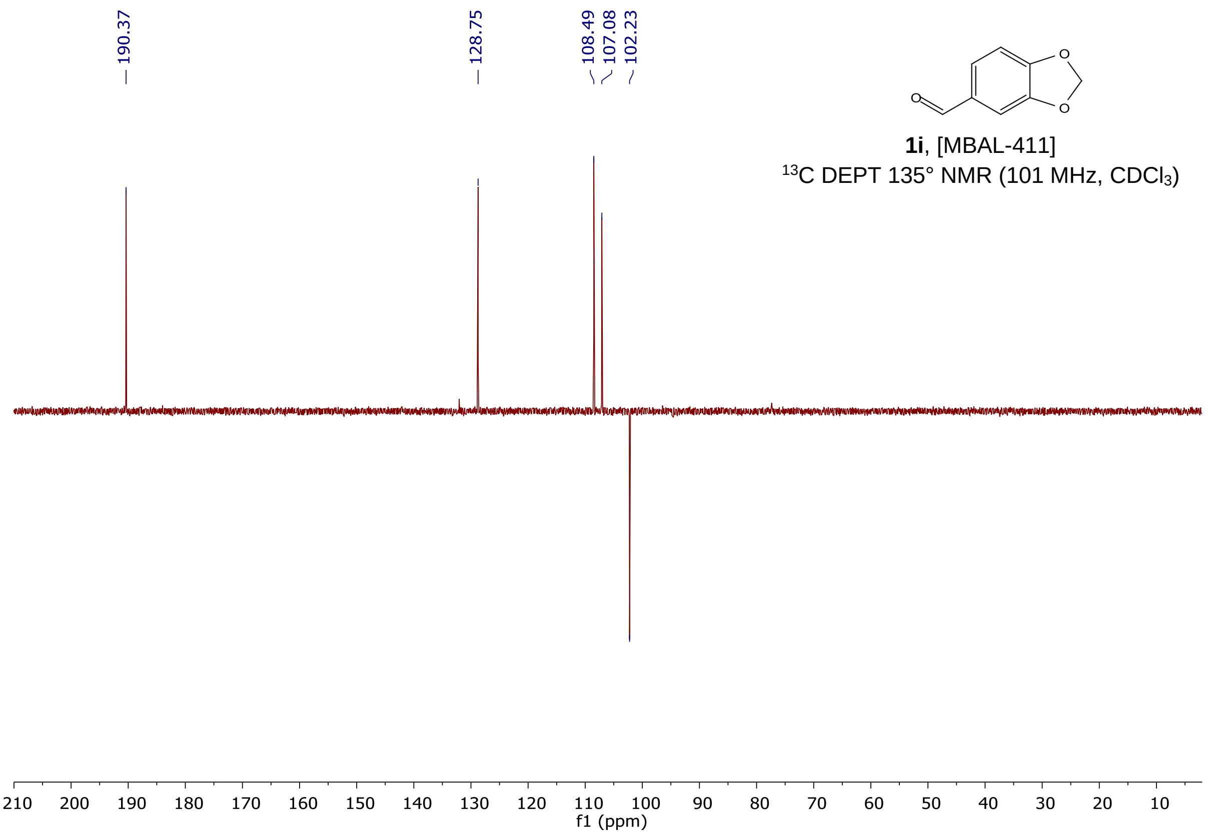
1g, [JBO-GM-126]
^{1}H COSY NMR (400 MHz, DMSO-d_6)



1i, [MBAL-411]
^{1}H NMR (400 MHz, $CDCl_3$)

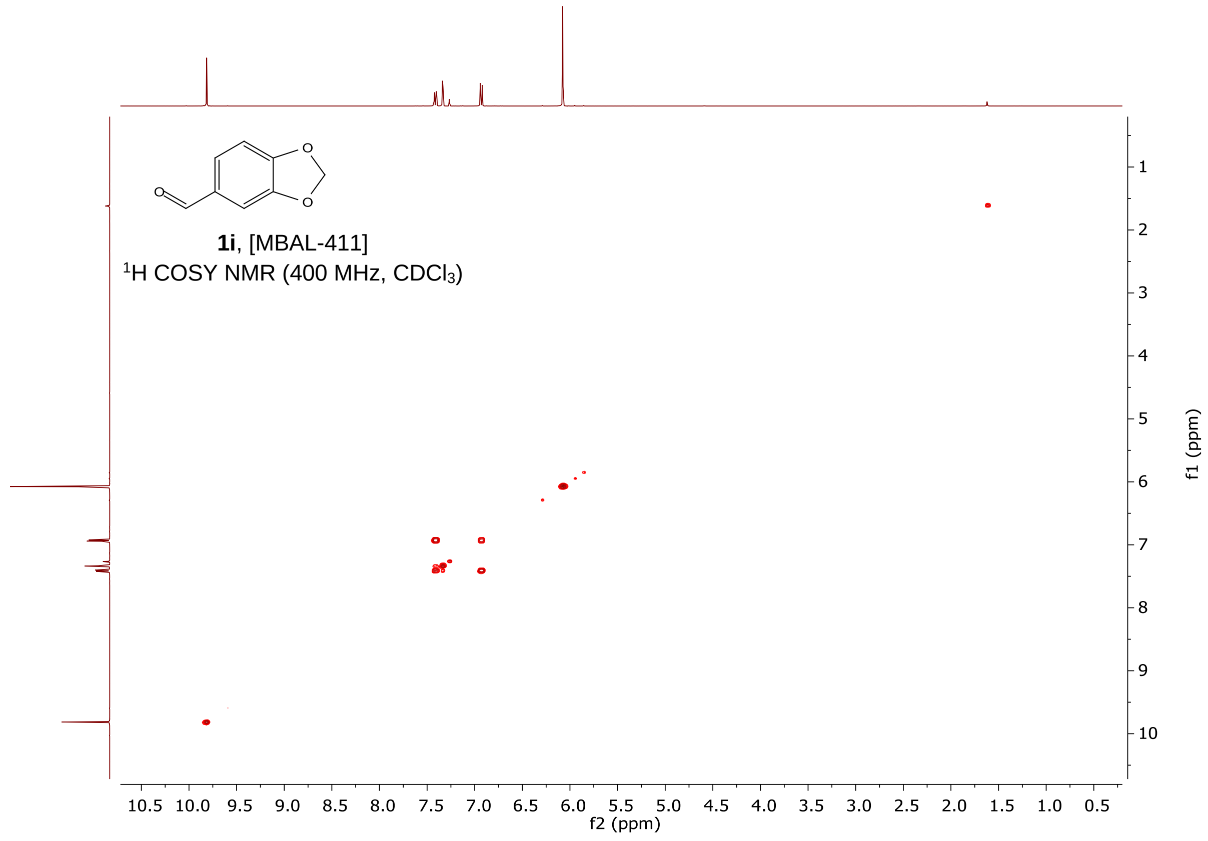


1i, [MBAL-411]
^{13}C NMR (101 MHz, $CDCl_3$)



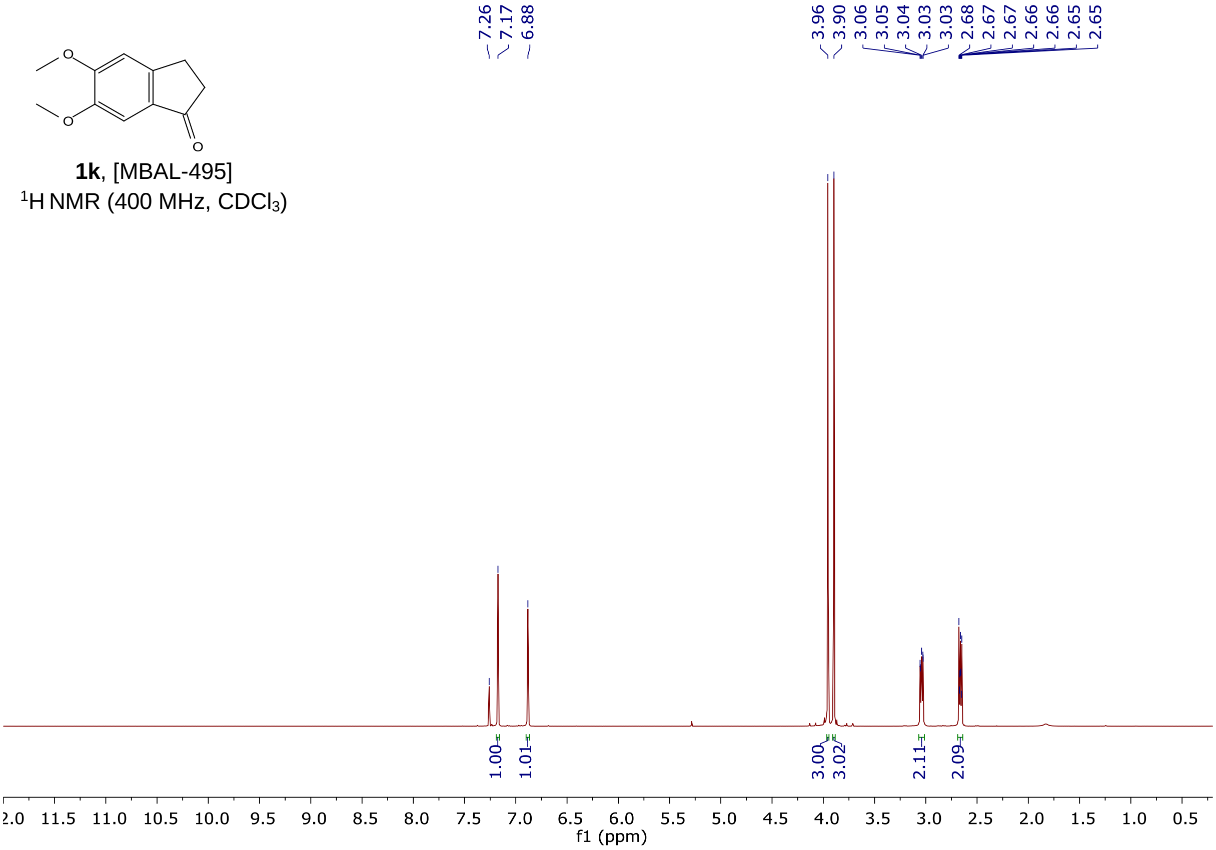
1i, [MBAL-411]

^{13}C DEPT 135° NMR (101 MHz, $CDCl_3$)

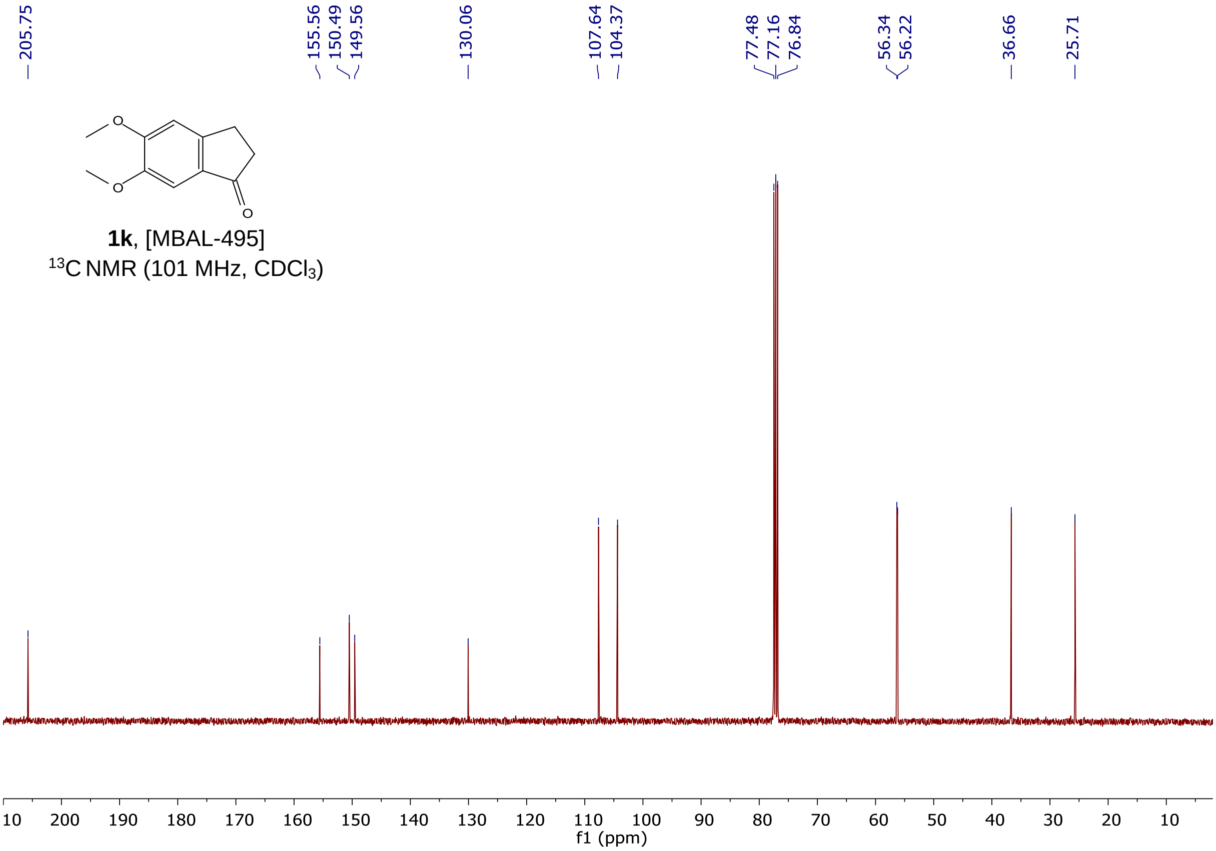


1i, [MBAL-411]

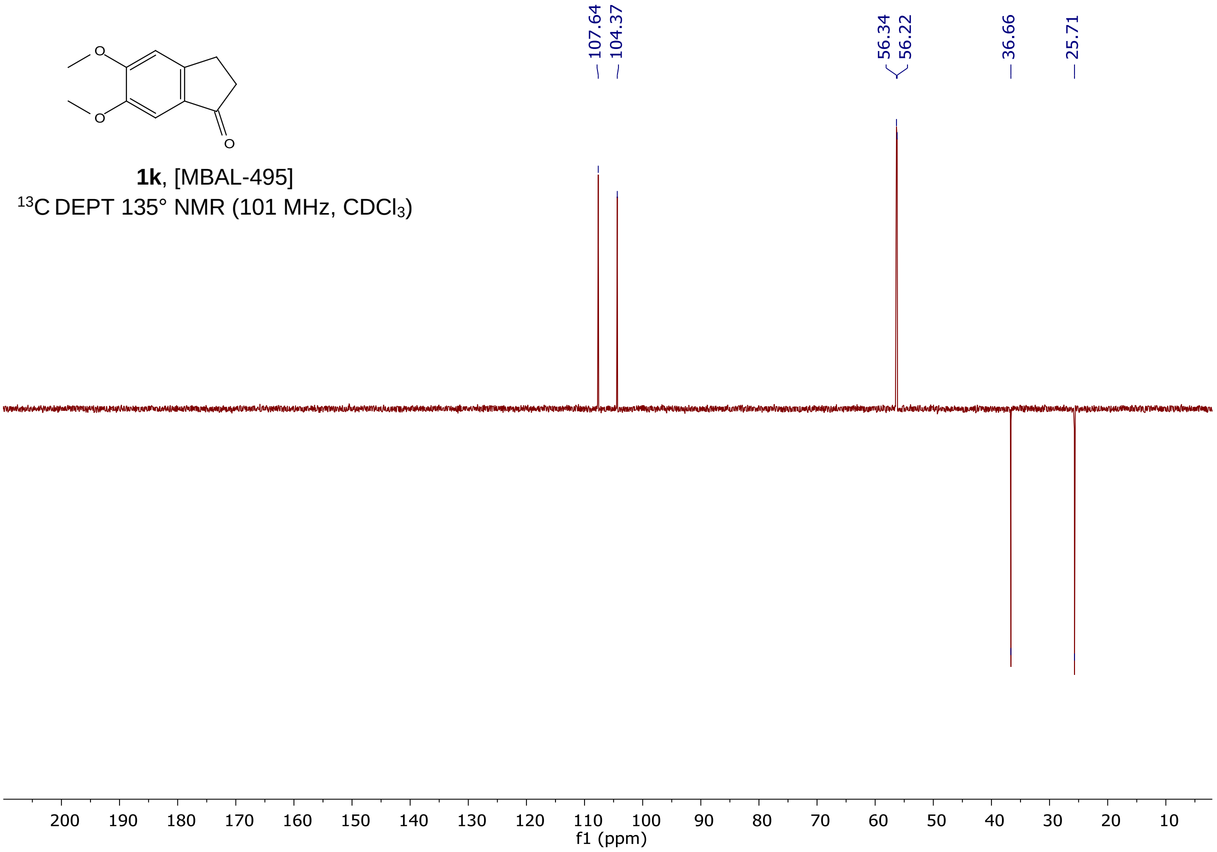
^{1}H COSY NMR (400 MHz, $CDCl_3$)



1k, [MBAL-495]
^1H NMR (400 MHz, $CDCl_3$)

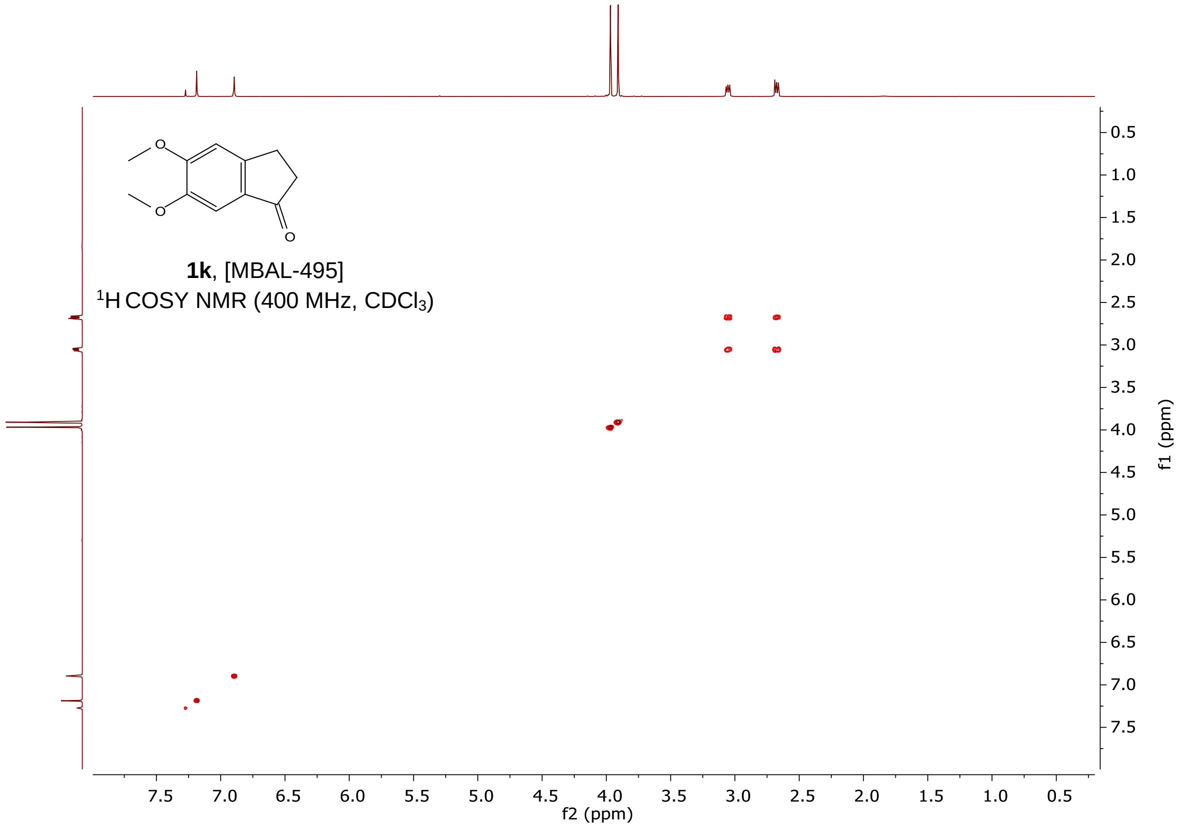


1k, [MBAL-495]
^{13}C NMR (101 MHz, $CDCl_3$)



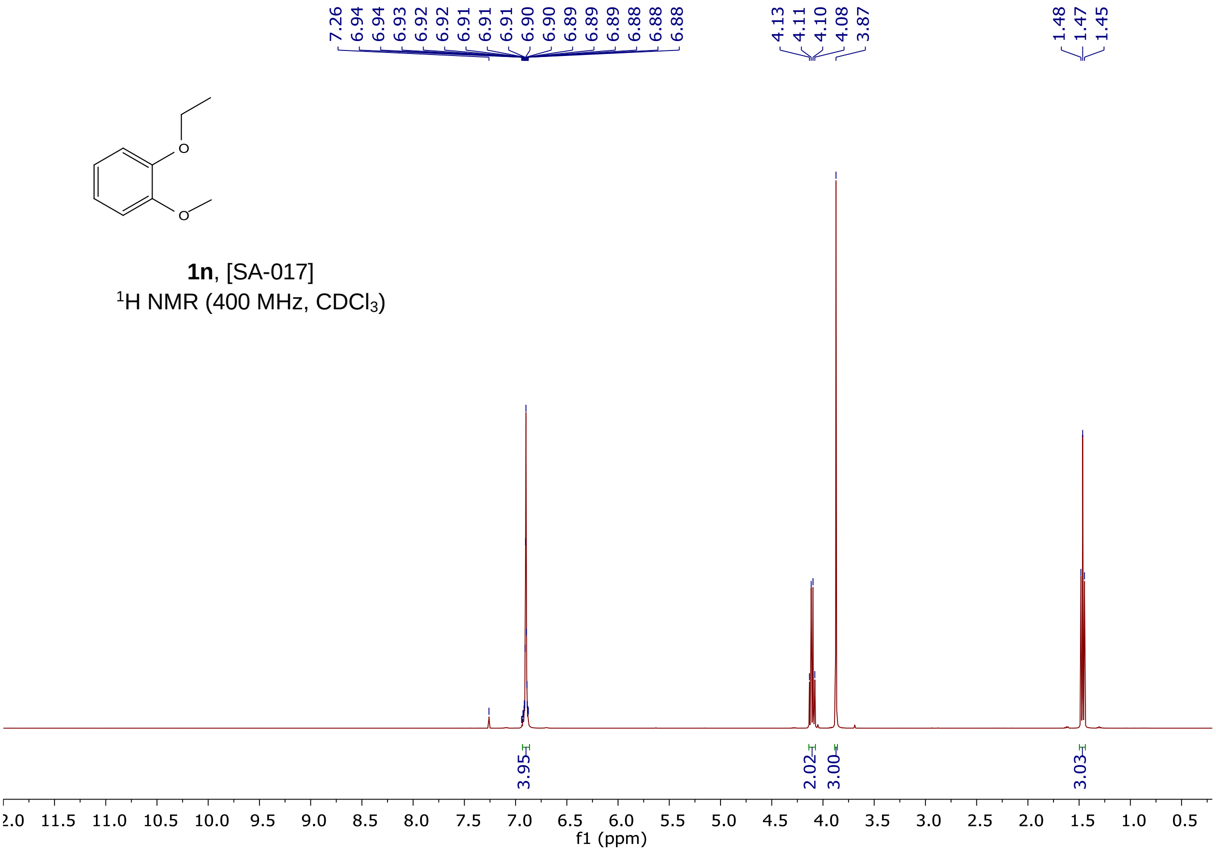
1k, [MBAL-495]

^{13}C DEPT 135° NMR (101 MHz, CDCl$_3$)

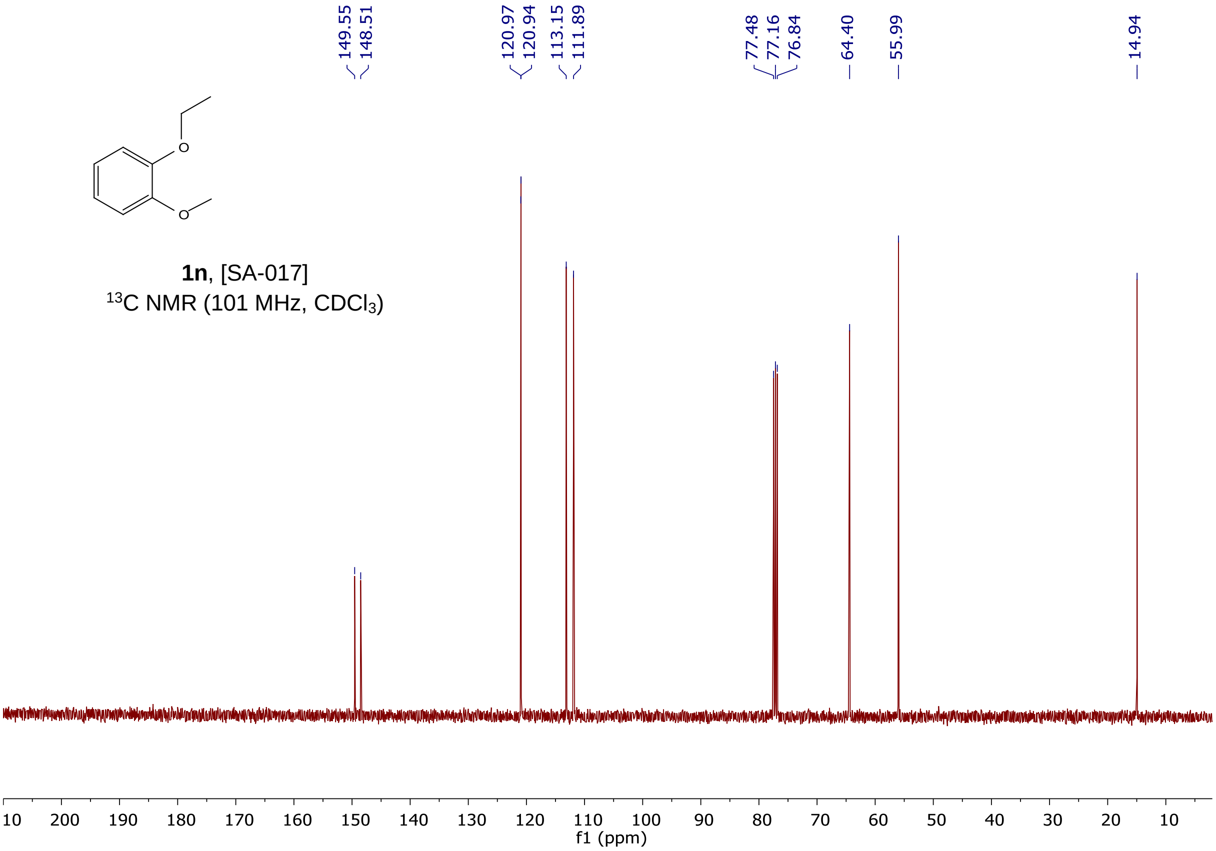


1k, [MBAL-495]

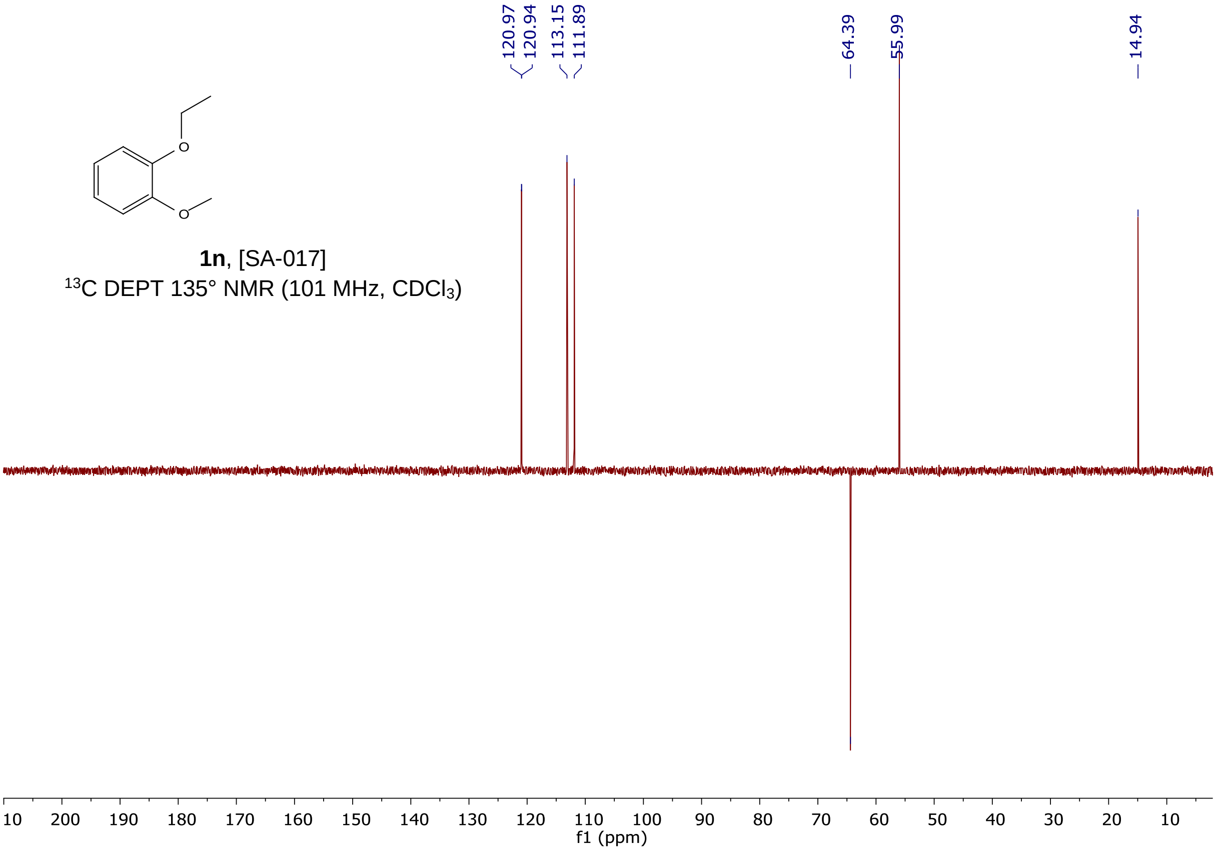
^{1}H COSY NMR (400 MHz, CDCl$_3$)



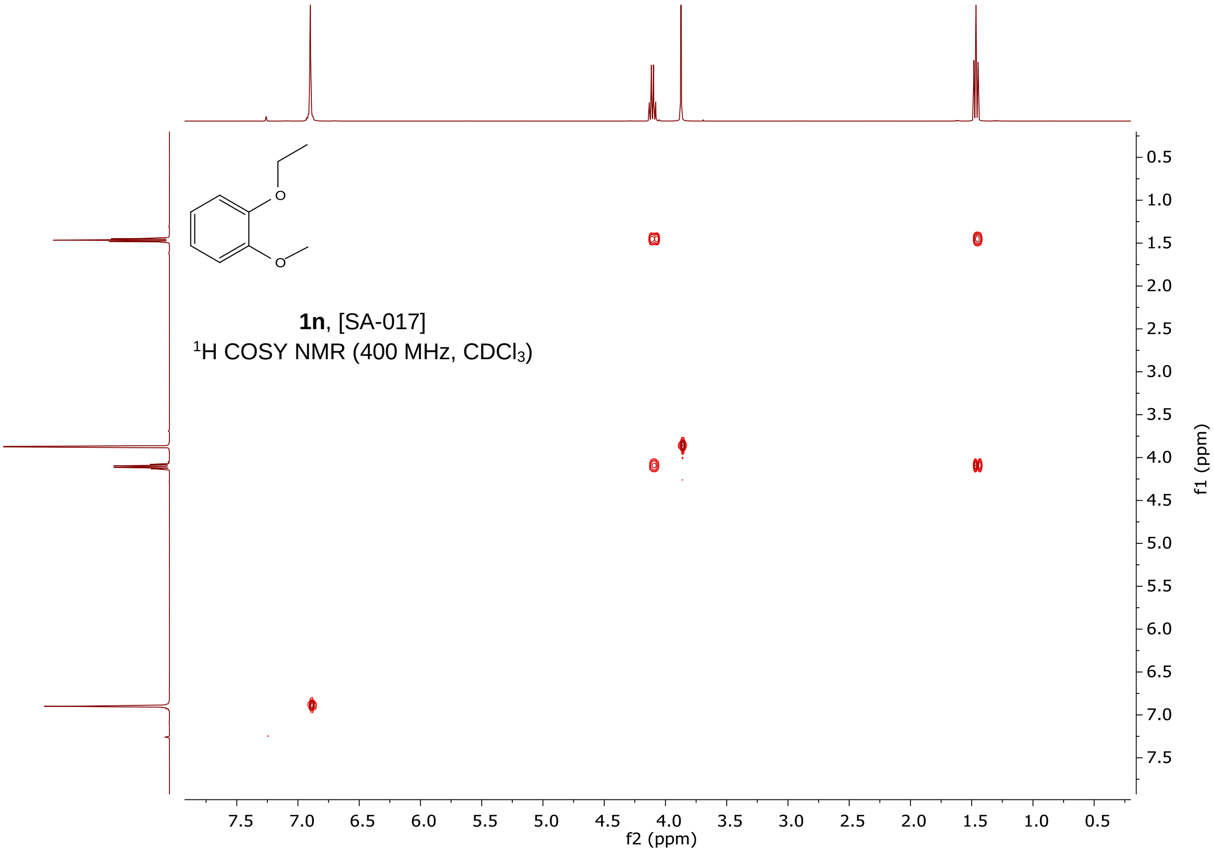
1n, [SA-017]
^{1}H NMR (400 MHz, $CDCl_3$)



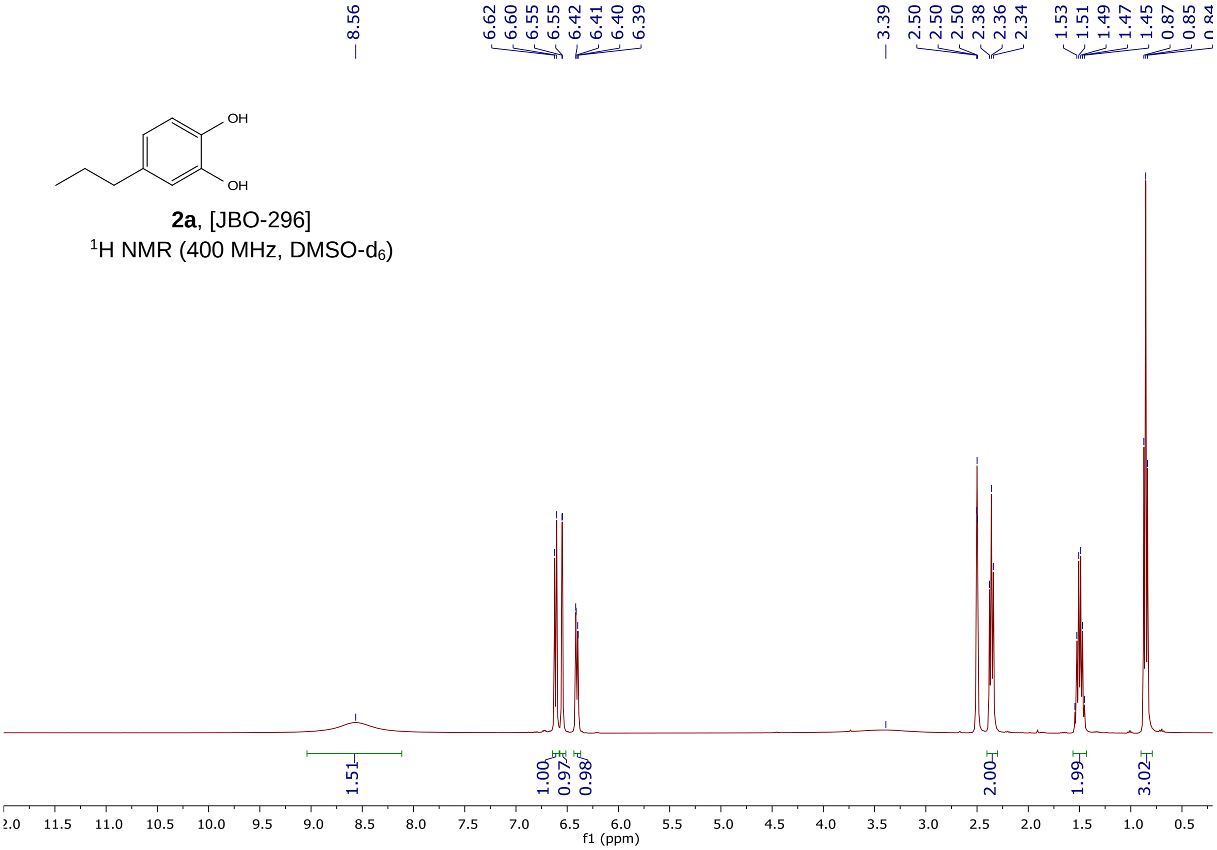
1n, [SA-017]
^{13}C NMR (101 MHz, $CDCl_3$)

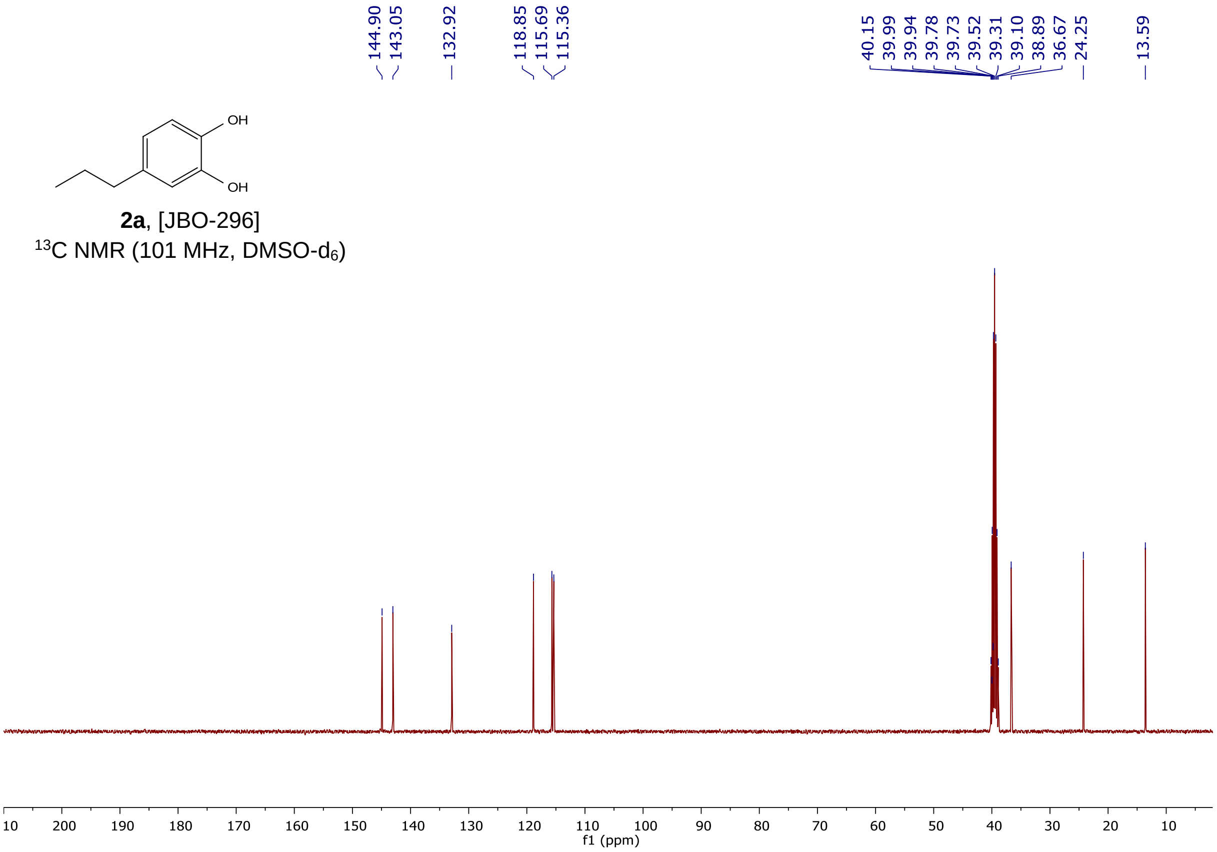


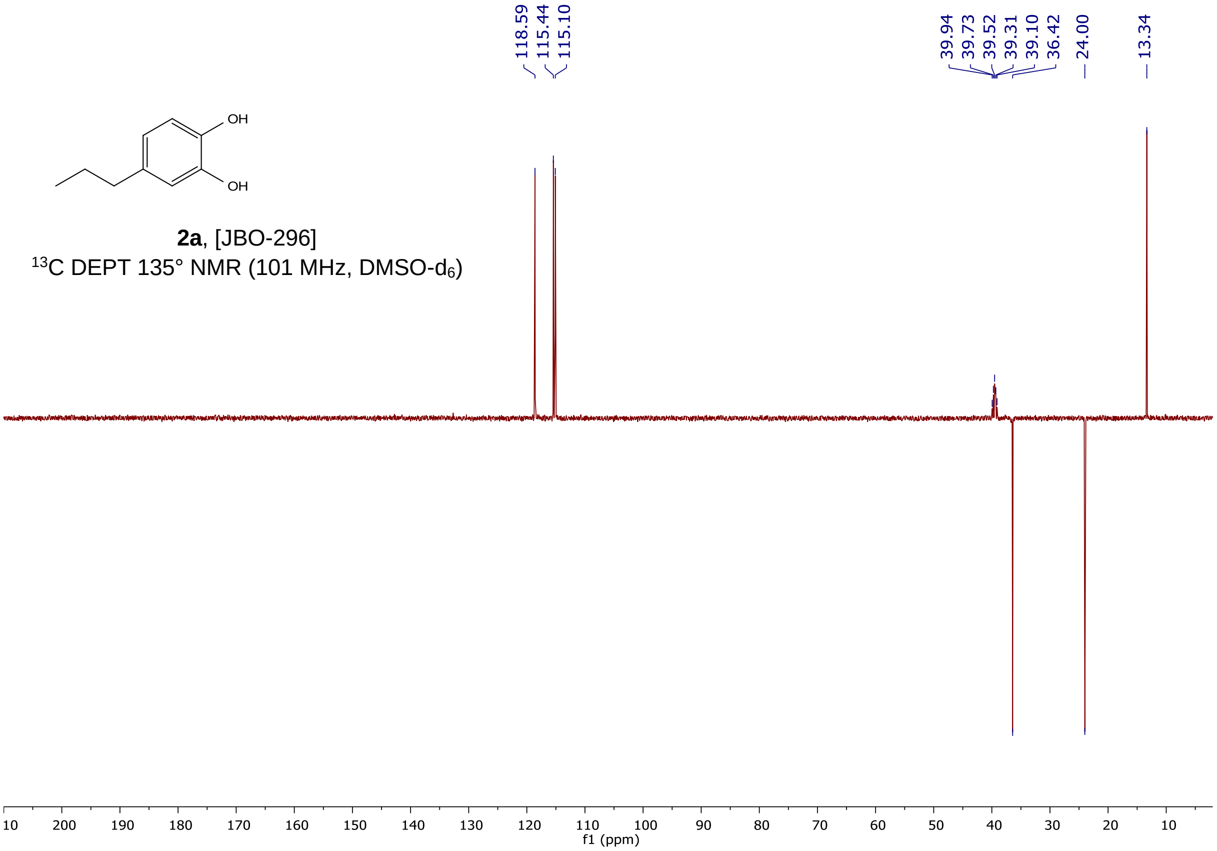
1n, [SA-017]
^{13}C DEPT 135° NMR (101 MHz, $CDCl_3$)



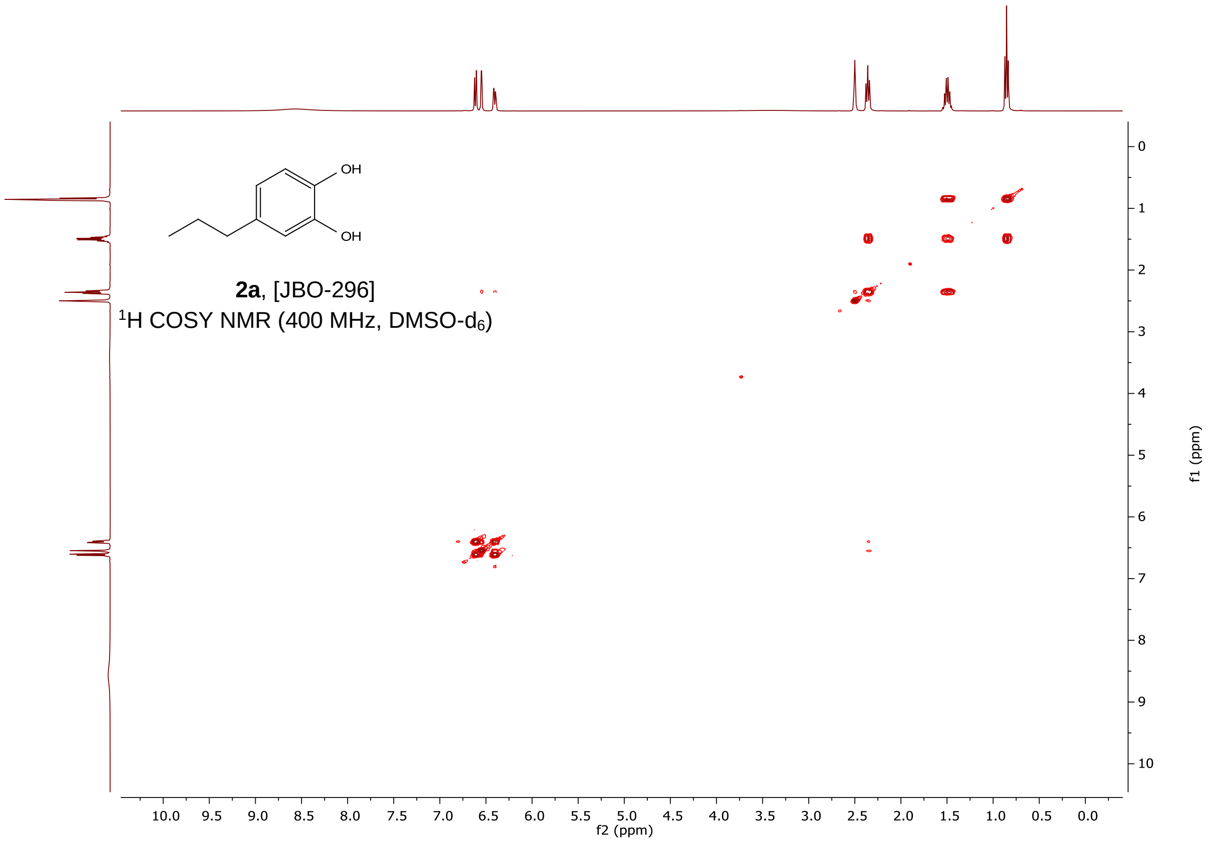
1n, [SA-017]
^{1}H COSY NMR (400 MHz, $CDCl_3$)


2a, [JBO-296]
^{1}H NMR (400 MHz, DMSO-d$_6$)

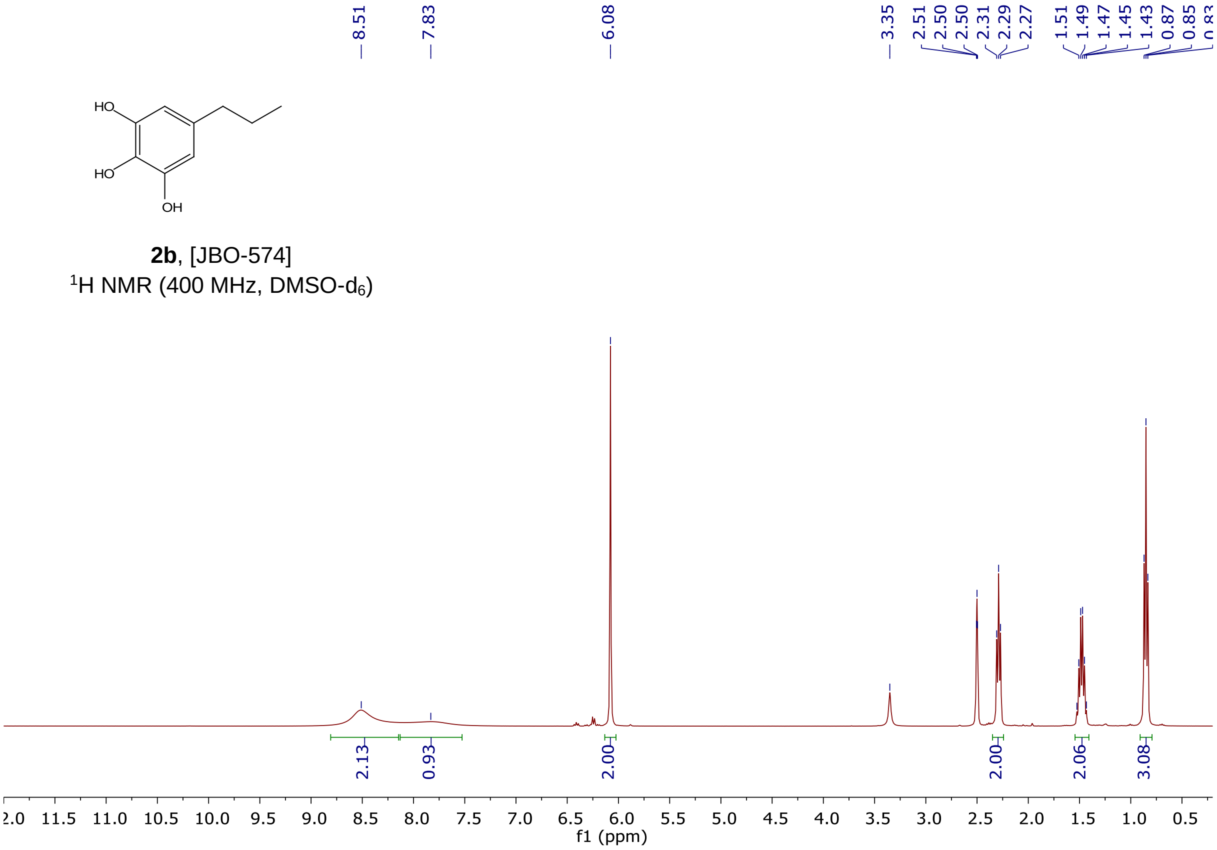

2a, [JBO-296]
^{13}C NMR (101 MHz, DMSO-d$_6$)



