Supporting information

Bio-based aromatic amines from lignin-derived monomers

Enguerrand Blondiaux,[a] Jeroen Bomon,[a] Michał Smoleń,[a] Nadya Kaval,[a] Filip Lemière,[a] Sergey Sergeyev,[a] Ludo Diels,[b] Bert Sels,[c] Bert U.W. Maes[a]*

[a] Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

[b] Flemish Inst Technol Res VITO, Boeretang 200, B-2400 Mol, Belgium

[c] Center for Surface Chemistry and Catalysis, KU Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

E-mail: Bert.Maes@UAntwerpen.be

Number of pages: 155

Number of tables: 9

Number of figures: 22

Table of Contents

1 General considerations S4

2 Methylation of **1a** using dimethyl carbonate S6

3 Oxidation of **2a** into **3a** S8

4 Oxidation of **8** into **9** S10

5 Synthesis of **2a** S11

6 Synthesis of **2b** S12

7 Synthesis of **2c** S14

8 Synthesis of **2g** and **2h** S15

9 Synthesis of **3a** S17

10 Synthesis of **4a** S19

11 Synthesis of **5a** from **4a** S21

12 Synthesis of **5a** from **1a** S22

13 Synthesis of **5b-c** from **1a** S26

14 Synthesis of **5g-h** from **1b** S30

15 Synthesis of **5d** from **1a** S34

16 Synthesis of **7** from **1a** S38

17 Synthesis of **8** from **2a** S42

18 Synthesis of **9** from **8** S43

19 Synthesis of **10** from **4a** S44

20 Evaluation of the green credentials for the synthesis of 3,4-dimethoxyaniline (**5a**) and 2-bromo-4,5-dimethoxyaniline (**7**) S45

20.1 Introduction S45

20.2 The CHEM21 Green Metrics Toolkit S46

20.2.1 Quantitative parameters S46

20.2.2 Qualitative parameters S48

20.3 Selection of a classical reference synthesis route for 3,4-dimethoxyaniline (**5a**) and 2-bromo-4,5-dimethoxyaniline (**7**) synthesis S50

20.4 Comments regarding the metrics calculations S52

20.5 Comparison of the green metrics for classical versus new route for 3,4-dimethoxyaniline (**5a**) and 2-bromo-4,5-dimethoxyaniline (**7**) synthesis S55

20.6 Ethylation of 4-propylguaiacol (**1a**) with diethylcarbonate.....S60

21 NMR spectra.....S63

22 Copies of the Excel Sheets used for Green Metrics calculations S105

22.1 Classical synthesis of 3,4-dimethoxyaniline (**5a**) S105

22.2 Classical synthesis of 2-Bromo-4,5-dimethoxyaniline (**7**) S119

22.3 New synthesis of 3,4-dimethoxyaniline (**5a**) S135

22.4 New synthesis of 2-bromo-4,5-dimethoxyaniline (**7**) S143

23 References S153

1 General considerations

Chemicals:

All chemicals, including solvents, were bought from classical chemical suppliers and were used as supplied by providers unless otherwise noted. **1a** was obtained from Sigma-Aldrich. **1b** was prepared from **1a** following a reported procedure.[1] Heptane was distilled prior to use.

NMR:

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III 400 Fourier Transform NMR spectrometer in $CDCl_3$ at 300 K (unless stated otherwise). For ^{1}H NMR, samples were prepared using ca. 2 mg of compound dissolved in 0.4 mL of $CDCl_3$ and for carbon NMR using about 10 mg of compound dissolved in 0.4 mL of $CDCl_3$. All spectra were referenced to the tetramethylsilane signal (δ = 0.00 ppm for ^{1}H NMR, δ = 0.0 ppm for $^{13}C\{^1H\}$ NMR). 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 = quintet, sext = sextet, sept = septet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, br = broad signal.

GC/MS:

Gas chromatography–mass spectrometry samples were prepared by dissolving 0.1-5 mg of the compound in acetone and further diluted to a concentration of 10^{-5}-10^{-6} M. 10 µL of the samples were injected. Apparatus was an Agilent Technologies 7890 A GC System coupled to an Agilent Technologies 5975 C inert MSD with triple-axis detector. Column was an Optima 725820.30 30 m × 250 µm × 0.25 µm. Carrier gas was helium.

HRMS:

High resolution mass spectrometry (HRMS) samples were prepared by dissolving 0.1-5 mg of the compound in MeOH/H_2O-8/2 containing 0.1% formic acid and further diluted to a concentration of 10^{-5}-10^{-6} M. 10 µL of each sample was injected using the CapLC system (Waters, Manchester, UK) and electrosprayed using a standard electrospray source. Samples were injected with an interval of 3 minutes. Positive ion mode accurate mass spectra were acquired using a Q-TOF II instrument (Waters, Manchester, UK). 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. Analytes were detected as protonated molecule. All measured masses are within a difference of 5 ppm compared to the calculated mass unless specified otherwise.

Melting points:

The melting points (uncorrected) were measured on Büchi Melting Point B-545 apparatus.