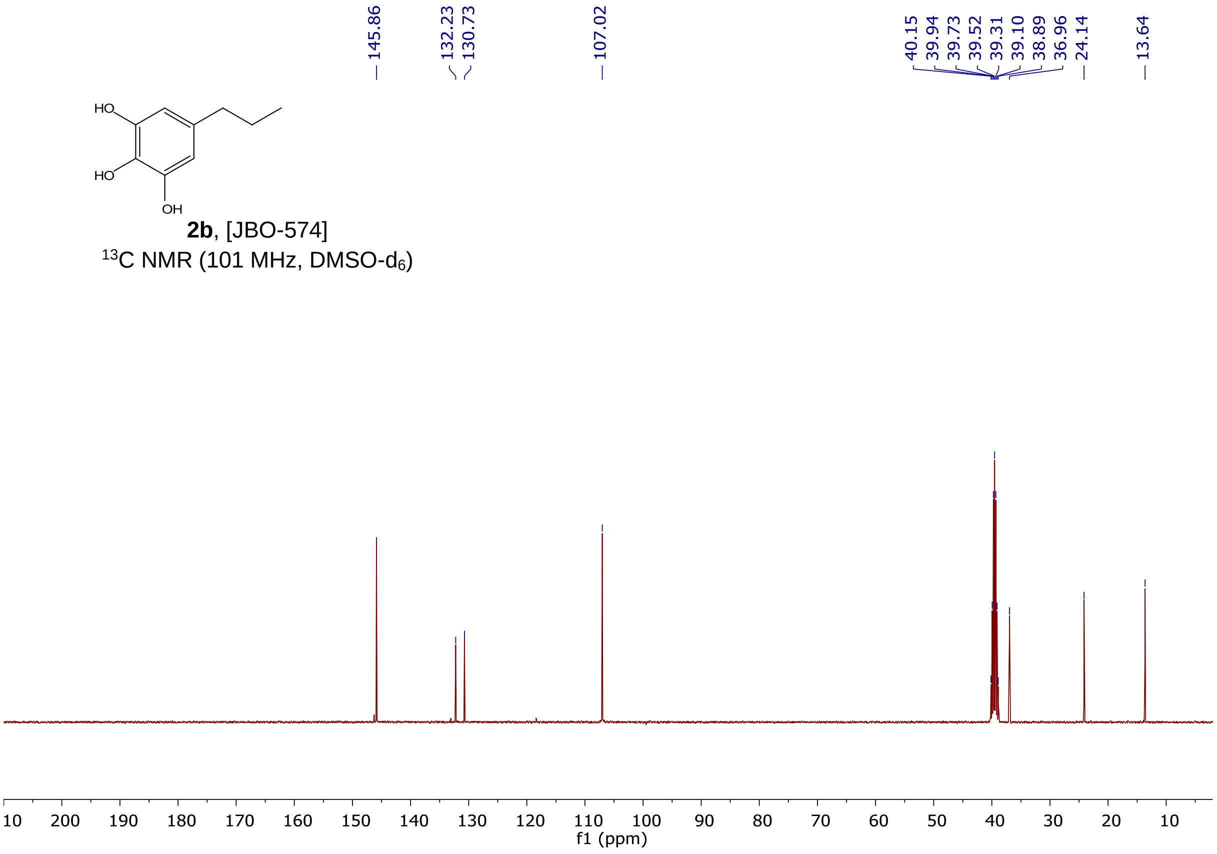
2a, [JBO-296]
^{13}C DEPT 135° NMR (101 MHz, DMSO-d_6)



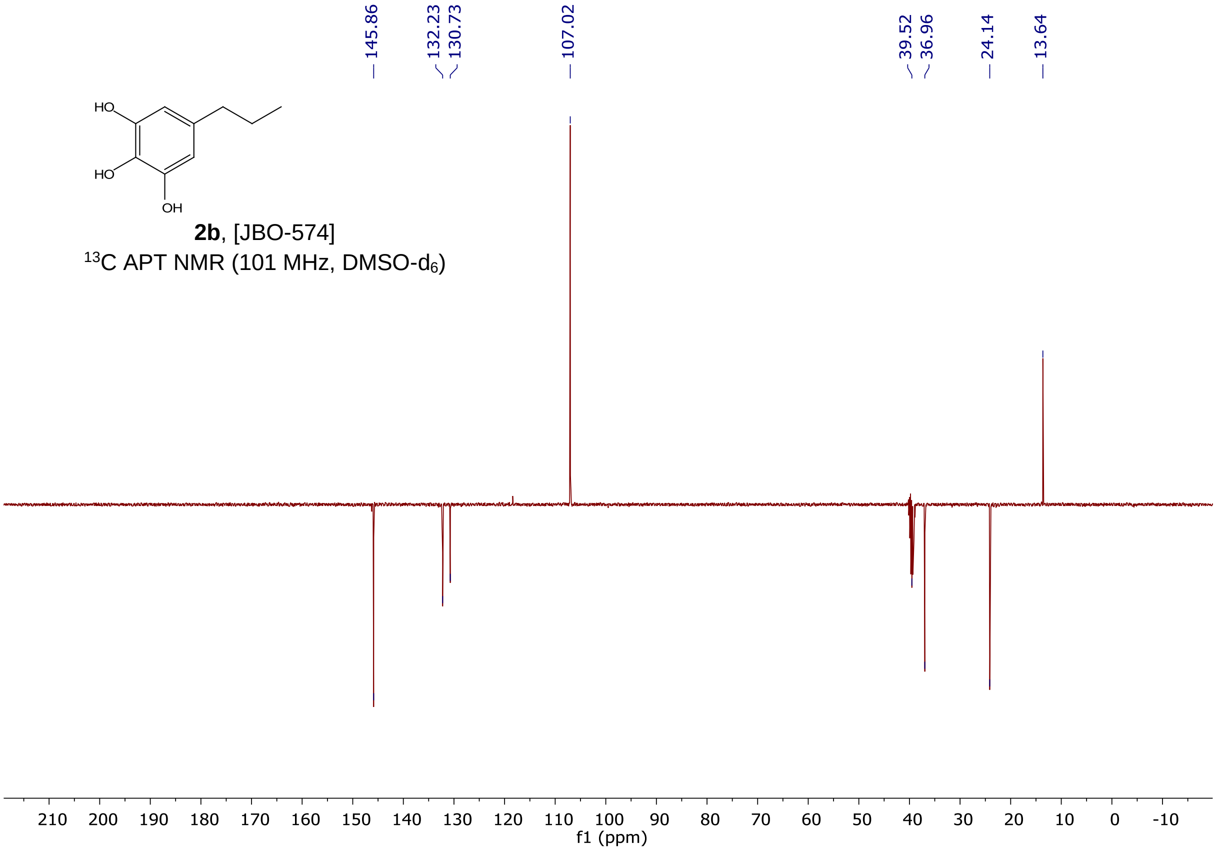
2a, [JBO-296]
^{1}H COSY NMR (400 MHz, DMSO-d_6)



2b, [JBO-574]
^{1}H NMR (400 MHz, DMSO-d_6)

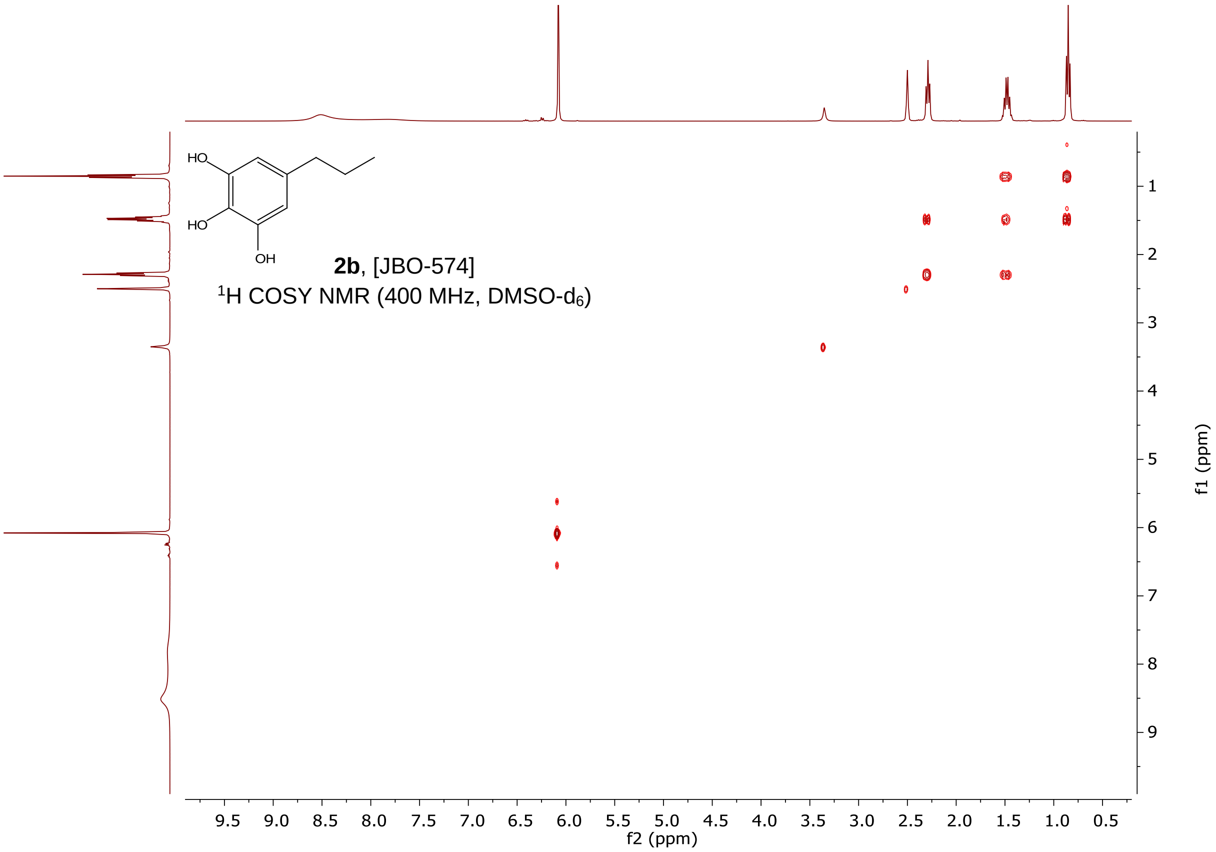


2b, [JBO-574]
^{13}C NMR (101 MHz, DMSO-d_6)



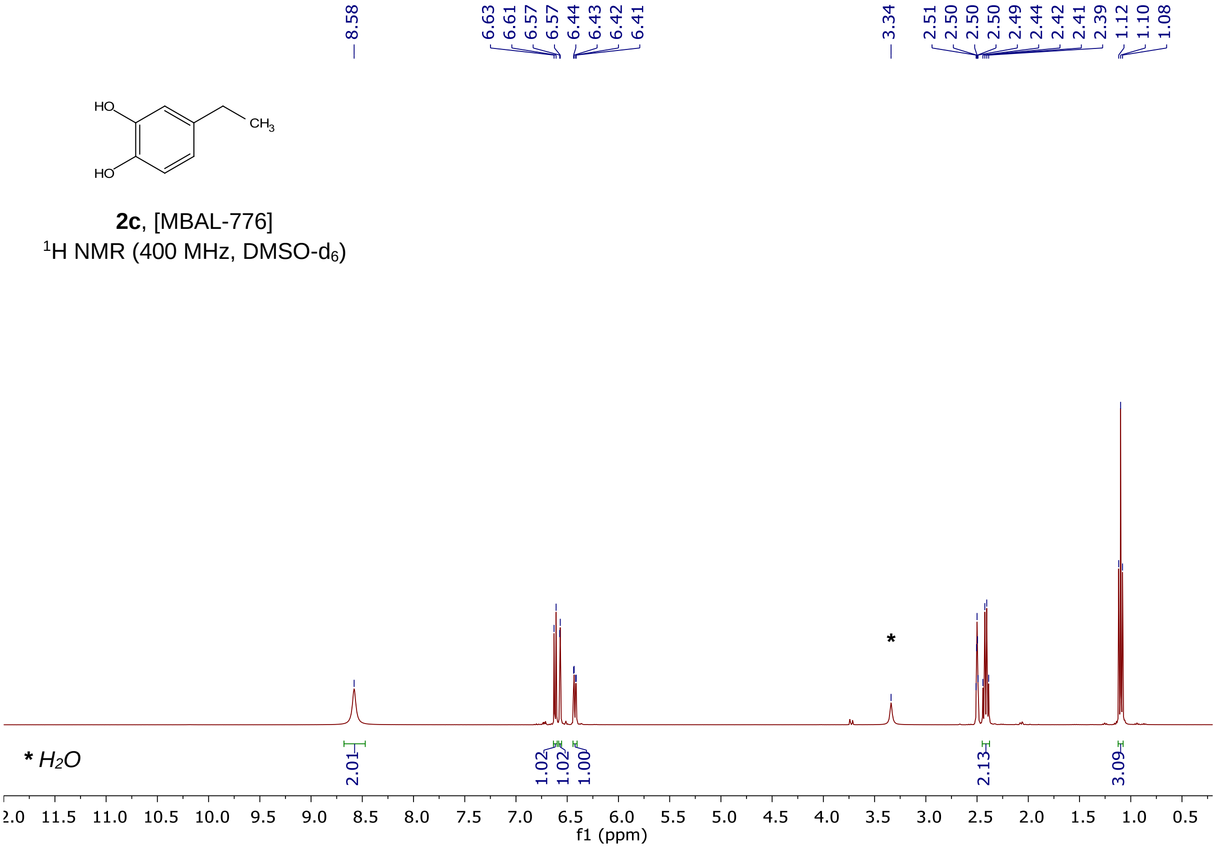
2b, [JBO-574]

^{13}C APT NMR (101 MHz, DMSO-d_6)



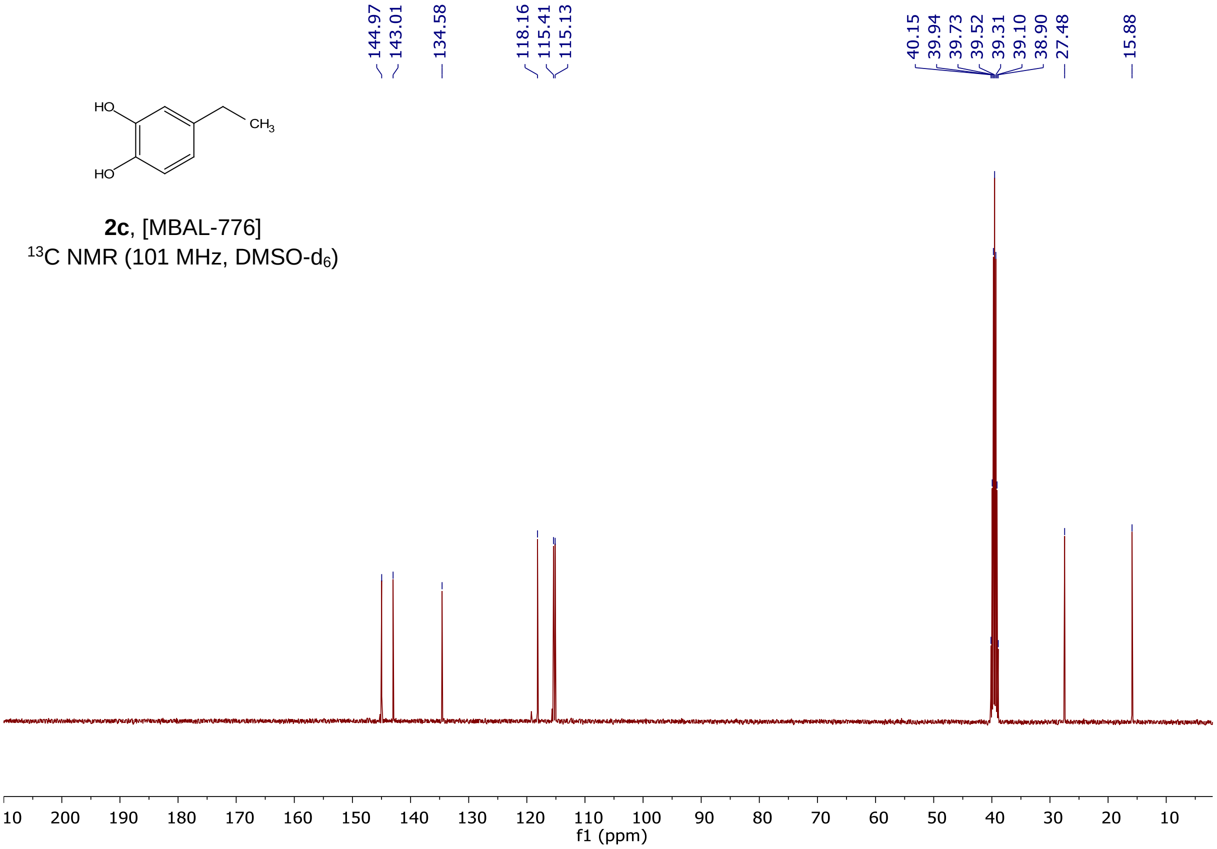
2b, [JBO-574]

^{1}H COSY NMR (400 MHz, DMSO-d_6)



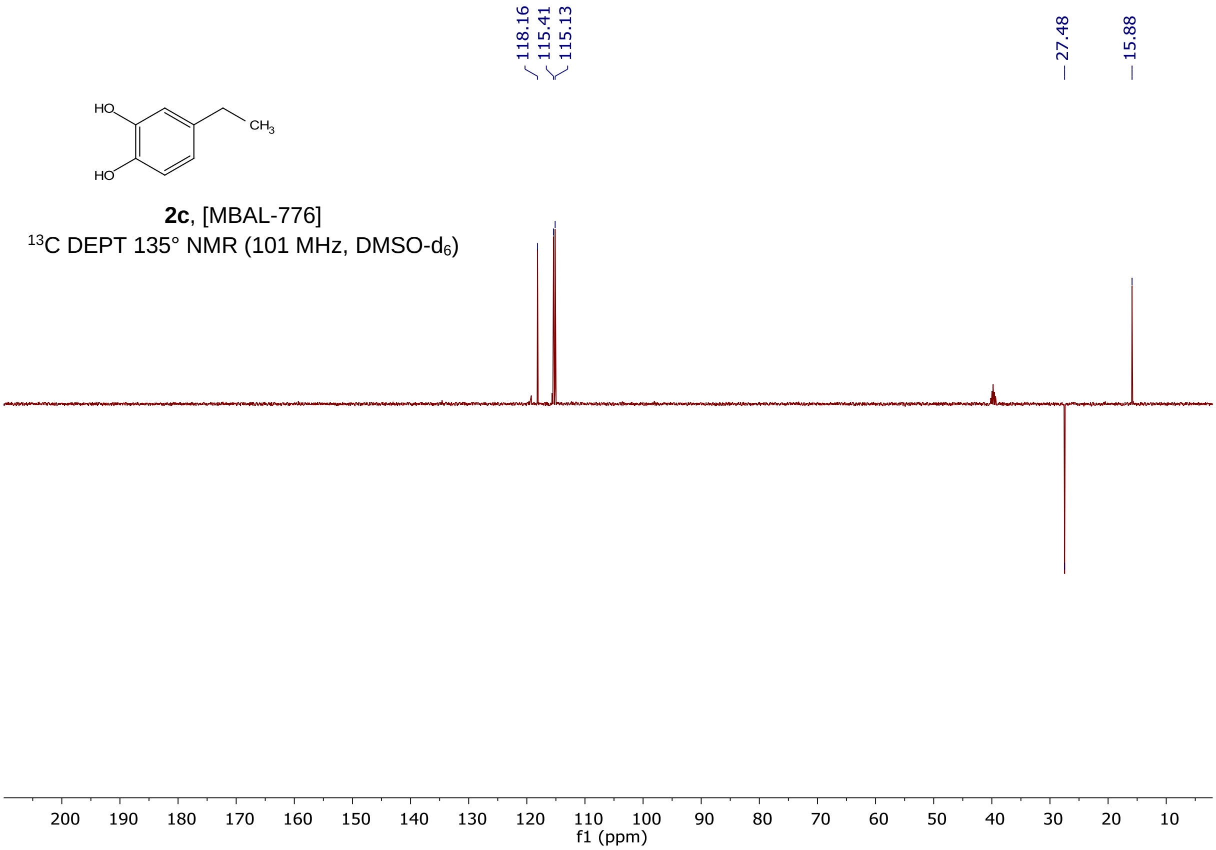
2c, [MBAL-776]

^{1}H NMR (400 MHz, DMSO-d_6)



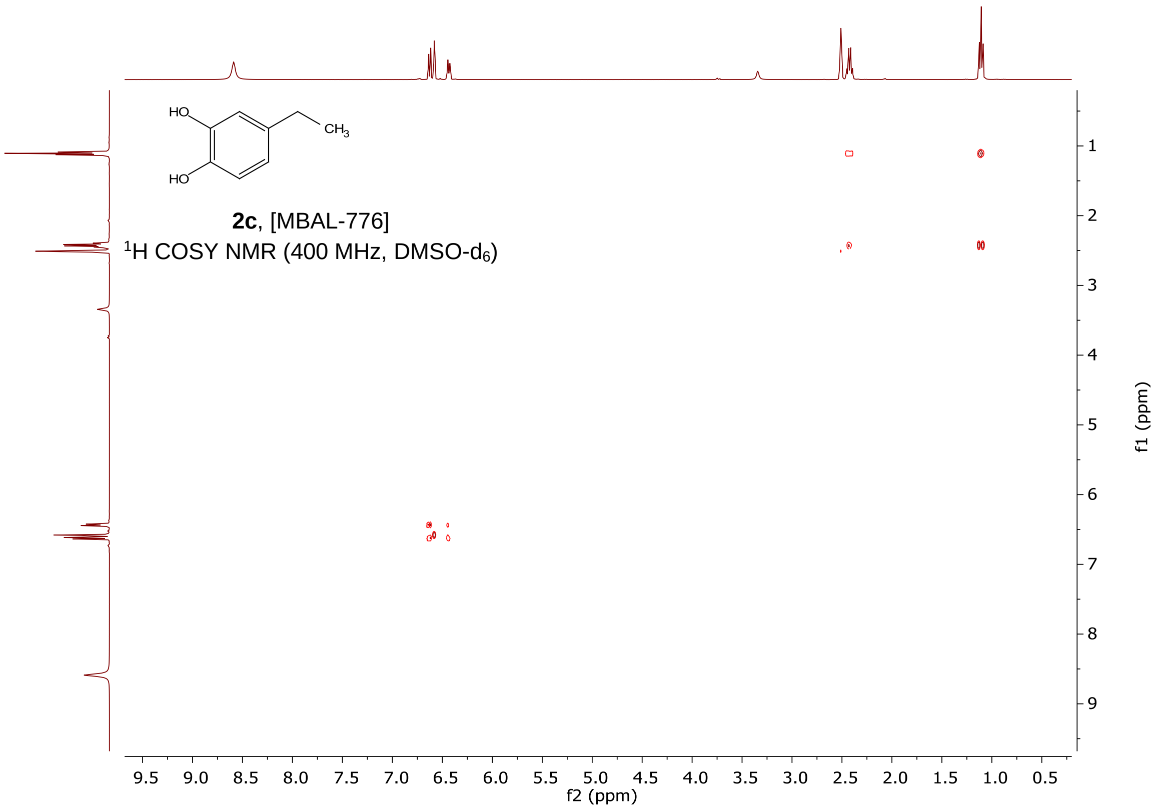
2c, [MBAL-776]

^{13}C NMR (101 MHz, DMSO-d_6)



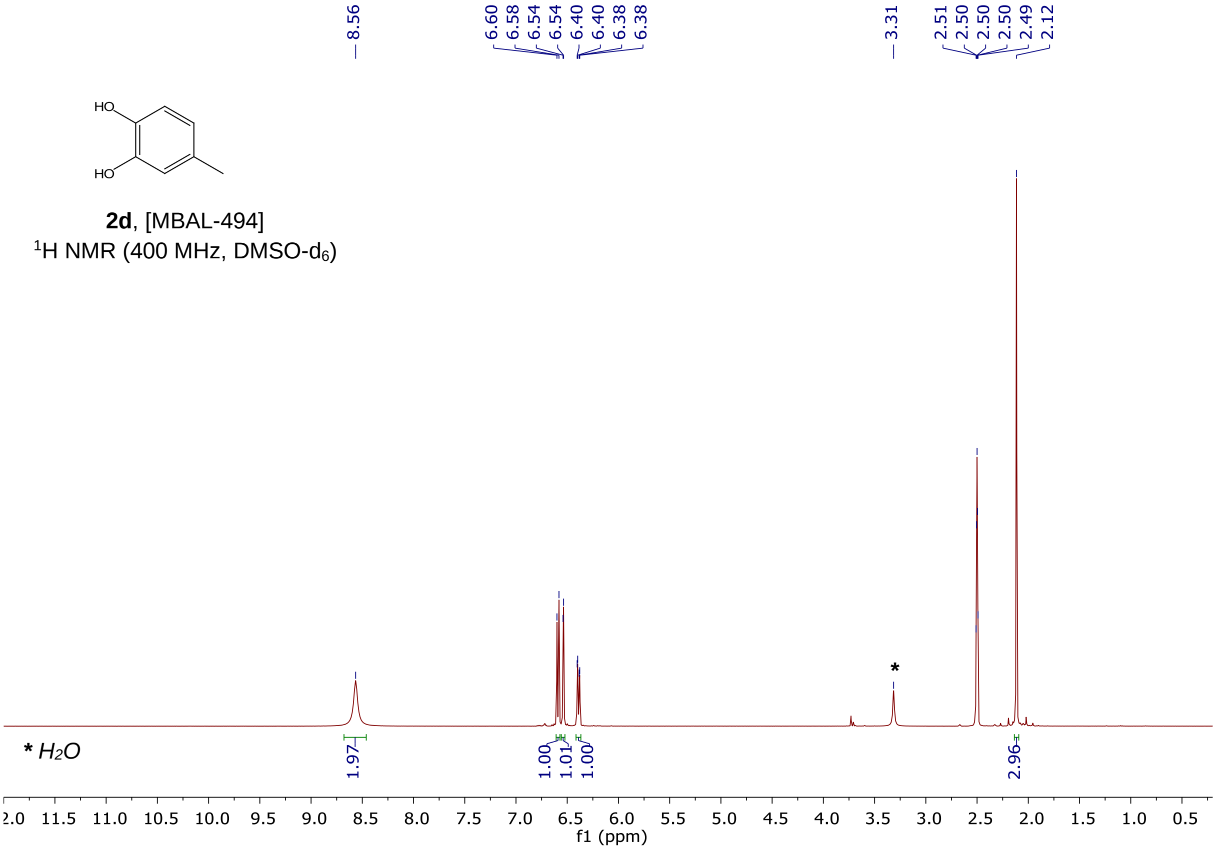
2c, [MBAL-776]

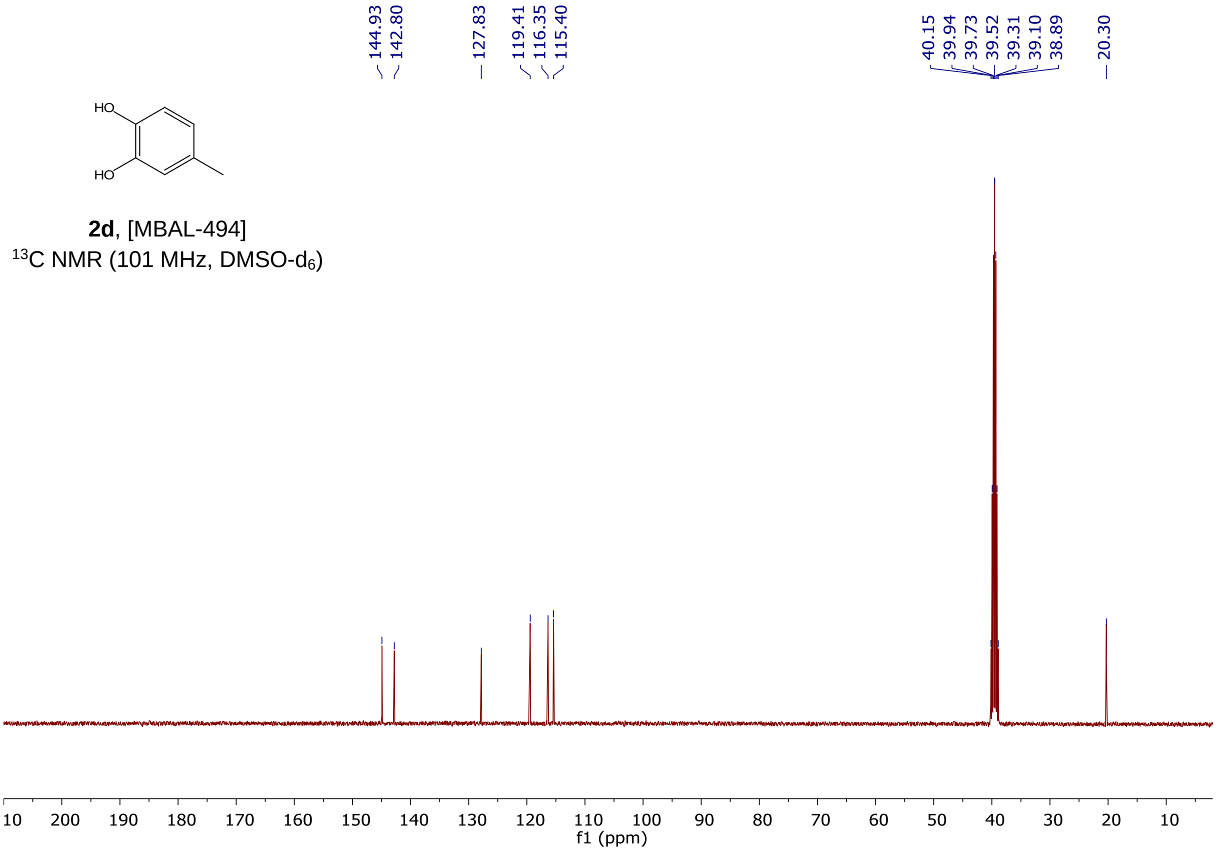
^{13}C DEPT 135° NMR (101 MHz, DMSO-d$_6$)

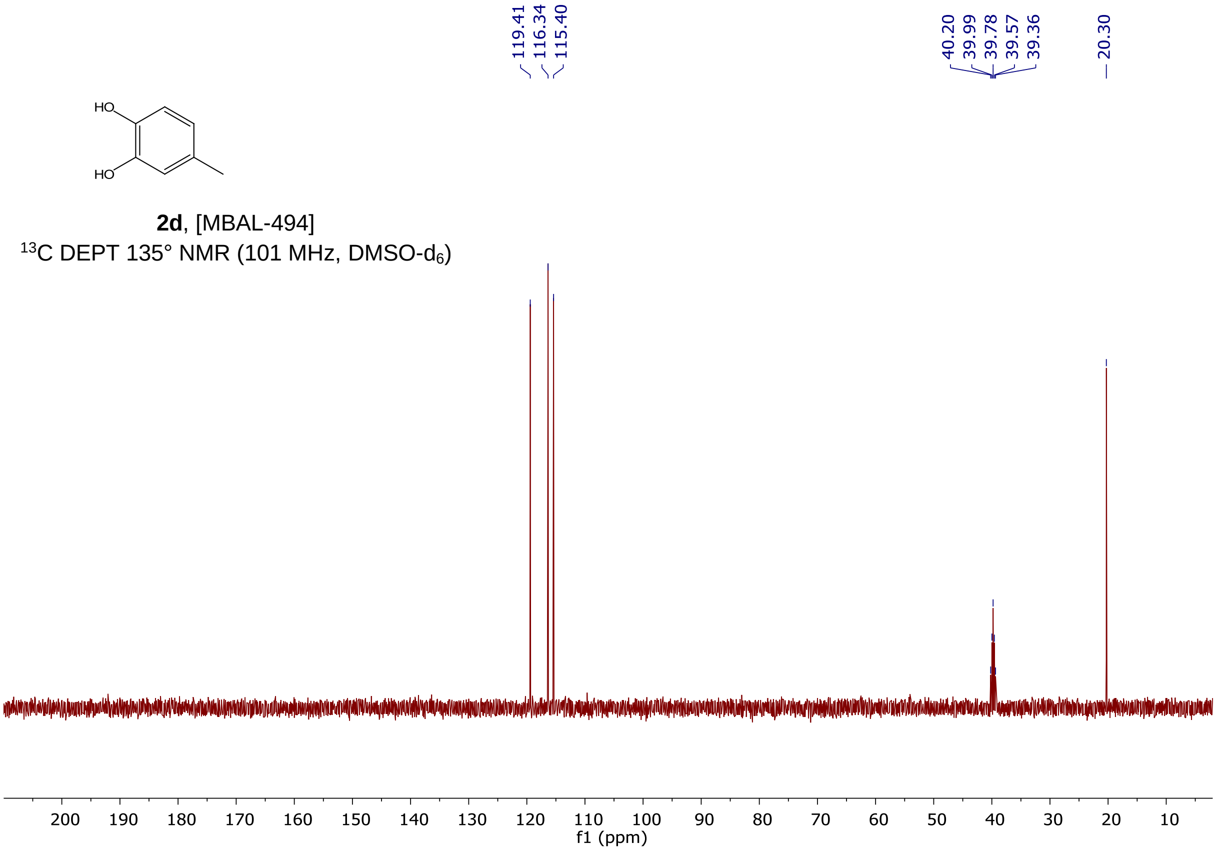


2c, [MBAL-776]

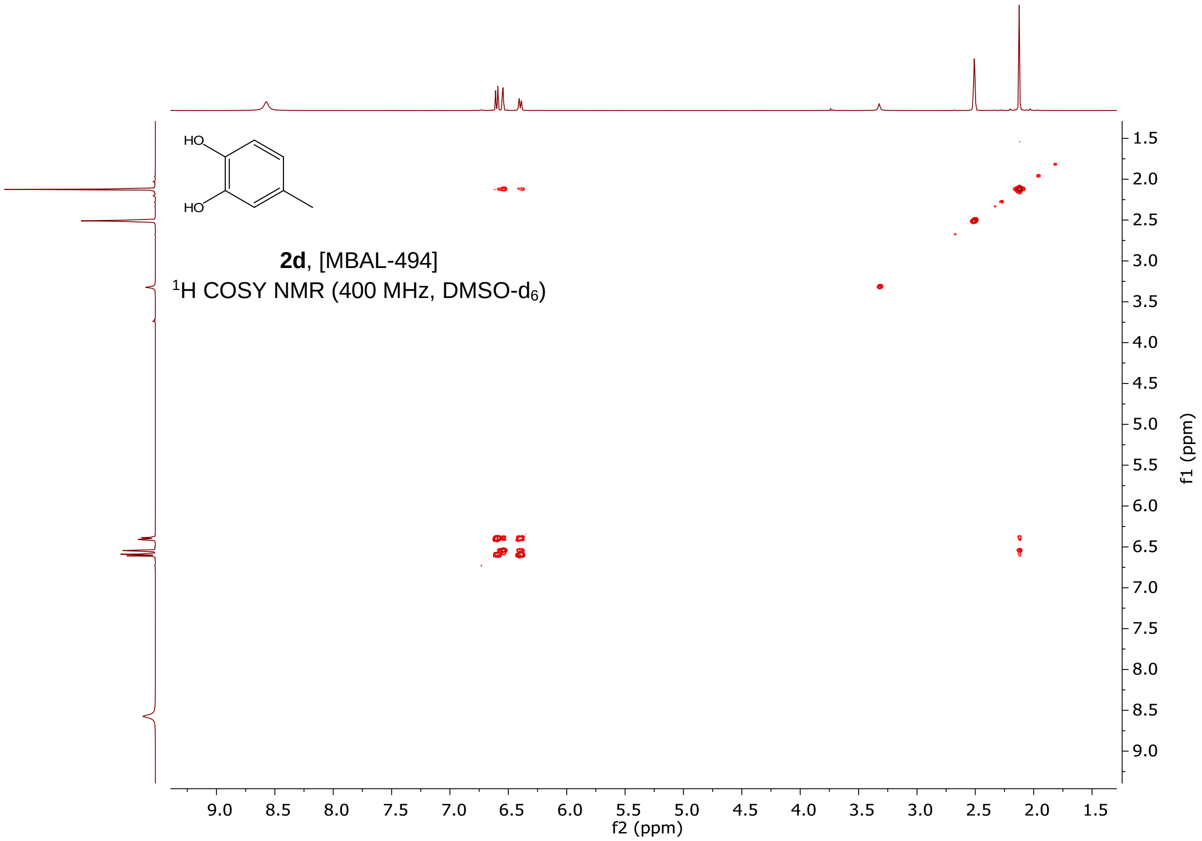
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)


2d, [MBAL-494]
^{1}H NMR (400 MHz, DMSO-d_6)

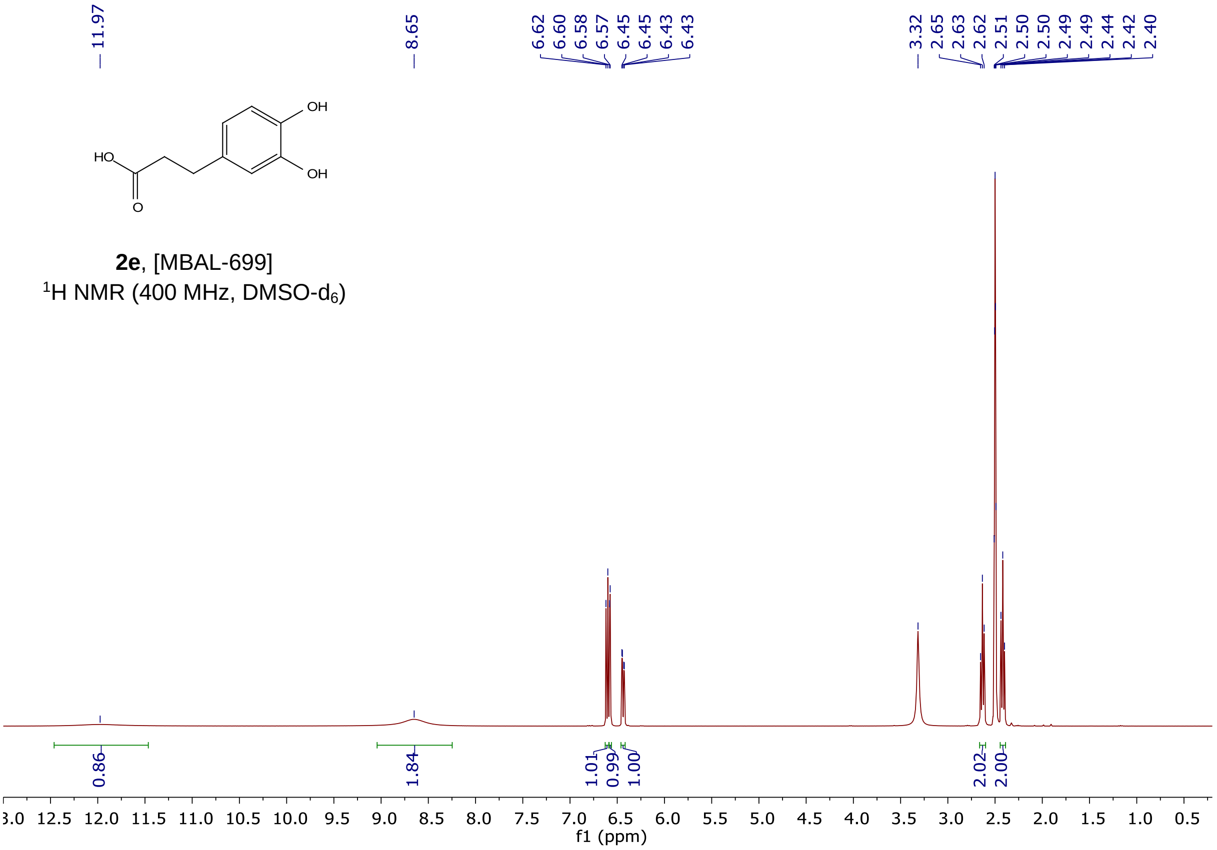

2d, [MBAL-494]
^{13}C NMR (101 MHz, DMSO-d_6)



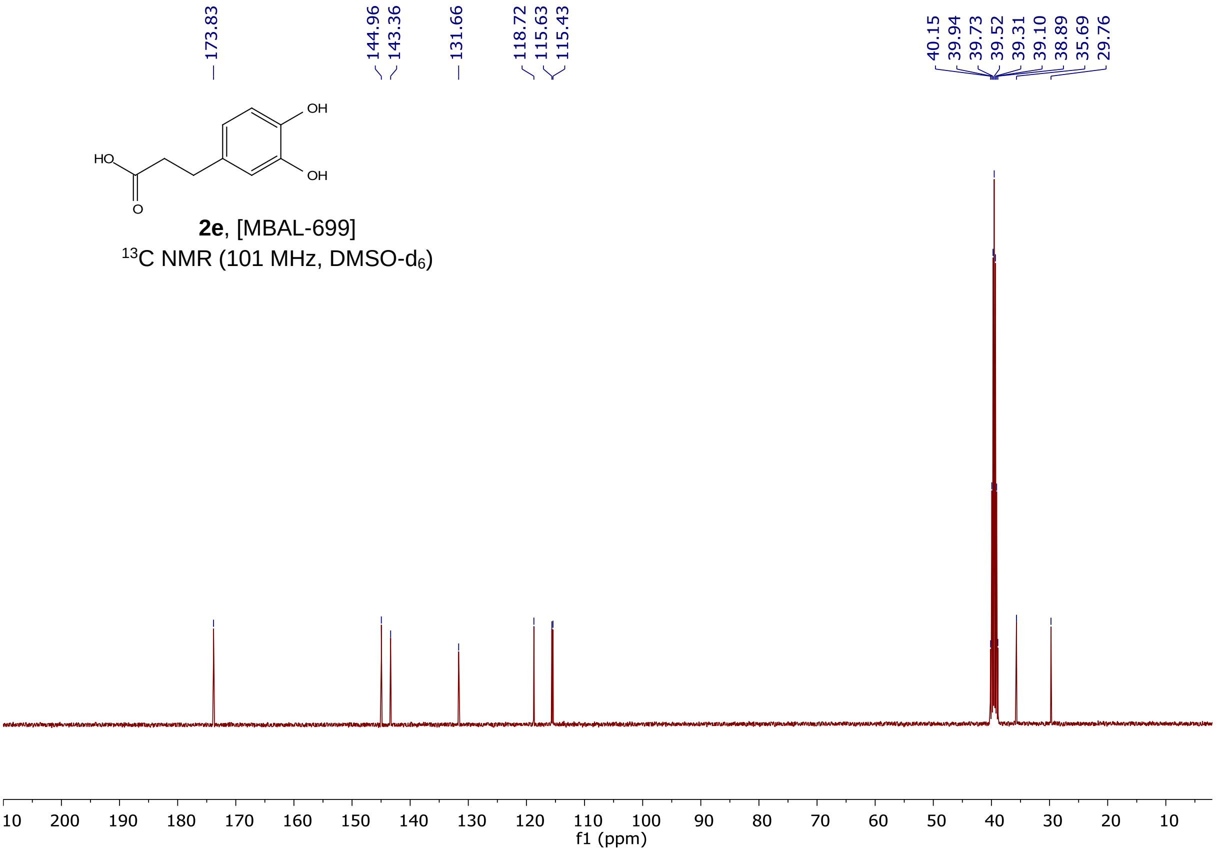
2d, [MBAL-494]
^{13}C DEPT 135° NMR (101 MHz, DMSO-d$_6$)



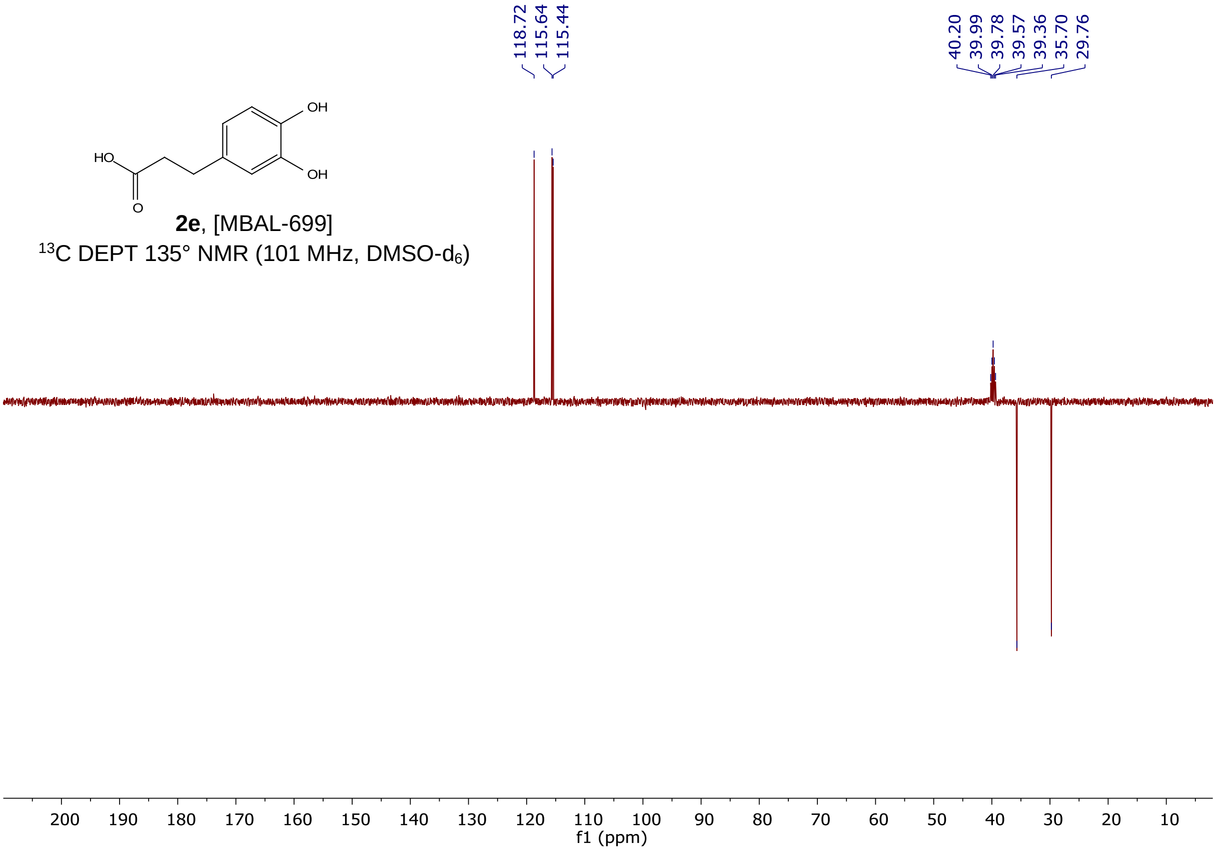
2d, [MBAL-494]
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)



2e, [MBAL-699]
^{1}H NMR (400 MHz, DMSO-d_6)

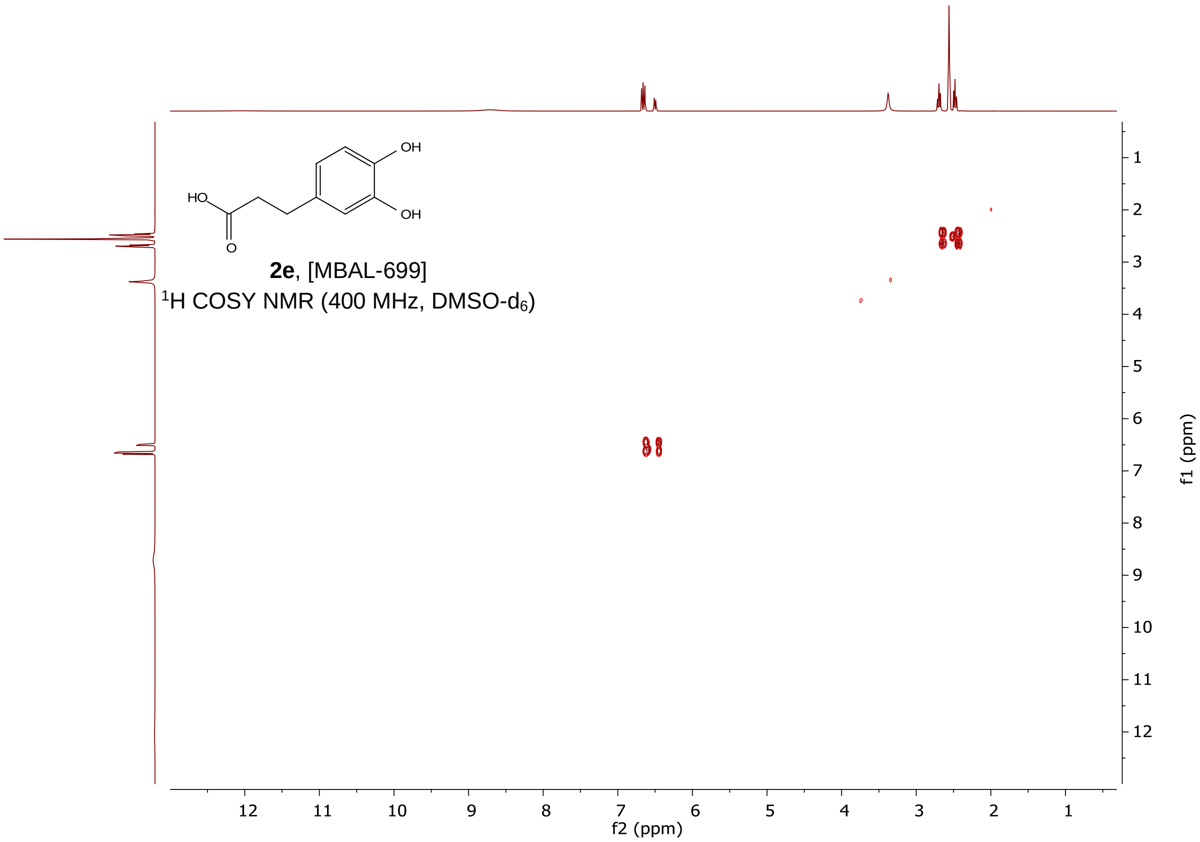


2e, [MBAL-699]
^{13}C NMR (101 MHz, DMSO-d_6)



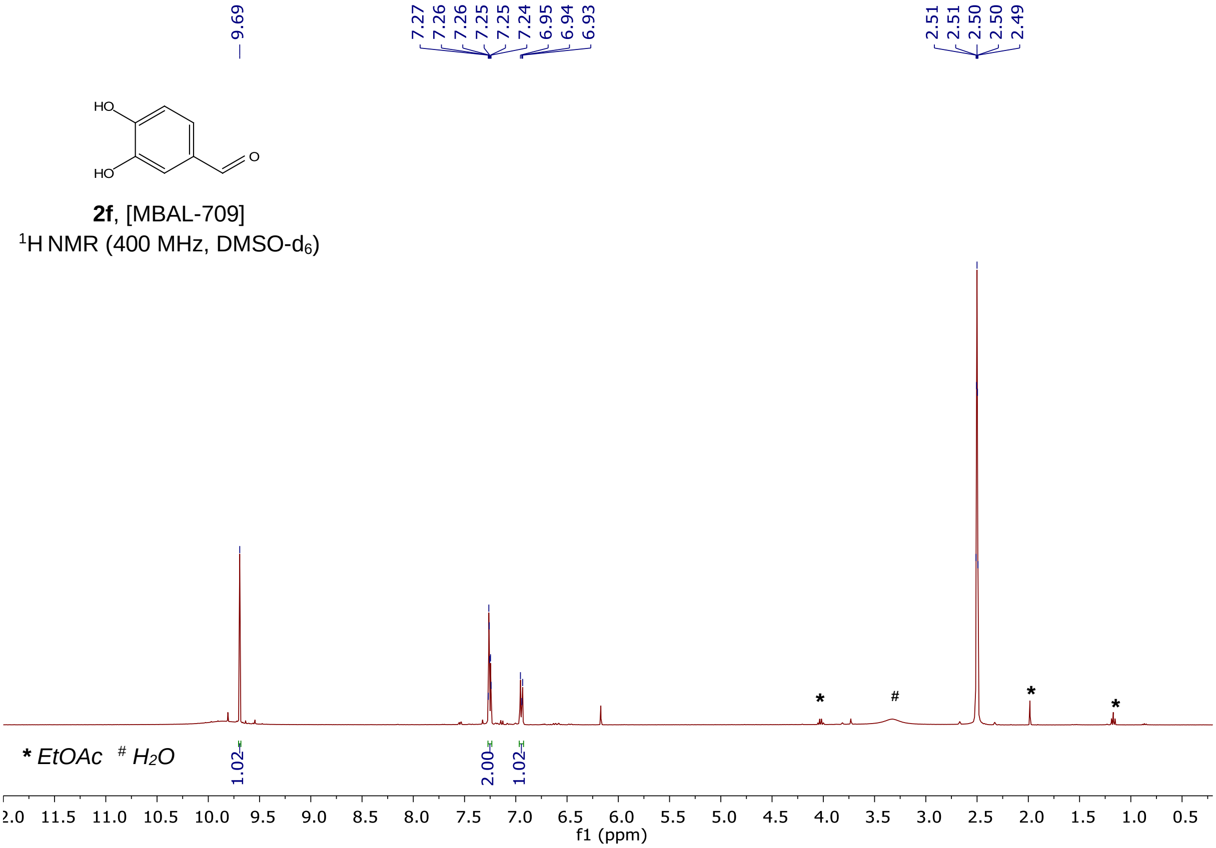
2e, [MBAL-699]

^{13}C DEPT 135° NMR (101 MHz, DMSO-d$_6$)

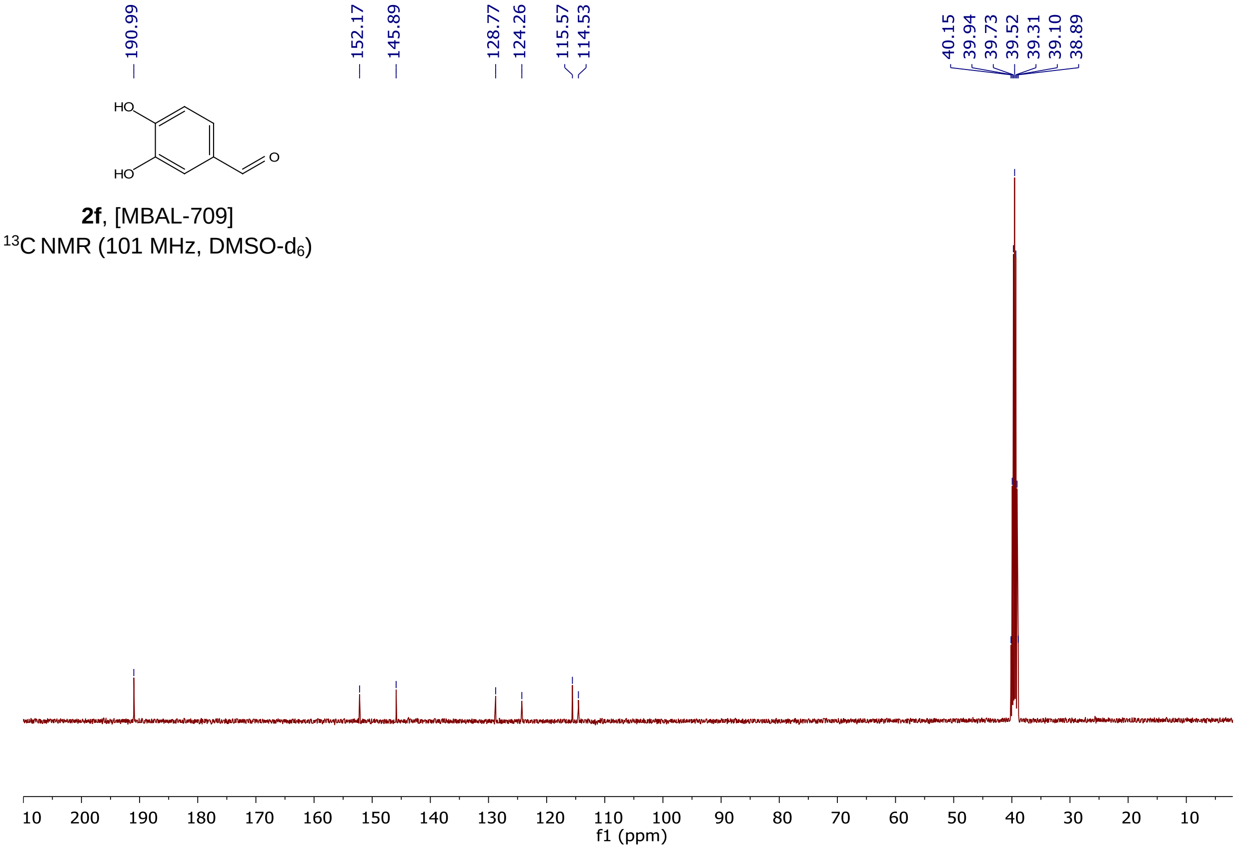


2e, [MBAL-699]

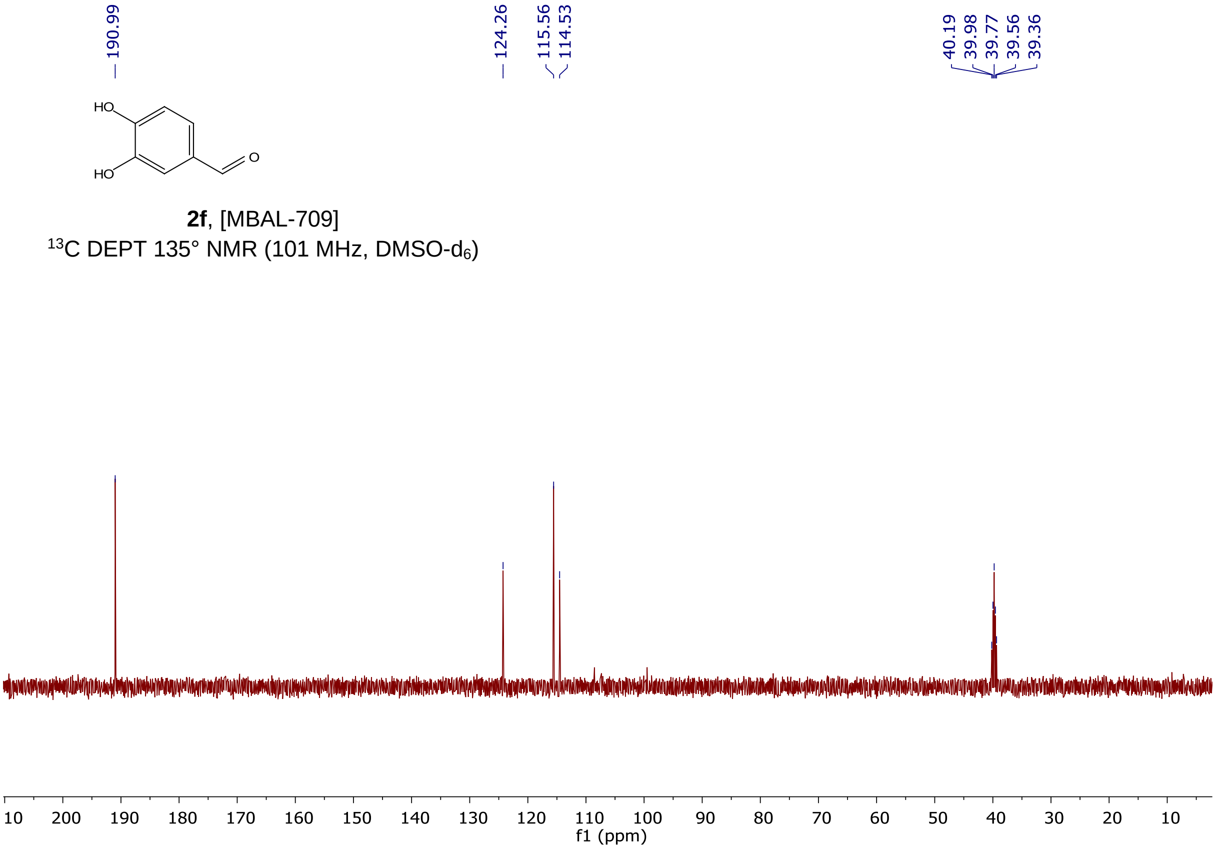
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)

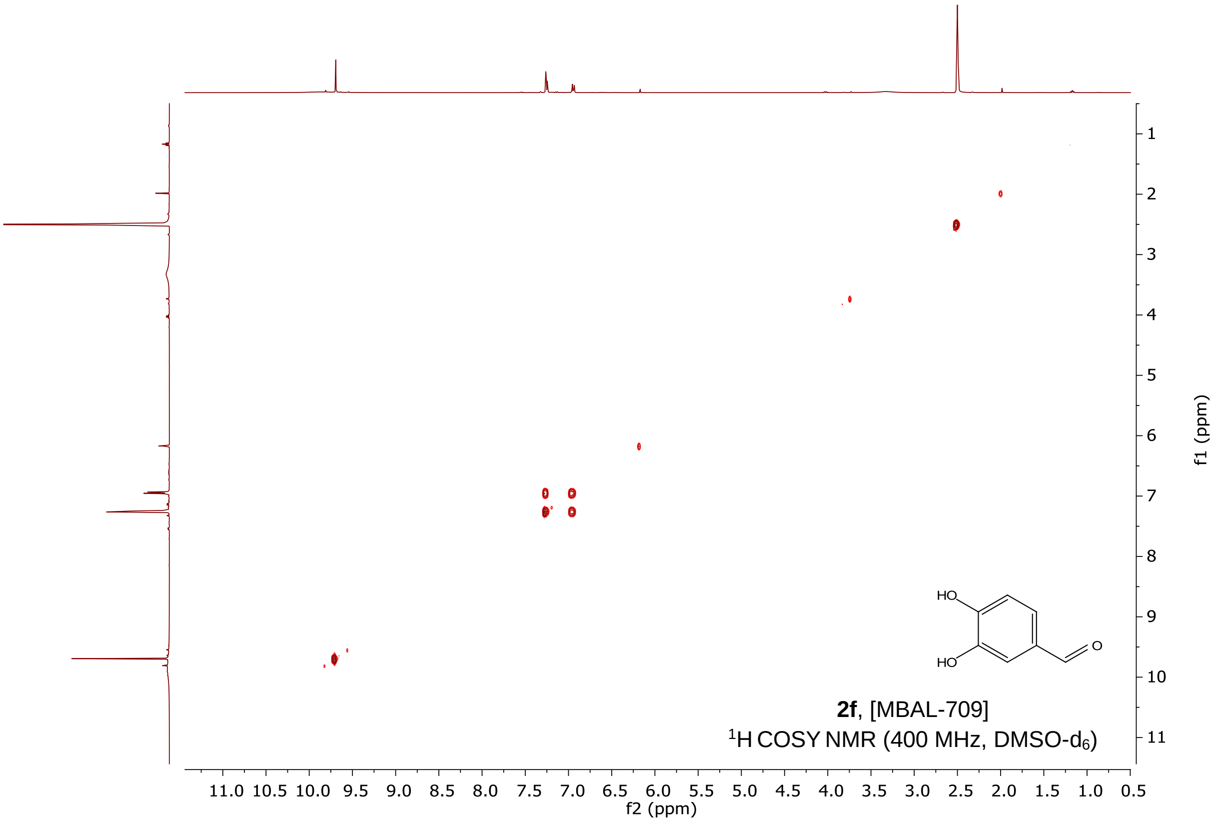


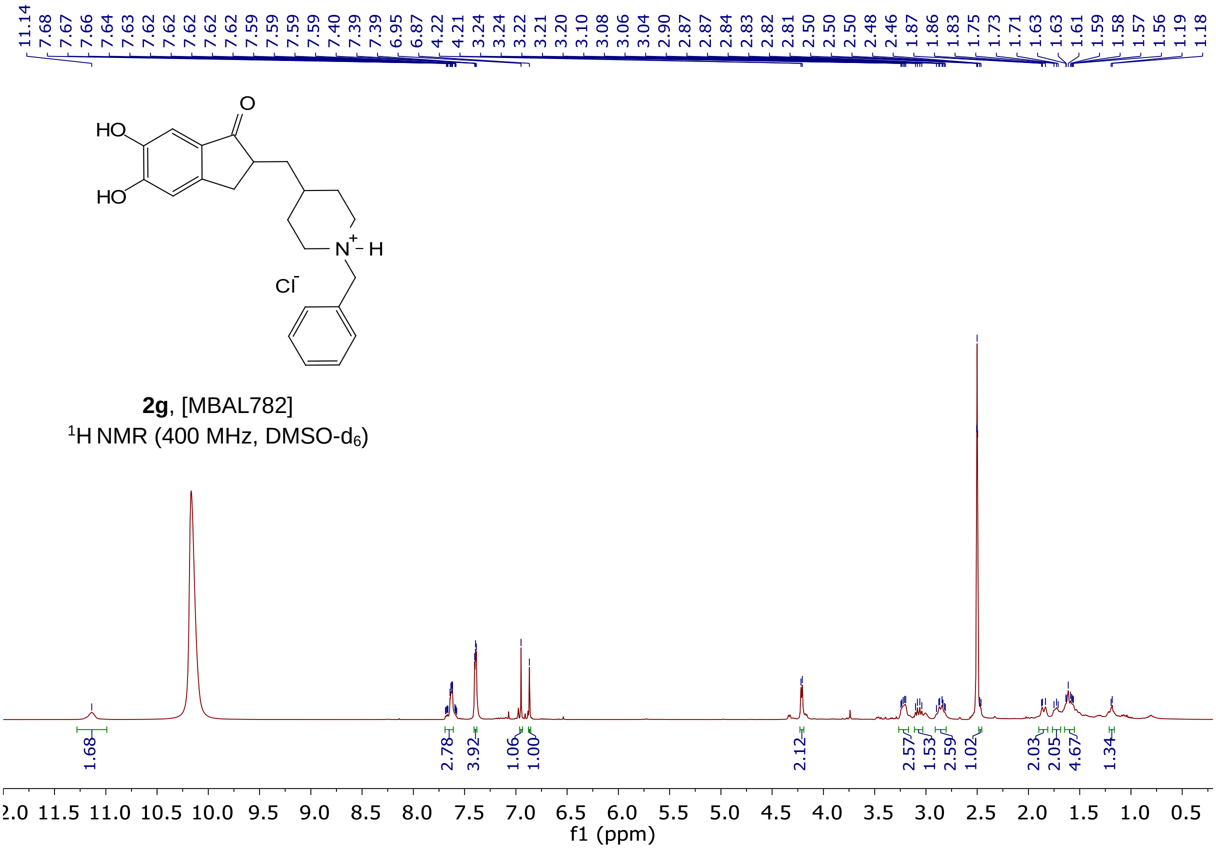
2f, [MBAL-709]
^{1}H NMR (400 MHz, DMSO-d_6)



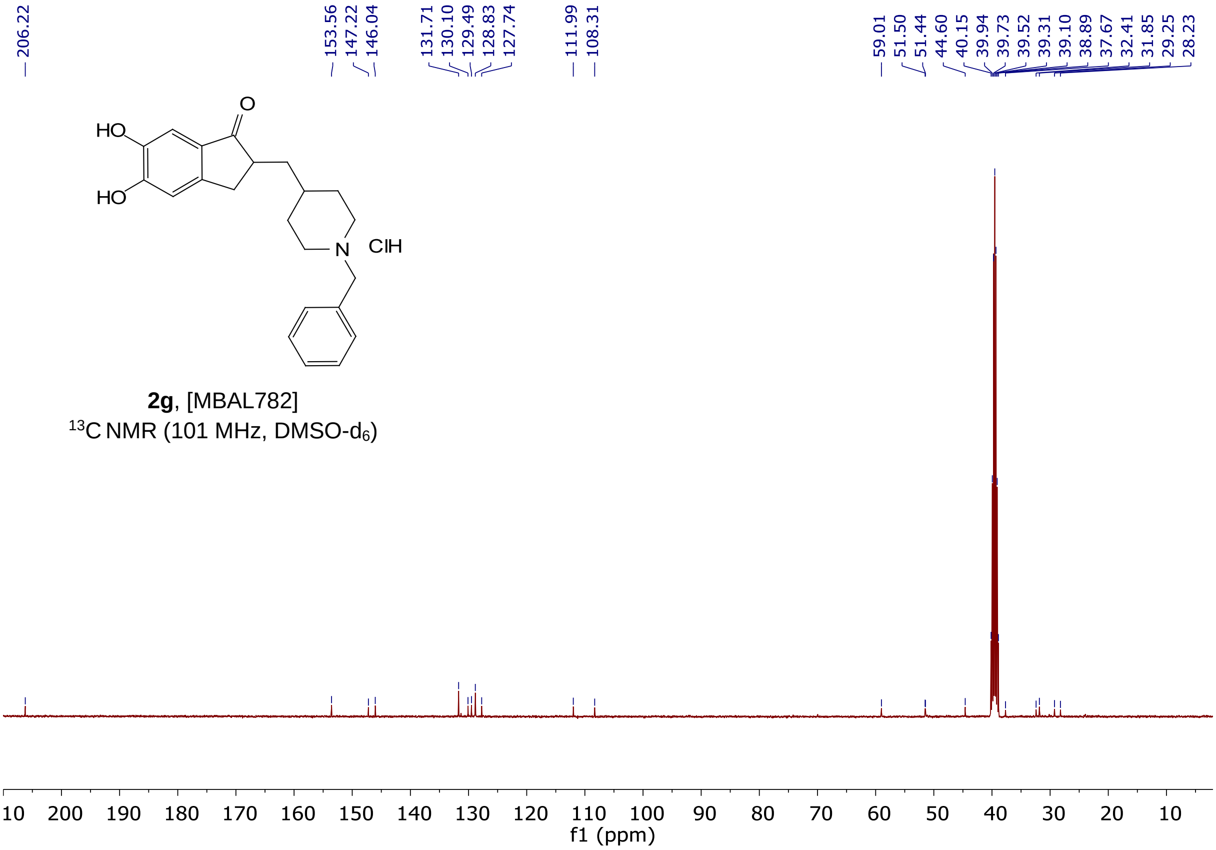
2f, [MBAL-709]
^{13}C NMR (101 MHz, DMSO-d_6)


2f, [MBAL-709]
^{13}C DEPT 135° NMR (101 MHz, DMSO-d$_6$)

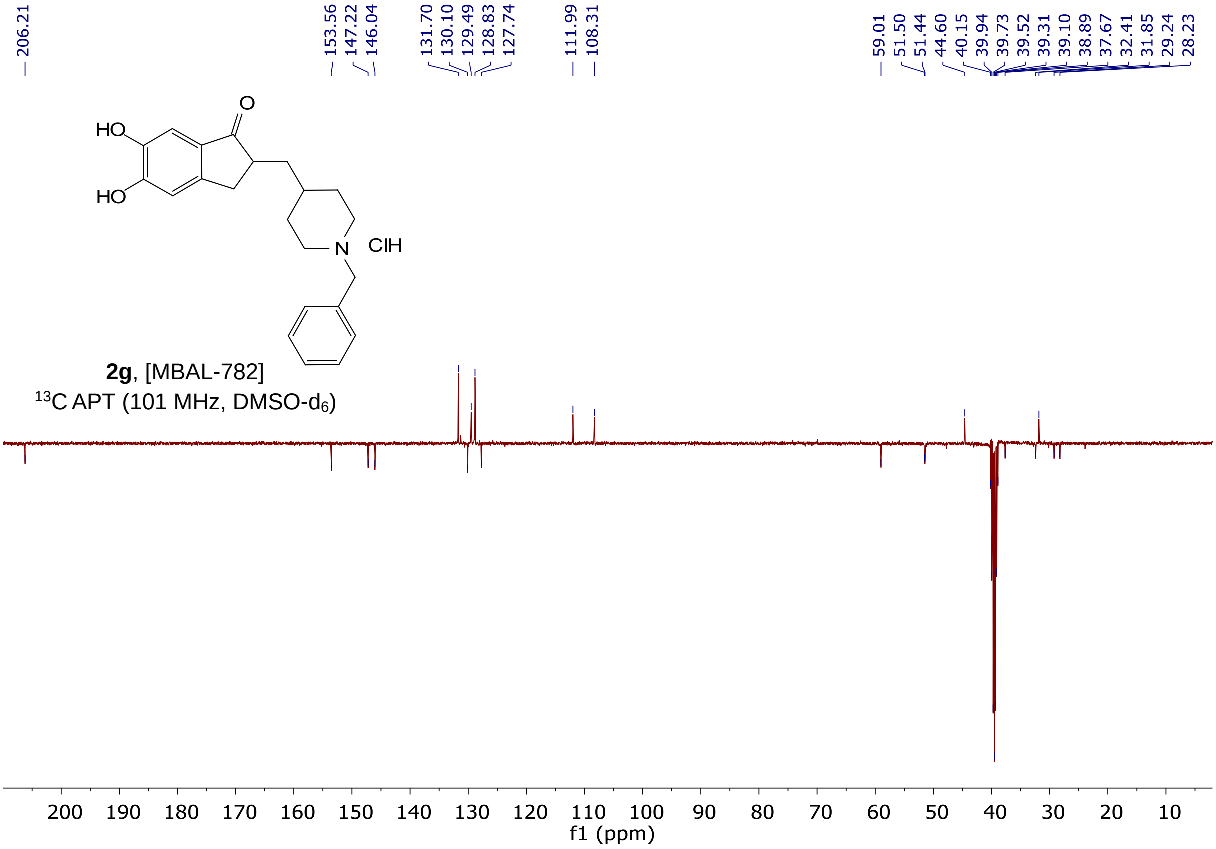

2f, [MBAL-709]
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)



2g, [MBAL782]
^{1}H NMR (400 MHz, DMSO-d_6)

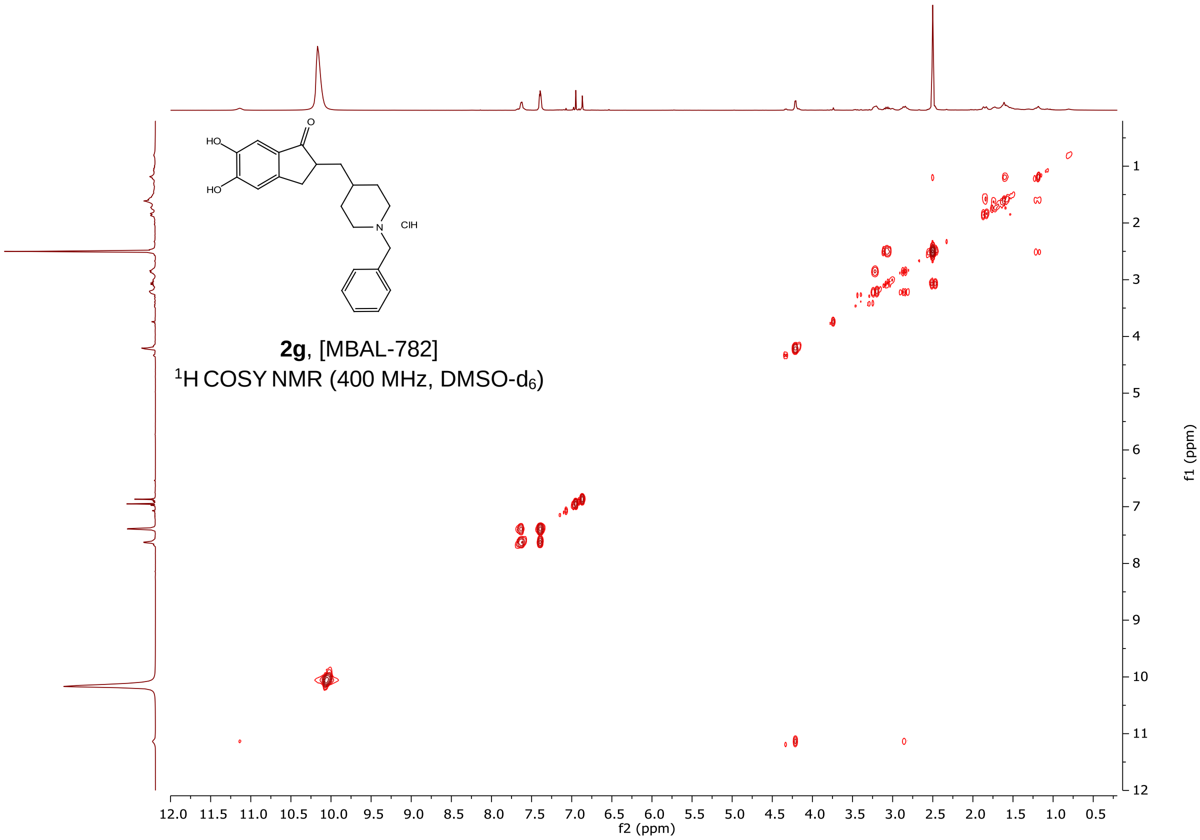


2g, [MBAL782]
^{13}C NMR (101 MHz, DMSO-d_6)



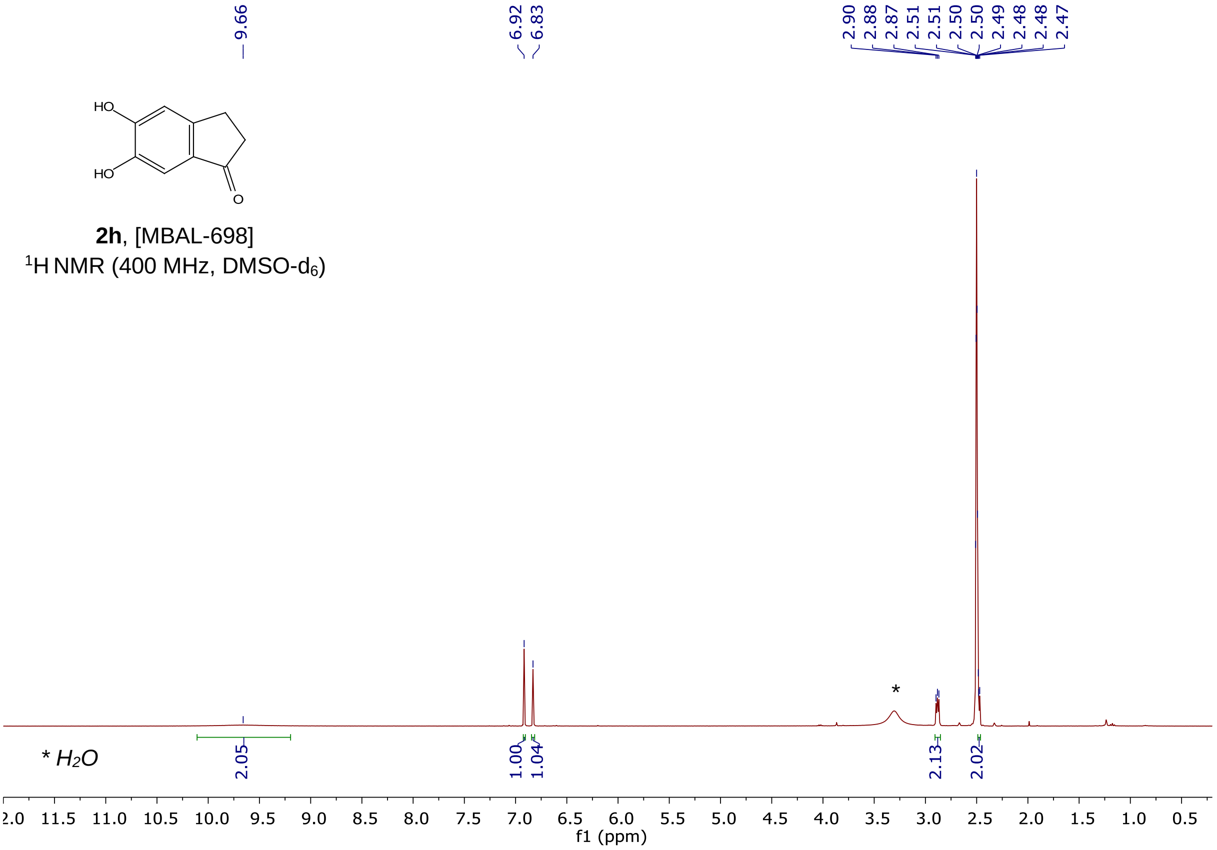
2g, [MBAL-782]

^{13}C APT (101 MHz, DMSO-d$_6$)

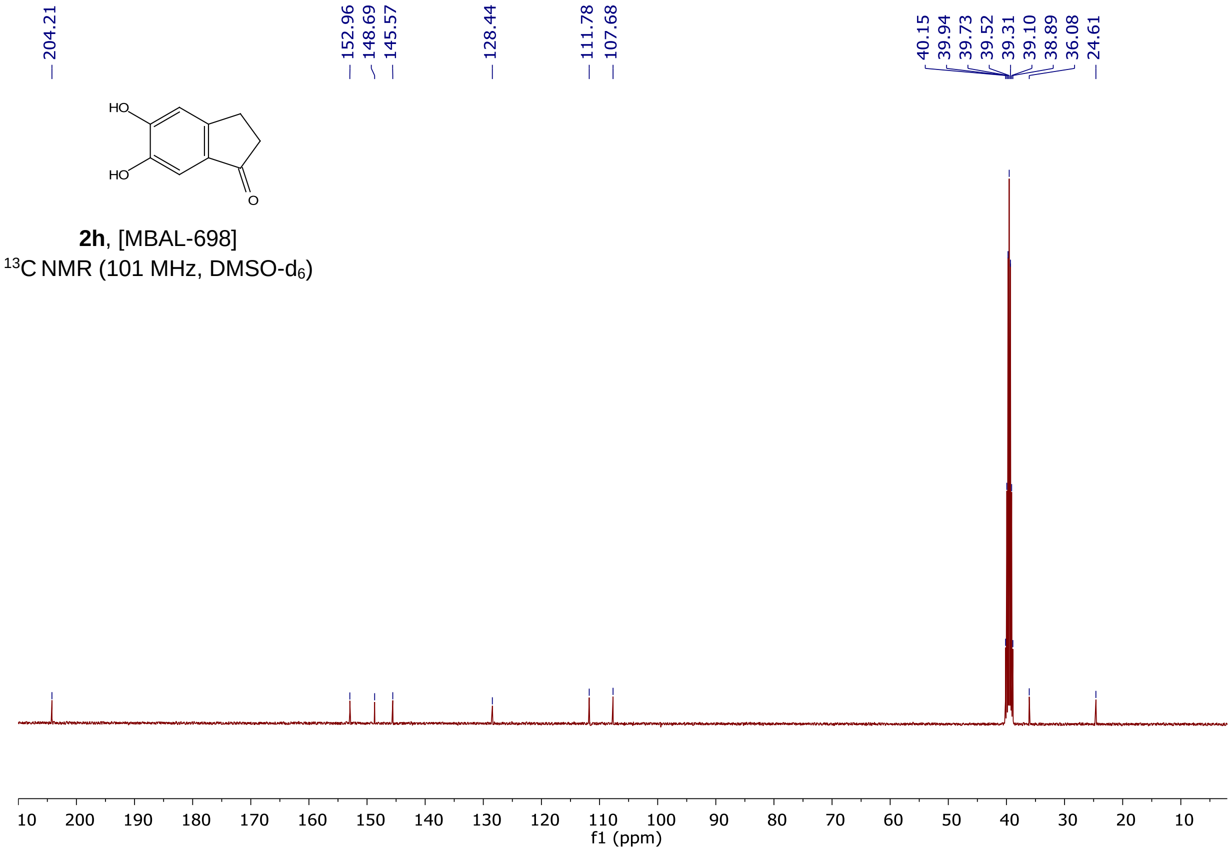


2g, [MBAL-782]

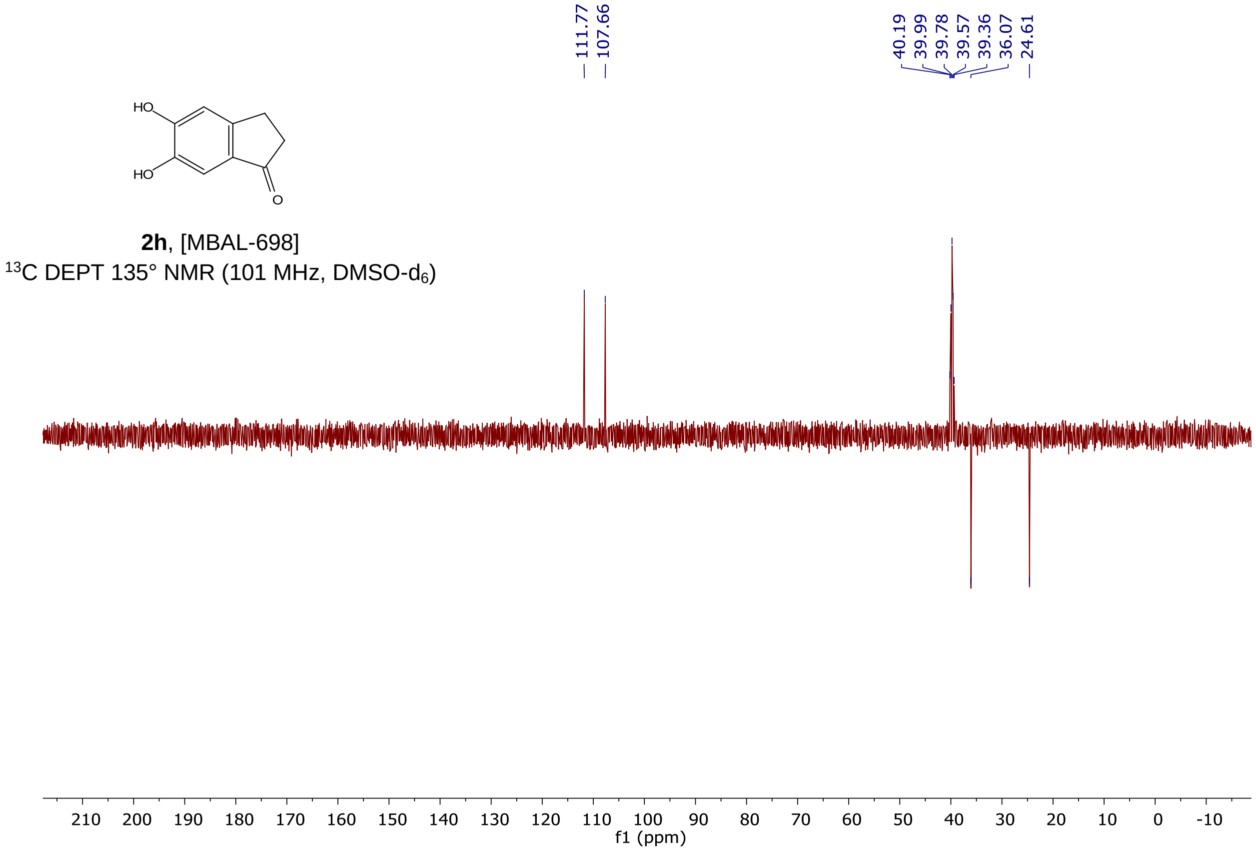
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)



2h, [MBAL-698]
^{1}H NMR (400 MHz, DMSO-d_6)

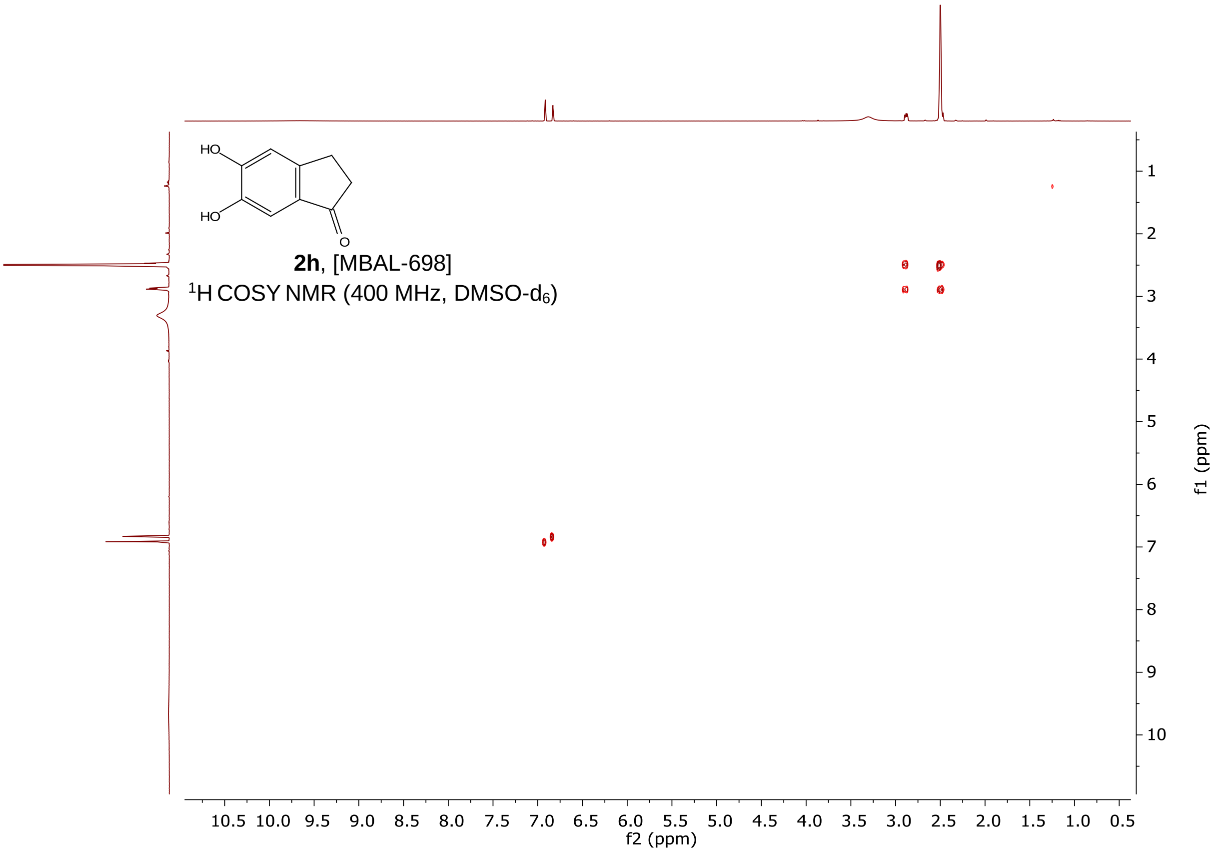


2h, [MBAL-698]
^{13}C NMR (101 MHz, DMSO-d_6)



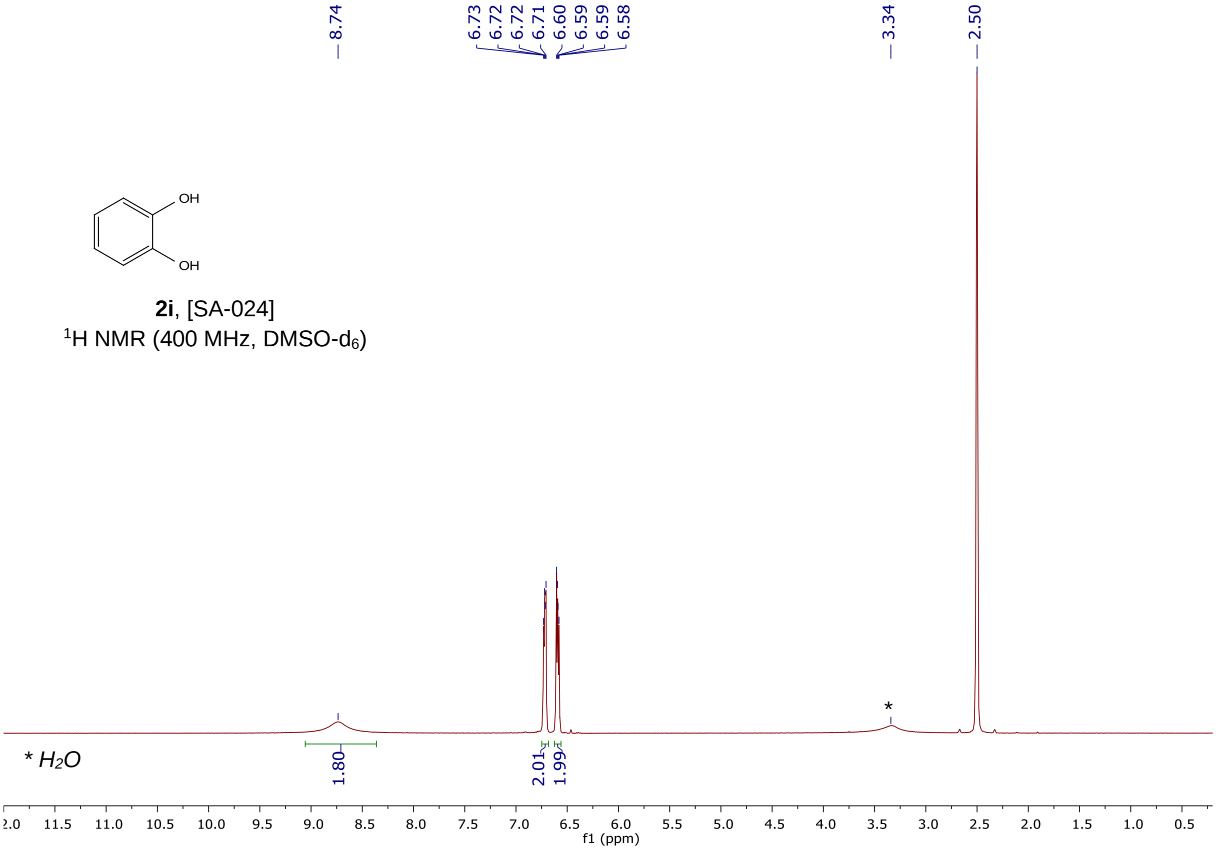
2h, [MBAL-698]

^{13}C DEPT 135° NMR (101 MHz, DMSO-d_6)

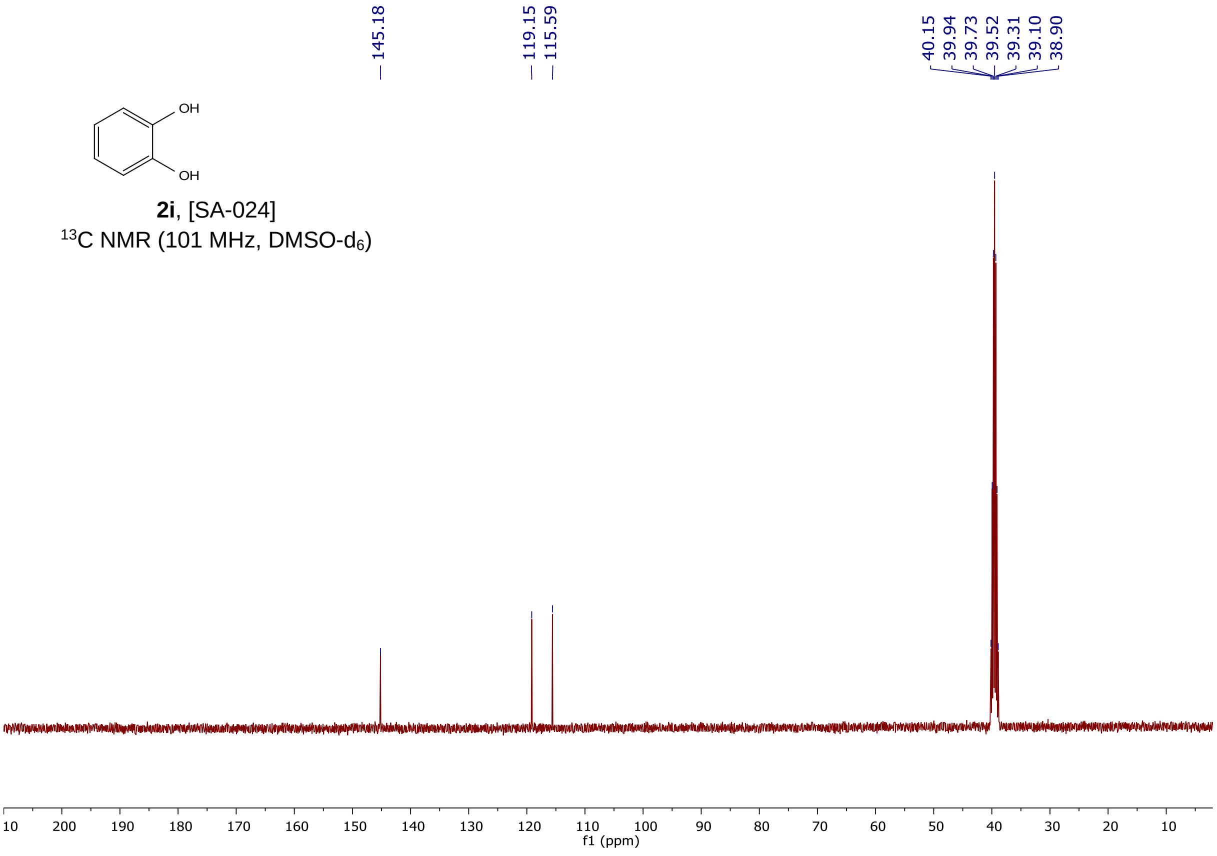


2h, [MBAL-698]

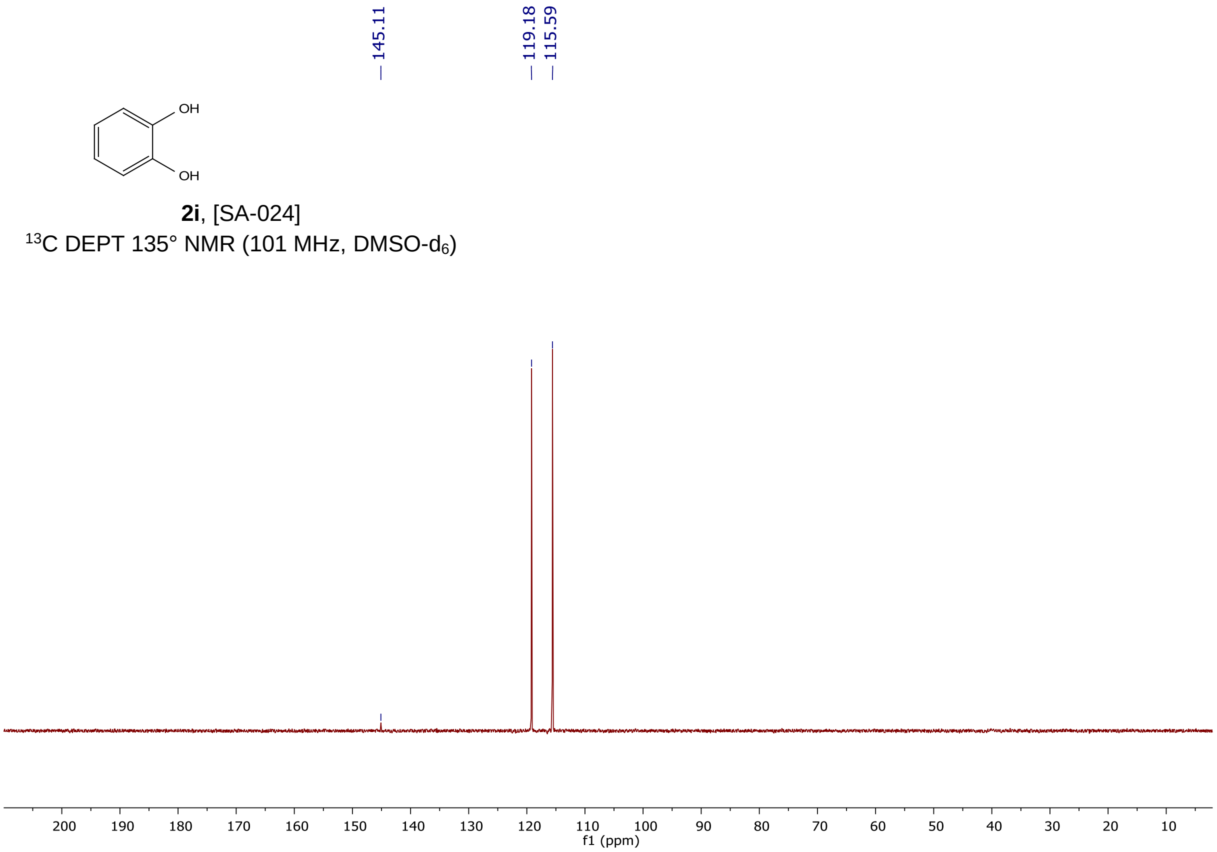
^{1}H COSY NMR (400 MHz, DMSO-d_6)



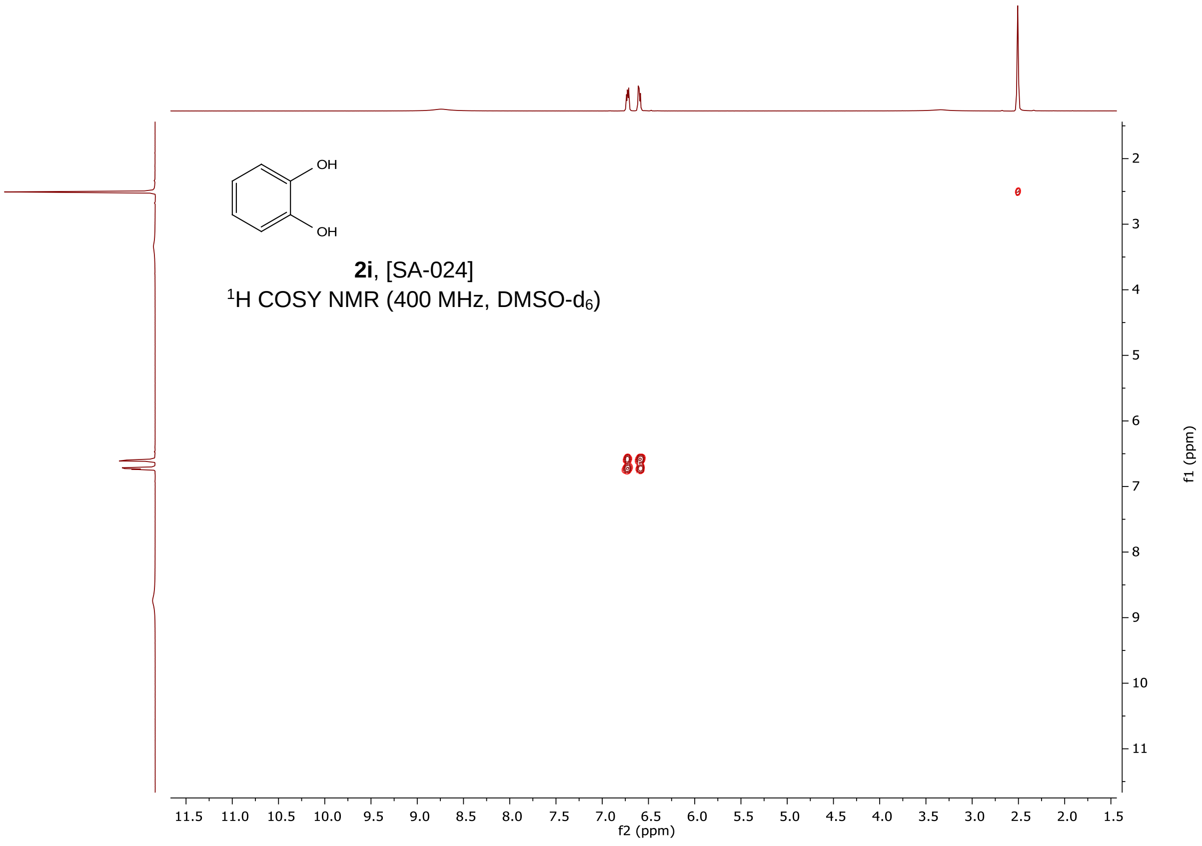
2i, [SA-024]
^{1}H NMR (400 MHz, DMSO-d_6)