Chromatography:

Chromatographic purification of products was performed by using an automated flash chromatography Biotage™ system eluting with a flow rate of 30 mL/min, otherwise indicated, utilizing commercially available Grace™ GraceResolv™ Silica Flash Cartridges.

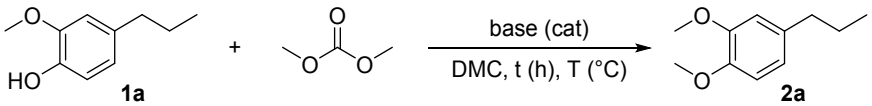
Chemicals prices:

Bulk chemical prices given in the article were based on the website zauba.com, relative to import/export data from India in 2016 and/or 2017. When no bulk chemical prices data were found, prices were selected from classical chemical suppliers like Sigma-Aldrich, Acros or TCI.

2 Methylation of 1a using dimethyl carbonate

The methylation of 4-propylguaiacol (**1a**) with DMC was tested using the following bases: K_2CO_3, Cs_2CO_3, Rb_2CO_3, NaOH, NEt_3 and Proton-sponge® (1,8-bis(dimethylamino)naphthalene) (Table S1 and S2). A quantitative yield was obtained after 24 h at 200 °C using a catalytic loading of 1 mol% K_2CO_3 (entry 5, Table S2).

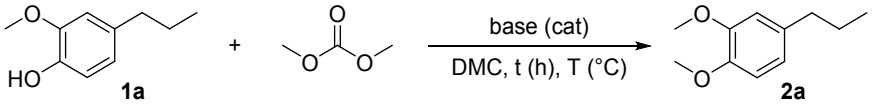
Table S1. Methylation of **1a** (0.50 mmol) using dimethyl carbonate.



Entry	Base	Eq.	t (h)	T (°C)	Yield (%)
1	K_2CO_3	0.20	15	160	**97**
2	K_2CO_3	1.5	1	160	**33**
3	K_2CO_3	0.20	7.5	160	**90**
4	K_2CO_3	0.50	7.5	160	**91**
5	Cs_2CO_3	0.20	2	160	**>99**
6	Cs_2CO_3	0.10	2	160	**>99**
7	Cs_2CO_3	0.20	2	150	**77**
8	Cs_2CO_3	0.20	2	140	**68**
9	Cs_2CO_3	0.040	2	160	**96**
10	Rb_2CO_3	0.20	2	160	**>99**
11	NaOH	0.20	6	160	**29**
12	NEt_3	0.20	6	160	**97**
13	Proton-sponge®	0.20	6	160	**0**

Reaction conditions: **1a** (0.50 mmol), dimethyl carbonate (1 mL), reactions run in a sealed pressure tube; yields determined by GC/MS using 1,3,5-trimethoxybenzene as an internal standard.

Table S2. Methylation of **1a** (2.80 mmol) using dimethyl carbonate with lower catalyst loading.



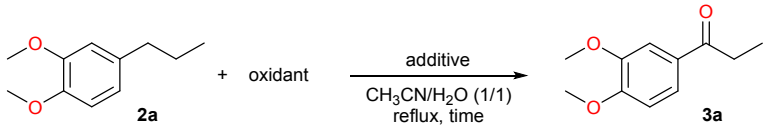
Entry	Base	Eq.	t (h)	T (°C)	Yield (%)
1	Cs_2CO_3	0.1	24	160	**94**
2	Cs_2CO_3	0.01	24	160	**90**
3	Cs_2CO_3	0.01	24	200	**>99**
4	Cs_2CO_3	0.005	24	200	**>99**
5	K_2CO_3	0.01	24	200	**>99**

Reaction conditions: **1a** (2.80 mmol), dimethyl carbonate (6 - 6.33 equiv.), reactions run in a sealed pressure tube; yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

3 Oxidation of 2a into 3a

The oxidation of 4-propylveratrole (**1a**) was performed using a combination of a peroxydisulfate as oxidant and an additive, as shown in Table S3. When using 2.0 eq. of potassium peroxydisulfate, 36% of **3a** was obtained after 3 h under reflux (Table S3, entry 1). Full conversion of **2a** was obtained, indicating significant degradation. Replacing the K^+ counterion by Na^+ or NH_4^+ under the same conditions gave 36% and 17% yield, respectively (Table S3, entries 2 and 3). Also in these cases a low mass balance was obtained. Other peroxide based oxidants such as Oxone® and H_2O_2 gave no conversion of the starting material (Table S3, entries 4 and 5). A set of additives was then screened in combination with sodium peroxydisulfate in order to increase the selectivity. Among the additives tested, 1.0 eq. of sodium acetate was found beneficial, giving a yield of 62%, while other bases gave only a marginal amount of reaction product (Table S3, entries 6−8). In particular, addition of H_2SO_4[2] was found unproductive (Table S3, entry 9). Decreasing the amount of sodium peroxydisulfate to 1.5 eq. led to a lower yield of 40% (Table S3, entry 10). When the quantity of sodium acetate was increased from 2.0 to 4.0 eq., the yield also decreased to 32% (Table S3, entry 11). On the contrary, decreasing the loading to 1.2 eq. the yield increased to 71% after 7 h (Table S3, entry 12). A similar yield was obtained when using 1.2 and 1.0 eq. NaOAc in 24 h (65%, Table S3, entries 13 and 14). However, the yield could be increased to 78% when increasing the oxidant loading to 2.5 eq. (Table S3, entry 15). The same yield was obtained after a reaction time of 16 h under the same conditions (Table S3, entry 16) or when slightly decreasing the $Na_2S_2O_8$ loading to 2.4 eq., keeping the NaOAc loading constant at 1.0 eq. (Table S3, entry 17). This last result is considered as the optimal reaction conditions for the benzylic oxidation.