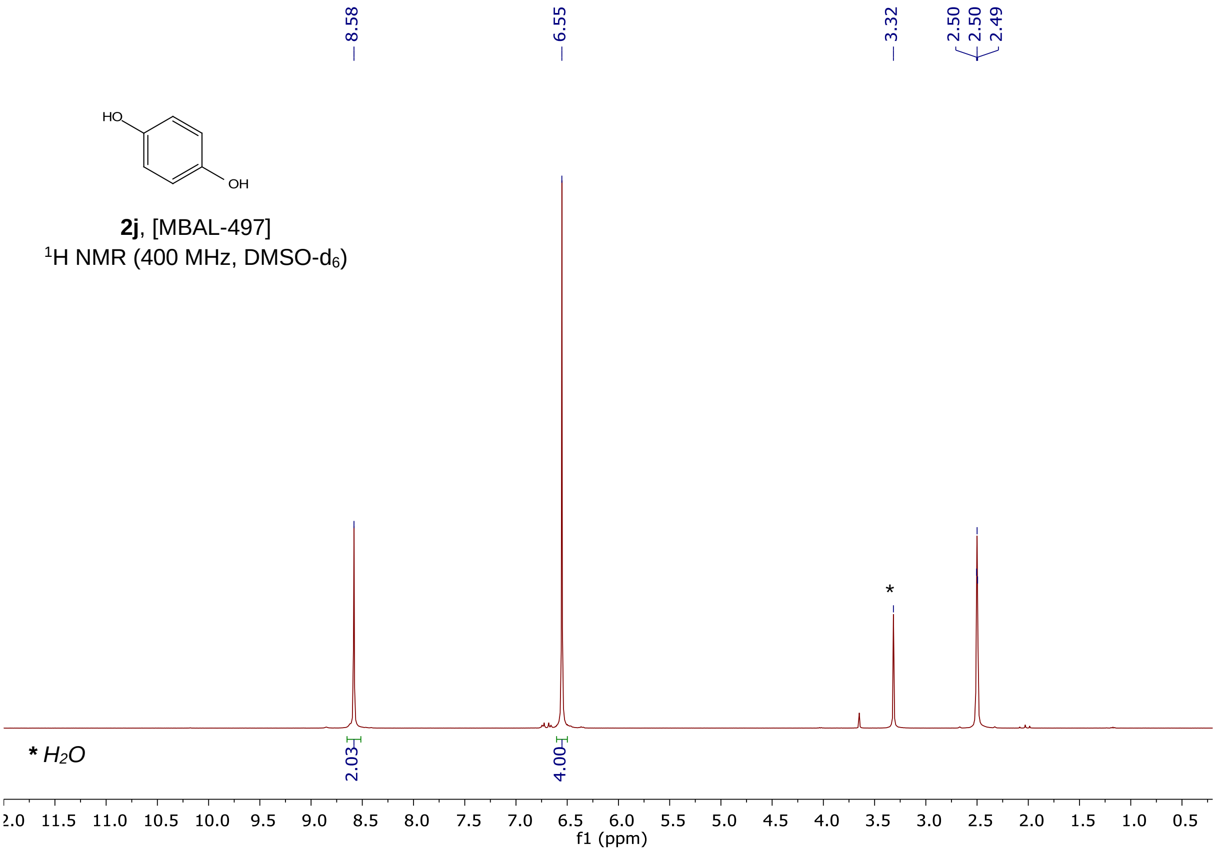
2i, [SA-024]
^{13}C NMR (101 MHz, DMSO-d_6)



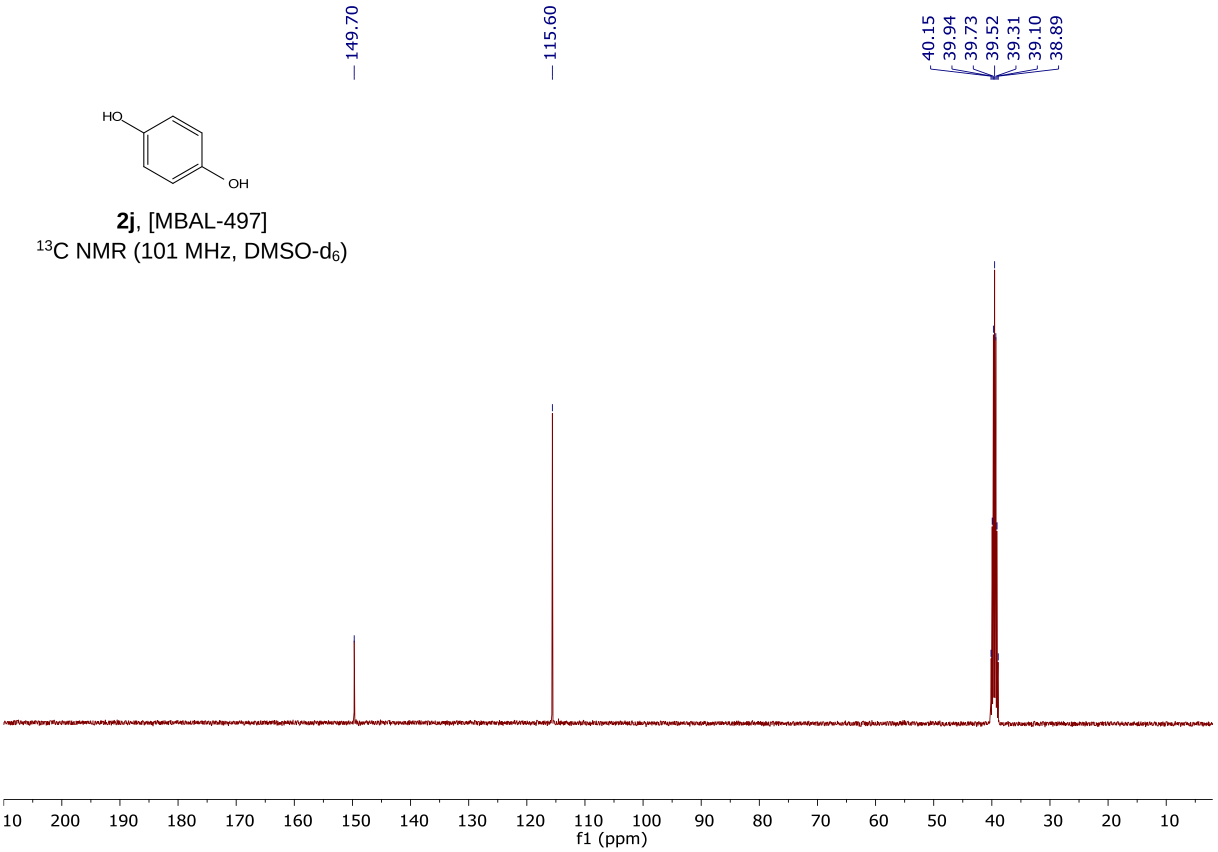
2i, [SA-024]
^{13}C DEPT 135° NMR (101 MHz, DMSO-d$_6$)



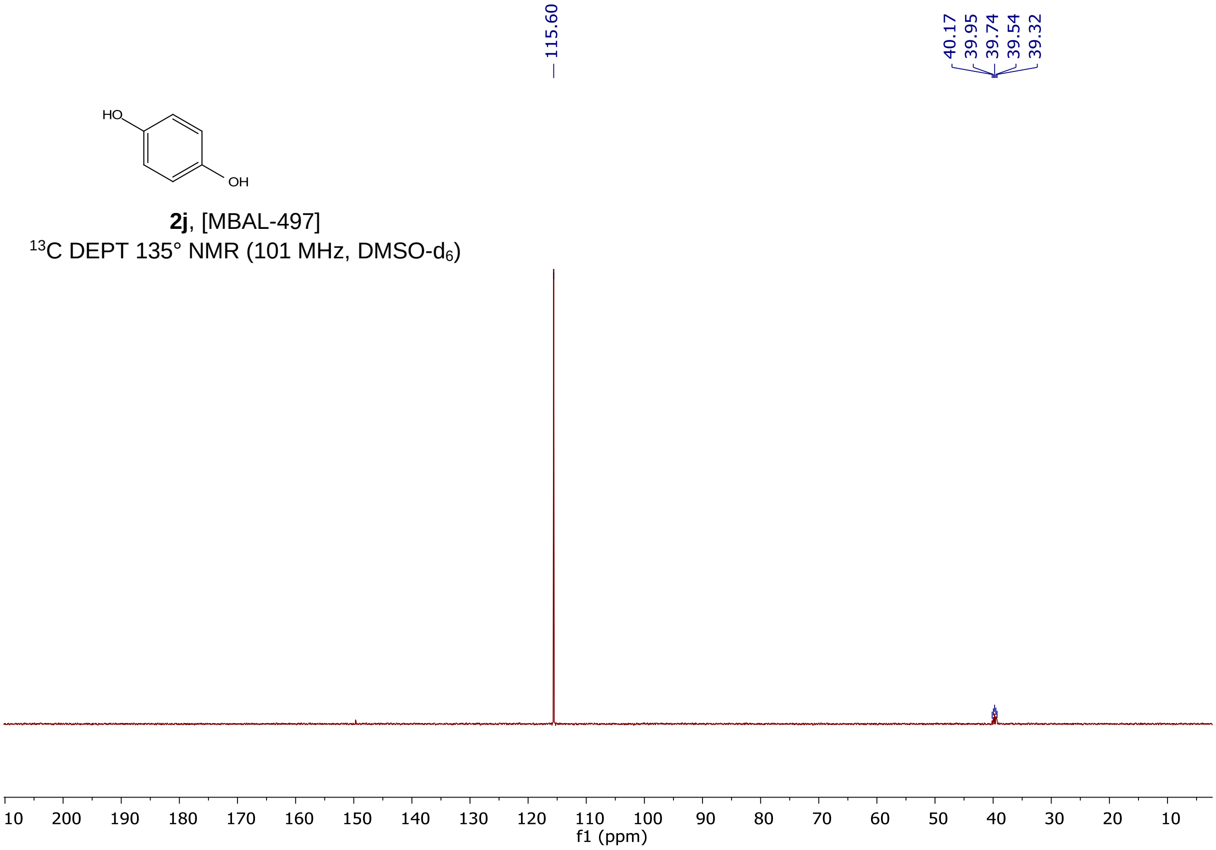
2i, [SA-024]
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)



2j, [MBAL-497]
^{1}H NMR (400 MHz, DMSO-d_6)

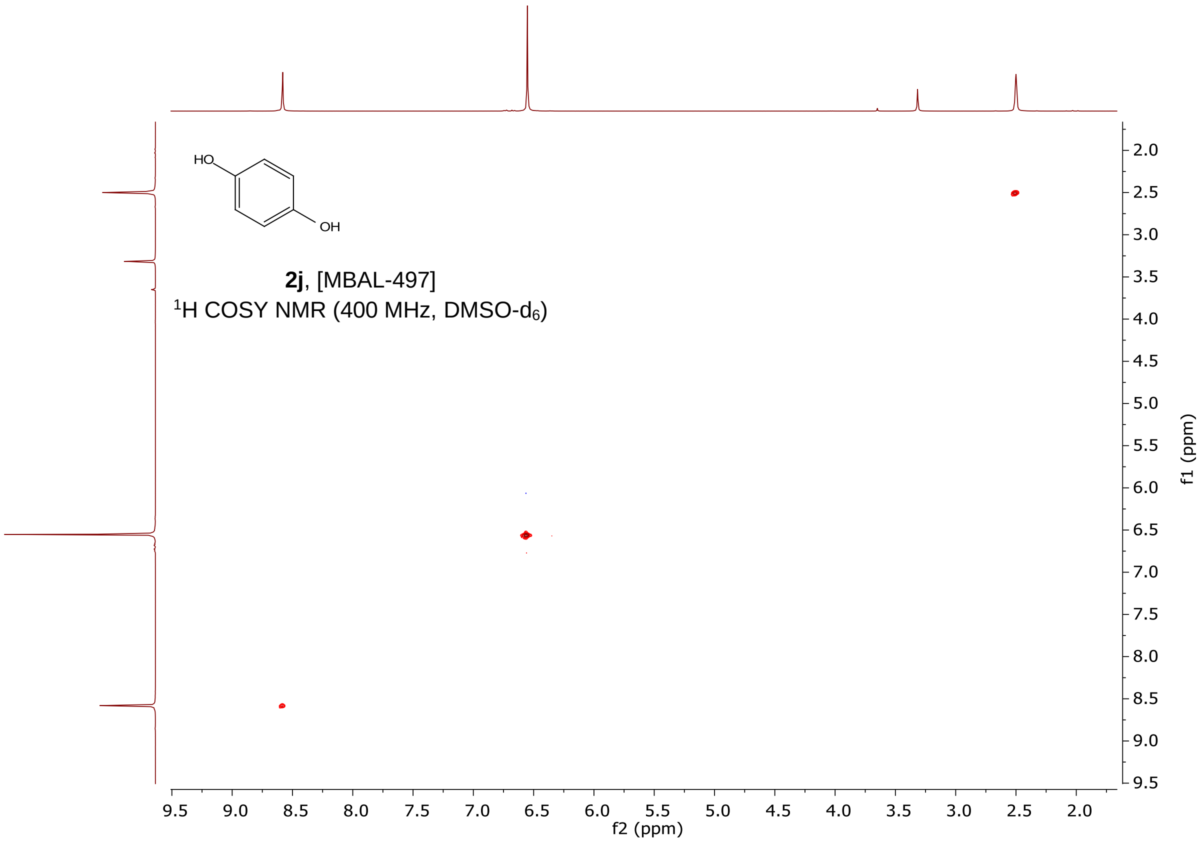


2j, [MBAL-497]
^{13}C NMR (101 MHz, DMSO-d_6)



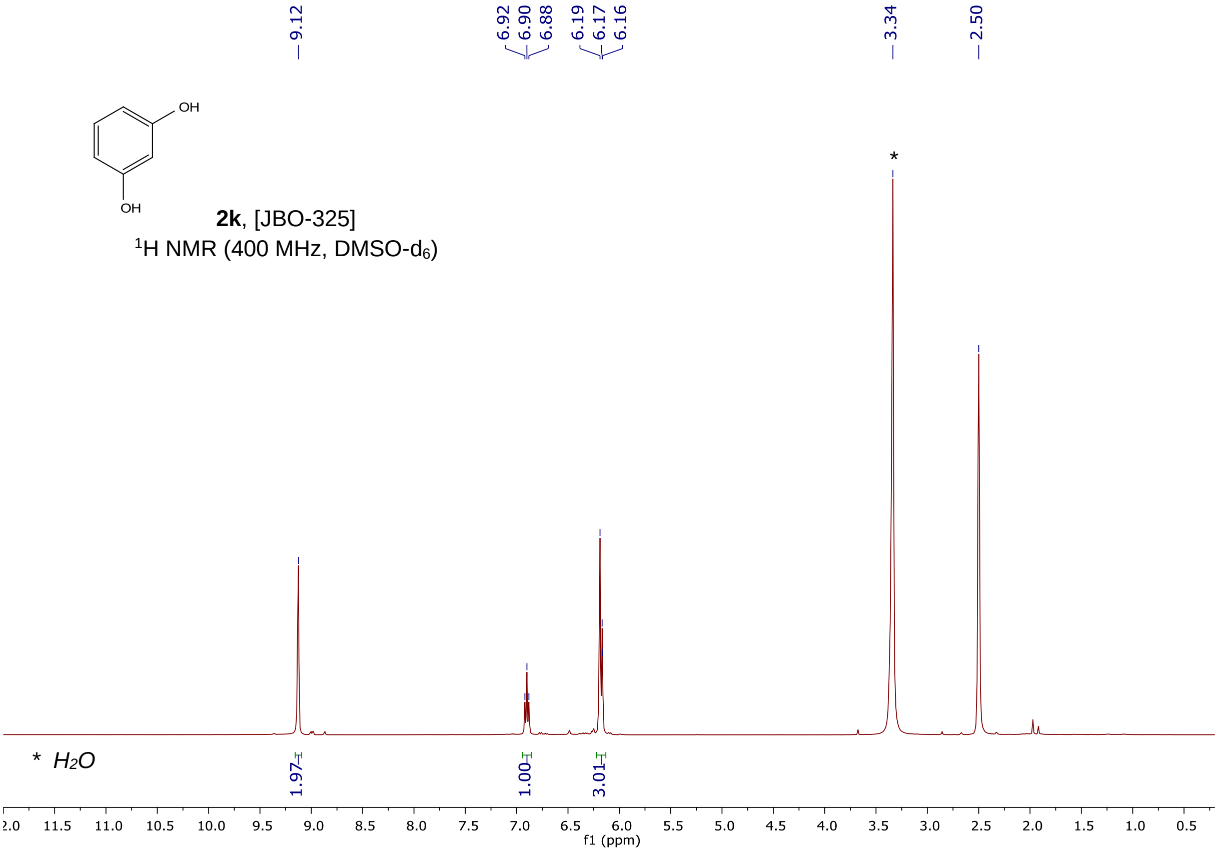
2j, [MBAL-497]

^{13}C DEPT 135° NMR (101 MHz, DMSO-d_6)

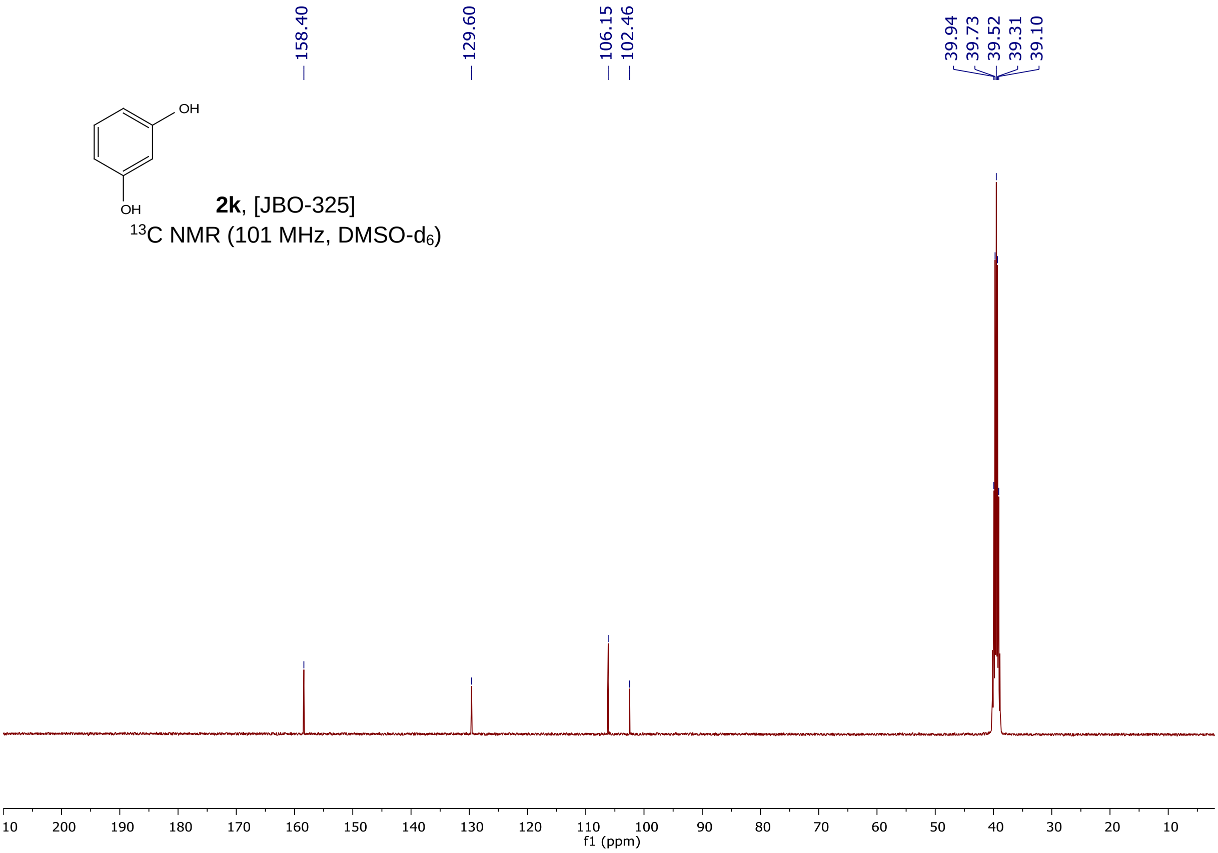


2j, [MBAL-497]

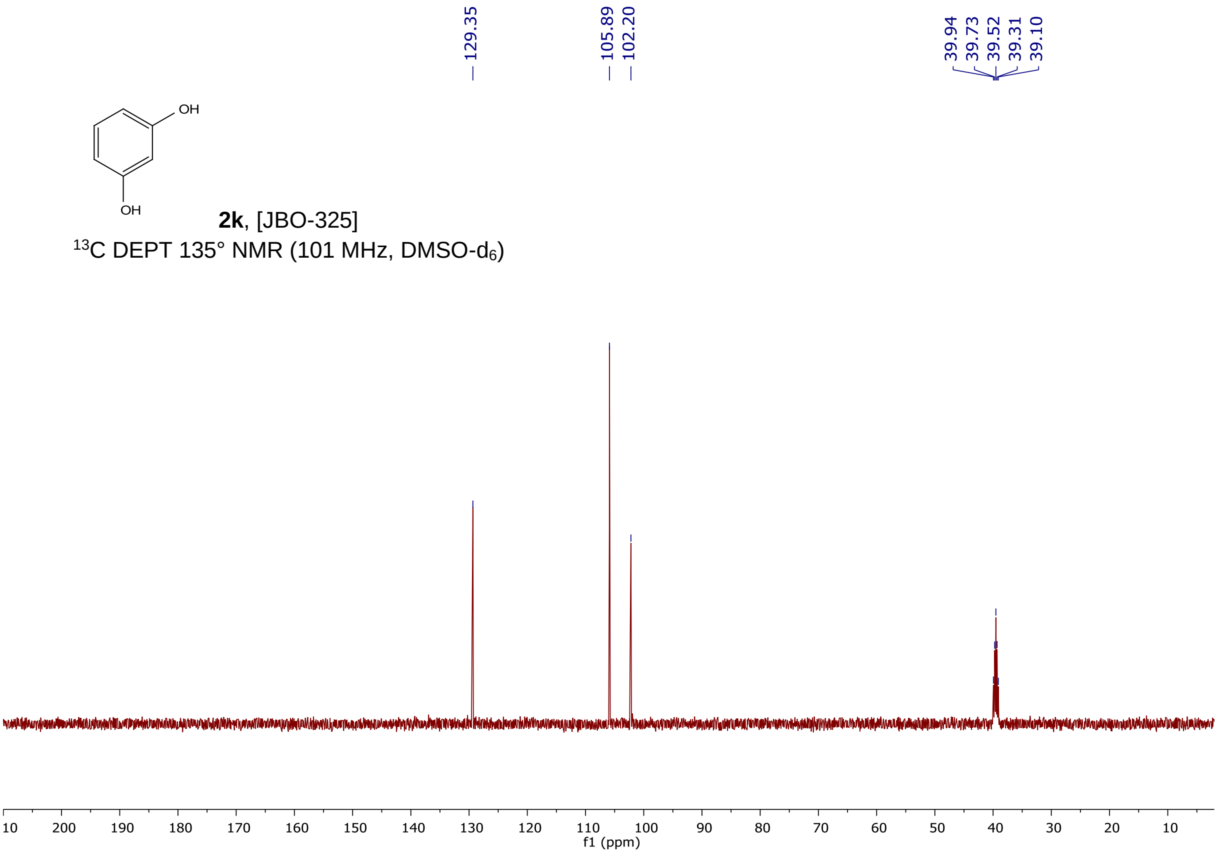
^{1}H COSY NMR (400 MHz, DMSO-d_6)



2k, [JBO-325]
^{1}H NMR (400 MHz, DMSO-d$_6$)

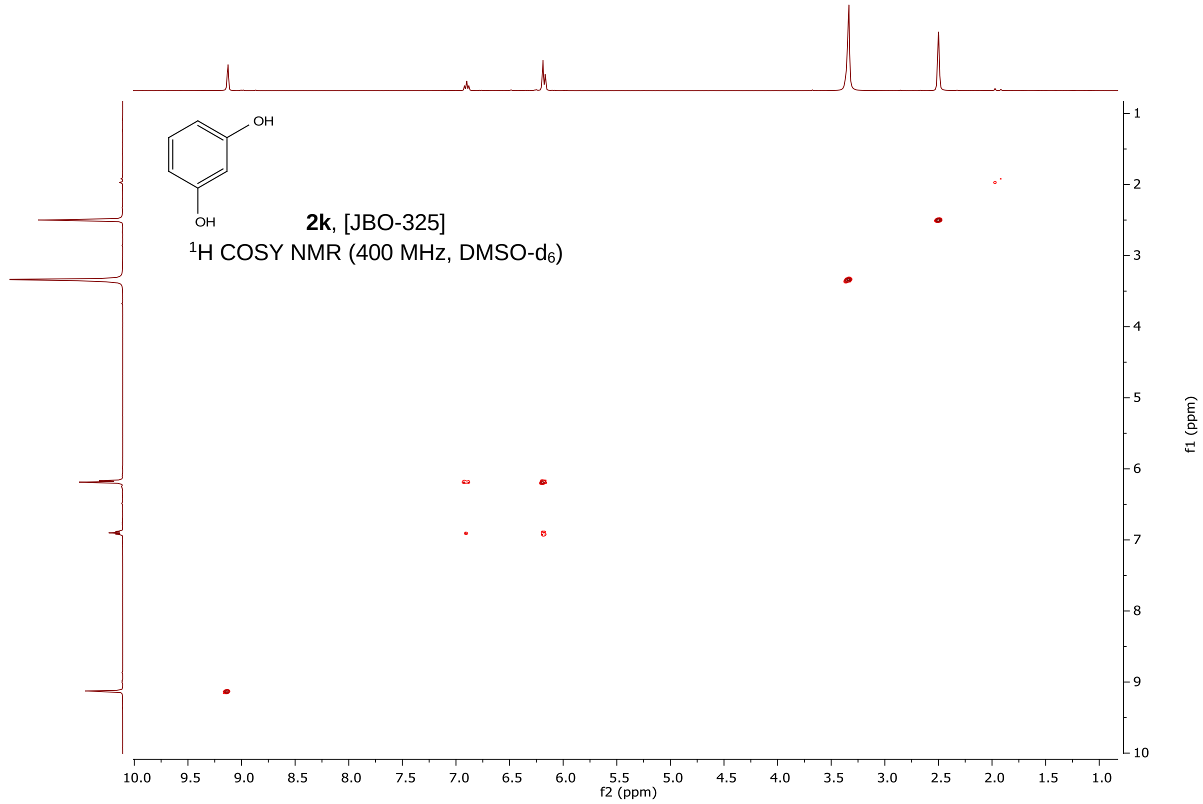


2k, [JBO-325]
^{13}C NMR (101 MHz, DMSO-d$_6$)



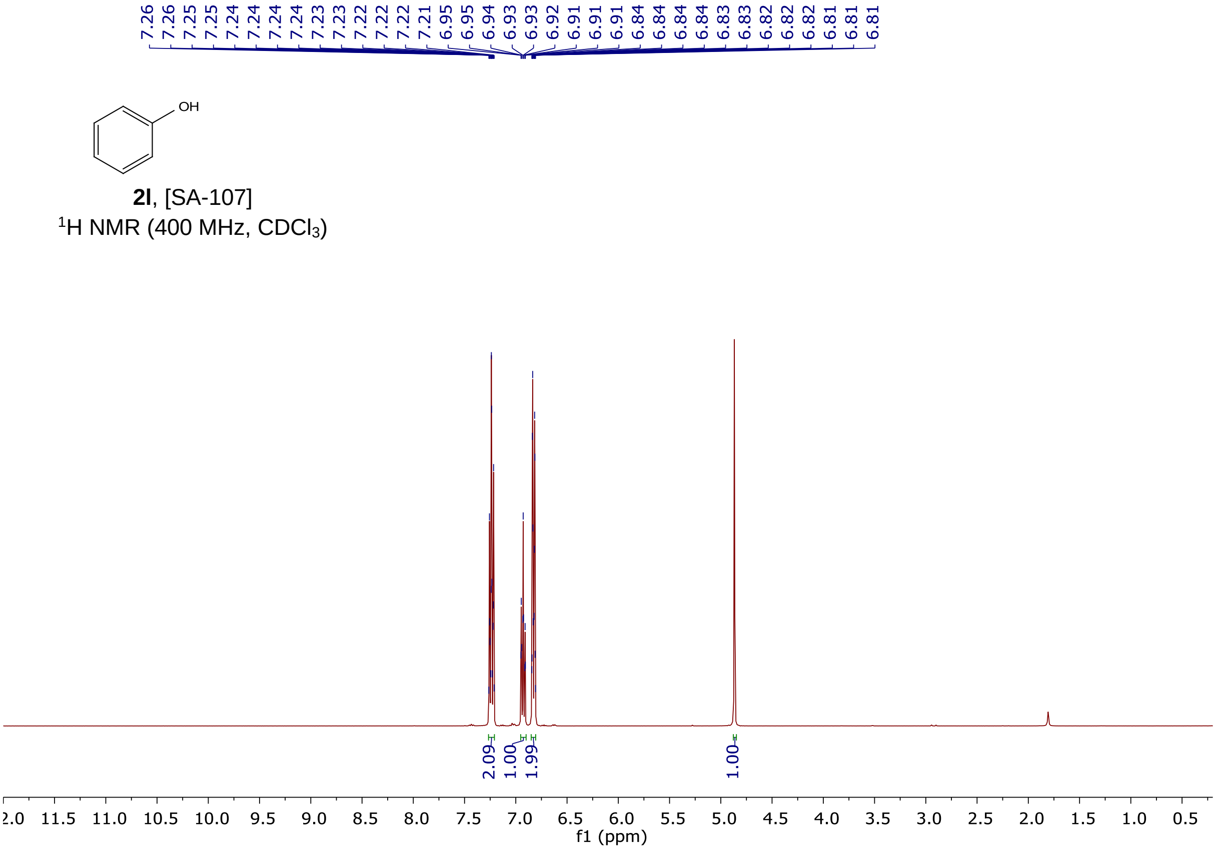
2k, [JBO-325]

^{13}C DEPT 135° NMR (101 MHz, DMSO-d_6)

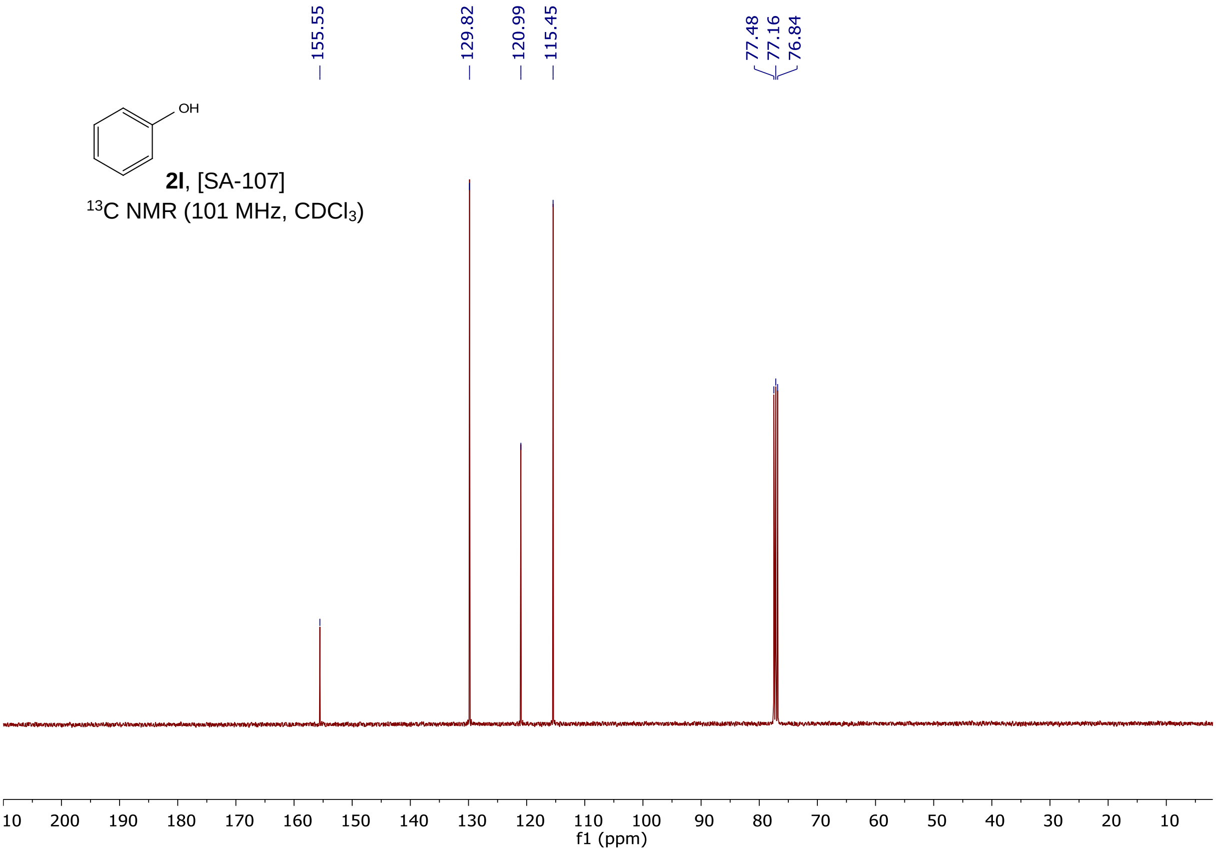


2k, [JBO-325]

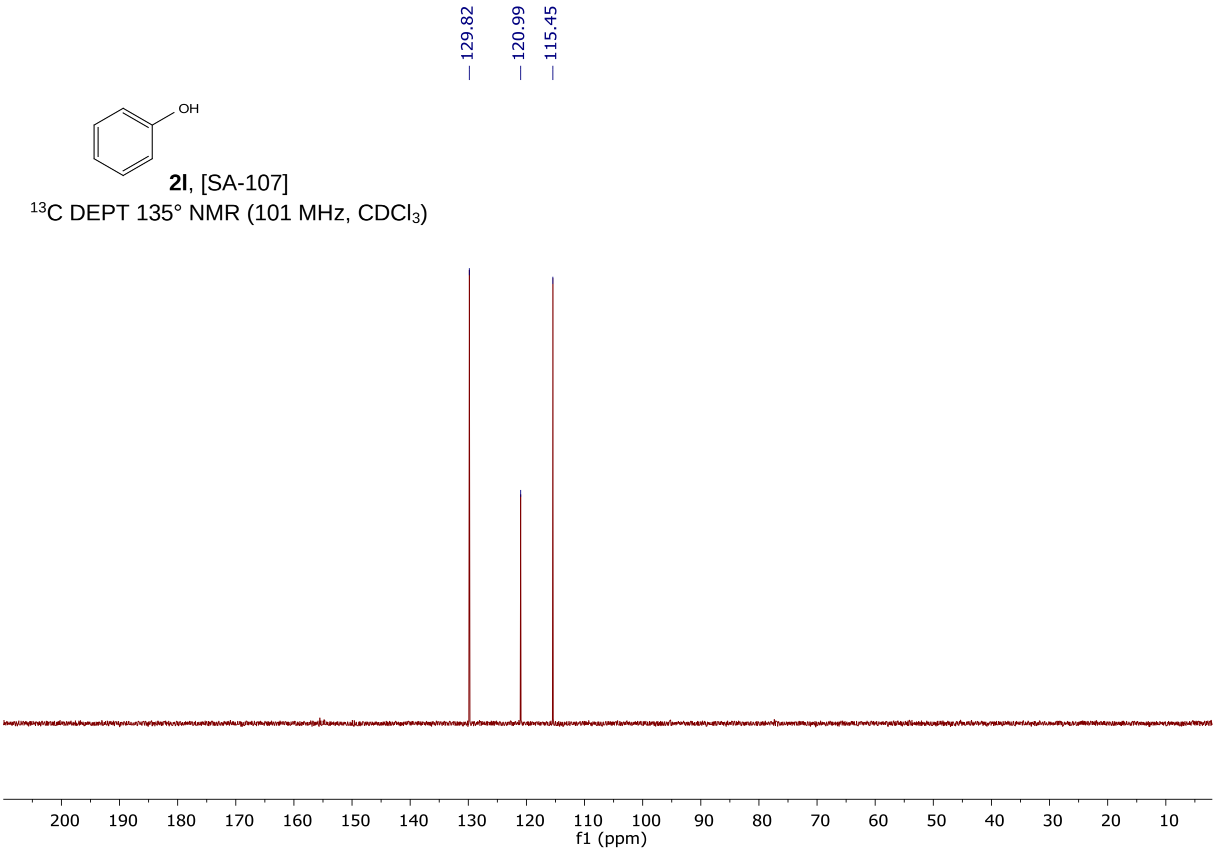
^{1}H COSY NMR (400 MHz, DMSO-d_6)



2l, [SA-107]
^{1}H NMR (400 MHz, $CDCl_3$)

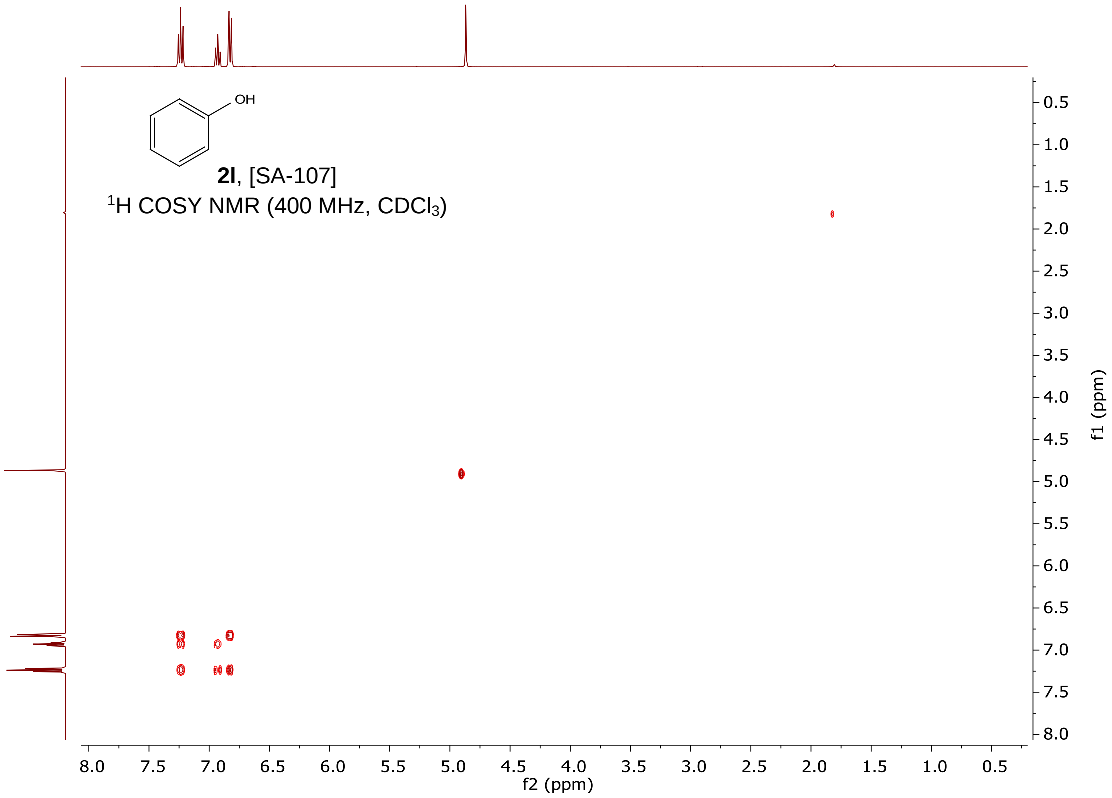


2l, [SA-107]
^{13}C NMR (101 MHz, $CDCl_3$)



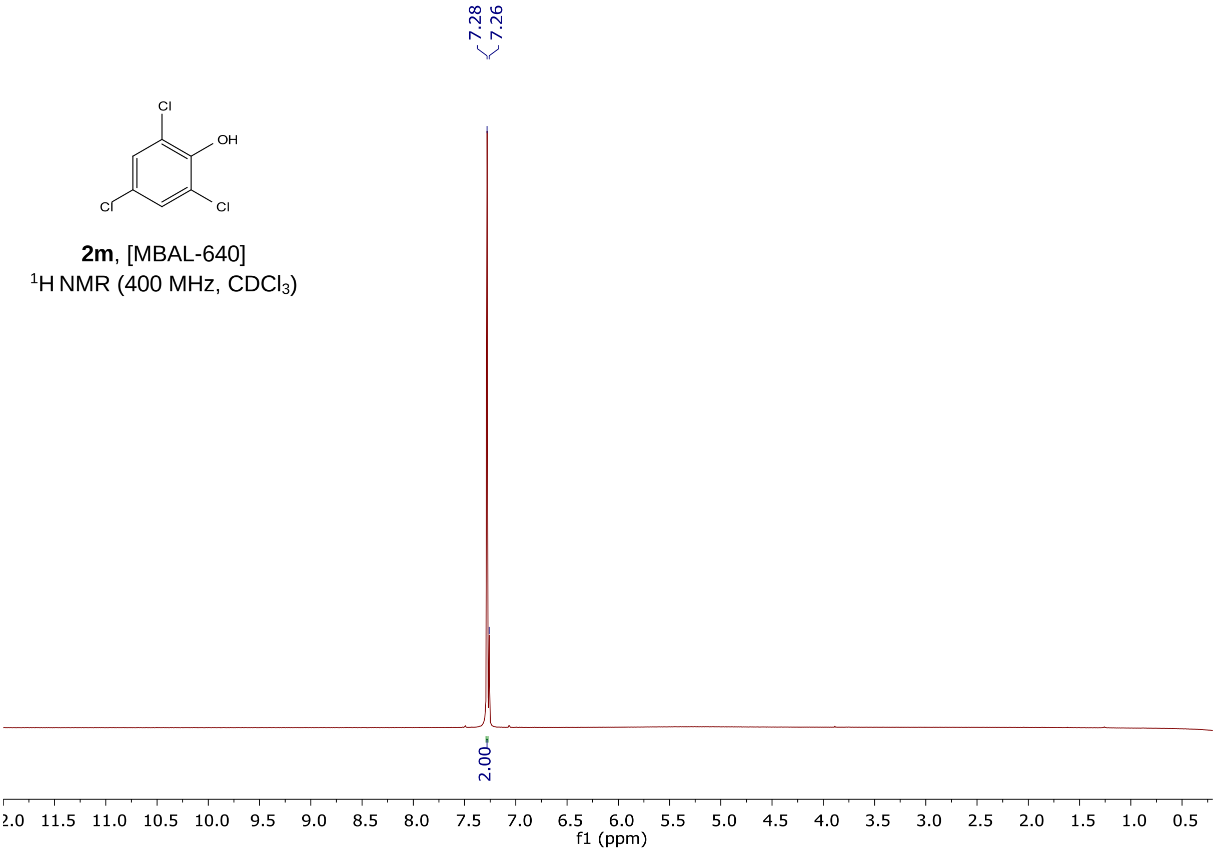
2l, [SA-107]

^{13}C DEPT 135° NMR (101 MHz, CDCl$_3$)

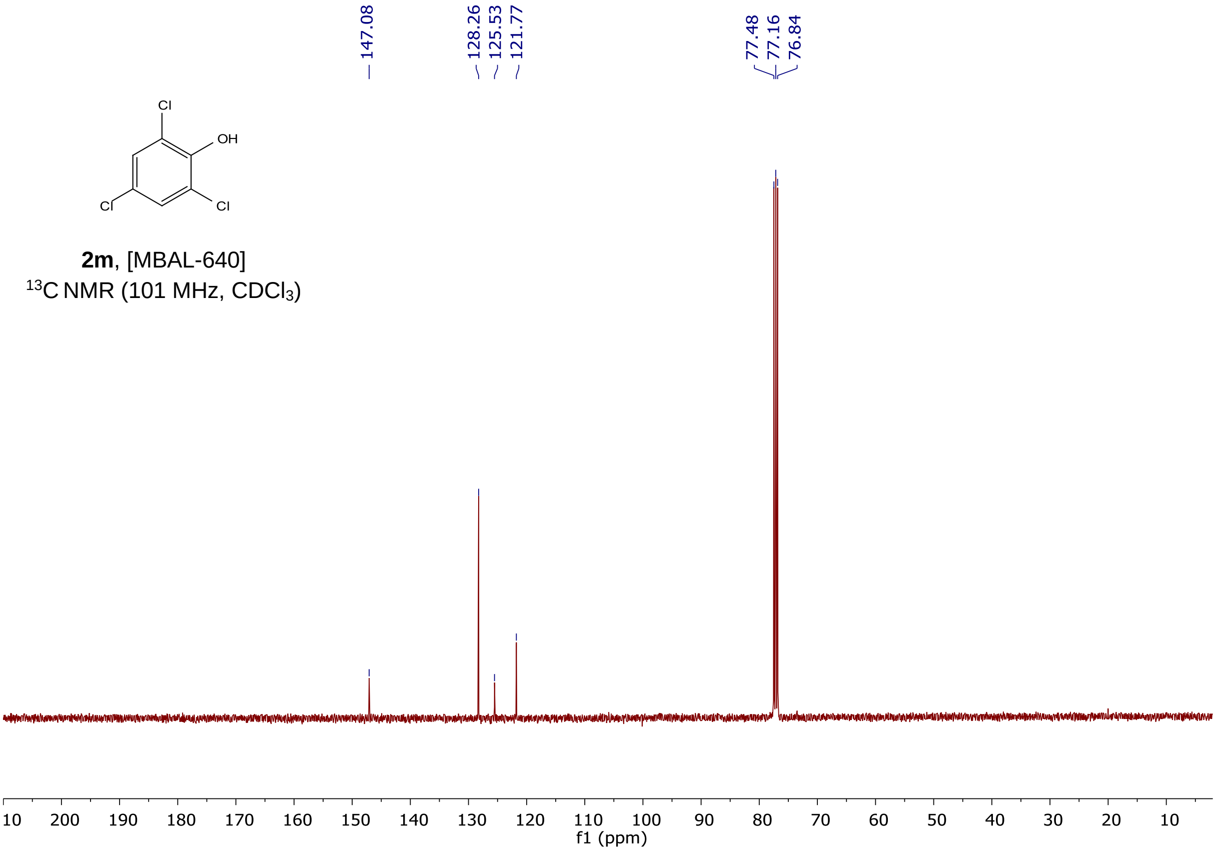


2l, [SA-107]

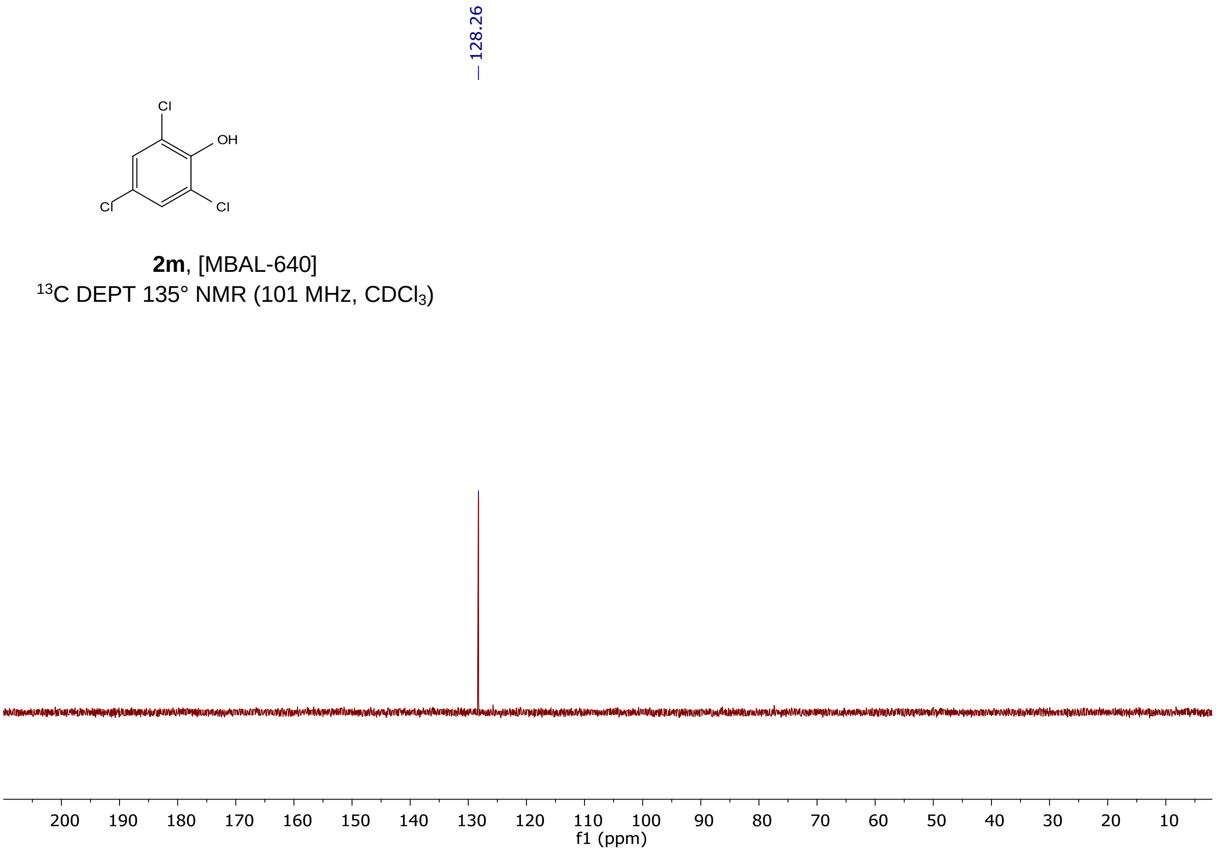
^{1}H COSY NMR (400 MHz, CDCl$_3$)



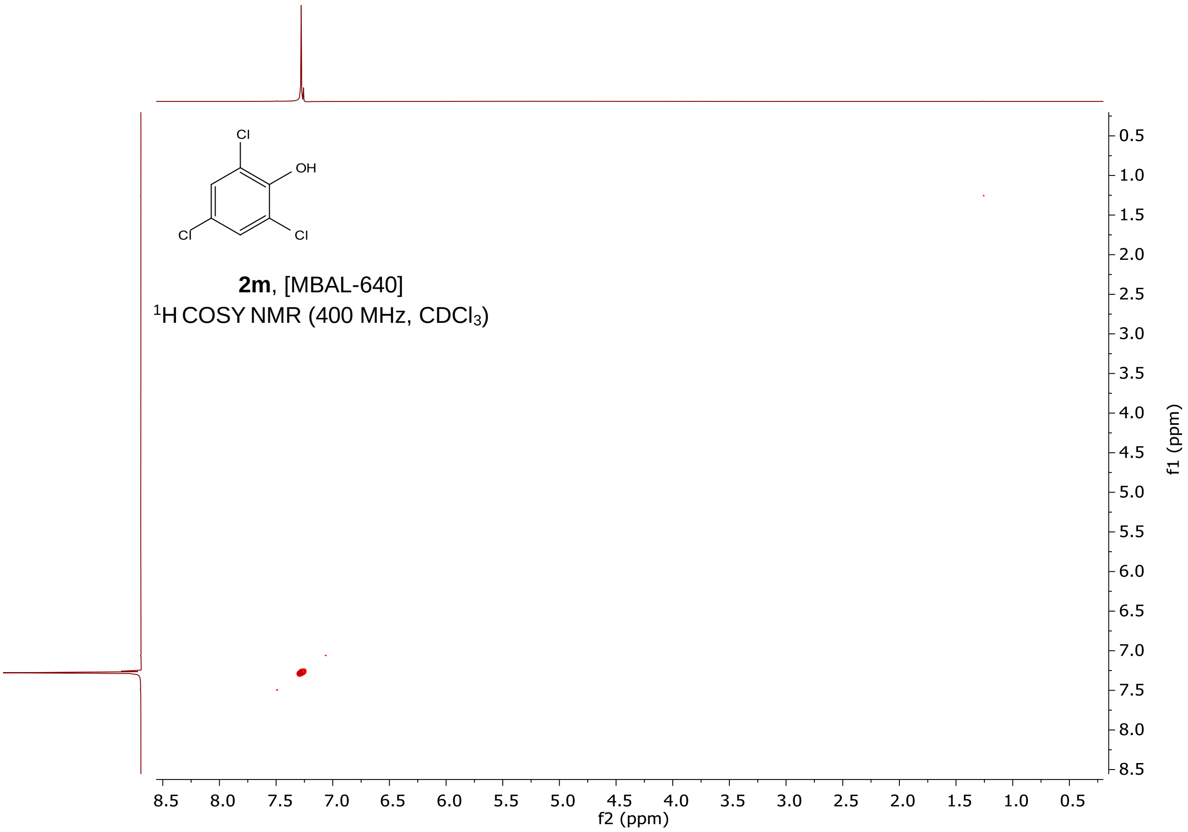
2m, [MBAL-640]
^{1}H NMR (400 MHz, $CDCl_3$)



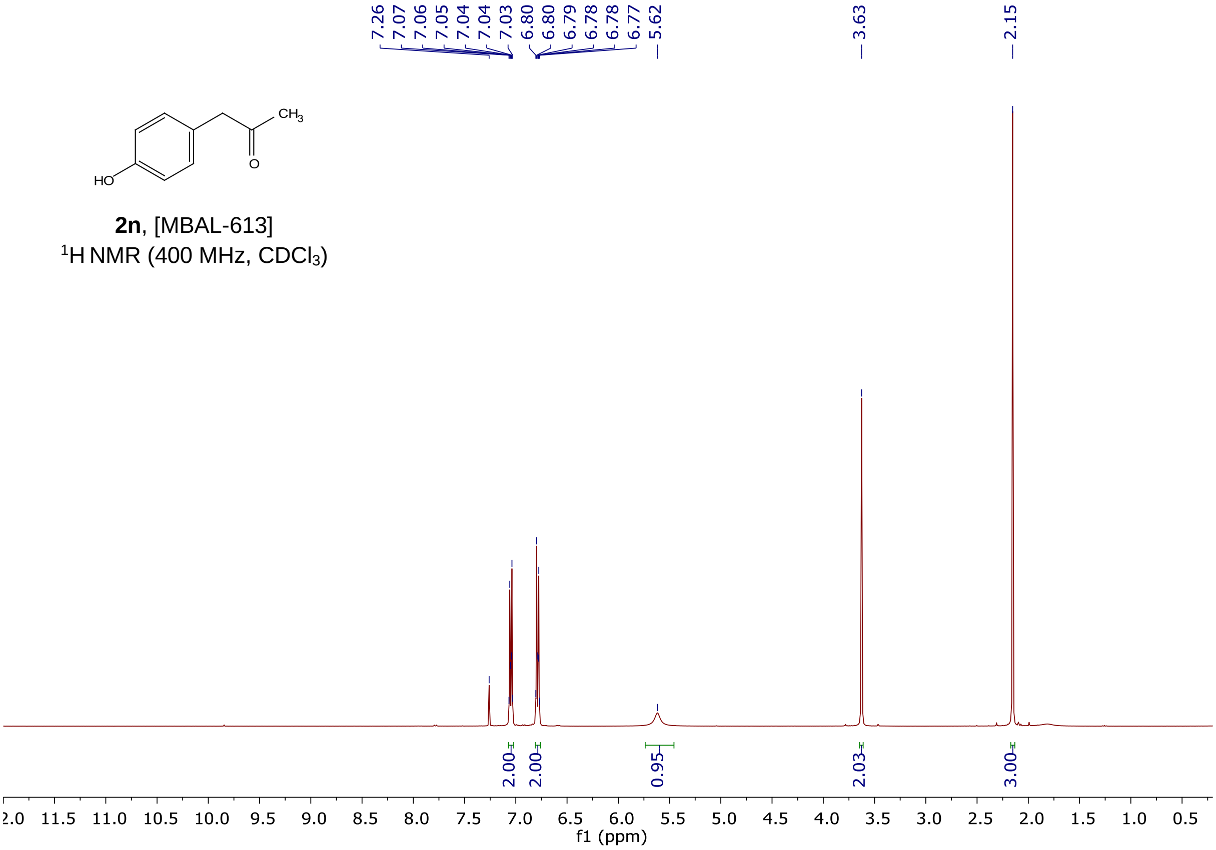
2m, [MBAL-640]
^{13}C NMR (101 MHz, $CDCl_3$)



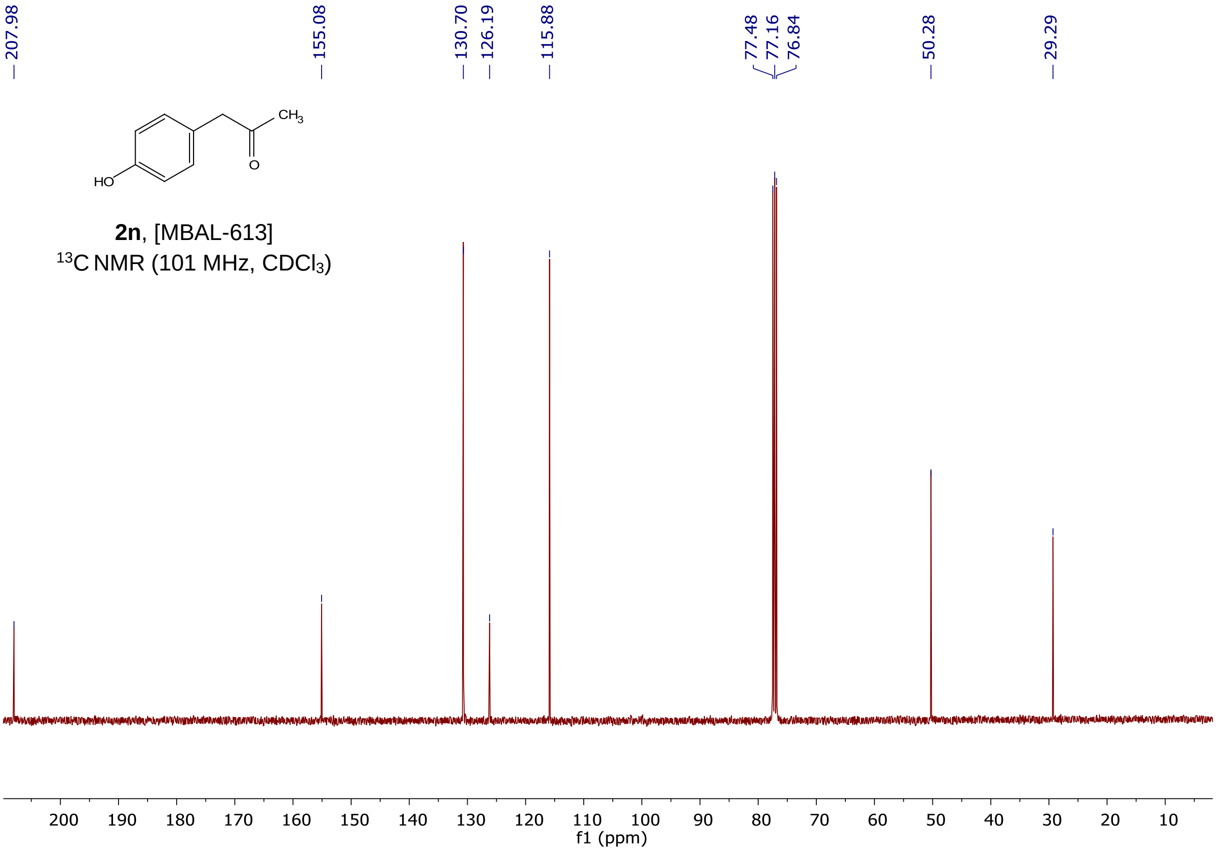
2m, [MBAL-640]
^{13}C DEPT 135° NMR (101 MHz, CDCl$_3$)



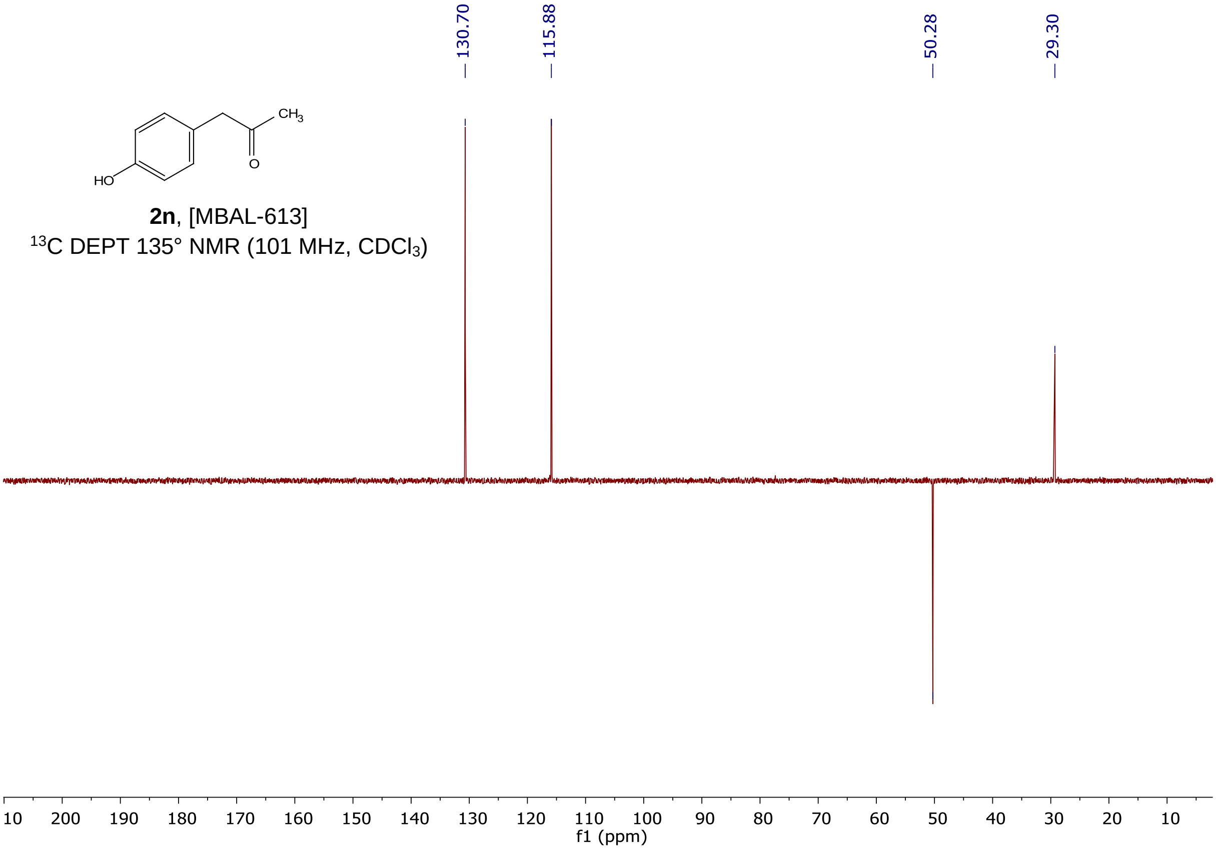
2m, [MBAL-640]
^{1}H COSY NMR (400 MHz, CDCl$_3$)



2n, [MBAL-613]
^{1}H NMR (400 MHz, $CDCl_3$)

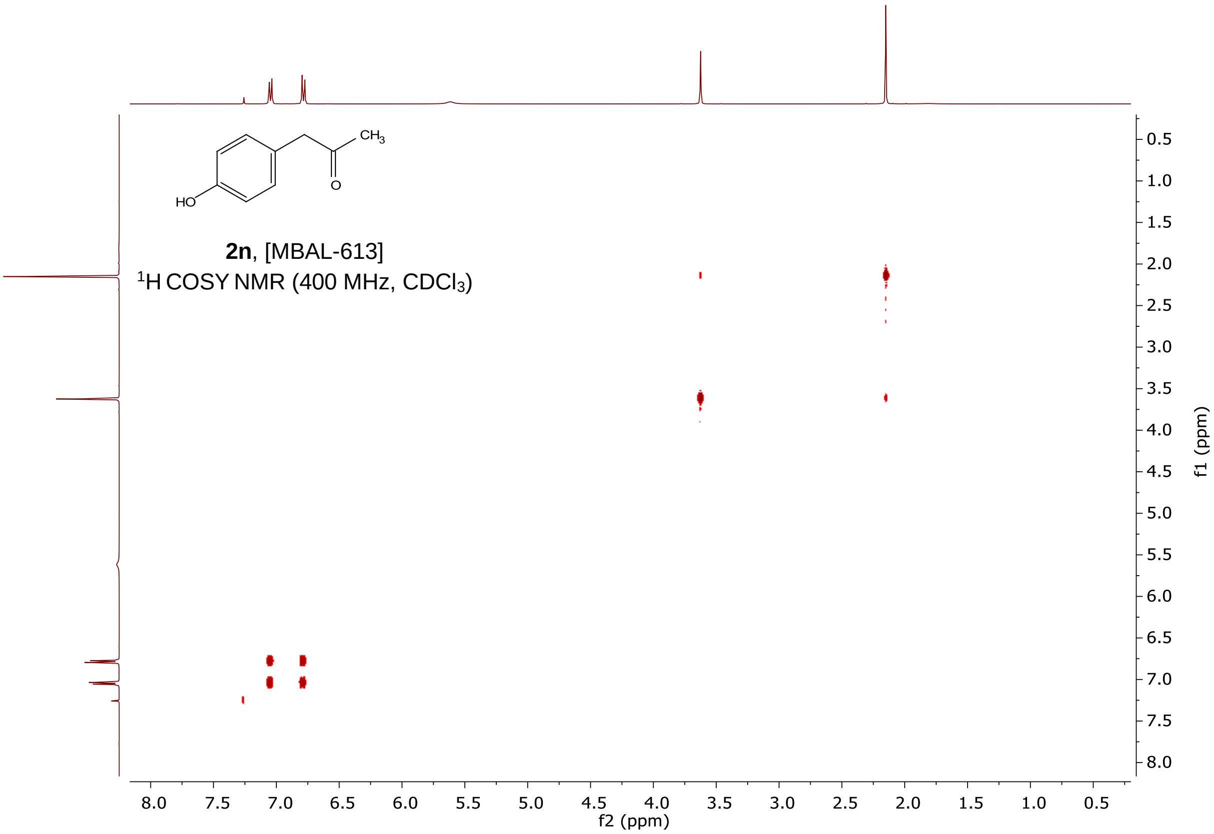


2n, [MBAL-613]
^{13}C NMR (101 MHz, $CDCl_3$)



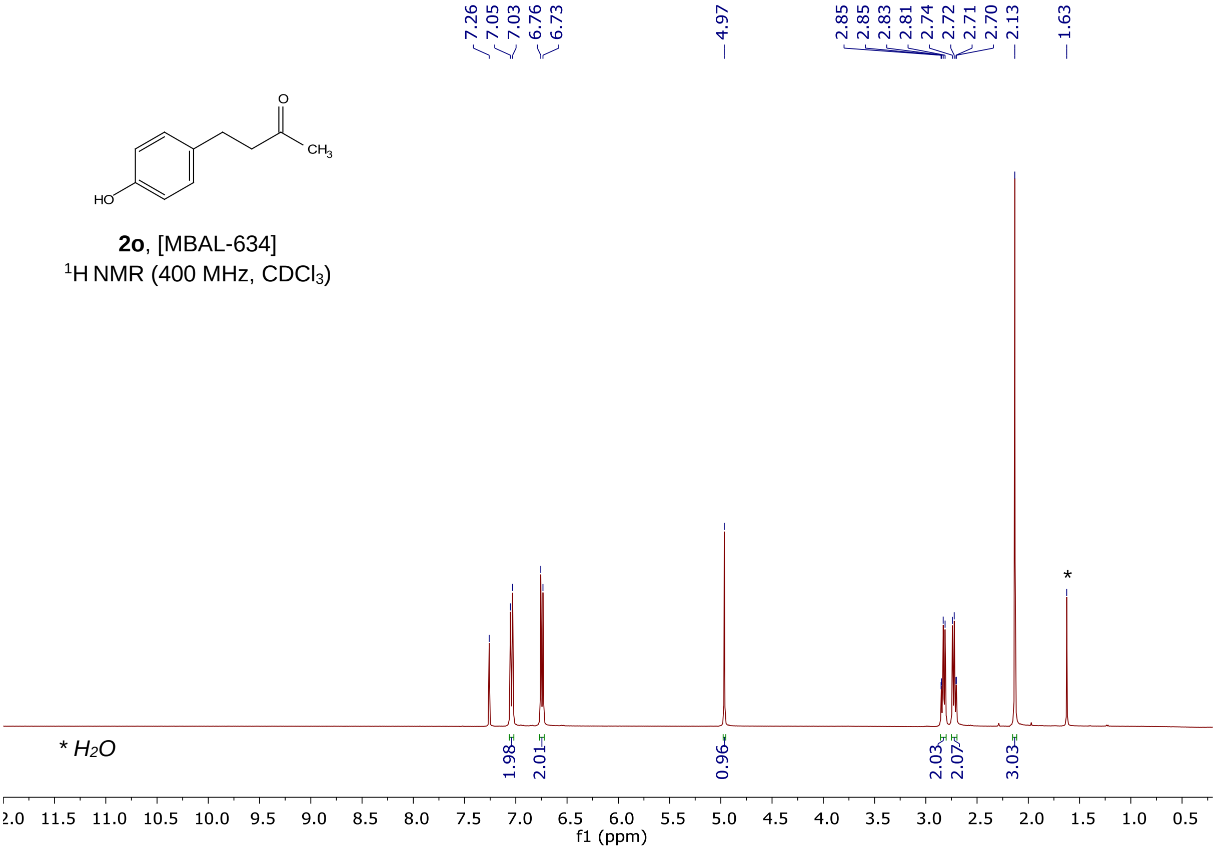
2n, [MBAL-613]

^{13}C DEPT 135° NMR (101 MHz, CDCl$_3$)



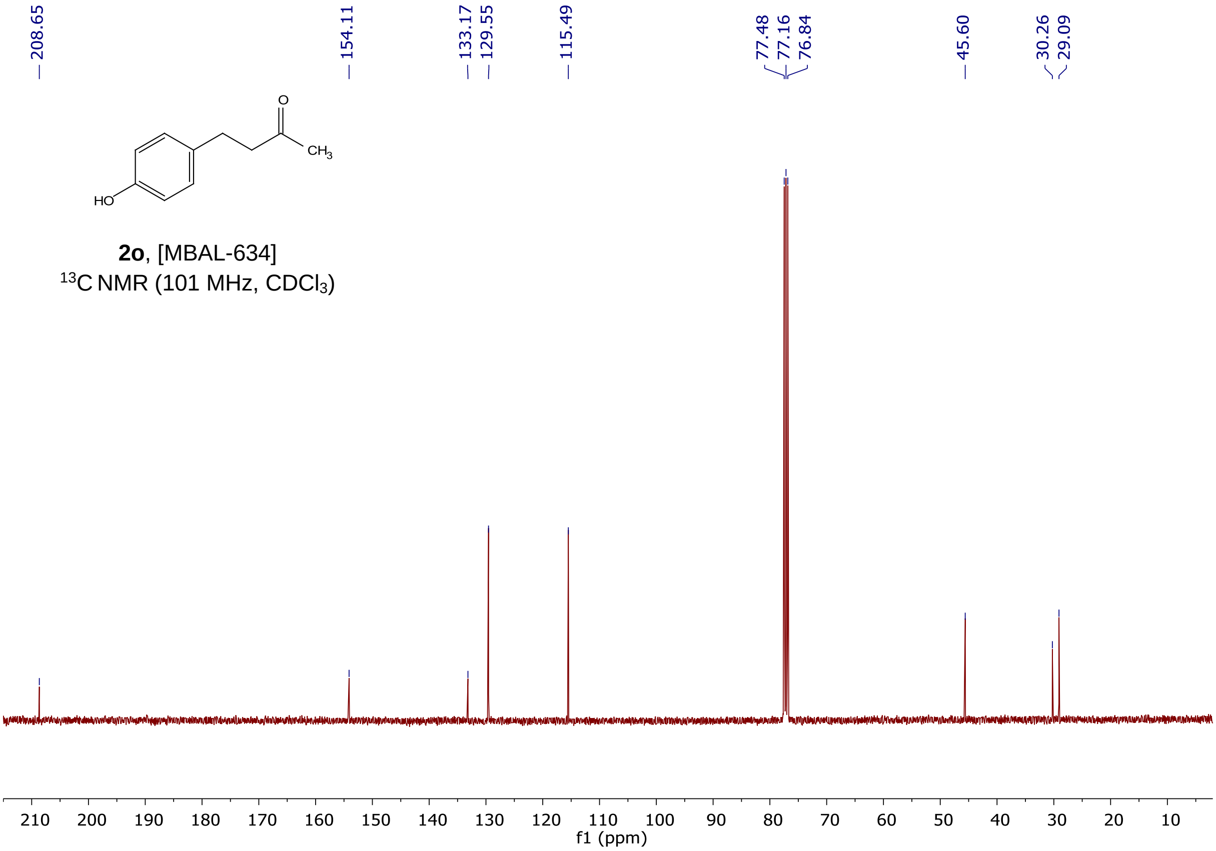
2n, [MBAL-613]

^{1}H COSY NMR (400 MHz, CDCl$_3$)



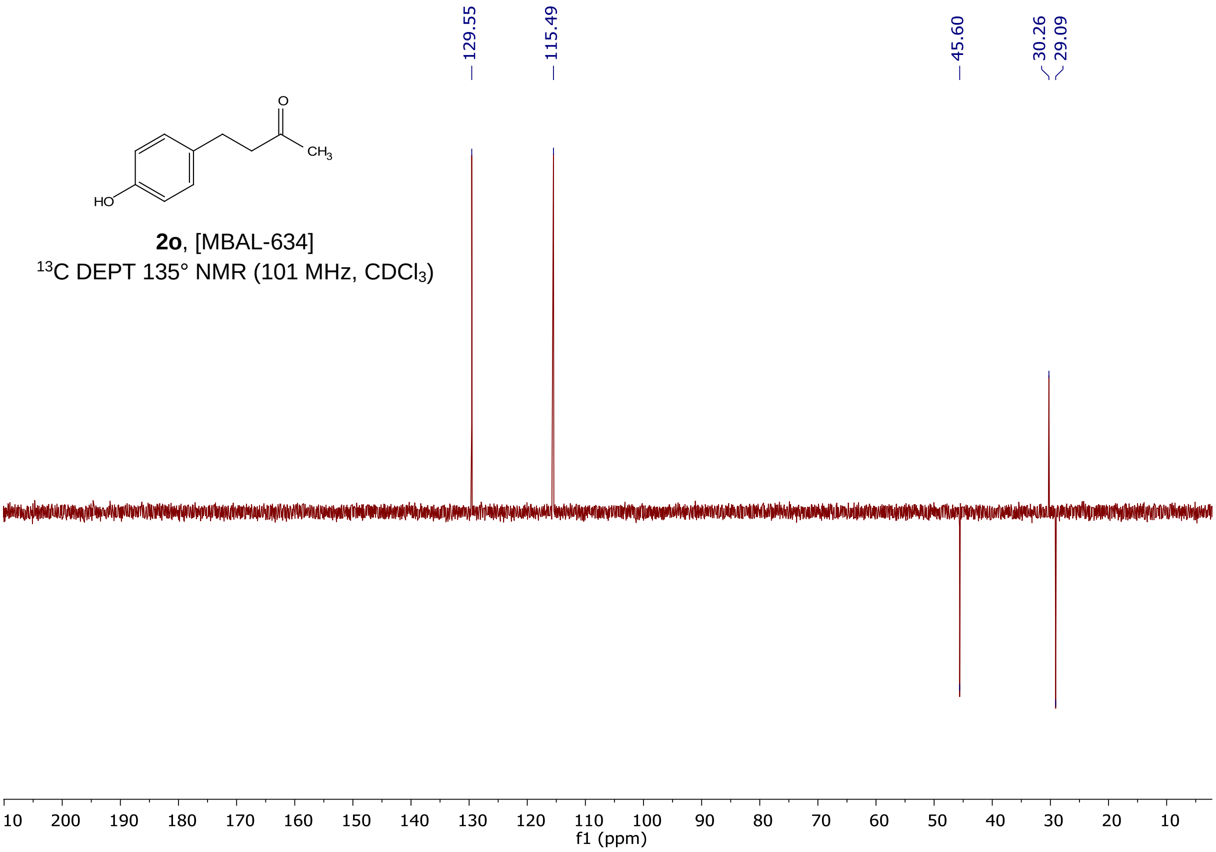
2o, [MBAL-634]

^{1}H NMR (400 MHz, $CDCl_3$)



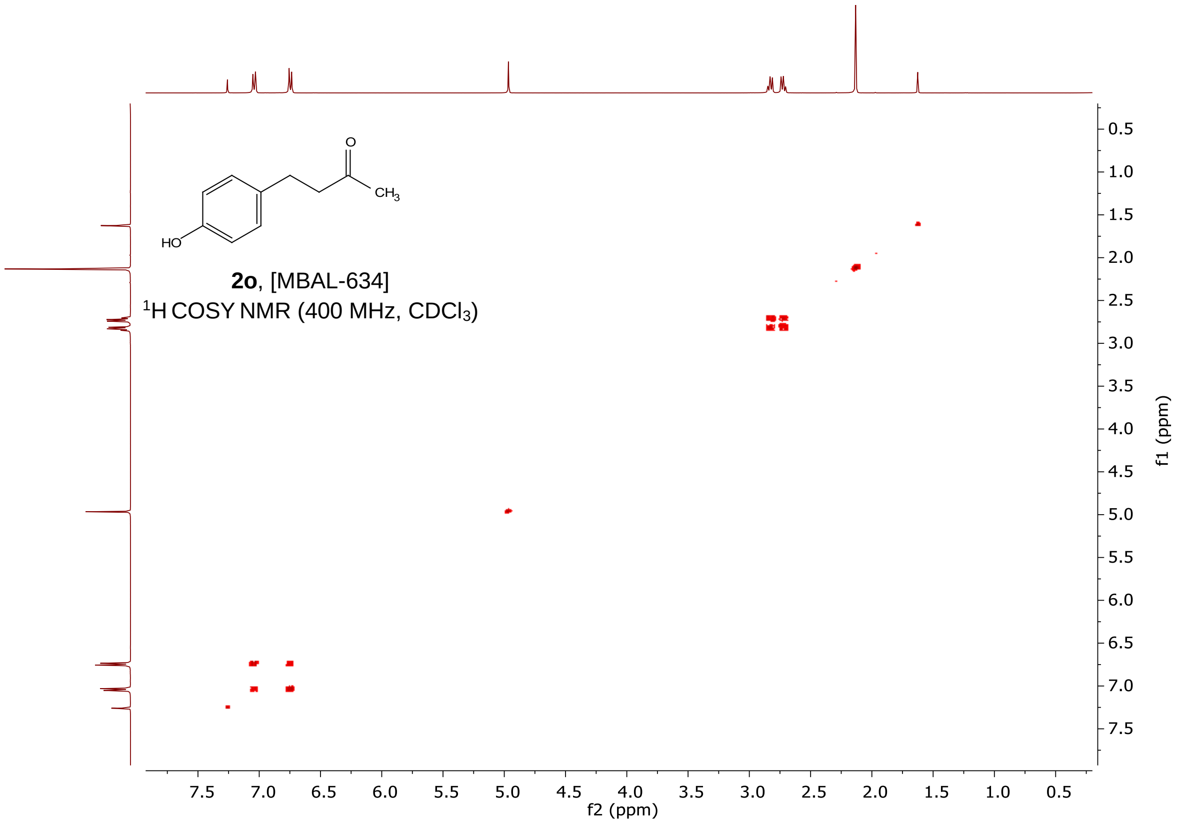
2o, [MBAL-634]

^{13}C NMR (101 MHz, $CDCl_3$)



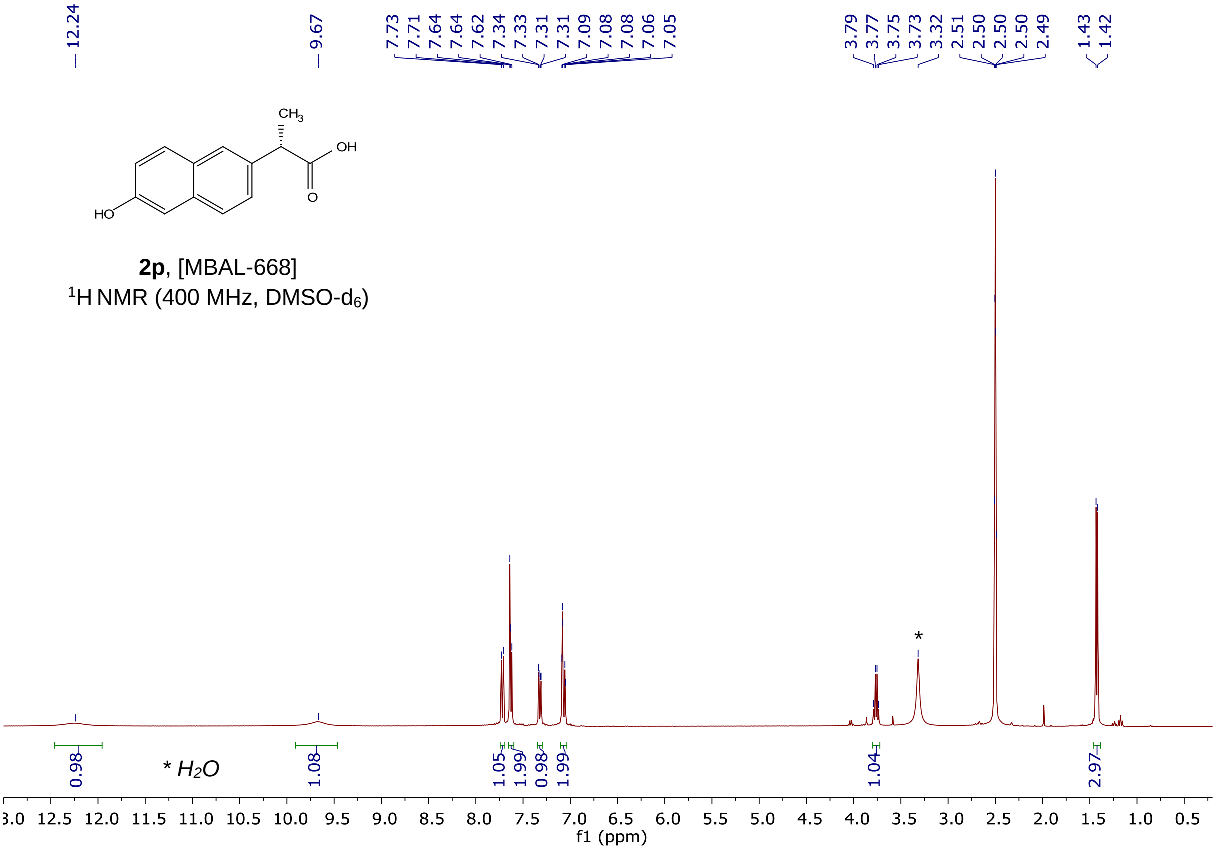
2o, [MBAL-634]

^{13}C DEPT 135° NMR (101 MHz, $CDCl_3$)

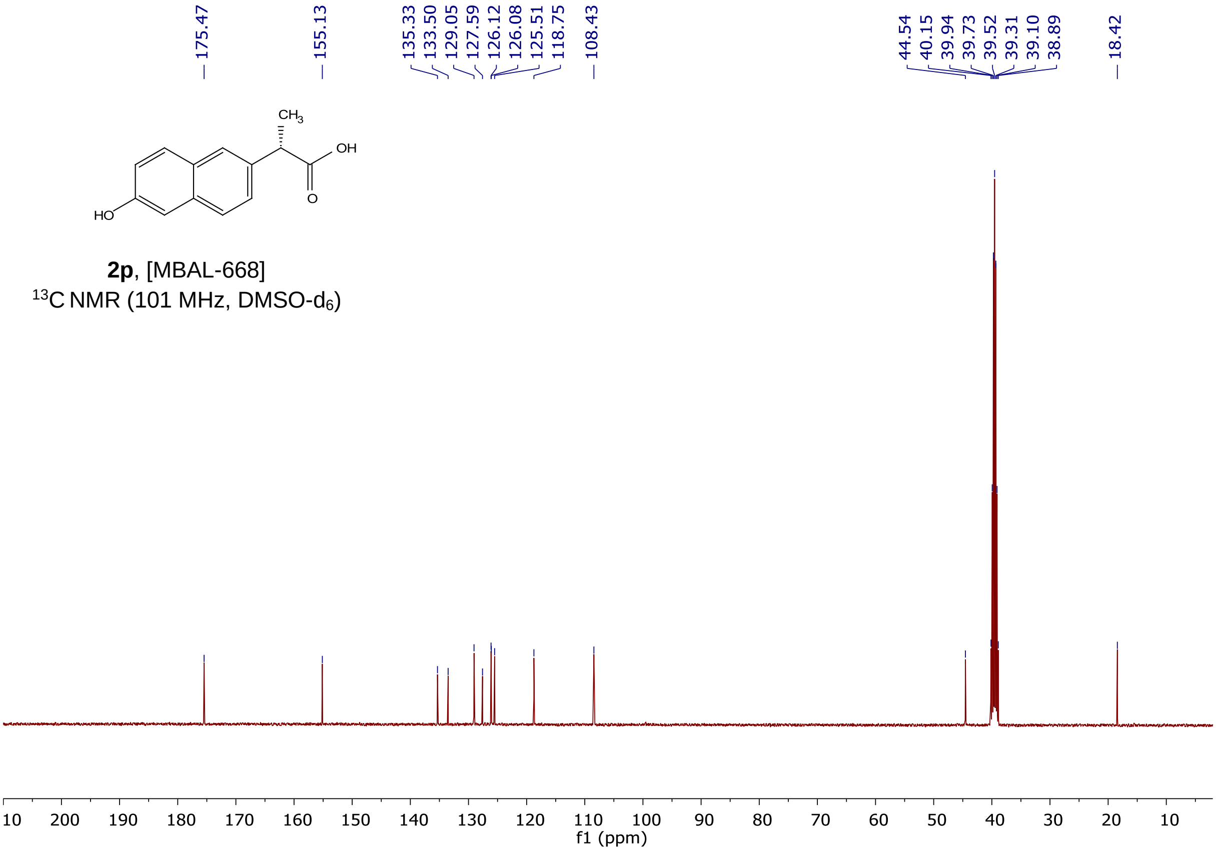


2o, [MBAL-634]

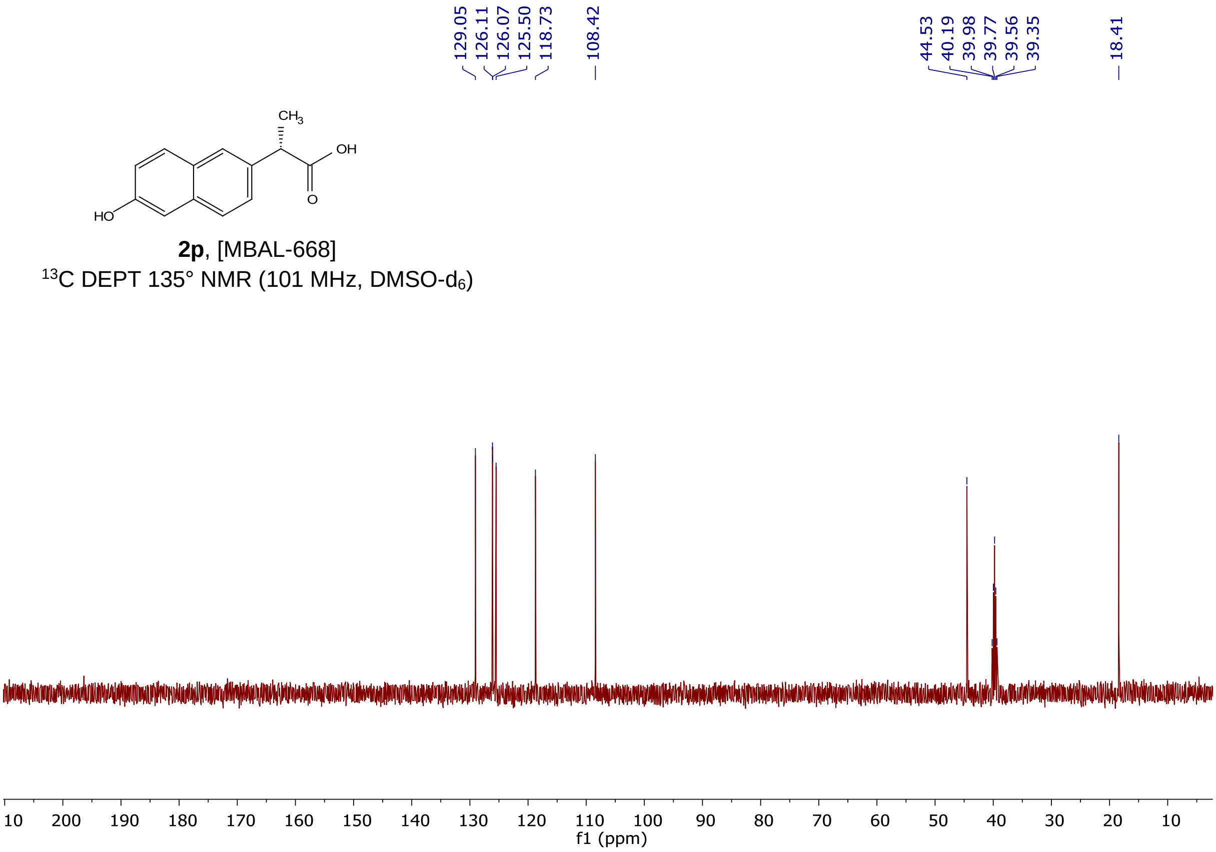
^{1}H COSY NMR (400 MHz, $CDCl_3$)



2p, [MBAL-668]
^{1}H NMR (400 MHz, DMSO-d$_6$)

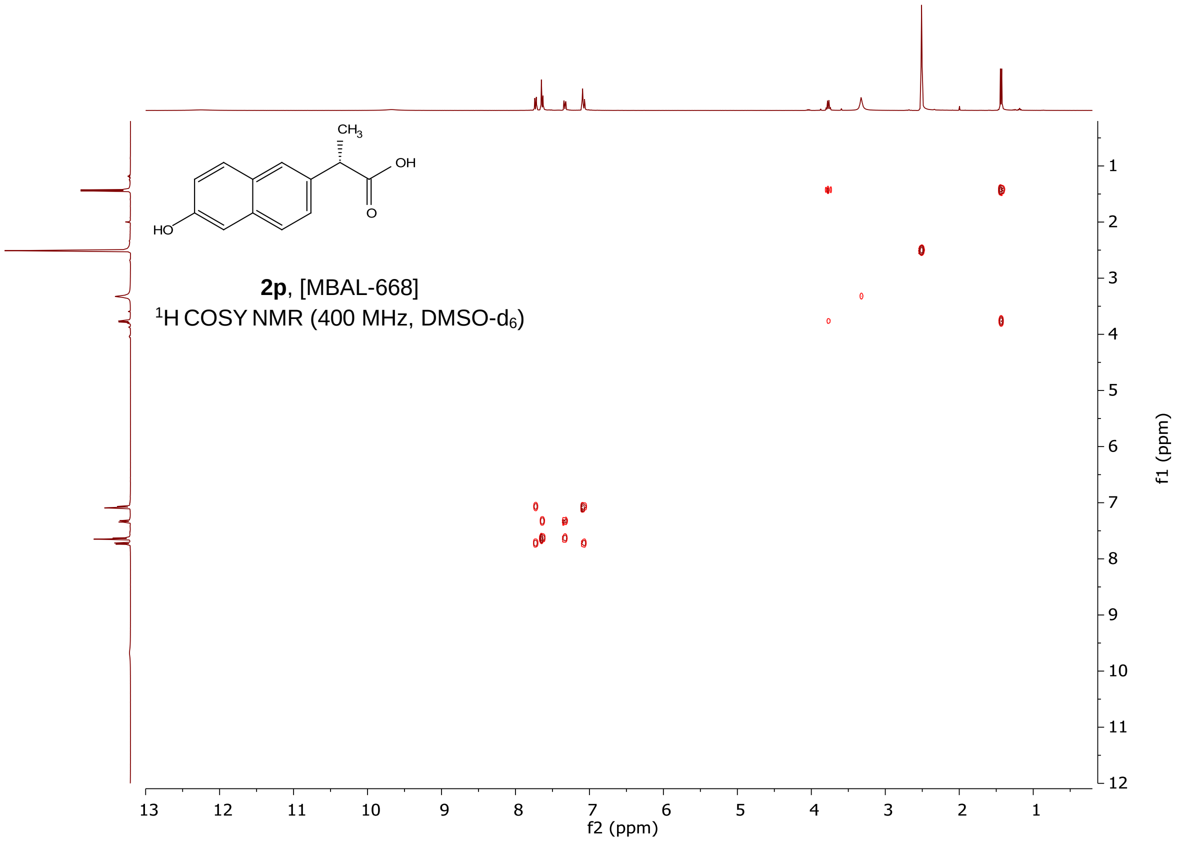


2p, [MBAL-668]
^{13}C NMR (101 MHz, DMSO-d$_6$)



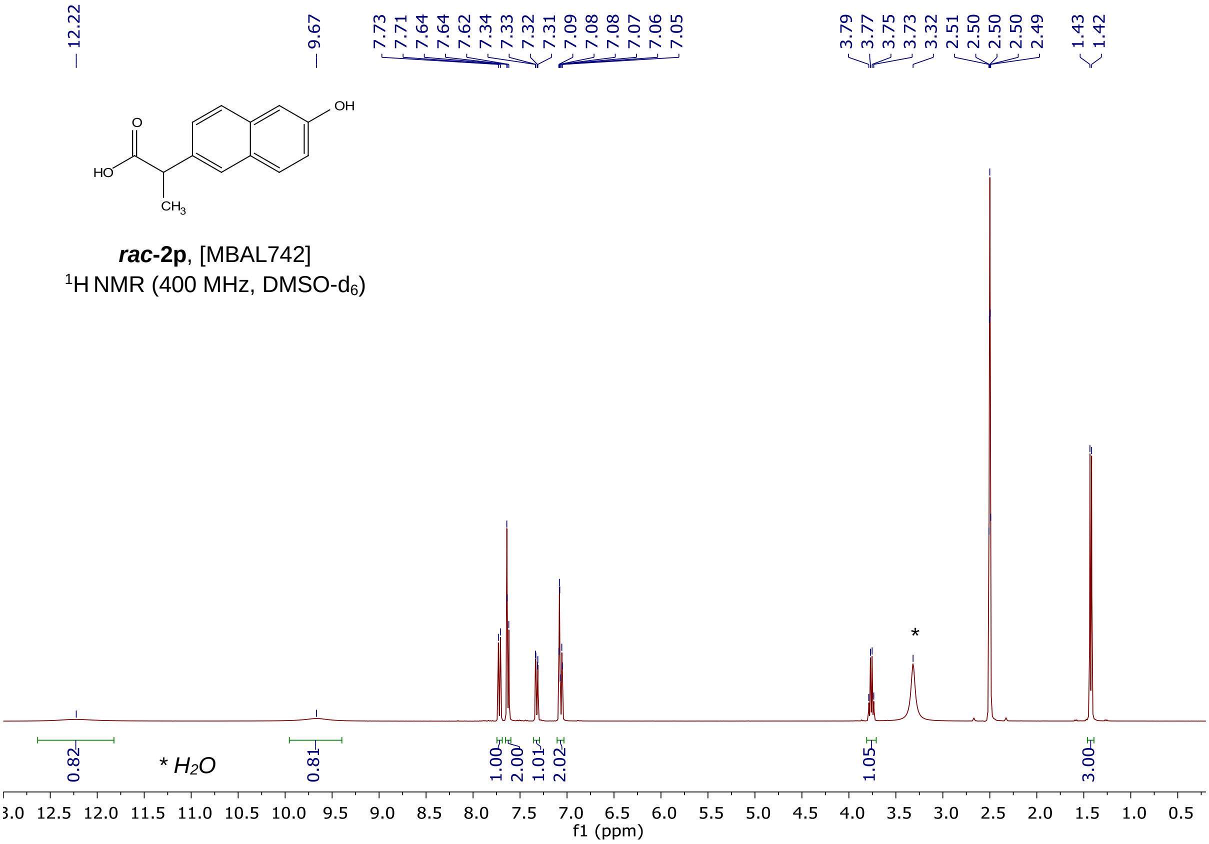
2p, [MBAL-668]

^{13}C DEPT 135° NMR (101 MHz, DMSO-d$_6$)

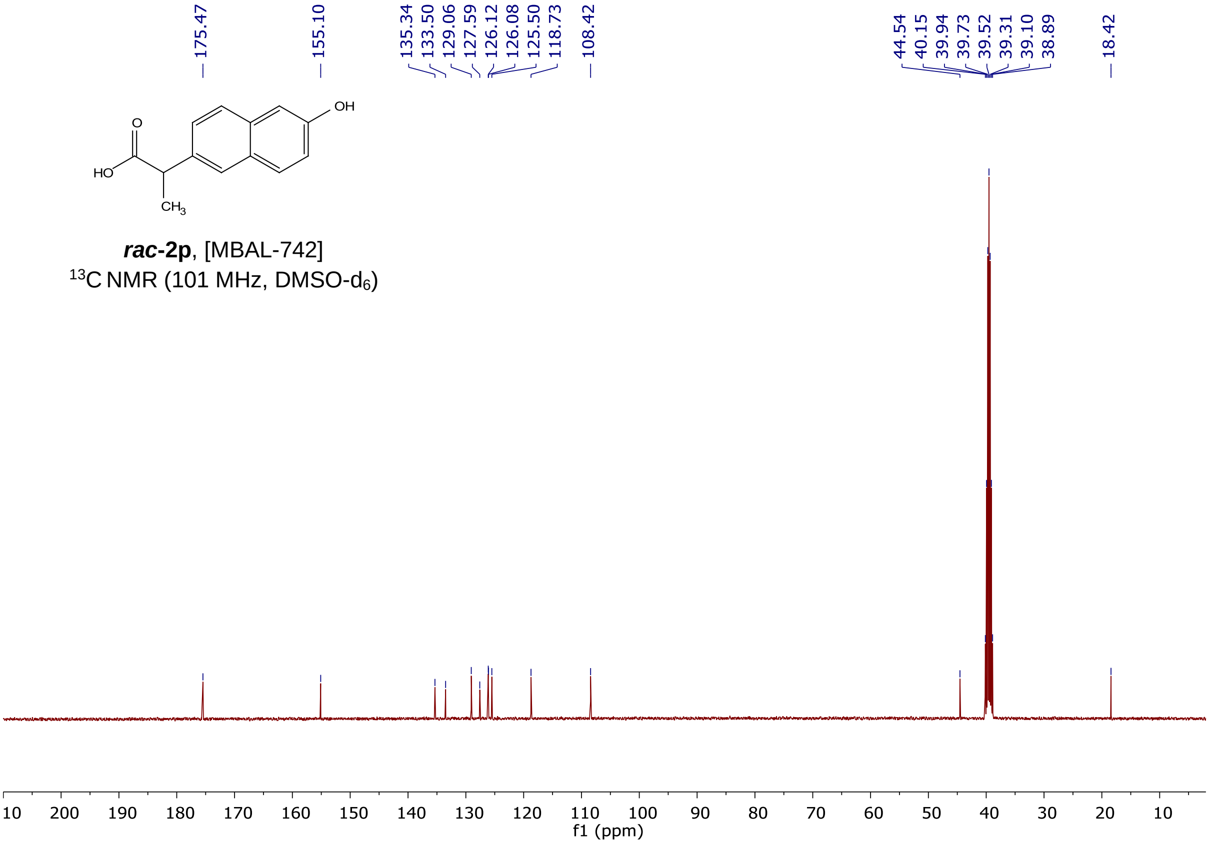


2p, [MBAL-668]

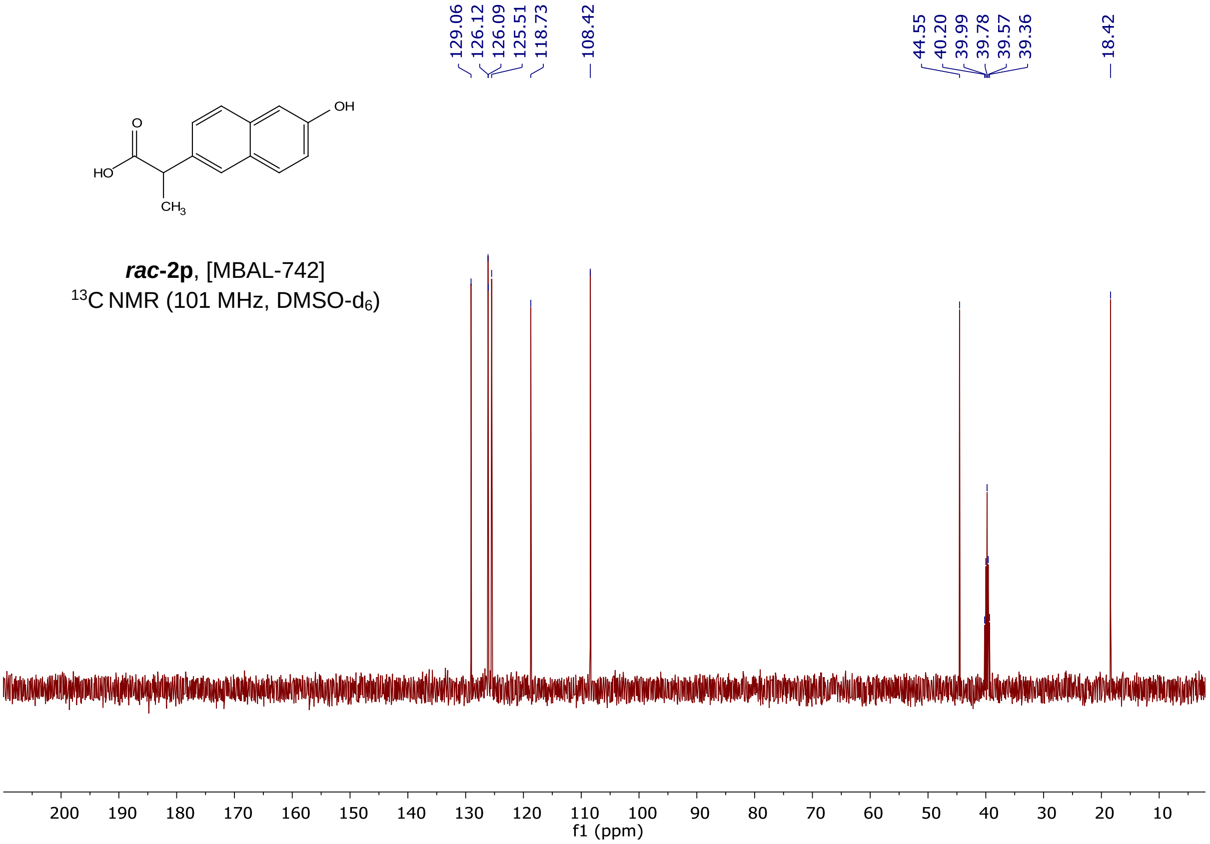
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)



***rac*-2p**, [MBAL742]
^{1}H NMR (400 MHz, DMSO-d$_6$)

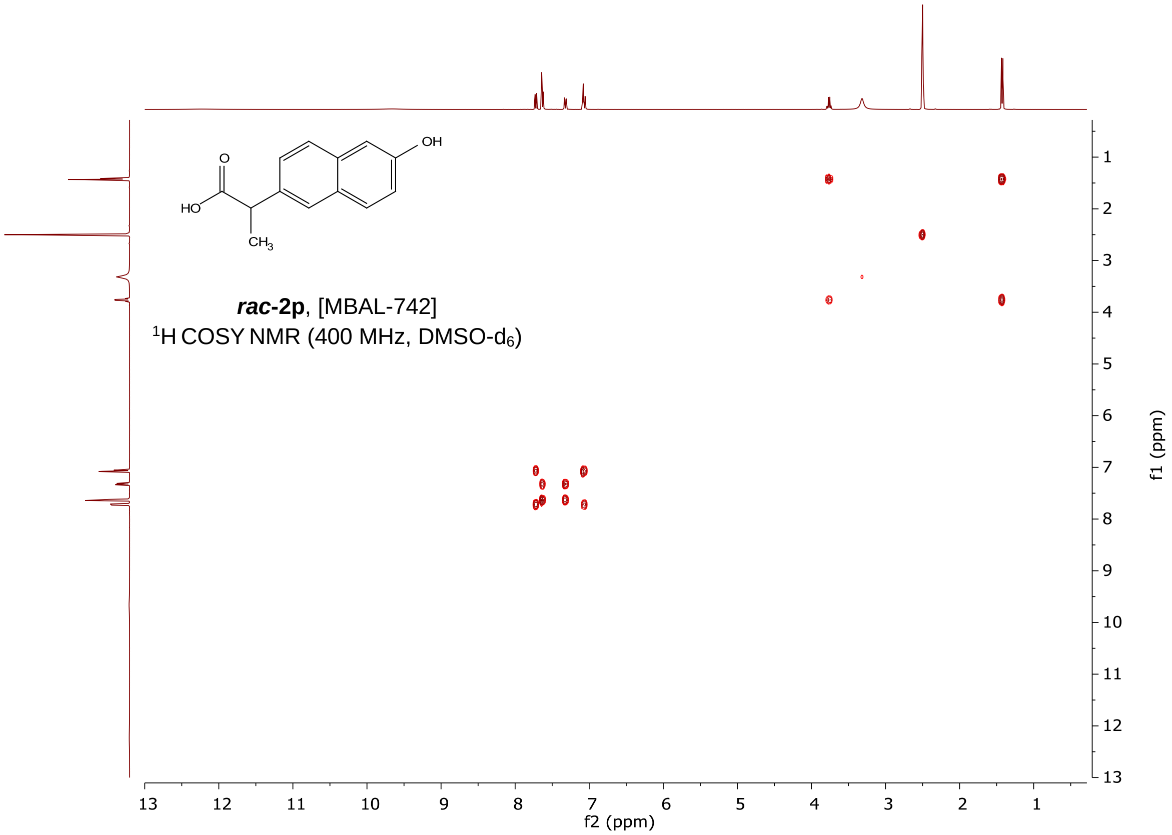


***rac*-2p**, [MBAL-742]
^{13}C NMR (101 MHz, DMSO-d$_6$)



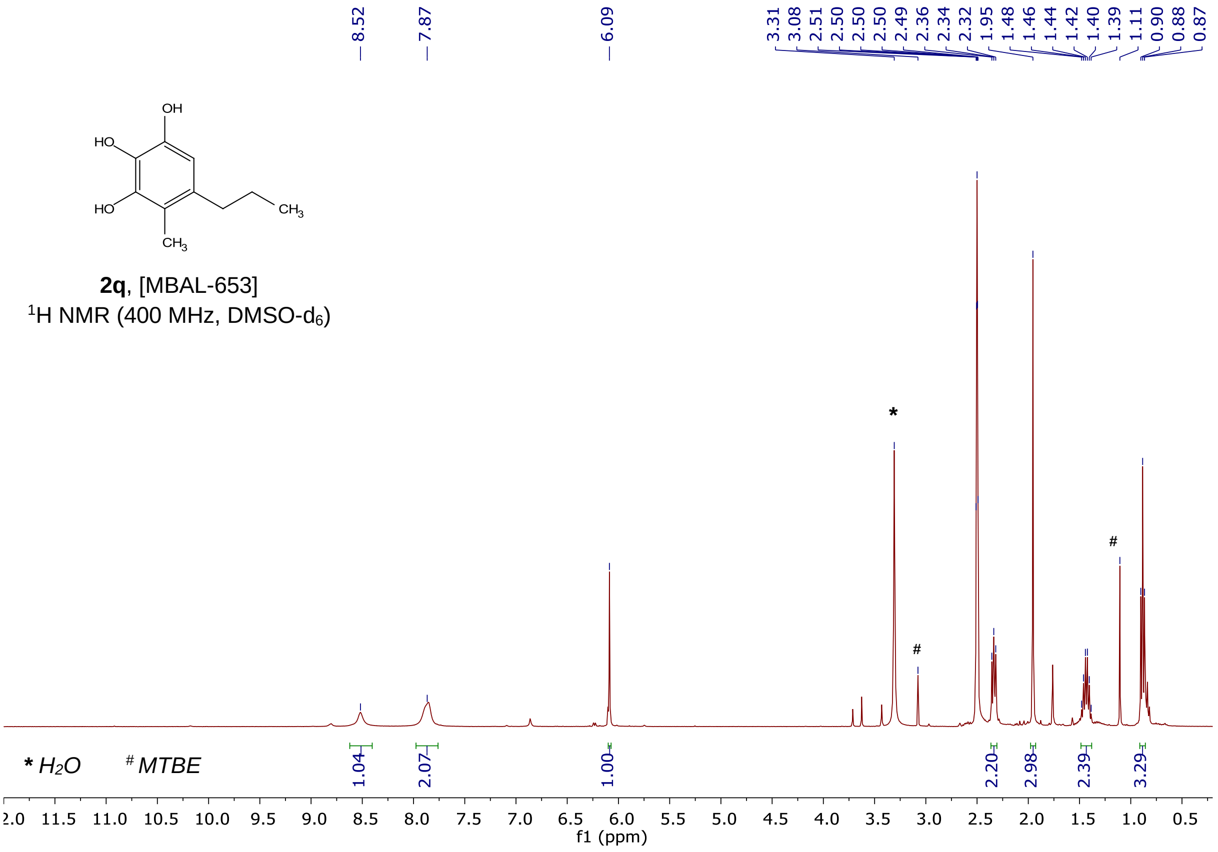
***rac*-2p**, [MBAL-742]

^{13}C NMR (101 MHz, DMSO-d$_6$)

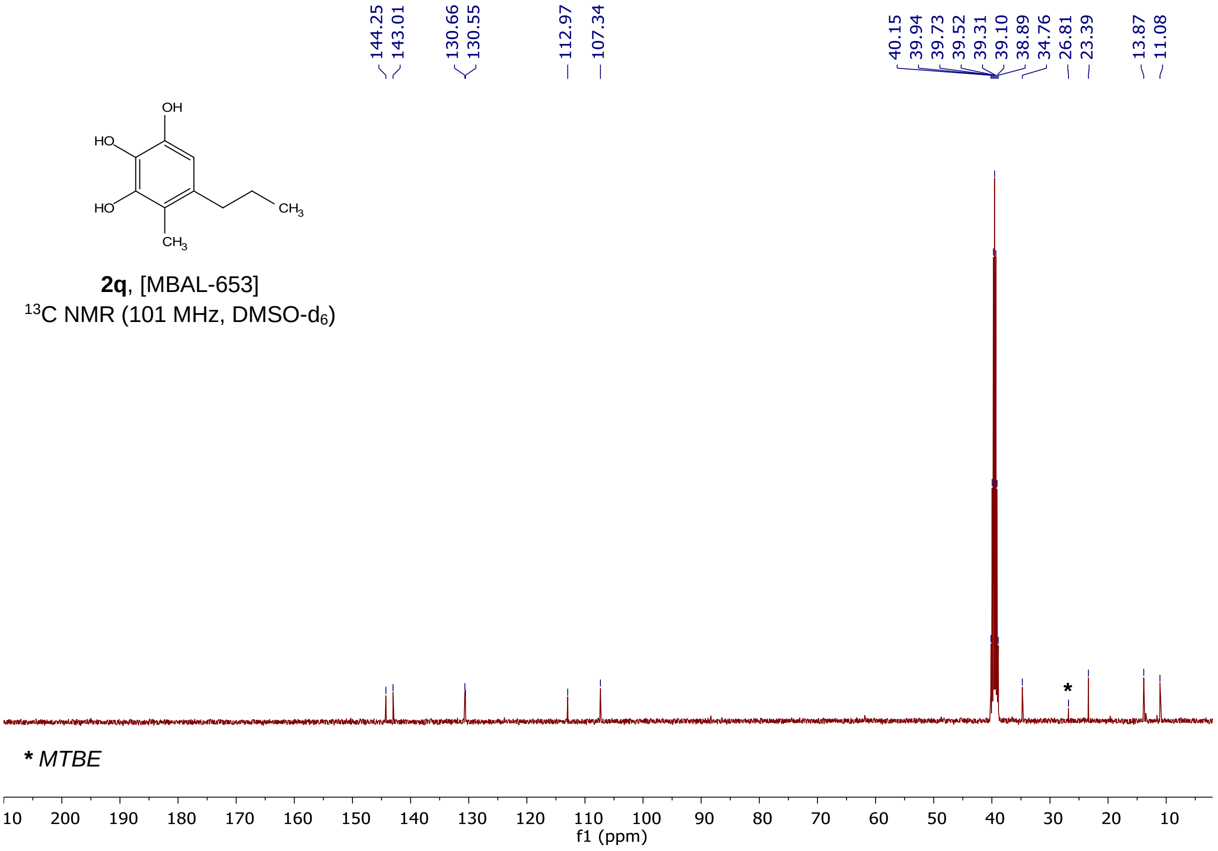


***rac*-2p**, [MBAL-742]

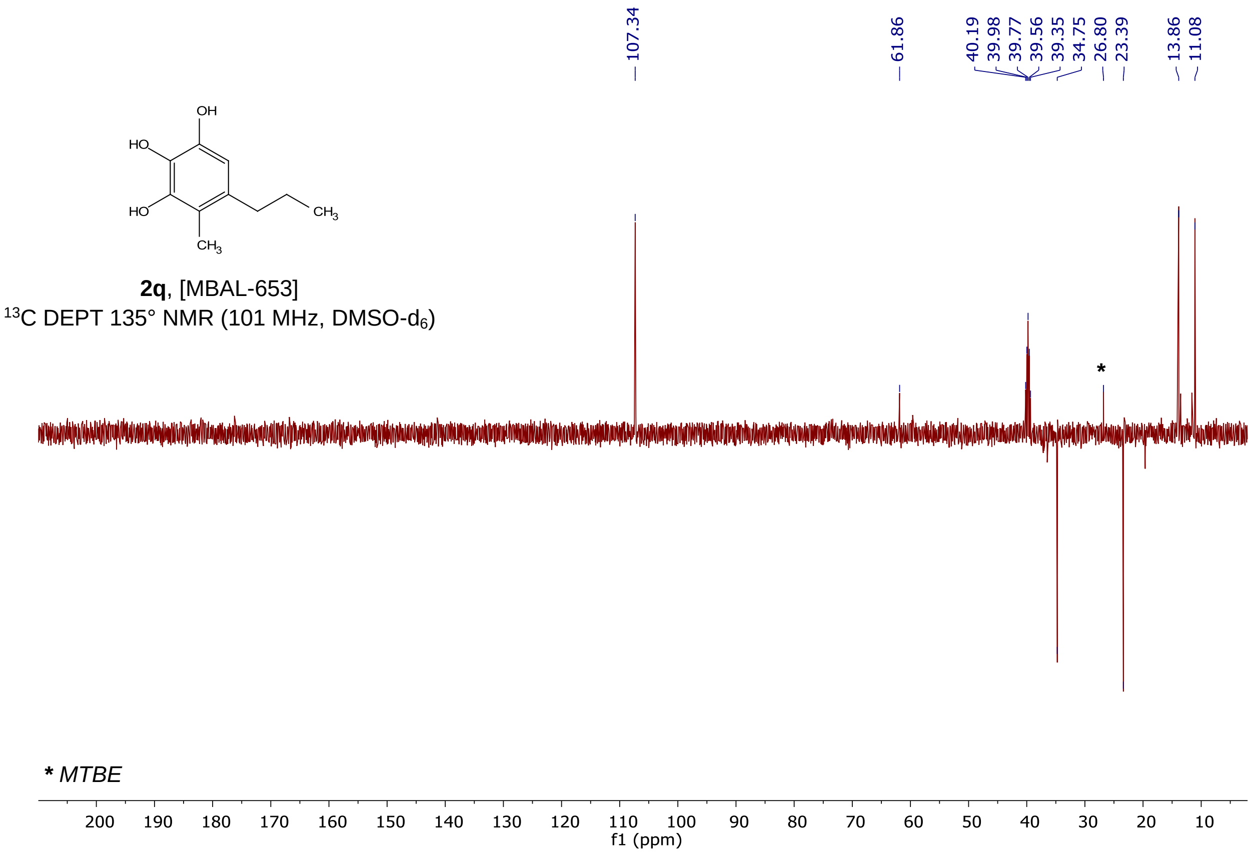
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)



2q, [MBAL-653]
^{1}H NMR (400 MHz, DMSO-d$_6$)



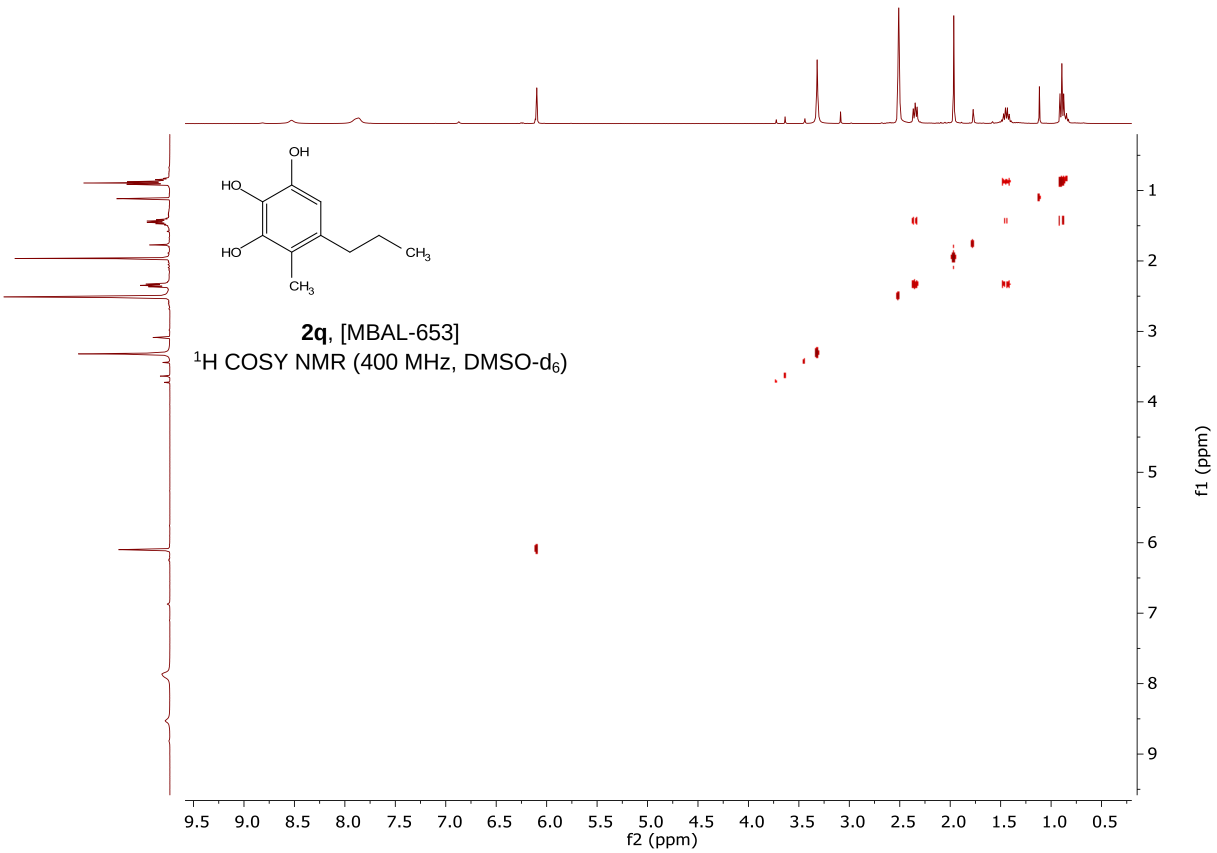
2q, [MBAL-653]
^{13}C NMR (101 MHz, DMSO-d$_6$)



2q, [MBAL-653]

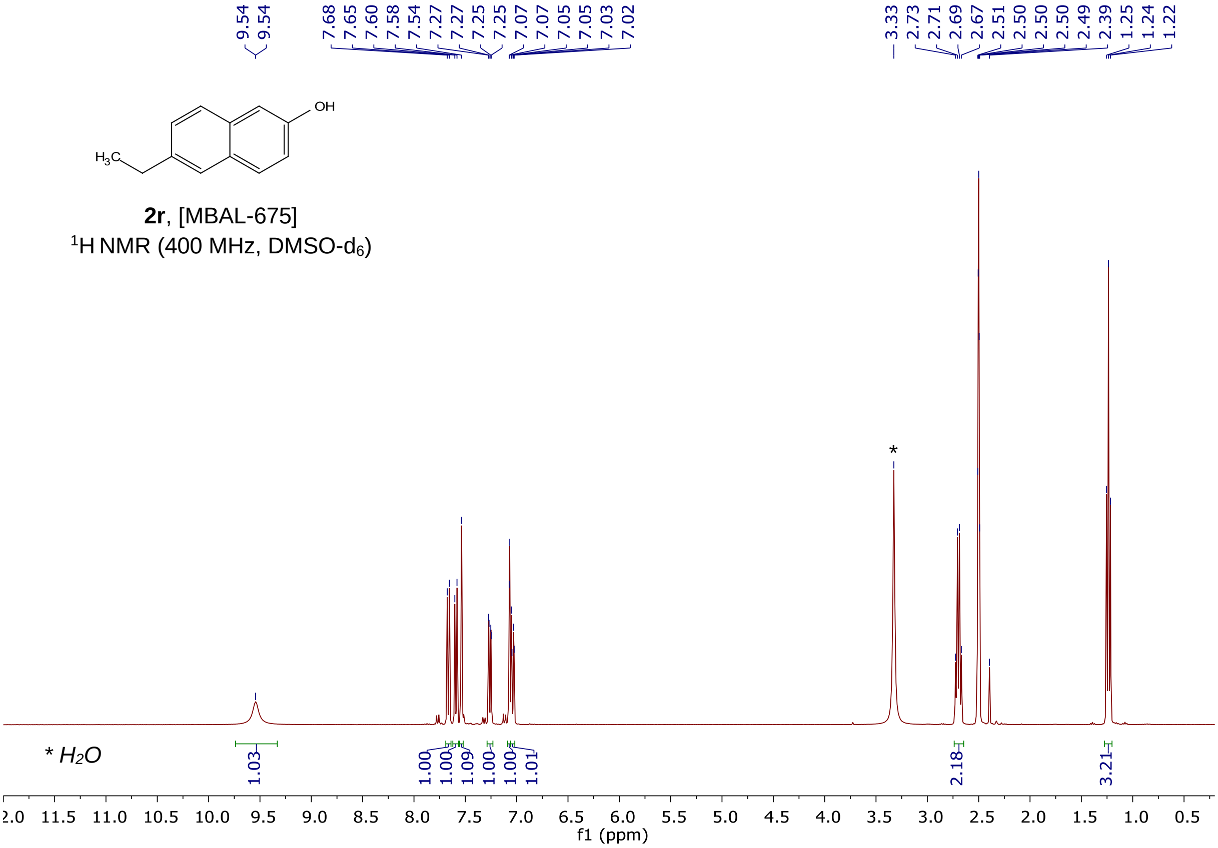
^{13}C DEPT 135° NMR (101 MHz, DMSO-d_6)

*** MTBE**

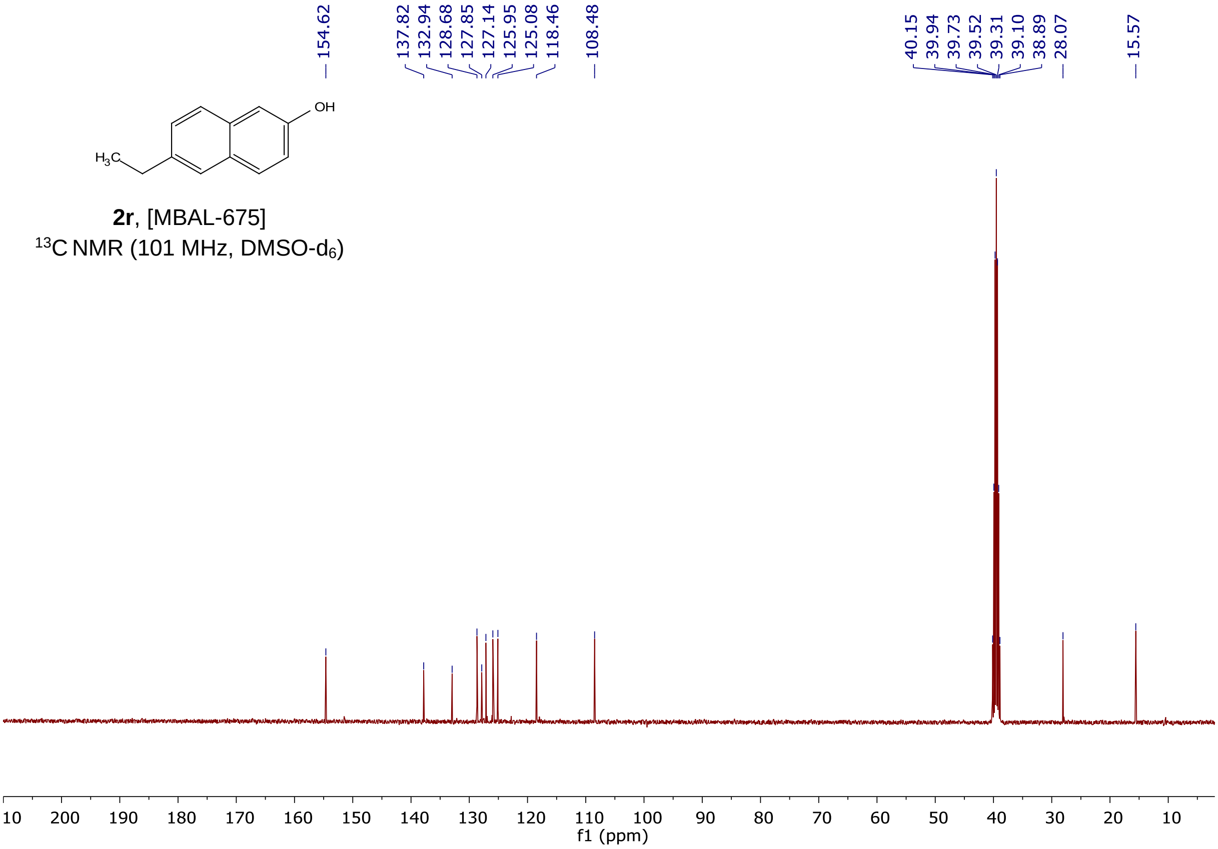


2q, [MBAL-653]

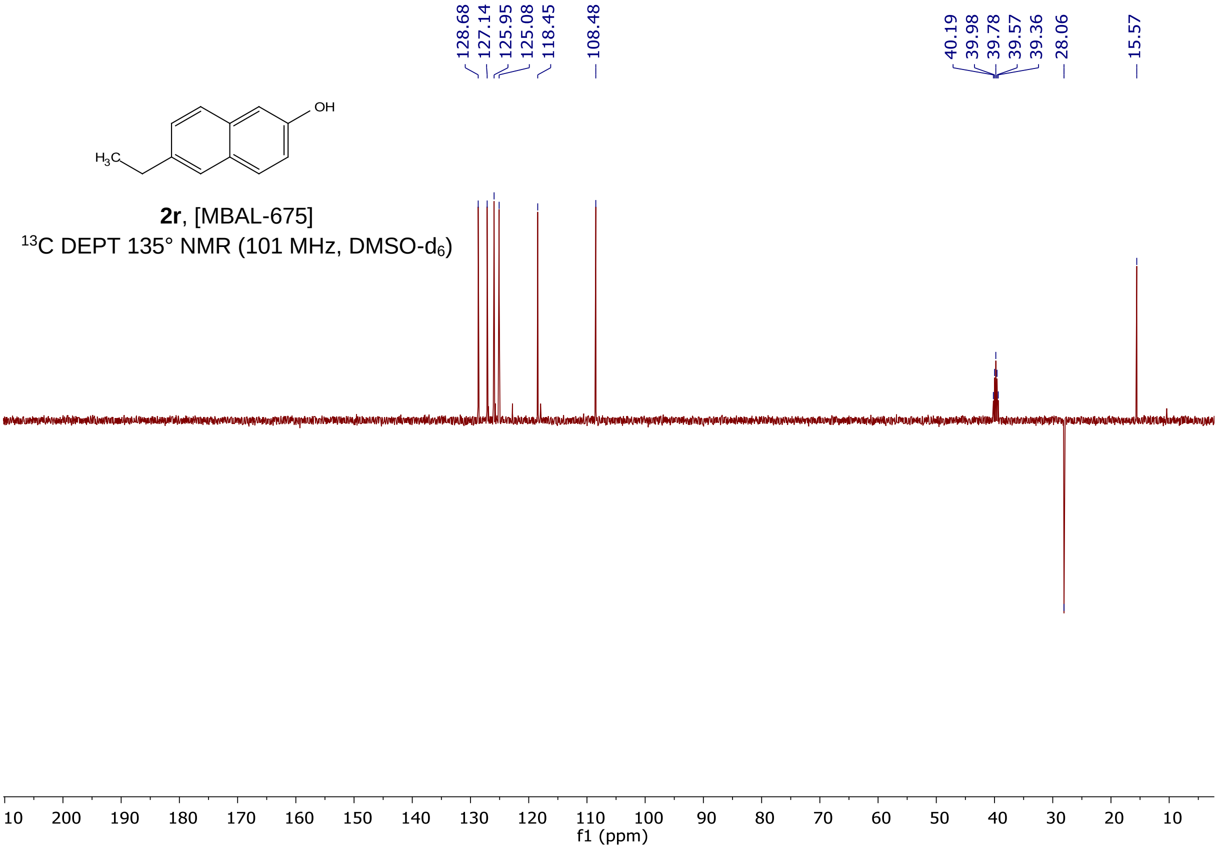
^{1}H COSY NMR (400 MHz, DMSO-d_6)



2r, [MBAL-675]
^{1}H NMR (400 MHz, DMSO-d$_6$)

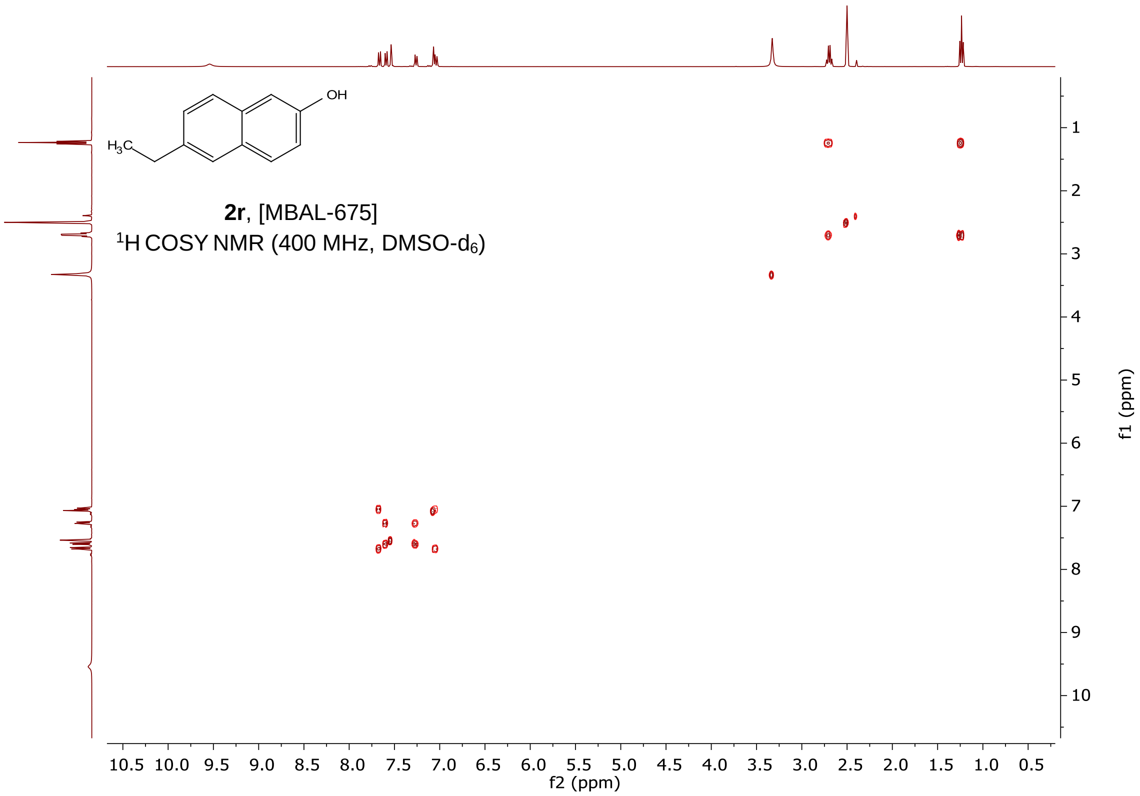


2r, [MBAL-675]
^{13}C NMR (101 MHz, DMSO-d$_6$)



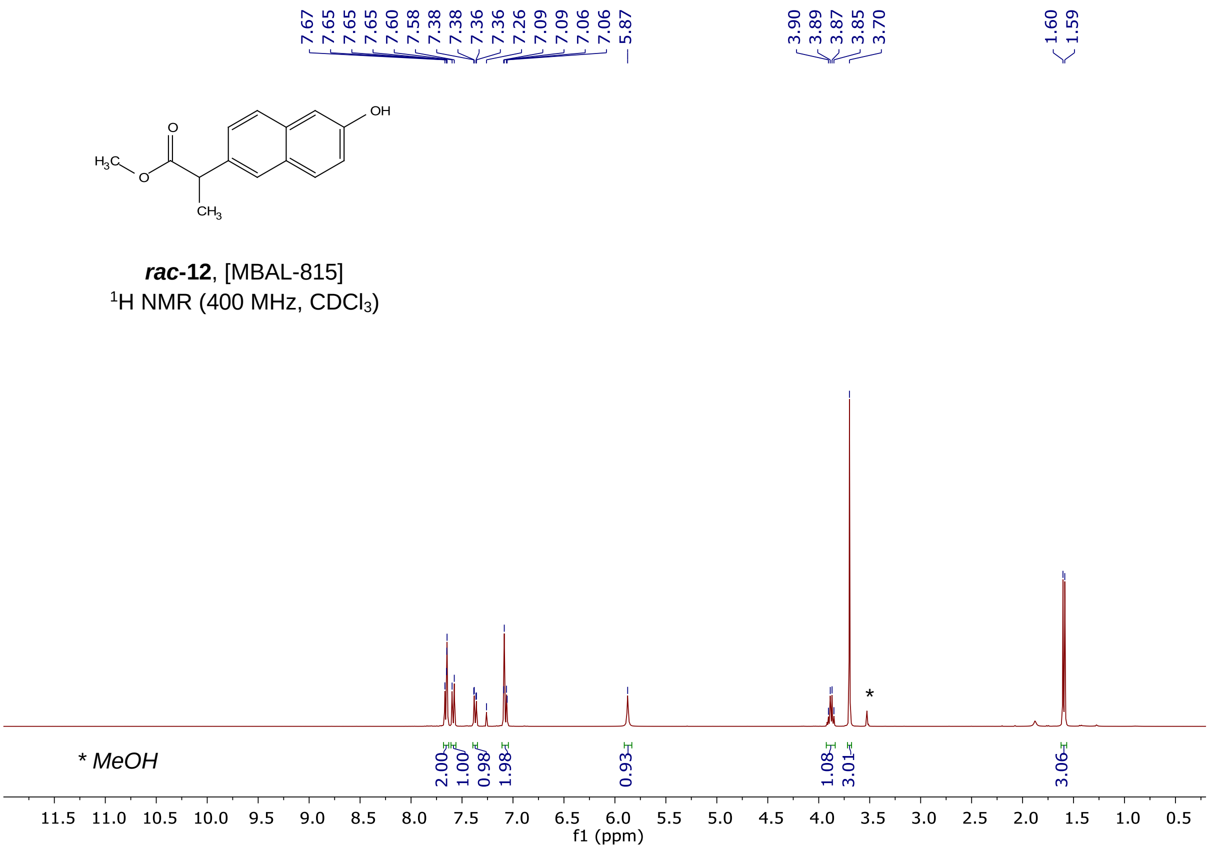
2r, [MBAL-675]

^{13}C DEPT 135° NMR (101 MHz, DMSO-d$_6$)

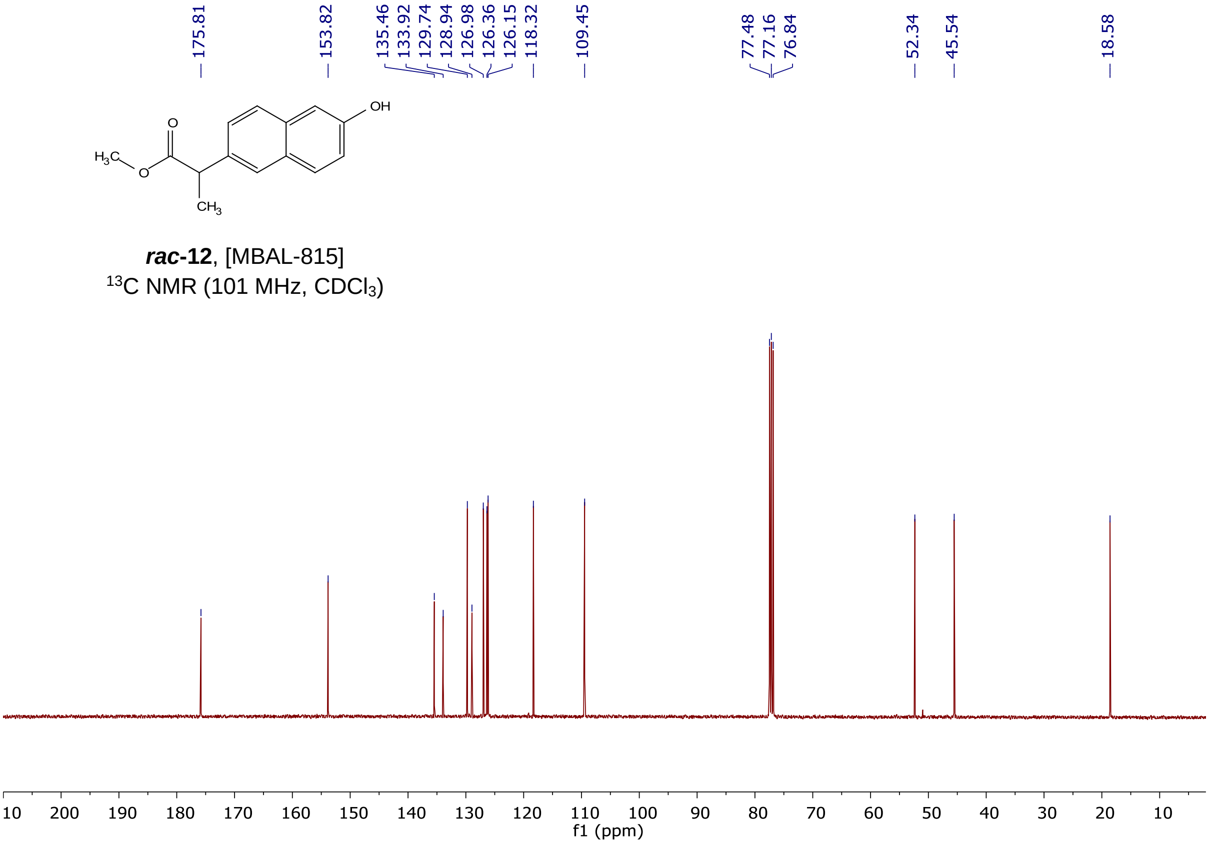


2r, [MBAL-675]

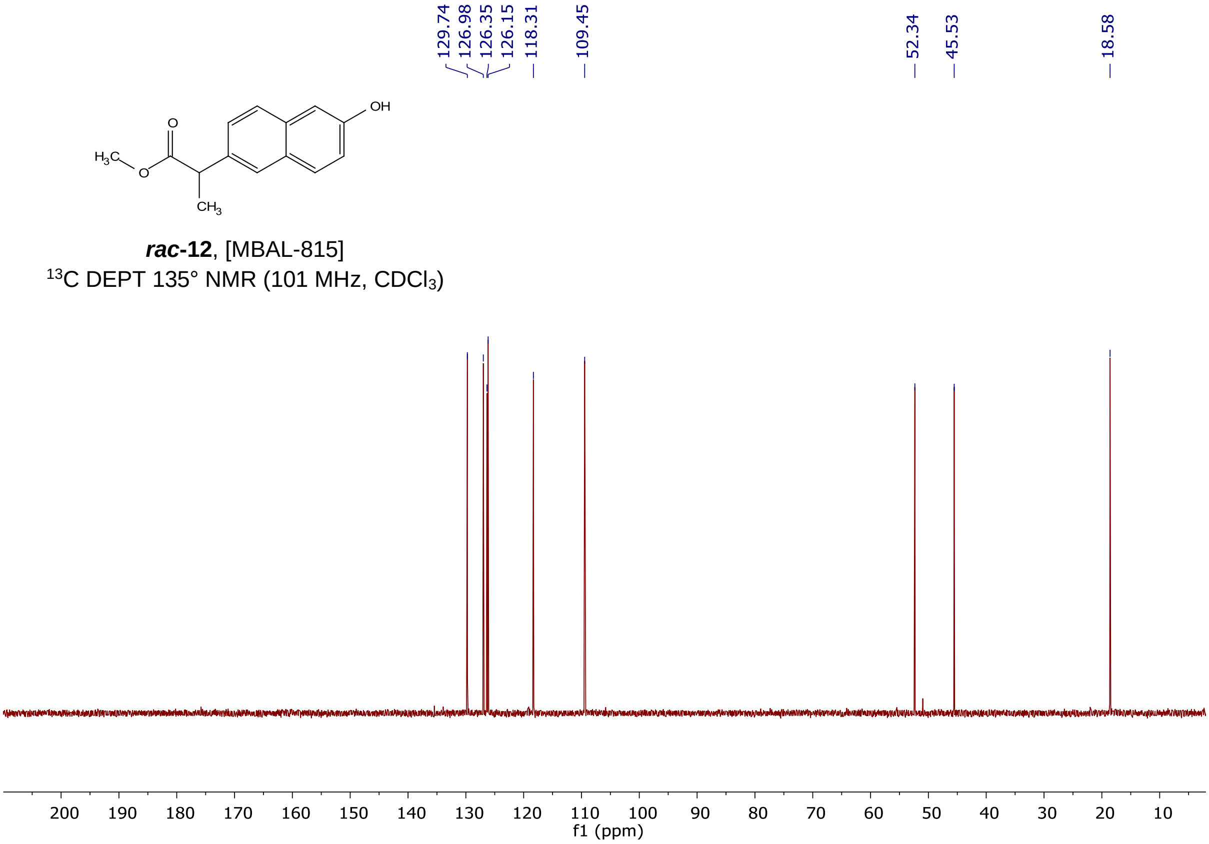
^{1}H COSY NMR (400 MHz, DMSO-d$_6$)



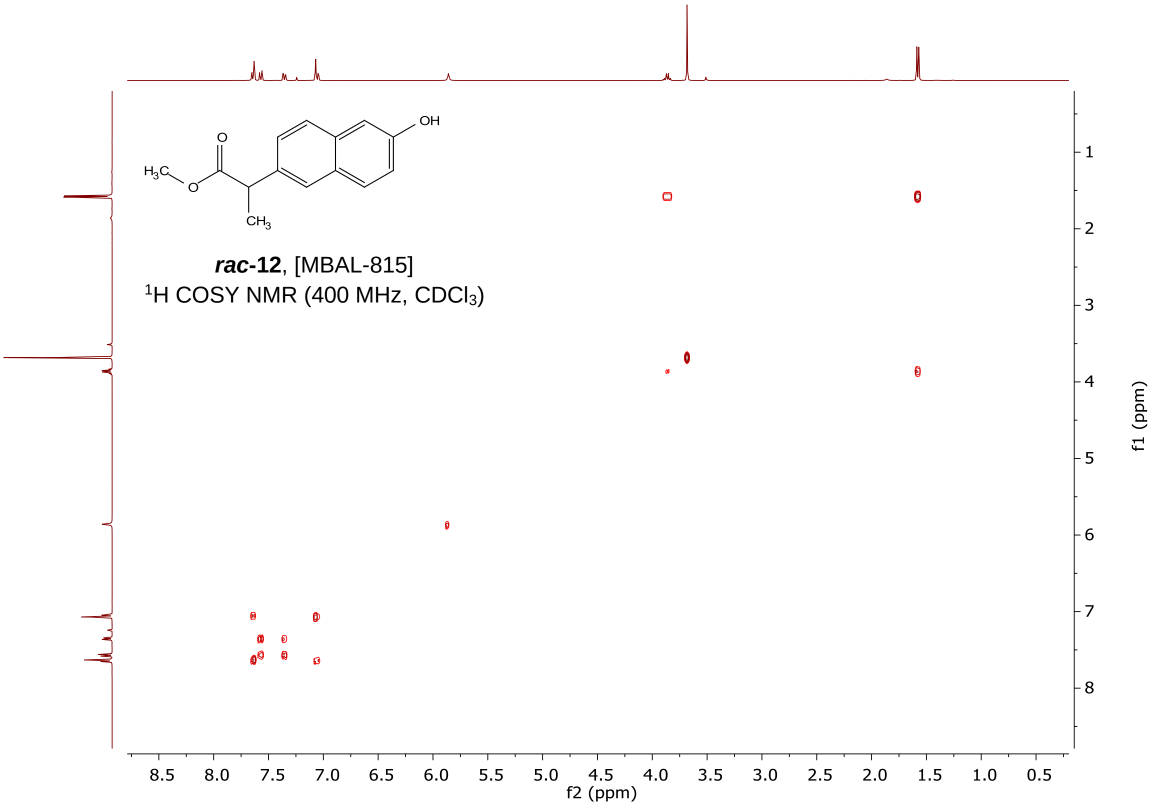
***rac*-12**, [MBAL-815]
^{1}H NMR (400 MHz, $CDCl_3$)



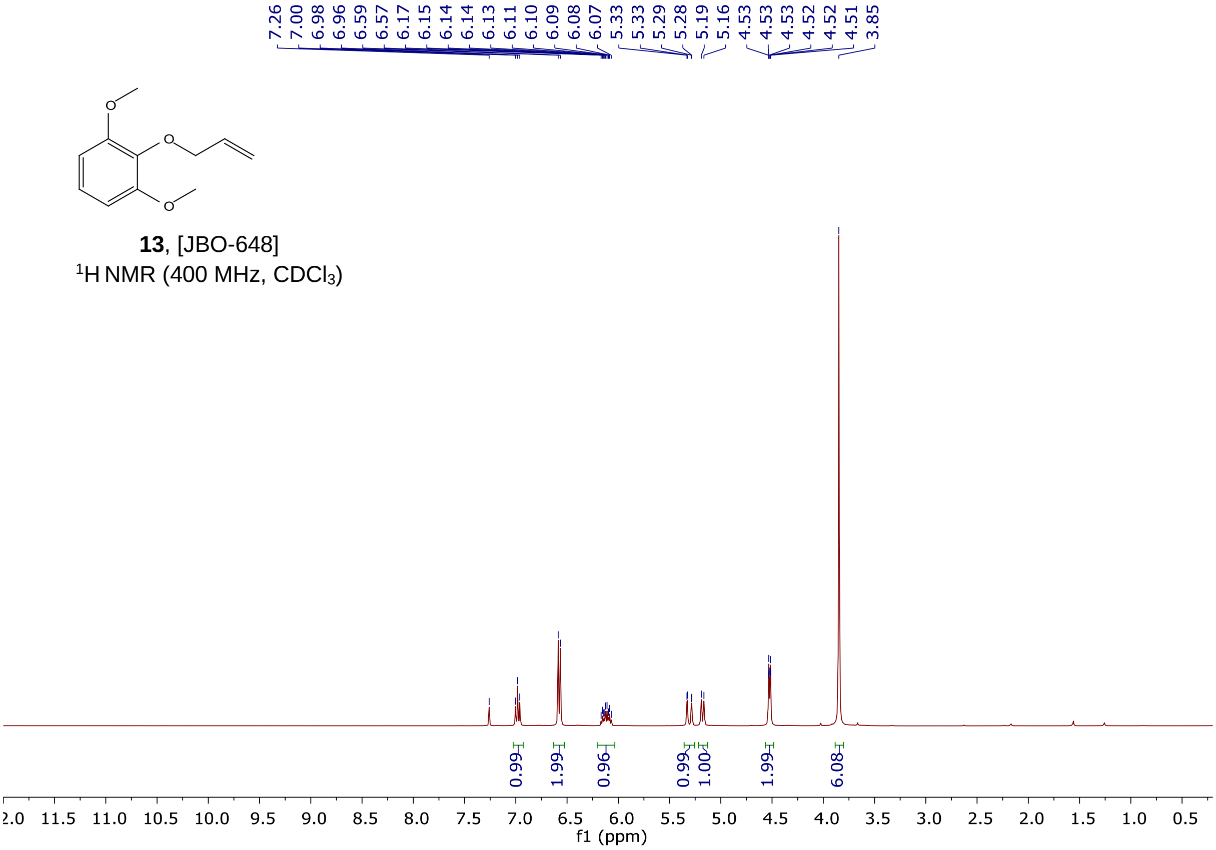
***rac*-12**, [MBAL-815]
^{13}C NMR (101 MHz, $CDCl_3$)

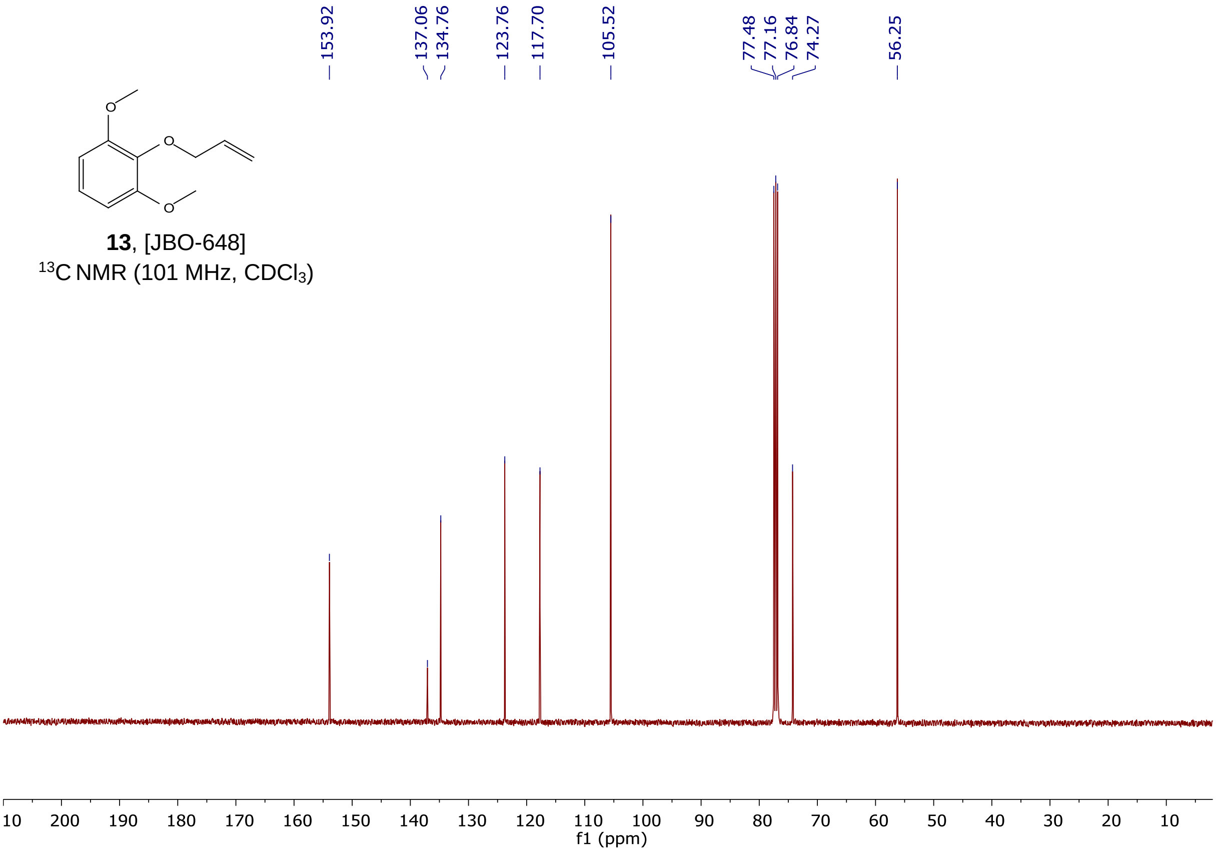


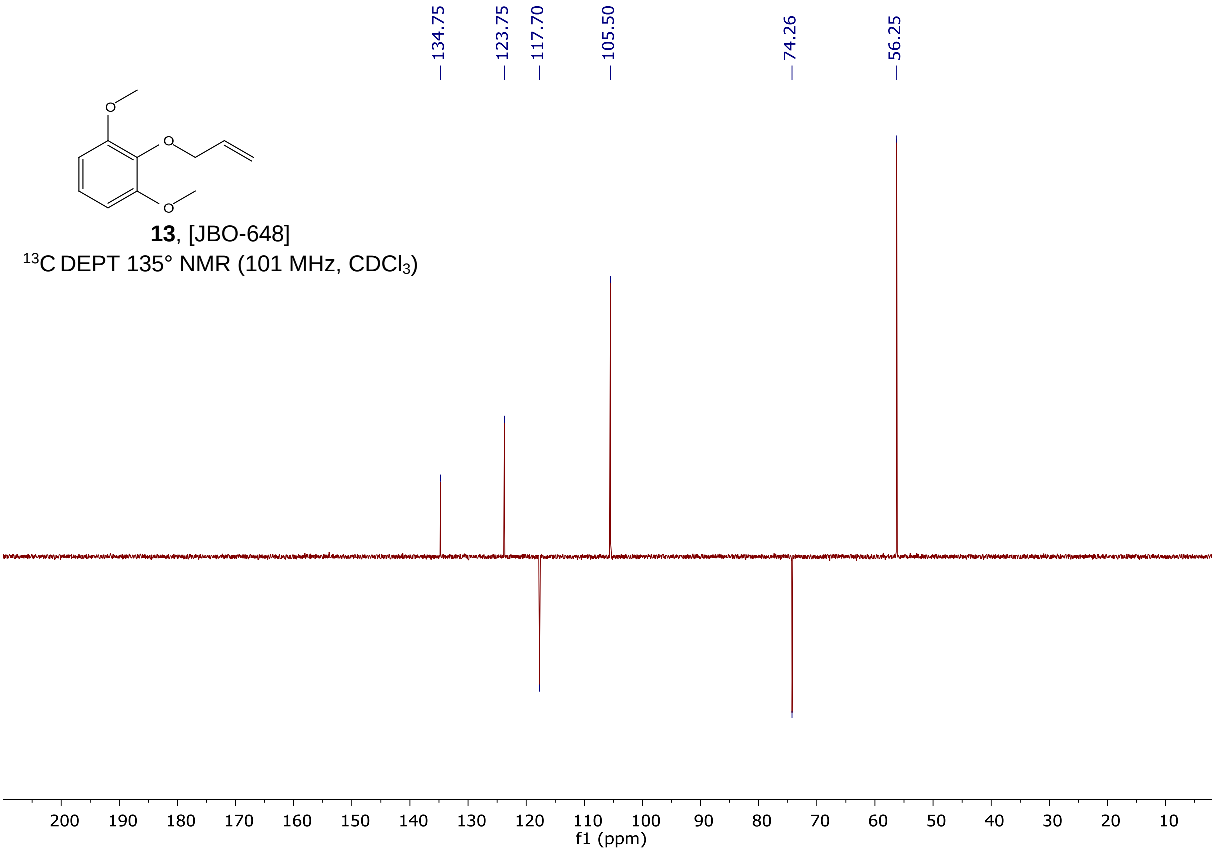
***rac*-12**, [MBAL-815]
^{13}C DEPT 135° NMR (101 MHz, $CDCl_3$)



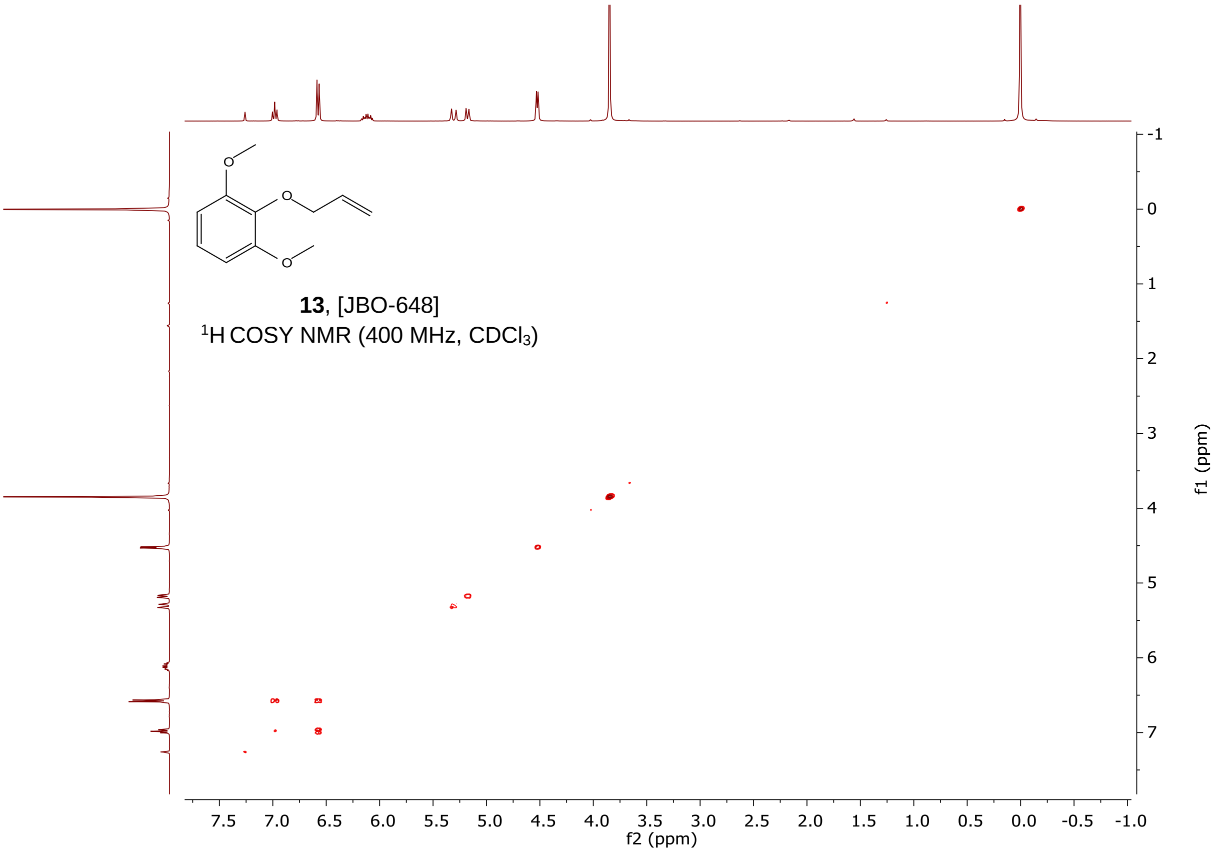
***rac*-12**, [MBAL-815]
^{1}H COSY NMR (400 MHz, $CDCl_3$)


13, [JBO-648]
^{1}H NMR (400 MHz, CDCl$_3$)

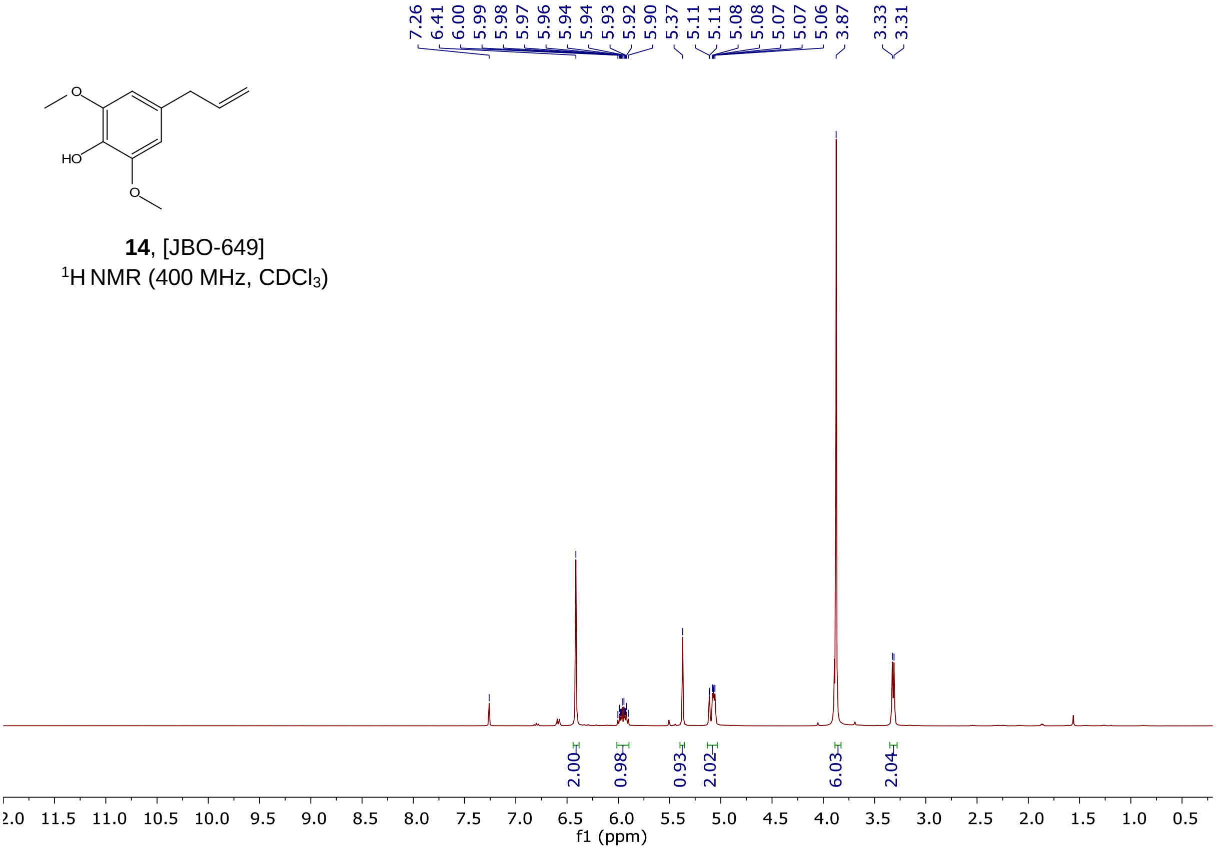

13, [JBO-648]
^{13}C NMR (101 MHz, CDCl$_3$)


13, [JBO-648]

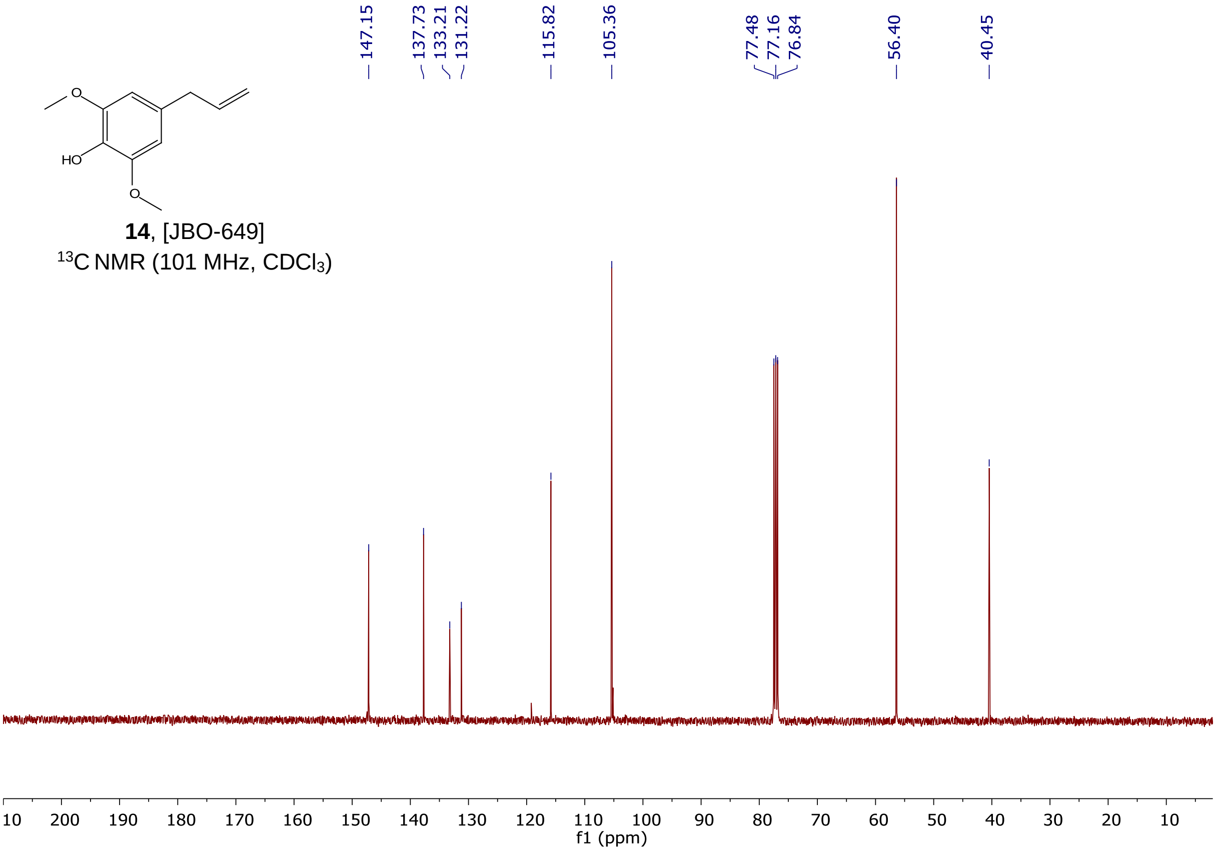
^{13}C DEPT 135° NMR (101 MHz, CDCl$_3$)


13, [JBO-648]

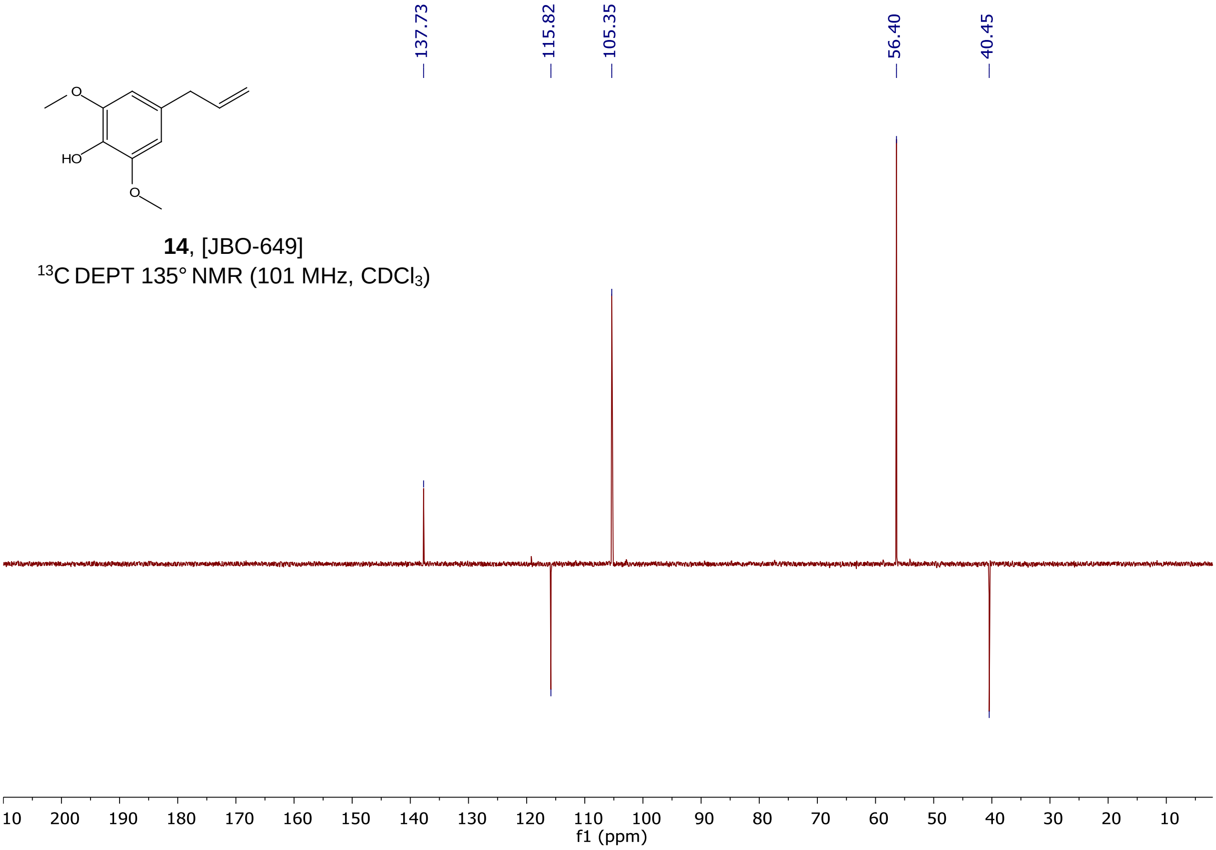
^{1}H COSY NMR (400 MHz, CDCl$_3$)



14, [JBO-649]
^{1}H NMR (400 MHz, $CDCl_3$)

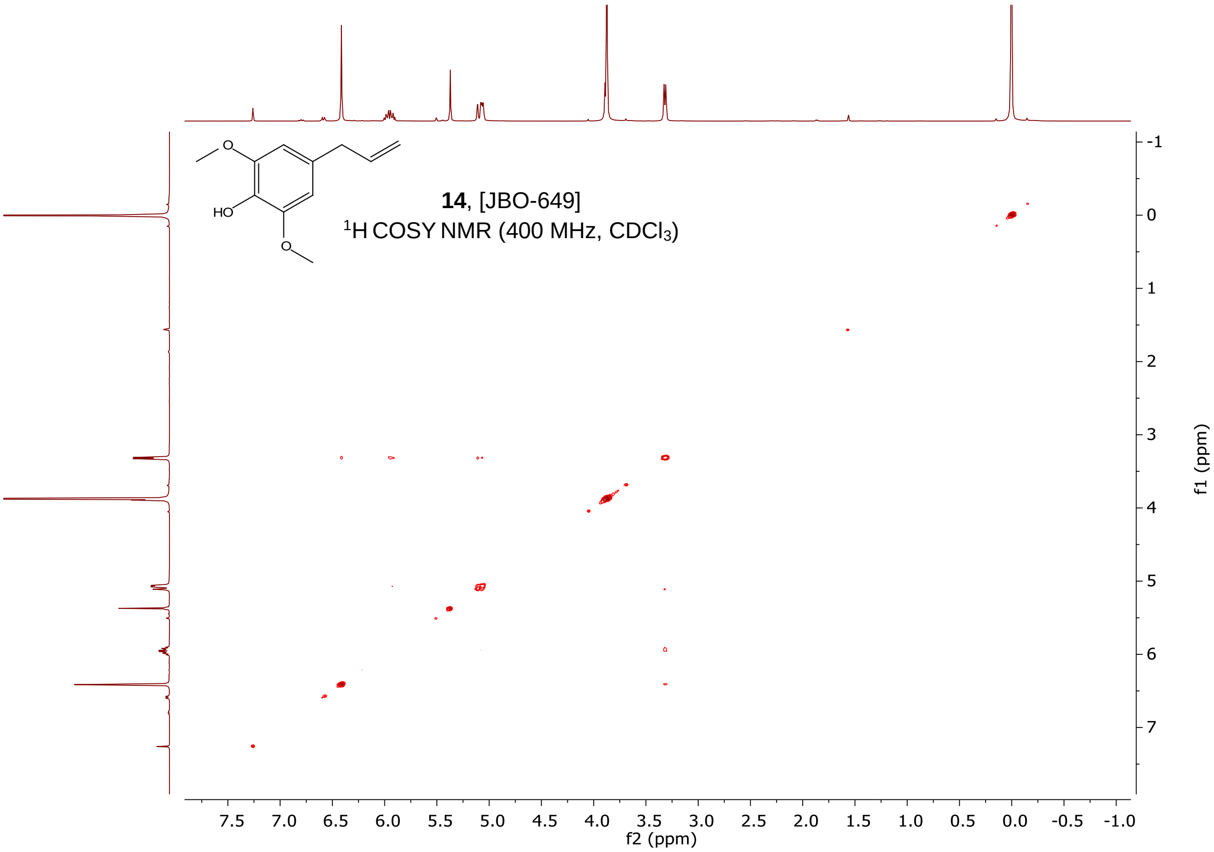


14, [JBO-649]
^{13}C NMR (101 MHz, $CDCl_3$)



14, [JBO-649]

^{13}C DEPT 135° NMR (101 MHz, $CDCl_3$)



14, [JBO-649]

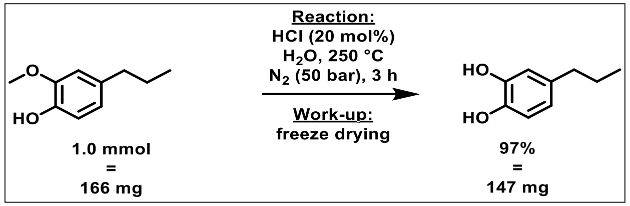
^{1}H COSY NMR (400 MHz, $CDCl_3$)

7 Copies of the Excel Sheets used for Green Metrics calculations

- Method A1 on 4-propylguaiacol (**1a**): [JBO-496]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	**Mass (g)**	**MW**	**Mol**	**Catalyst**	**Mass (g)**	**Reagent**	**Mass (g)**	**Reaction solvent**	**Volume (cm^3)**	**Density (g ml^{-1})**	**Mass (g)**	**Work up chemical**	**Mass (g)**	**Workup solvent**	**Volume (cm^3)**	**Density (g ml^{-1})**	**Mass (g)**
4-Propylguaiacol	0,166	166,22	1,00E-03	HCl	0,007			H_2O	1,982	1,00	1,98						
H_2O	0,018	18,02	1,00E-03														
Total	0,18	184,23			0,01		0,00				1,98		0,00				0,00



		Flag	
Yield	96,59	●	96,6
Conversion	100,00	●	100,0
Selectivity	96,59	●	96,6
AE	82,61		
RME	79,79	OE	96,6
PMI total	14,79		
PMI Reaction	14,79		
PMI Workup	0,00		
PMI Workup chemical	0,00		
PMI workup solvents	0,00		
PMI RRC	1,30		
PMI FI Total	12,21		
PMI FI React	12,21		
PMI FI Workup	0,00		
PMI FI RRC	1,08		
AE FI	100,00		
RME FI	96,59		
E factor	13,79		
E factor FI	11,21		

	Mass	MW	Mol
Product	0,147	152,19	9,66E-04
	mass		
Unreacted limiting reactant	0,00		
	Mass	MW	Mol
Co-Product	0,031	32,04	9,66E-04
	excluding co-products	including co-	
Generated waste	2,027	1,996	

Experimental [JBO-496]
The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (166 mg, 1.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.20 mmol, 0.2 equiv.) and H_2O (1.8 mL) as regents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment wa repeated 5 times and samples were freeze-dried to remove all volatiles. The residue was pure product.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

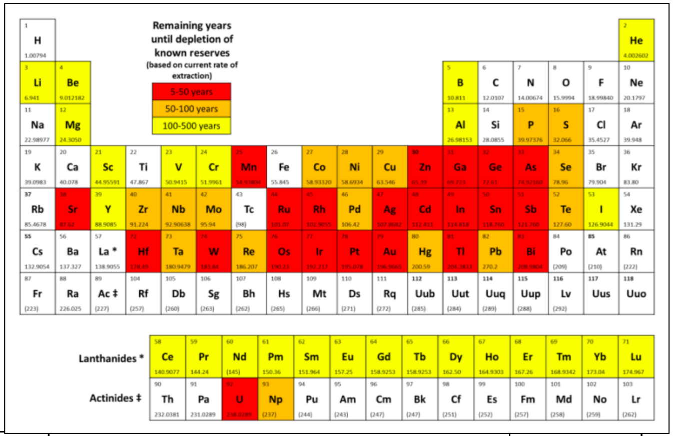
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Sublimation
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H2O HCl
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

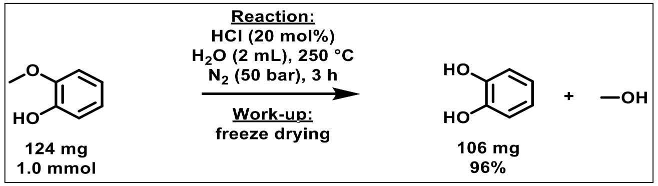
Use of chemicals of environmental concern

		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method A1 on guaiacol (**1l**): [SA-024]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
Guaiacol	0,124	124,14	1,00E-03	HCl	0,007			H_2O	1,982	1,00	1,98						
H_2O	0,018	18,02	1,00E-03														
Total	0,14	142,16			0,01		0,00				1,98		0,00				0,00



		Flag	
Yield	96,27	●	96,3
Conversion	100,00	●	100,0
Selectivity	96,27	●	96,3
AE	77,46		
RME	74,57	OE	96,3
PMI total	20,11		
PMI Reaction	20,11		
PMI Workup	0,00		
PMI Workup chemical	0,00		
PMI workup solvents	0,00		
PMI RRC	1,41		
PMI FI Total	15,58		
PMI FI Reaction	15,58		
PMI FI Workup	0,00		
PMI FI RRC	1,09		
AE FI	100,00		
RME FI	96,26		
E factor	19,11		
E factor FI	14,58		

	Mass	MW	Mol
Product	0,106	110,11	9,63E-04
	mass		
Unreacted limiting reactant	0,00		
	Mass	MW	Mol
Co-Product	0,031	32,04	9,63E-04
	excluding co-products	including co-products	
Generated waste	2,025	1,995	

Experimental [SA-024]

The reaction was performed using General Procedure C, using 2-methoxyphenol (124 mg, 1.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.20 mmol, 0.2 equiv.) and H_2O (1.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were freeze-dried to remove all volatiles. The residue was pure product.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

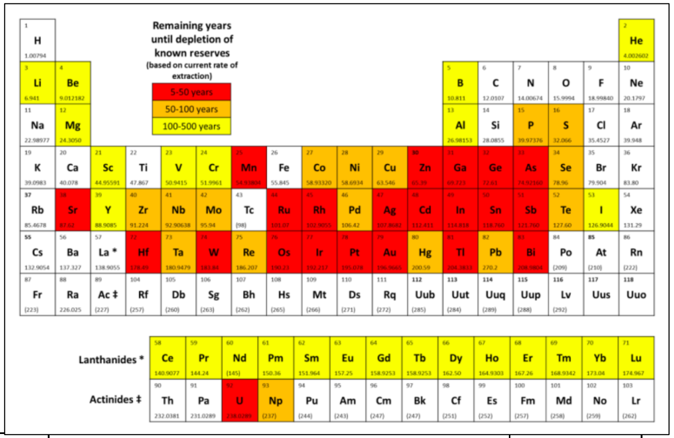
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Sublimation
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

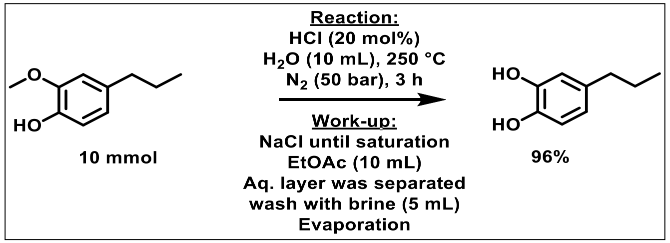
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H2O HCl
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		**List substances of very high concern**
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method A2 on 4-propylguaiacol (**1a**): [MBAL-766]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-Propylguaiacol	0,332	166,22	2,00E-03	HCl	0,015			H_2O	1,964	1,00	1,96	NaCl	0,40	EtOAc	2,00	0,90	1,79
H_2O	0,036	18,02	2,00E-03									NaCl	0,36	H_2O	1,00	1,00	1,00
Total	0,37	184,23			0,01		0,00				1,96		0,76				2,79



		Flag	
Yield	95,97	●	96,0
Conversion	100,00	●	100,0
Selectivity	95,97	●	96,0
AE	82,61		
RME	79,27	OE	96,0
PMI total	20,20		
PMI Reaction	8,03		
PMI Workup	12,17		
PMI Workup chemical	2,60		
PMI workup solvents	9,57		
PMI RRC	1,31		
PMI FI Total	16,69		
PMI FI React	6,64		
PMI FI Workup	10,05		
PMI FI RRC	1,08		
AE FI	100,00		
RME FI	95,96		
E factor	19,20		
E factor FI	15,69		

	Mass	MW	Mol
Product	0,292	152,19	1,92E-03
	mass		
Unreacted limiting reactant	0,00		
	Mass	MW	Mol
Co-Product	0,061	32,04	1,92E-03
	excluding co-products	including co-	
Generated waste	5,609	5,547	

Experimental [MBAL-766]

The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (332 mg, 2.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.4 mL, 0.40 mmol, 0.2 equiv.) and H_2O (1.6 mL) as reagents as reagent. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was performed 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The residue was pure product.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

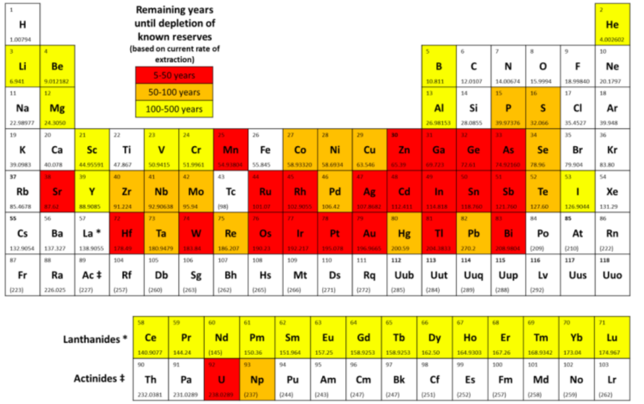
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X


Remaining years until depletion of known reserves (based on current rate of extraction)

🟥 5-50 years
🟧 50-100 years
🟨 100-500 years

Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Sublimation
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H2O HCl NaCl EtOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

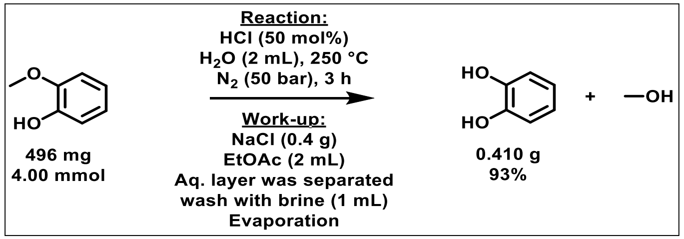
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method A2 on guaiacol (**1l**): [MBAL-467]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
Guaiacol	0,496	124,14	4,00E-03	HCl	0,073			H_2O	1,928	1,00	1,93	NaCl	0,40	EtOAc	2,00	0,90	1,79
H_2O	0,072	18,02	4,00E-03									NaCl	0,36	H_2O	1,00	1,00	1,00
Total	0,57	142,16			0,07		0,00				1,93		0,76				2,79

Yield	93,19
Conversion	100,00
Selectivity	93,19
AE	77,46
RME	72,19
PMI total	14,93
PMI Reaction	6,27
PMI Workup	8,67
PMI Workup chemical	1,85
PMI workup solvents	6,81
PMI RRC	1,56
PMI FI Total	11,57
PMI FI Reaction	4,85
PMI FI Workup	6,71
PMI FI RRC	1,21
AE FI	100,00
RME FI	93,19
E factor	13,93
E factor FI	10,57



	Mass	MW	Mol
Product	0,410	110,11	3,72E-03
	mass		
Unreacted limiting reactant	0,00		
	Mass	MW	Mol
Co-Product	0,119	32,04	3,72E-03
	excluding co-products	including co-products	
Generated waste	5,713	5,594	

Experimental [MBAL467]

The reaction was performed using General Procedure C, using 2-methoxyphenol (496 mg, 4.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.00 mmol, 0.5 equiv.) as reagent. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was performed 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The residue was pure product.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

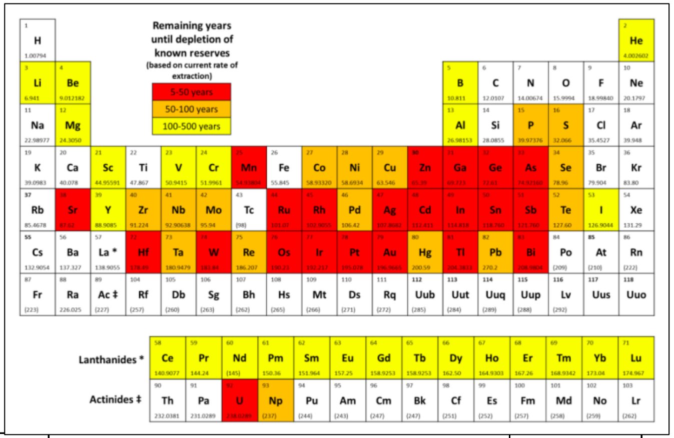
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Sublimation
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H2O HCl NaCl EtOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

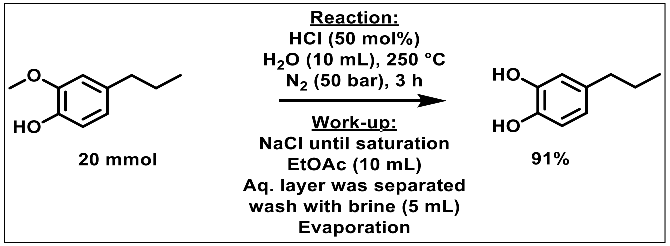
- Method A3: [JBO-643]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)
4-Propylguaiacol	0,665	166,22	4,00E-03	HCl	0,073			H_2O	1,928	1,00	1,93	NaCl	0,40	EtOAc	2,00	0,90	1,79
H_2O	0,072	18,02	4,00E-03									NaCl	0,36	H_2O	1,00	1,00	1,00
Total	0,74	184,23			0,07		0,00				1,93		0,76				2,79

		Flag		
Yield	91,00	●	91,0	
Conversion	100,00	●	100,0	
Selectivity	91,00	●	91,0	
AE	82,61			
RME	75,18	OE		91,0
PMI total	11,36			
PMI Reaction	4,94			
PMI Workup	6,42			
PMI Workup chemical	1,37			
PMI workup solvents	5,04			
PMI RRC	1,46			
PMI FI Total	9,38			
PMI FI React	4,08			
PMI FI Workup	5,30			
PMI FI RRC	1,21			
AE FI	100,00			
RME FI	91,00			
E factor	10,36			
E factor FI	8,38			

	Mass	MW	Mol
Product	0,554	152,19	3,64E-03
	mass		
Unreacted limiting reactant	0,00		
	Mass	MW	Mol
Co-Product	0,117	32,04	3,64E-03
	excluding co-products	including co-	
Generated waste	5,738	5,621	



Experimental [JBO-643]

The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (666 mg, 4.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.00 mmol, 0.5 equiv.) as reagent. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was performed 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The residue was pure product.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

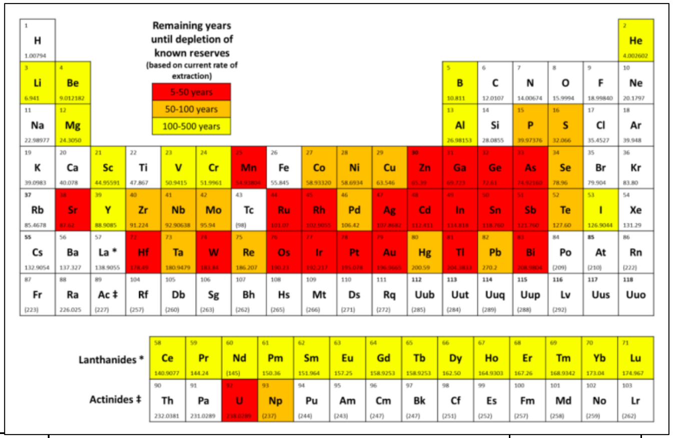
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X


Remaining years until depletion of known reserves (based on current rate of extraction)
5-50 years
50-100 years
100-500 years

Energy (First Pass)

		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}C at atmospheric	Green Flag	Evaporation Sublimation
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

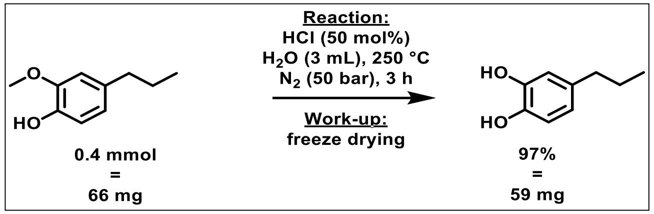
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O HCl NaCl EtOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		**List substances of very high concern**
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method A4: [JBO-1658]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-Propylguaiacol	0,066	166,22	4,00E-04	HCl	0,007			H_2O	2,993	1,00	2,99						
H_2O	0,007	18,02	4,00E-04														
Total	0,07	184,23			0,01		0,00				2,99		0,00				0,00



		Flag	
Yield	96,92	●	96,9
Conversion	100,00	●	100,0
Selectivity	96,92	●	96,9
AE	82,61		
RME	80,06	OE	96,9
PMI total	52,10		
PMI Reaction	52,10		
PMI Workup	0,00		
PMI Workup chemical	0,00		
PMI workup solvents	0,00		
PMI RRC	1,37		
PMI FI Total	43,04		
PMI FI Reaction	43,04		
PMI FI Workup	0,00		
PMI FI RRC	1,13		
AE FI	100,00		
RME FI	96,92		
E factor	51,10		
E factor FI	42,04		

	Mass	MW	Mol
Product	0,059	152,19	3,88E-04
	mass		
Unreacted limiting reactant	0,00		
	Mass	MW	Mol
Co-Product	0,012	32,04	3,88E-04
	excluding co-products	including co-products	
Generated waste	3,015	3,002	

Experimental [JBO-1658]

The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (66 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.20 mmol, 0.5 equiv.) and H_2O (2.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were freeze-dried to remove all volatiles. The residue was pure product.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt**,** sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

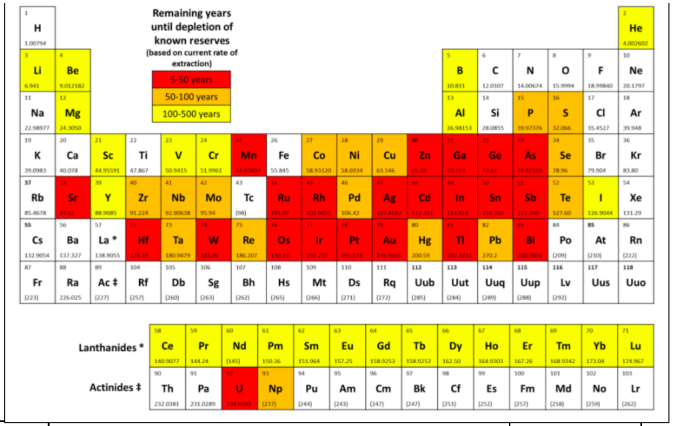
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Sublimation
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

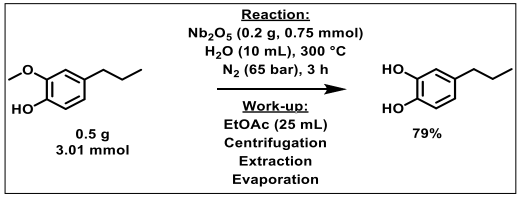
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O HCl
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method B: Nb_2O_5.[12]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-Propylguaiacol	0,50	166,22	3,0E-03	Nb_2O_5	0,20			H_2O	9,95	1,00	9,95			EtOAc	25,00	0,90	22,55
H_2O	0,05	18,02	3,0E-03														
Total	0,55	184,24			0,20		0,00				9,95		0,00				22,55



		Flag	
Yield	78,64	●	78,6
Conversion	97,00	●	97,0
Selectivity	81,07	●	81,1
AE	82,61		
RME	64,96	OE	78,6
PMI total	92,36		
PMI Reaction	29,72		
PMI Workup	62,64		
PMI Workup chemical	0,00		
PMI workup solvents	62,64		
PMI RRC	2,09		
E factor	91,36		

	Mass	MW	Mol
Product	0,360	152,19	2,37E-03
	mass		
Unreacted limiting reactant	0,02		

	Mass
Generated waste	32,890

Experimental [MBAL-810]
The Parr® 4596 reactor (25 mL internal volume) was charged with 2-methoxy-4-propylphenol (0.50 g, 3.01 mmol), Nb_2O_5 (0.20 g, 0.75 mmol) and H_2O (10 mL). The reactor was closed properly, flushed with N_2 gas (3 × 10 bar) and filled with N_2 gas (65 bar). Subsequently, stirring (mechanical overhead stirring, 400 rpm) was started and the reactor and its contents were heated to 300 °C. After the temperature reached it desired value, stirring was continued for 3 h at this temperature. Subsequently the reactor and its contents were cooled to r.t. (using an ice bath), gas was released and the reactor was opened. The crude reaction mixture was extracted with EtOAc (1 x 15 mL, 2 x 5 mL). The combined organic fractions were centrifuged for 30 min at 4500 rpm. The organic solvent was subsequently evaporated under reduced pressure to afford a mixture of 4-propylcatechol (79%, 0.36 g, 2.37 mmol), catechol (6%, 19 mg, 0.17 mmol) and 2-methoxy-4-propylphenol (3%, 15 mg, 0.09 mmol) as an orange oil.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

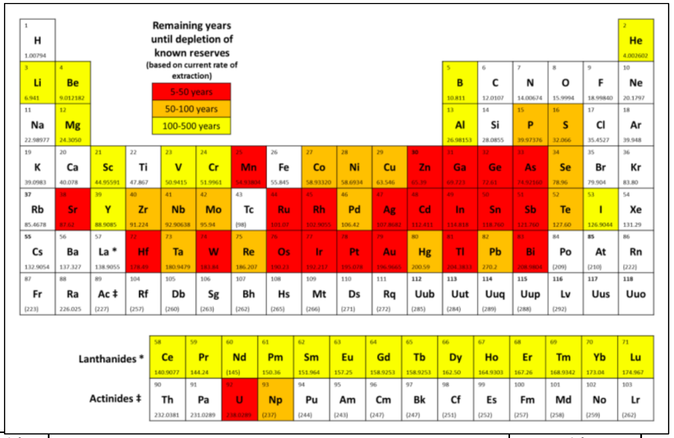
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	X

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	Nb
+500 years	Green Flag	



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Centrifugation
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

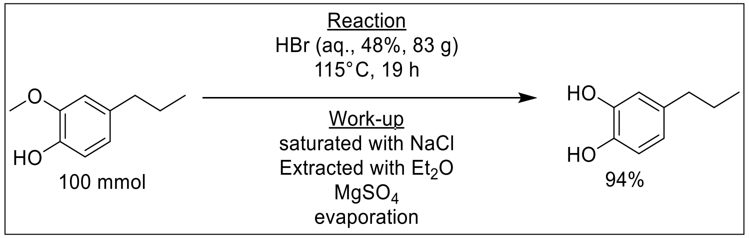
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O EtOAc Nb_2O_5
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		**List substances of very high concern**
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method C1: HBr.[2]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	16,60	166,22	0,100			H_2O	1,80	H_2O	41,36	1,00	41,36	NaCl	15,54	Et_2O	299,61	0,71	213,85
HBr	39,84	80,91	0,49									$MgSO_4$	99,87				
Total	56,44	247,13			0,00		1,80				41,36		115,41				213,85

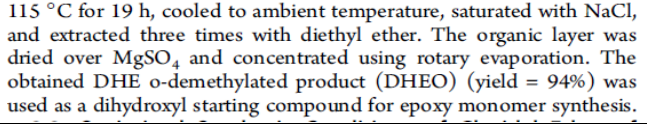


		Flag	
Yield	94,00	●	94,0
Conversion	100,00	●	100,0
Selectivity	94,00	●	94,0
AE	61,58		
RME	25,31	OE	41,1
PMI total	30,02		
PMI Reaction	6,97		
PMI Workup	23,05		
PMI Workup chemical	8,08		
PMI workup solvents	14,97		
PMI RRC	4,08		
E factor	29,02		

	Mass	MW	Mol
Product	14,287	152,19	0,09
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	414,574

Experimental: copied from Abu-Omar *et al.*, *Biomacromolecules* **2015**, *16*, 2025.



2.1. o-Demethylation of DHE To Make Propylcatechol (DHEO). DHE (16.6 g, 0.1 mol) was added to 83 g of 48% aqueous hydrobromic acid. The reaction mixture was magnetically stirred at 115 °C for 19 h, cooled to ambient temperature, saturated with NaCl, and extracted three times with diethyl ether. The organic layer was dried over $MgSO_4$ and concentrated using rotary evaporation. The obtained DHE o-demethylated product (DHEO) (yield = 94%) was used as a dihydroxyl starting compound for epoxy monomer synthesis.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	Et_2O

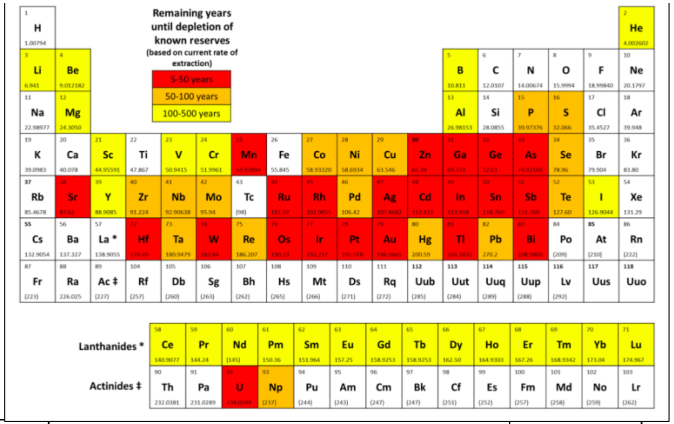
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	X
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

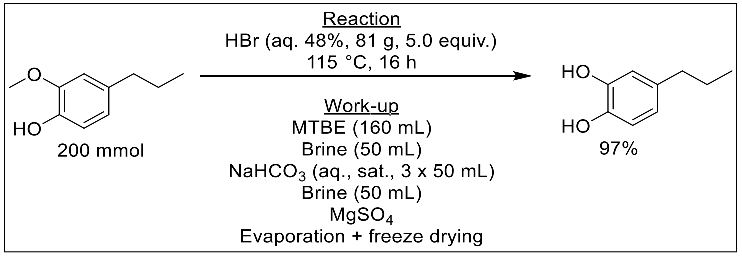
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Et_2O: H224	H_2O NaCl
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311 HBr: H331	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method C2: HBr.[13]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	33,24	166,22	0,200			H_2O	3,600	H_2O	84,15	1,00	84,15	NaCl	18,00	MTBE	160,00	0,74	118,40
HBr	81,00	80,91	1,001									$NaHCO_3$	15,00	H_2O (brine)	50,00	1,00	50,00
												NaCl	18,00	H_2O ($NaHCO_3$)	150,00	1,00	150,00
														H_2O (brine)	50,00	1,00	50,00
Total	114,24	247,13			0,00		3,60				84,15		51,00				368,40

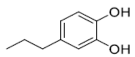


		Flag	
Yield	97,25	●	97,2
Conversion	100,00	●	100,0
Selectivity	97,25	●	97,2
AE	61,58		
RME	25,91	OE	42,1
PMI total	20,99		
PMI Reaction	6,82		
PMI Workup	14,17		
PMI Workup chemical	1,72		
PMI workup solvents	12,45		
PMI RRC	3,98		
E factor	19,99		

	Mass	MW	Mol
Product	29,60	152,19	0,19
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	591,793

Experimental: copied from Maes *et al.*, *ChemSusChem* **2019**, *12*, 3103.



A 250 mL roundbottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 2-methoxy-4-propylphenol (**1**) (32.2 g, 200.0 mmol, 1 equiv) and 48% aq. HBr (81.0 g, 1000.0 mmol, 5 equiv). The obtained mixture was stirred for 16 h at 115 °C. After cooling down to room temperature, it was diluted with 160 ml MTBE (2-methoxy-2-methylpropane), washed with 50 ml brine, 3x50 ml saturated $NaHCO_3$ solution, and again with 50 ml brine. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequently, the residue was freeze dried in order to remove the last traces of solvent and to obtain pure 4-propylcatechol (**2**) as an off-white solid (29.6 g, 97%). The obtained spectroscopic data (NMR in $CDCl_3$) of the product are in accordance with literature.[5]

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	MTBE
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

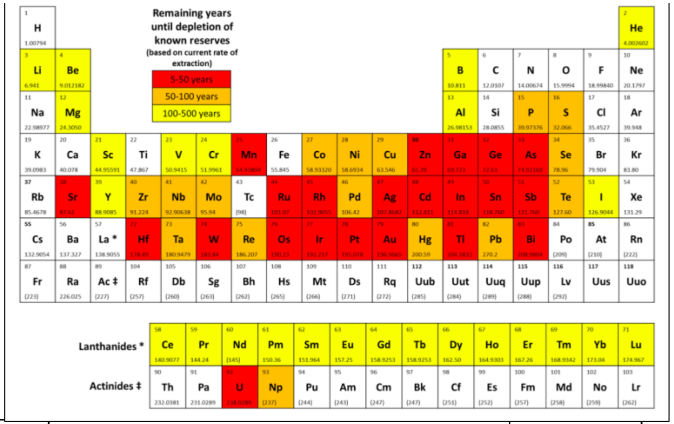
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	X
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Freeze drying
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

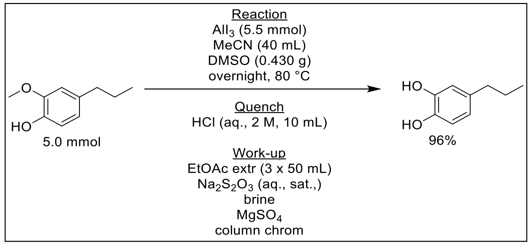
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O MTBE NaCl $NaHCO_3$
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311 HBr: H331	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		**List substances of very high concern**
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method D: AlI_3 + DMSO.[14]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	0,83	166,22	0,005			AlI_3	2,24	MeCN	40,00	0,79	31,44	HCl	0,55	H_2O	10,00	1,00	10,00
HCl	0,18	36,46	0,005			DMSO	0,43					$Na_2S_2O_3$	2,09	EtOAc	150,00	0,90	134,55
												NaCl	3,60	H_2O ($Na_2S_2O_3$)	10,00	1,00	10,00
												$MgSO_4$	5,00	H_2O (NaCl)	10,00	1,00	10,00
												SiO_2	40,00	Heptane	400,00	0,68	273,20
														EtOAc	100,00	0,90	89,70
Total	1,01	202,68			0,00		2,67				31,44		51,24				527,45

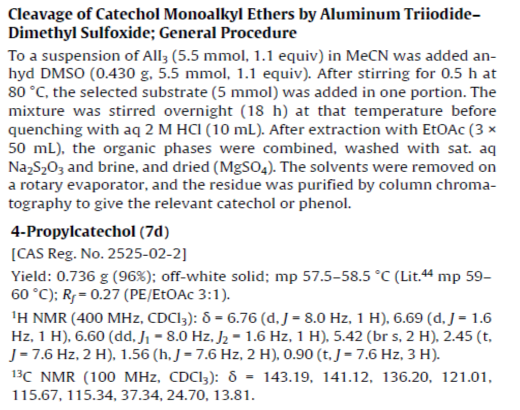


		Flag			
Yield	96,72	●	96,7		
Conversion	100,00	●	100,0		
Selectivity	96,72	●	96,7		
AE	75,09				
RME	72,63	OE			96,7
PMI total	833,98				
PMI Reaction	47,72				
PMI Workup	786,26				
PMI Workup chemical	69,62				
PMI workup solvents	716,64				
PMI RRC	5,01				
E factor	832,98				

	Mass	MW	Mol
Product	0,736	152,19	0,00
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	613,076

Experimental: copied from Tian *et al.*, *Synthesis* **2019**, *51*, 704.



Cleavage of Catechol Monoalkyl Ethers by Aluminum Triiodide–Dimethyl Sulfoxide; General Procedure

To a suspension of AlI_3 (5.5 mmol, 1.1 equiv) in MeCN was added anhyd DMSO (0.430 g, 5.5 mmol, 1.1 equiv). After stirring for 0.5 h at 80 °C, the selected substrate (5 mmol) was added in one portion. The mixture was stirred overnight (18 h) at that temperature before quenching with aq 2 M HCl (10 mL). After extraction with EtOAc (3 × 50 mL), the organic phases were combined, washed with sat. aq $Na_2S_2O_3$ and brine, and dried ($MgSO_4$). The solvents were removed on a rotary evaporator, and the residue was purified by column chromatography to give the relevant catechol or phenol.

4-Propylcatechol (7d)

[CAS Reg. No. 2525-02-2]

Yield: 0.736 g (96%); off-white solid; mp 57.5–58.5 °C (Lit.[44] mp 59–60 °C); R_f = 0.27 (PE/EtOAc 3:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.76 (d, J = 8.0 Hz, 1 H), 6.69 (d, J = 1.6 Hz, 1 H), 6.60 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 5.42 (br s, 2 H), 2.45 (t, J = 7.6 Hz, 2 H), 1.56 (h, J = 7.6 Hz, 2 H), 0.90 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.19, 141.12, 136.20, 121.01, 115.67, 115.34, 37.34, 24.70, 13.81.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	DMSO MeCN Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

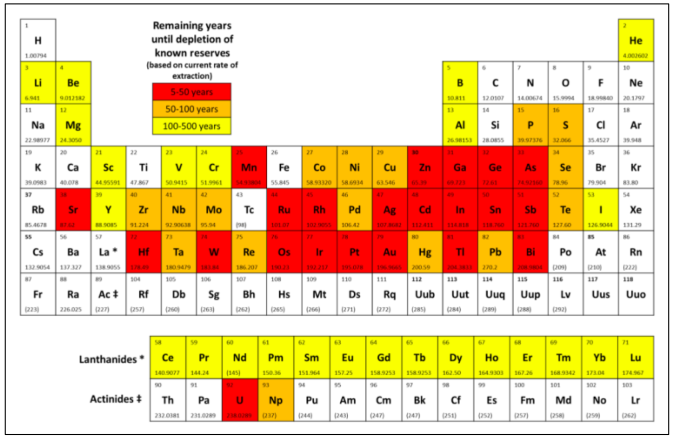
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	I, Al, S
+500 years	Green Flag	



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	X
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Column chrom.

Health & safety

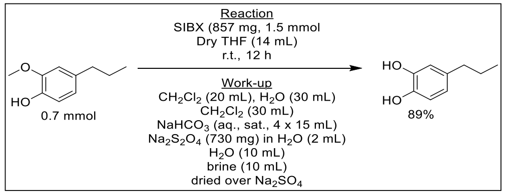
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			AlI_3 CH_3CN DMSO HCl $Na_2S_2O_3$
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method E: SIBX.[15]

Yield, AE, RME, MI/PMI and OE

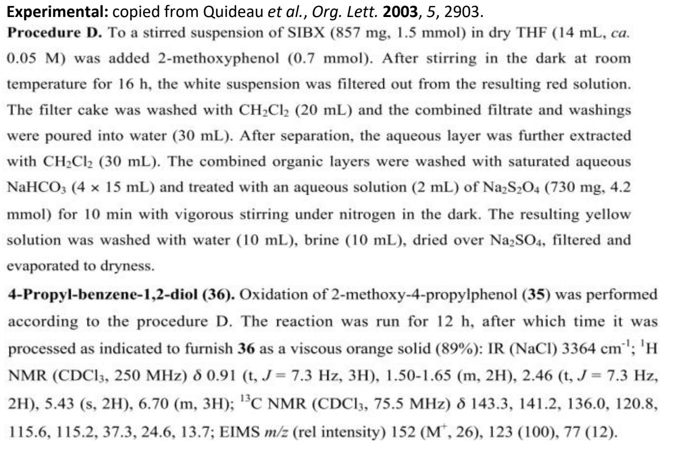
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	0,116	166,22	7,00E-04			SIBX	0,857	THF	14,00	0,89	12,40	$NaHCO_3$	6,00	CH_2Cl_2	50,00	1,33	66,50
												$Na_2S_2O_4$	0,73	H_2O	30,00	1,00	30,00
												NaCl	3,60	H_2O ($NaHCO_3$)	60,00	1,00	60,00
												Na_2SO_4	0,70	H_2O ($Na_2S_2O_4$)	2,00	1,00	2,00
														H_2O	10,00	1,00	10,00
														H_2O (brine)	10,00	1,00	10,00
Total	0,12	166,22			0,00		0,86				12,40		11,03				178,50



		Flag	
Yield	89,00	●	89,0
Conversion	100,00	●	100,0
Selectivity	89,00	●	89,0
AE	91,56		
RME	81,49	OE	89,0
PMI total	2140,05		
PMI Reaction	141,09		
PMI Workup	1998,96		
PMI Workup chemical	116,33		
PMI workup solvents	1882,63		
PMI RRC	10,27		
E factor	2139,05		

	Mass	MW	Mol
Product	0,095	152,19	6,23E-04
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	202,813



Experimental: copied from Quideau *et al.*, *Org. Lett.* **2003**, *5*, 2903.

Procedure D. To a stirred suspension of SIBX (857 mg, 1.5 mmol) in dry THF (14 mL, *ca.* 0.05 M) was added 2-methoxyphenol (0.7 mmol). After stirring in the dark at room temperature for 16 h, the white suspension was filtered out from the resulting red solution. The filter cake was washed with CH_2Cl_2 (20 mL) and the combined filtrate and washings were poured into water (30 mL). After separation, the aqueous layer was further extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (4 × 15 mL) and treated with an aqueous solution (2 mL) of $Na_2S_2O_4$ (730 mg, 4.2 mmol) for 10 min with vigorous stirring under nitrogen in the dark. The resulting yellow solution was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and evaporated to dryness.

4-Propyl-benzene-1,2-diol (36). Oxidation of 2-methoxy-4-propylphenol (**35**) was performed according to the procedure D. The reaction was run for 12 h, after which time it was processed as indicated to furnish **36** as a viscous orange solid (89%): IR (NaCl) 3364 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.91 (t, J = 7.3 Hz, 3H), 1.50-1.65 (m, 2H), 2.46 (t, J = 7.3 Hz, 2H), 5.43 (s, 2H), 6.70 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 143.3, 141.2, 136.0, 120.8, 115.6, 115.2, 37.3, 24.6, 13.7; EIMS m/z (rel intensity) 152 (M^+, 26), 123 (100), 77 (12).

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	THF
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	CH_2Cl_2
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

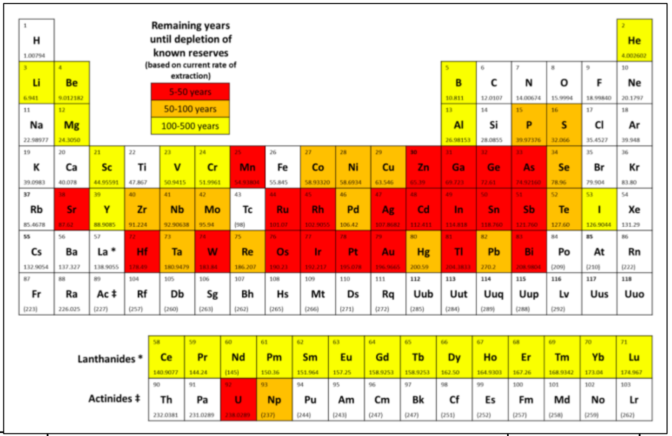
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	I, S
+500 years	Green Flag	



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

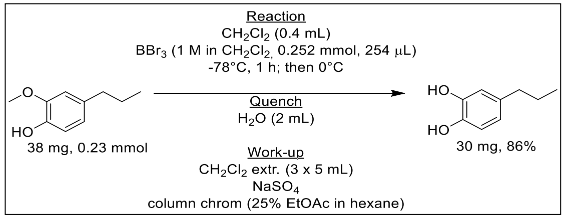
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			IBX Benzoic acid Isophthalic acid THF $NaHCO_3$ $Na_2S_2O_8$ NaCl Na_2SO_4
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			CH_2Cl_2: H315	
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method F1: BBr_3.[16]

Yield, AE, RME, MI/PMI and OE

Reactant **(Limiting Reactant First)**	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	0,0380	166,22	2,286E-04			BBr_3	0,063	CH_2Cl_2	0,40	1,33	0,53	Na_2SO_4	0,23	H_2O	2,00	1,00	2,00
H_2O	0,0041	18,02	2,286E-04					CH_2Cl_2	0,25	1,33	0,34	SiO_2	2,29	CH_2Cl_2	15,00	1,33	19,95
														Hexane	17,15	0,66	11,23
														EtOAc	5,72	0,90	5,16
Total	0,04	184,23			0,00		0,06				0,87		2,51				38,33

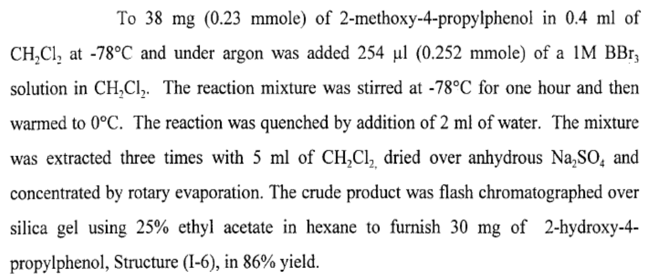


		Flag	
Yield	86,22	●	86,2
Conversion	100,00	●	100,0
Selectivity	86,22	●	86,2
AE	82,61		
RME	71,23	OE	86,2
PMI total	1394,06		
PMI Reaction	32,50		
PMI Workup	1361,56		
PMI Workup chemical	83,83		
PMI workup solvents	1277,73		
PMI RRC	3,51		
E factor	1393,06		

	Mass	MW	Mol
Product	0,030	152,19	1,971E-04
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	41,792

Experimental: copied from Ghosh *et al.*, WO9937294A2, **1999**.


To 38 mg (0.23 mmole) of 2-methoxy-4-propylphenol in 0.4 ml of CH_2Cl_2 at -78°C and under argon was added 254 µl (0.252 mmole) of a 1M BBr_3 solution in CH_2Cl_2. The reaction mixture was stirred at -78°C for one hour and then warmed to 0°C. The reaction was quenched by addition of 2 ml of water. The mixture was extracted three times with 5 ml of CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude product was flash chromatographed over silica gel using 25% ethyl acetate in hexane to furnish 30 mg of 2-hydroxy-4-propylphenol, Structure (I-6), in 86% yield.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	Hexane CH_2Cl_2
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

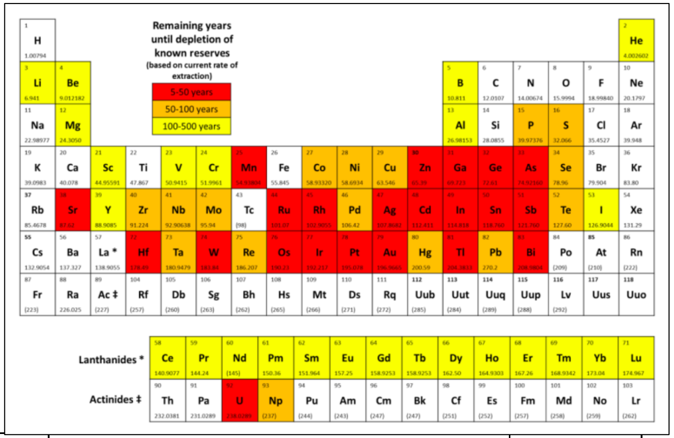
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}C at atmospheric	Green Flag	Quenching
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Column chrom

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O Na_2SO_4 SiO_2 EtOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,		BBr_3: H300, H330	4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			CH_2Cl_2: H351	
Environmental implications	H400, H410, H411, H420	H401, H412		Hexane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method F2: BBr_3 [BL-10]

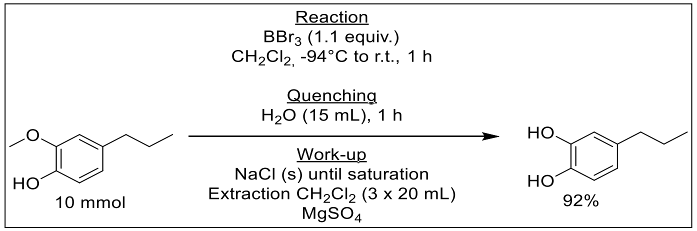
Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	1,66	166,22	0,0100			BBr_3	2,80	CH_2Cl_2	15,00	1,33	19,88	NaCl	5,40	CH_2Cl_2	60,00	1,33	79,80
H_2O	0,18	18,02	0,0100									$MgSO_4$	10,00	H_2O	14,82	1,00	14,82
Total	1,84	184,24			0,00		2,80				19,88		15,40				94,62

		Flag	
Yield	92,07	●	92,1
Conversion	100,00	●	100,0
Selectivity	92,07	●	92,1
AE	82,61		
RME	76,05	OE	92,1
PMI total	96,03		
PMI Reaction	17,50		
PMI Workup	78,53		
PMI Workup chemical	10,99		
PMI workup solvents	67,54		
PMI RRC	3,31		
E factor	95,03		

	Mass	MW	Mol
Product	1,40	152,19	0,0092
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	133,137



Experimental [BL-10]:
In a flame-dried and argon flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (15 mL). The obtained mixture was cooled to -94 °C and subsequently, BBr_3 (1.06 mL, 11.0 mmol, 1.1 equiv.) was added dropwise. The cooling bath was removed and the reaction was allowed to reach r.t. The mixture was stirred for 1 h and subsequently, ice cold H_2O (15 mL) was added dropwise. The obtained suspension was stirred for 1 h and NaCl (s) was added until saturation and the product was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol was obtained with a yield of 92% (1.40 g,

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	CH_2Cl_2
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

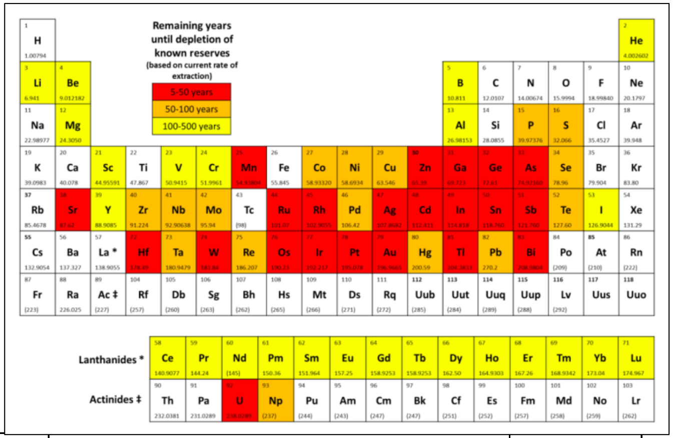
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	B
+500 years	Green Flag	Br, Cl



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Quenching, Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

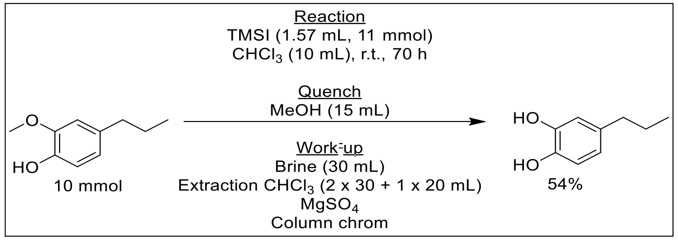
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			NaCl H_2O
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,		BBr_3: H300, H330	4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			CH_2Cl_2: H351, H373	
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method G1: TMSI [BL-20]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)
4-propylguaiacol	1,66	166,22	0,0100			TMSI	2,21	$CHCl_3$	10,00	1,48	14,80	NaCl	10,80	$CHCl_3$	80,00	1,48	118,40
MeOH	0,32	32,04	0,0100									$MgSO_4$	10,00	MeOH	14,60	0,79	11,55
												SiO_2	40,00	EtOAc	112,50	0,90	101,25
														heptane	997,50	0,68	682,09
														H_2O	30,00	1,00	30,00
Total	1,98	198,26			0,00		2,21				14,80		60,80				943,29



		Flag	
Yield	53,62	●	53,6
Conversion	74,37	●	74,4
Selectivity	72,10	●	72,1
AE	76,76		
RME	41,16	OE	53,6
PMI total	1253,77		
PMI Reaction	23,27		
PMI Workup	1230,50		
PMI Workup chemical	74,51		
PMI workup solvents	1155,99		
PMI RRC	5,13		
E factor	1252,77		

	Mass	MW	Mol
Product	0,82	152,19	0,0054
	mass		
Unreacted limiting reactant	0,43		

	Mass
Generated waste	1022,264

Experimental [BL-20]:

In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (1.57 mL, 11.0 mmol, 1.1 equiv.) were dissolved in dry $CHCl_3$ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 mL·min^{-1}, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol was obtained in 54% yield (0.82 g, 5.36 mmol). Furthermore, 2-methoxy-4-propylphenol was recovered for 26% (0.43 g, 2.56 mmol). The obtained spectroscopic data are in accordance with those reported before.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, MeOH, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	$CHCl_3$

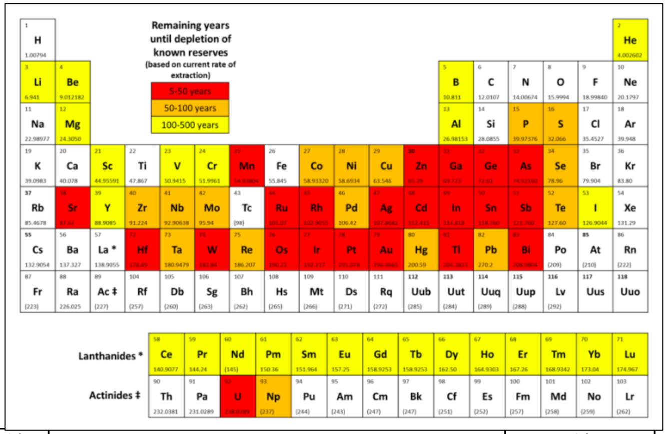
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	I
+500 years	Green Flag	Cl, Na



Energy (First Pass)

		Tick
Reaction run between 0 to 70^{o}C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}C at atmospheric	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Chromatography

Health & safety

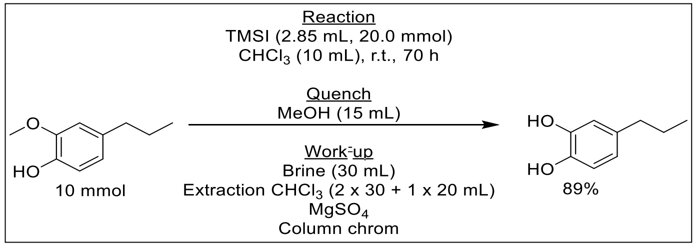
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			TMSI EtOAc NaCl H_2O
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		$CHCl_3$: H372 MeOH: H370		
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method G2: TMSI [BL-22]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	1,66	166,22	0,0100			TMSI	4,01	$CHCl_3$	10,00	1,48	14,80	NaCl	10,80	$CHCl_3$	80,00	1,48	118,40
MeOH	0,32	32,04	0,0100									$MgSO_4$	10,00	MeOH	14,60	0,79	11,55
												SiO_2	40,00	EtOAc	112,50	0,90	101,25
														heptane	997,50	0,68	682,09
														H_2O	30,00	1,00	30,00
Total	1,98	198,26			0,00		4,01				14,80		60,80				943,29



		Flag		
Yield	88,98	●	89,0	
Conversion	100,00	●	100,0	
Selectivity	88,98	●	89,0	
AE	76,76			
RME	68,30	OE		89,0
PMI total	756,93			
PMI Reaction	15,35			
PMI Workup	741,57			
PMI Workup chemical	44,90			
PMI workup solvents	696,67			
PMI RRC	4,42			
E factor	755,93			

	Mass	MW	Mol
Product	1,35	152,19	0,0089
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	1023,526

Experimental [BL-22]:
In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry $CHCl_3$ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 x 30 mL and 1 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes / EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 mL/min, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol was obtained in 89% yield (1.35 g, 8.9 mmol).

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, MeOH, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	$CHCl_3$

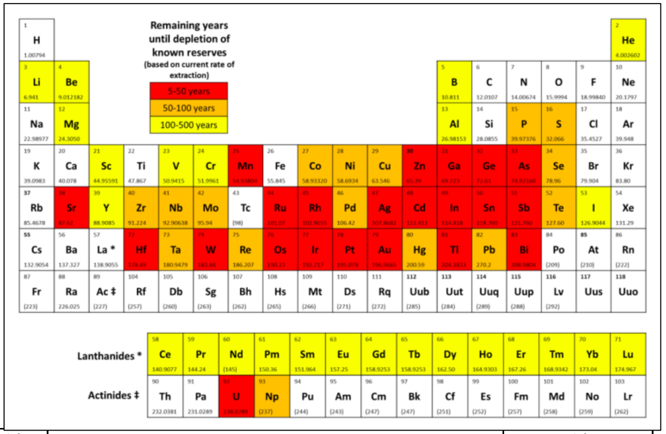
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	I
+500 years	Green Flag	Cl, Na



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Chromatography

Health & safety

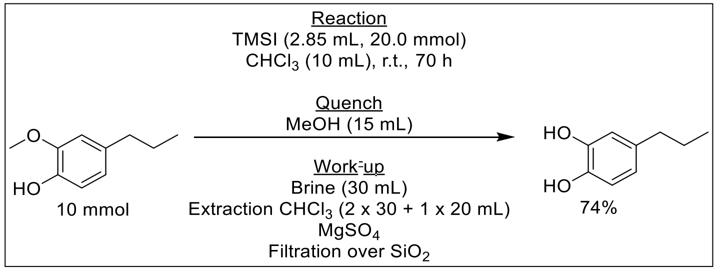
				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			TMSI EtOAc NaCl H_2O
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		$CHCl_3$: H372 MeOH: H370		
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method G3: TMSI [BL-32]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	1,66	166,22	0,0100			TMSI	4,01	$CHCl_3$	10,00	1,48	14,80	$MgSO_4$	10,00	MeOH	14,60	0,79	11,55
MeOH	0,32	32,04	0,0100									SiO_2	20,00	H_2O	30,00	1,00	30,00
														$CHCl_3$	80,00	1,48	118,40
														MTBE	30,00	0,74	22,20
Total	1,98	198,26			0,00		4,01				14,80		30,00				182,15



		Flag	
Yield	74,13	●	74,1
Conversion	100,00	●	100,0
Selectivity	74,13	●	74,1
AE	76,76		
RME	56,90	OE	74,1
PMI total	206,50		
PMI Reaction	18,43		
PMI Workup	188,07		
PMI Workup chemical	26,59		
PMI workup solvents	161,48		
PMI RRC	5,31		
E factor	205,50		

	Mass	MW	Mol
Product	1,13	152,19	0,0074
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	231,809

Experimental [BL-32]:
In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry $CHCl_3$ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 x 30 mL and 1 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated by dissolving the crude material in MTBE (30 mL) and filtering it over a layer of silica. Volatiles were evaporated under reduced pressure and pure product was obtained in 74% yield (1.13 g, 7.4 mmol).

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, MeOH
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	$CHCl_3$

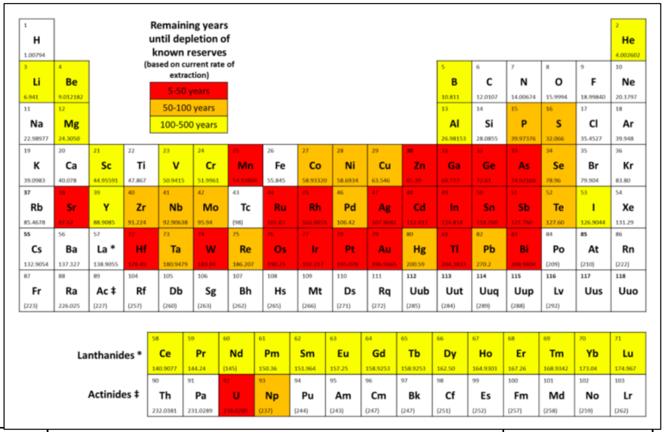
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	I
+500 years	Green Flag	Si, Na, Cl


Remaining years until depletion of known reserves (based on current rate of extraction)

5-50 years

50-100 years

100-500 years

Energy (First Pass)

		Tick
Reaction run between 0 to 70^{o}C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}C at atmospheric	Green Flag	filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	solvent exchange
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Column chrom.

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			TMSI NaCl H_2O
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		$CHCl_3$: H372; MeOH: H370		
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		**List substances of very high concern**
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method H: Al + I_2 [JBO-GM-119]

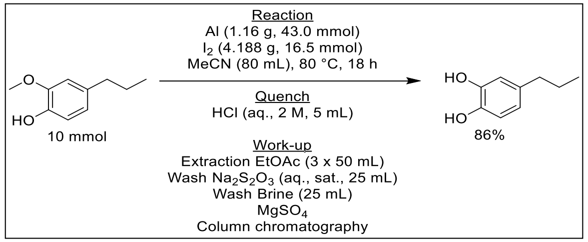
Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
4-*n*-propylguaiacol	1,66	166,22	0,010			Al	1,16	CH_3CN	80,00	0,79	62,88	NaCl	9,00	H_2O	55,00	1,00	55,00
HCl	0,36	36,46	0,010			I_2	4,19					$Na_2S_2O_3$	17,53	EtOAc	150,00	0,90	134,55
												$MgSO_4$	9,99	heptane	1074,00	0,68	730,32
												SiO_2	40,00	EtOAc	126,00	0,90	113,02
Total	2,02	202,68			0,00		5,35				62,88		76,51				1032,89

		Flag	
Yield	86,7	●	86,7
Conversion	100,0	●	100,0
Selectivity	86,7	●	86,7
AE	75,1		
RME	65,1	OE	86,7
PMI total	895,5		
PMI Reaction	53,3		
PMI Workup	842,18		
PMI Workup chemical	58,08		
PMI workup solvents	784,10		
PMI RRC	5,60		
E factor	894,51		

	Mass	MW	Mol
Product	1,32	152,19	0,0087
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	1178,341



Reaction
Al (1.16 g, 43.0 mmol)
I_2 (4.188 g, 16.5 mmol)
MeCN (80 mL), 80 °C, 18 h

Quench
HCl (aq., 2 M, 5 mL)

Work-up
Extraction EtOAc (3 x 50 mL)
Wash $Na_2S_2O_3$ (aq., sat., 25 mL)
Wash Brine (25 mL)
$MgSO_4$
Column chromatography

Experimental [JBO-GM-119]:
In a 250 mL roundbottomed flask, equipped with reflux condenser and magnetic stirring bar, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in acetonitrile (80 mL). Subsequently, aluminium powder (1.160 g, 43.0 mmol, 4.3 equiv.) was added to the solution and then I_2 (4.188 g, 16.5 mmol, 1.7 equiv.) was added in one portion. The obtained mixture was stirred for 18 hr at 80 °C. After cooling to r.t., the mixture was quenched with HCl (aq., 2 M, 5 mL), and extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with $Na_2S_2O_3$ (aq., sat., 25 mL), brine (25 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified with an automatic column chromatography system (column: 40 g SiO_2 cartridge; flow rate: 30 mL/min; eluent: heptanes, 2 min; heptanes to 15% EtOAc in

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H_2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	CH_3CN, heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

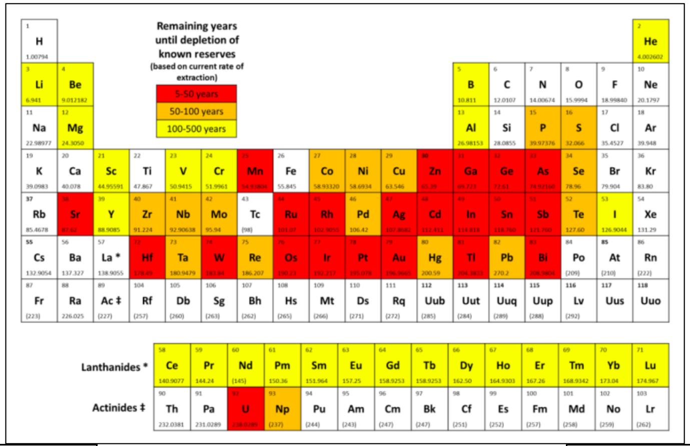
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	Al, I, S
+500 years	Green Flag	Na, Cl,



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	X
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Quenching Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Column chrom.

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			NaCl $Na_2S_2O_3$ CH_3CN EtOAc HCl
Explosive thermal runaway	H230, H240, H250	H241		Al: H250		
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		I_2: H372		
Environmental implications	H400, H410, H411, H420	H401, H412		I_2: H400 heptane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method I1: $AlCl_3$ + NaI [BL-47]

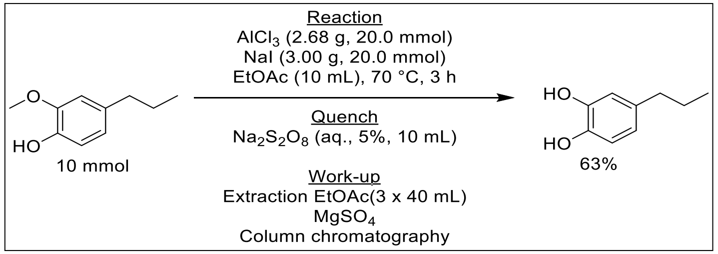
Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	1,66	166,22	0,0100			$AlCl_3$	2,68	EtOAc	10,00	0,90	9,00	$Na_2S_2O_3$	63,76	EtOAc (extr)	120,00	0,90	108,00
water	0,18	18,02	0,0100			NaI	3,00					$MgSO_4$	10,00	EtOAc (column)	135,00	0,90	121,50
												silica	40,00	heptane	1275,00	0,68	867,00
														H_2O	9,82	1,00	9,82
Total	1,84	184,24			0,00		5,68				9,00		113,76				1106,32

		Flag	
Yield	63,02	🔴	63,0
Conversion	97,83	🟢	97,8
Selectivity	64,42	🔴	64,4
AE	82,61		
RME	52,06	OE	63,0
PMI total	1289,47		
PMI Reaction	17,23		
PMI Workup	1272,24		
PMI Workup chemical	118,62		
PMI workup solvents	1153,62		
PMI RRC	7,84		
E factor	1288,47		

	Mass	MW	Mol
Product	0,96	152,19	0,0063
	mass		
Unreacted limiting reactant	0,036		

	Mass
Generated waste	1235,641



Experimental: [BL-47]
A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with $AlCl_3$ (2.68 g, 20.0 mmol, 2.0 equiv.) and NaI (3.00 g, 20.0 mmol, 2.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (1.60 mL, 10.0 mmol, 1.0 equiv.) and dry EtOAc (10 mL) were added through the septum. The septum was removed and the tube was closed properly. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with $Na_2S_2O_3$ (aq., 5%, 10 mL). The obtained mixture was extracted with EtOAc (3 x 40 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes / EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 mL/min, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 30 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol was obtained in 63% yield (0.96 g, 6.3 mmol). 2-Methoxy-4-propylphenol was recovered for 2% (36 mg, 0,2 mmol).

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

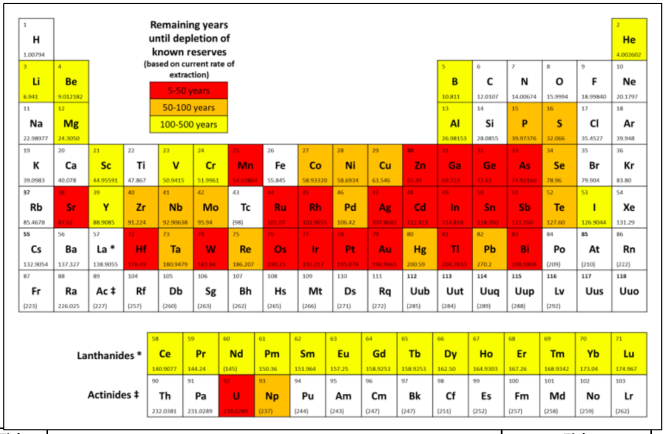
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	x

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	Al, I
+500 years	Green Flag	Cl, Na



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	X
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Column chrom.

Health & safety

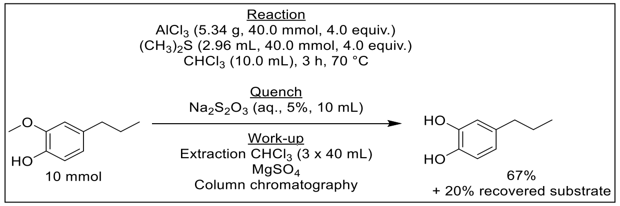
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			$AlCl_3$ EtOAc H_2O $Na_2S_2O_3$
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410; NaI: H400		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method I2: $AlCl_3$ + Me_2S [BL-44]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	1,66	166,22	0,0100			$AlCl_3$	5,34	$CHCl_3$	10,00	1,48	14,80	$Na_2S_2O_3$	0,50	$CHCl_3$	120,00	1,48	177,60
H_2O	0,18	18,02	0,0100			$(CH_3)_2S$	2,49					$MgSO_4$	10,00	EtOAc	135,00	0,90	121,50
												SiO_2	40,00	heptane	1275,00	0,68	867,00
														H_2O	9,82	1,00	9,82
Total	1,84	184,24			0,00		7,83				14,80		50,50				1175,92



		Flag	
Yield	66,70	🔴	66,7
Conversion	80,14	🟠	80,1
Selectivity	83,22	🟠	83,2
AE	82,61		
RME	55,10	OE	66,7
PMI total	1232,40		
PMI Reaction	24,11		
PMI Workup	1208,29		
PMI Workup chemical	49,75		
PMI workup solvents	1158,54		
PMI RRC	9,53		
E factor	1231,40		

	Mass	MW	Mol
Product	1,02	152,19	0,0067
	mass		
Unreacted limiting reactant	0,33		

	Mass
Generated waste	1249,872

Experimental: [BL-44]
A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with $AlCl_3$ (5.34 g, 40.0 mmol, 4.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.), $(CH_3)_2S$ (2.96 mL, 40.0 mmol, 4.0 equiv.) and dry $CHCl_3$ (10 mL) were added through the septum. The septum was removed and the tube was closed properly. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with $Na_2S_2O_3$ (aq., 5%, 10 mL). The obtained mixture was extracted with $CHCl_3$ (3 x 40 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes / EtOAc gradient (40 g SiO_2 cartridge, flow rate: 30 mL/min, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 30 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol was obtained in 67% yield (1.02 g, 6.7 mmol). 2-Methoxy-4-propylphenol was recovered for 20% (330 mg, 2.0 mmol).

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	$CHCl_3$

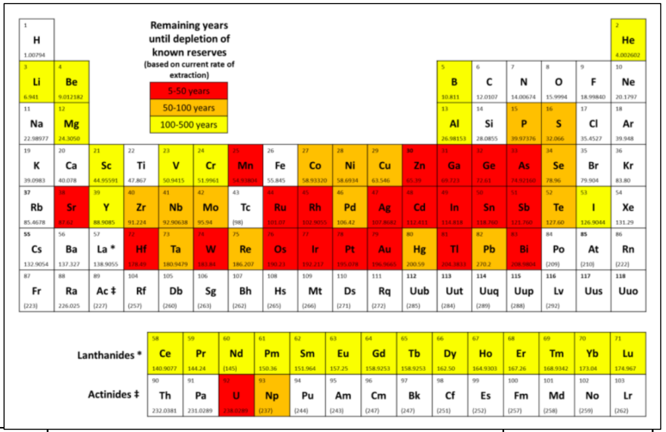
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	Al, S
+500 years	Green Flag	Cl, Na



Energy (First Pass)

		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	X
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}C at atmospheric	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	Column chrom.

Health & safety

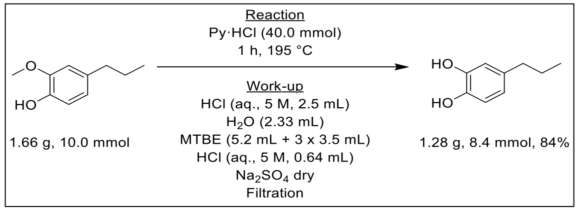
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			$AlCl_3$ $(CH_3)_2S$ EtOAc H_2O $Na_2S_2O_3$
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		$CHCl_3$: H372		
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method J: Py·HCl [MBAL-642]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	**Mass (g)**	**MW**	**Mol**	**Catalyst**	**Mass (g)**	**Reagent**	**Mass (g)**	**Reaction solvent**	**Volume (cm^3)**	**Density (g ml^{-1})**	**Mass (g)**	**Work up chemical**	**Mass (g)**	**Workup solvent**	**Volume (cm^3)**	**Density (g ml^{-1})**	**Mass (g)**
4-propylguaiacol	1,66	166,22	0,010			Py·HCl	3,066					Na_2SO_4	9,99	MTBE	15,70	0,74	11,62
Py·HCl	1,55	155,56	0,010									HCl	0,57	H_2O	2,33	1,00	2,33
														H_2O (HCl)	3,14	1,00	3,14
																	0,00
Total	3,21	321,78			0,00		3,07				0,00		10,56				17,09



		Flag			
Yield	84,21	●	84,2		
Conversion	100,00	●	100,0		
Selectivity	84,21	●	84,2		
AE	47,30				
RME	39,83	OE			84,2
PMI total	26,51				
PMI Reaction	4,91				
PMI Workup	21,60				
PMI Workup chemical	8,25				
PMI workup solvents	13,35				
PMI RRC	4,91				
E factor	25,51				

	Mass	**MW**	**Mol**
Product	1,28	152,19	0,0084
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	32,654

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	MTBE
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Experimental [MBAL-462]:
A 50 mL two-necked roundbottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 2-methoxy-4-propylphenol (**xx**, 1.66 g, 10.0 mmol, 1 equiv.) and Py·HCl (4.62 g, 40.0 mmol, 4.0 equiv.). The obtained mixture was stirred for 1 h at 195 °C, after which it was allowed to cool to 90 °C. Subsequently, HCl (aq., 5 M, 2.5 mL, 12.5 mmol, 1.25 equiv.) and H_2O (2.33 mL) were added. Stirring was continued allowing the temperature of the mixture to reach 35 °C. Subsequently, to the crude mixture was added MTBE (5.2 mL). The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 3.5 mL). The combined organix fractions were washed with HCl (aq., 5 M, 0.64 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (**xx**) was obtained in 84% yield (1.28 g, 8.40 mmol).

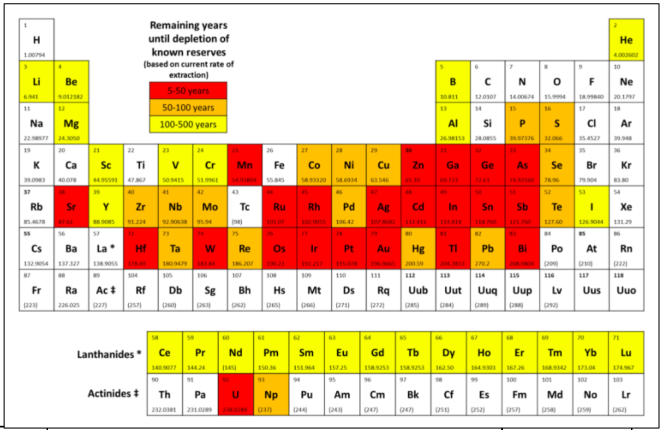
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	X



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Filtration quenching
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

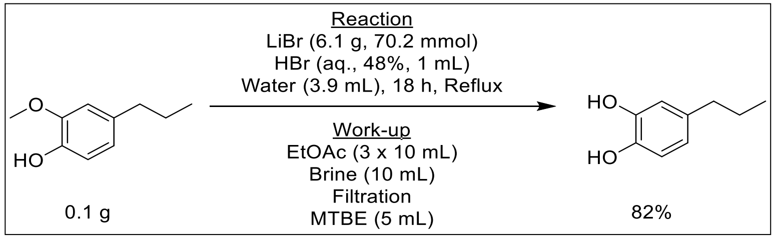
				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O MTBE Py·HCl
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method K: LiBr and HBr [MBAL-795]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	0,10	166,22	6,016E-04			H_2O	0,011	H_2O (HBr)	0,78	1,00	0,78	NaCl	3,60	EtOAc	30,00	0,90	27,06
HBr	0,72	80,91	8,899E-03			LiBr	6,10	H_2O	3,89	1,00	3,89	Celite	1,20	H_2O (brine)	10,00	1,00	10,00
														MTBE	5,00	0,74	3,70
																	0,00
Total	0,82	247,13			0,00		6,11				4,67		4,80				40,76



		Flag	
Yield	81,91	●	81,9
Conversion	100,00	●	100,0
Selectivity	81,91	●	81,9
AE	61,58		
RME	9,15	OE	14,9
PMI total	762,20		
PMI Reaction	154,67		
PMI Workup	607,54		
PMI Workup chemical	64,04		
PMI workup solvents	543,49		
PMI RRC	92,41		
E factor	761,20		

	Mass	MW	Mol
Product	0,075	152,19	4,93E-04
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	57,090

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	MTBE
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Experimental [MBAL-795]:

In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, LiBr (6.10 g, 70.2 mmol, 117 equiv.) was dissolved in H_2O (3.9 mL). When LiBr was completely dissolved, 2-methoxy-4-propylphenol (0.10 g, 0.60 mmol, 1.0 equiv.) and HBr (aq., 48%, 1.50 g, 8.84 mmol, 14.7 equiv.) were added. The mixture was stirred for 18 h under reflux, after which it was cooled to r.t. in ice water. The crude mixture was diluted with brine (10 mL), extracted with EtOAc (3 × 10 mL) and evaporated under reduced pressure. The crude product was re-dissolved in MTBE (5 mL) and filtered over a plug of Celite. Volatiles were evaporated under reduced pressure, delivering 4-propylbenzene-1,2-diol in 82% yield (75 mg, 0.47 mmol). The obtained spectroscopic data are in accordance with those reported before.

Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

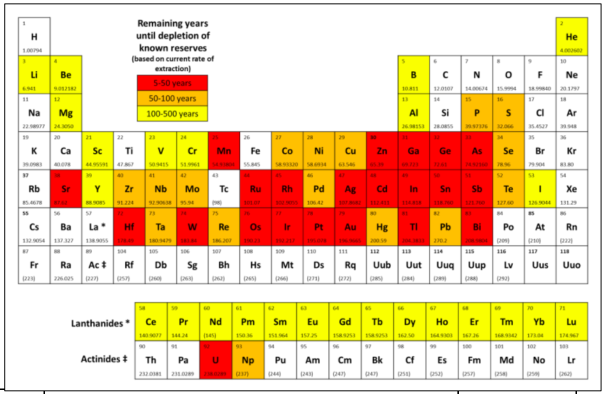
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	Li
+500 years	Green Flag	



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	X
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	Evaporation Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

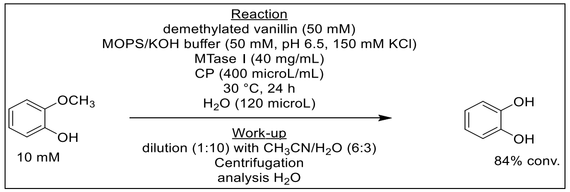
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O MTBE NaCl EtOAc LiBr
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311 HBr: H331	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		**List substances of very high concern**
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method L1: MTase I.[23]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
Guaiacol	1,49E-04	124,14	1,20E-06	MTase I	4,80E-03	MOPS	1,256E-03	H_2O	0,12	1,00	0,12			CH_3CN	0,72	0,79	0,57
Demethylated vanillin	8,29E-04	138,12	6,00E-06	CP	2,64E-03	KCl	1,342E-03							H_2O	0,36	1,00	0,36
Total	0,00	262,26			0,01		0,00				0,12		0,00				0,93



Reaction
demethylated vanillin (50 mM)
MOPS/KOH buffer (50 mM, pH 6.5, 150 mM KCl)
MTase I (40 mg/mL)
CP (400 microL/mL)
30 °C, 24 h
H_2O (120 microL)

Work-up
dilution (1:10) with CH_3CN/H_2O (6:3)
Centrifugation
analysis H_2O

Yield	84,00
Conversion	84,00
Selectivity	100,00
AE	41,99
RME	11,35
PMI total	9522,67
PMI Reaction	1180,41
PMI Workup	8342,26
PMI Workup chemical	0,00
PMI workup solvents	8342,26
PMI RRC	99,24
PMI FI total	3998,15
PMI FI Reaction	495,60
PMI FI Workup	3502,55
PMI FI RRC	41,67
AE FI	100,00
RME FI	27,04
E factor	9521,67
E factor FI	3997,15

	Mass	MW	Mol
Product	1,11E-04	110,11	1,01E-06
	mass		
Unreacted limiting reactant	2,38E-05		
	Mass	MW	Mol
Co Product	1,53E-04	152,15	1,01E-06
	excluding co-products	including co-products	
Generated waste	1,057	1,057	

Experimental: copied from Kroutil *et al*. Nature Communications. **2018**, *1:82*,DOI 10.1038/s42004-018-0083-2.

Representative biotransformation procedure. Analytical biotransformation reactions were carried out on 120 µL scale as follows: MTase I (10–20 mU, 40 mg mL^{-1} CFE or 13 mg mL^{-1} pure enzyme, respectively) was dissolved in *holo*-CP solution (400 µL mL^{-1}, containing 67 mg mL^{-1} CFE or 22 mg mL^{-1} pure enzyme, respectively). Then appropriate amounts of substrate (10–50 mM final concentration) and co-substrate (10–50 mM final concentration) dissolved in MOPS/KOH buffer (50 mM, pH 6.5, 150 mM KCl) were added and the reaction samples were shaken at 30 °C and 800 rpm. See Supplementary Note 2 for details with respect to the use of an O_2-scavenger system during initial experiments. After 24 h an aliquot of the reaction was withdrawn and diluted (1:10) with MeCN (6 parts) and deionized water (3 parts). Precipitated protein was removed by centrifugation (14,000 rpm, 15 min) and the clear supernatant was filtered and directly analyzed by reversed-phase HLPC.

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H_2O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	CH_3CN
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

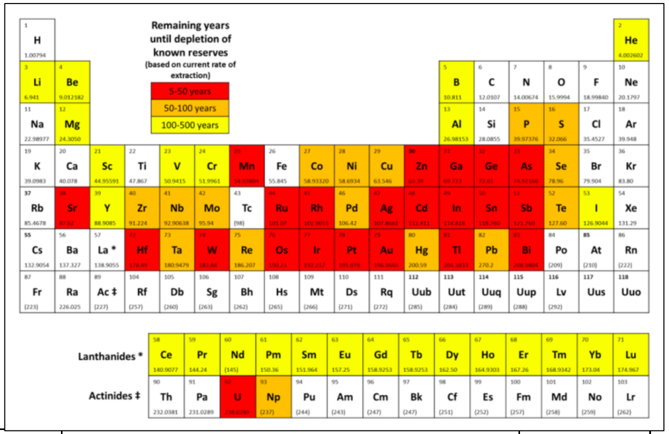
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	X

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	S
+500 years	Green Flag	



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			MeCN KCl MOPS MTase I CP
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern

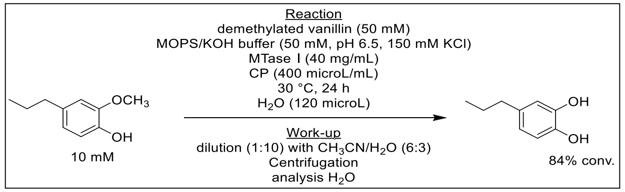
		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

- Method L2: MTase I.[23] Simulated data.

Yield, AE, RME, MI/PMI and OE

Reactant **(Limiting Reactant First)**	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)
4-propylguaiacol	1,99E-04	166,22	1,20E-06	MTase I	4,80E-03	MOPS	1,256E-03	H_2O	0,12	1,00	0,12			CH_3CN	0,72	0,79	0,57
Demethylated vanillin	8,29E-04	138,12	6,00E-06	CP	2,64E-03	KCl	1,342E-03							H_2O	0,36	1,00	0,36
Total	0,00	304,34			0,01		0,00				0,12		0,00				0,93

Yield	84,00
Conversion	84,00
Selectivity	100,00
AE	50,01
RME	14,92
PMI total	6890,05
PMI Reaction	854,36
PMI Workup	6035,69
PMI Workup chemical	0,00
PMI workup solvents	6035,69
PMI RRC	72,13
PMI FI total	3445,51
PMI FI Reaction	427,24
PMI FI Workup	3018,27
PMI FI RRC	36,07
AE FI	100,00
RME FI	29,84
E factor	6889,05
E factor FI	3444,51



	Mass	MW	Mol
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	mass		
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		List solvents below
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Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

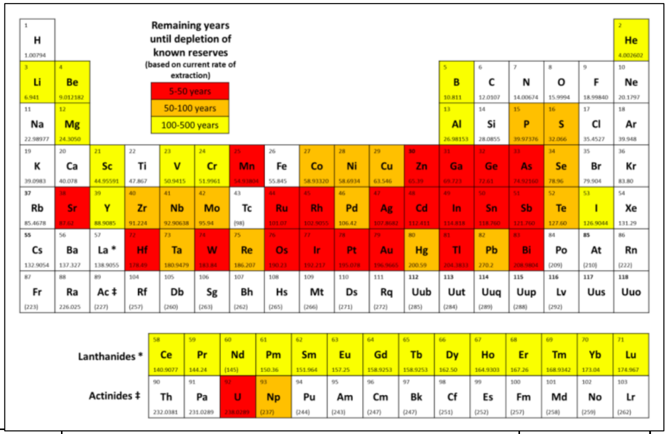
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	X
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	X

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	S
+500 years	Green Flag	



Energy (First Pass)

		Tick
Reaction run between 0 to 70°C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	X

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	
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Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
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Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern

		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

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