Table S3. Oxidation of **2a** into **3a**.



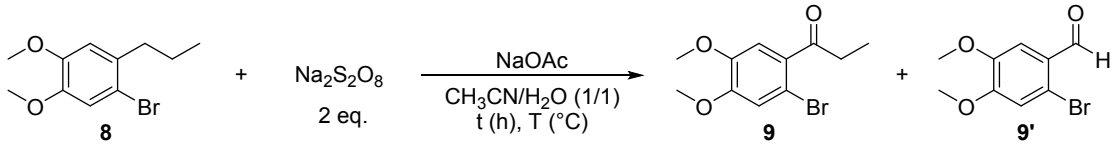
Entry	Oxidant	Eq.	Additive	Eq.	Time (h)	Conv. **2a** (%)	Yield **3a** (%)
1	$K_2S_2O_8$	2.0	–	–	3	100	**36**
2	$Na_2S_2O_8$	2.0	–	–	3	100	**36**
3	$(NH_4)_2S_2O_8$	2.0	–	–	3	88	**17**
4	Oxone®	2.0	–	–	3	0	**0**
5	H_2O_2	2.0	–	–	3	0	**0**
6	$Na_2S_2O_8$	2.0	NaOAc	2.0	3	100	**62**
7	$Na_2S_2O_8$	2.0	NaOH	2.0	3	54	**6**
8	$Na_2S_2O_8$	2.0	Na_2CO_3	2.0	3	54	**3**
9	$Na_2S_2O_8$	2.0	H_2SO_4	2.0	3	29	**0**
10	$Na_2S_2O_8$	1.5	NaOAc	2.0	3	75	**40**
11	$Na_2S_2O_8$	2.0	NaOAc	4.0	3	100	**32**
12	$Na_2S_2O_8$	2.0	NaOAc	1.2	7	100	**71**
13	$Na_2S_2O_8$	2.0	NaOAc	1.2	24	100	**65**
14	$Na_2S_2O_8$	2.0	NaOAc	1.0	24	100	**65**
15	$Na_2S_2O_8$	2.5	NaOAc	1.0	24	100	**78**
16	$Na_2S_2O_8$	2.5	NaOAc	1.0	16	100	**78**
17	$Na_2S_2O_8$	2.4	NaOAc	1.0	16	100	**78**

Reaction conditions: **2a** (2.80 mmol) in CH_3CN/H_2O (50 mL, 1/1 mixture, Conc. = 0.056 M). Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

4 Oxidation of 8 into 9

Oxidation of **8** was performed using $Na_2S_2O_8$ and variable quantities of NaOAc. **9** was obtained together with the corresponding aldehyde (**9'**). The best yield of **9** was obtained with 2.0 eq. NaOAc (34%, %, Table S4, entry 2) whereas the best yield of **9'** was obtained with 4.0 eq. NaOAc (29%, Table S4, entry 3).

Table S4. Oxidation of **8** into **9**.



Entry	Base	Eq.	t (h)	T (°C)	Conv (%)	Yield **9** (%)	Yield **9'** (%)
1	–	–	16	80	100	**19**	**2**
2	NaOAc	2	16	80	100	**34**	**20**
3	NaOAc	4	16	80	100	**5**	**29**
4	NaOAc	8	16	80	100	**5**	**20**

Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard.

5 Synthesis of 2a

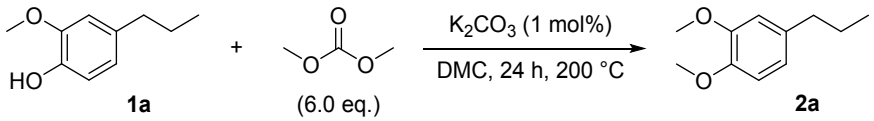
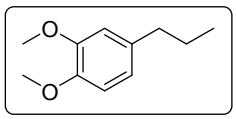


Figure S1. Methylation of 4-propylguaiacol (**1a**) with the use of dimethyl carbonate (DMC).

Procedure (MS538):

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with potassium carbonate (26 mg, 0.19 mmol, 0.01 eq.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 3.00 mL, 18.8 mmol, 1.0 eq.) and dimethyl carbonate (10.13 g, 9.47 mL, 112 mmol, 6.0 eq.). The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to room temperature. The contents of the pressure tube was transferred with EtOAc (5 mL), filtered through cotton-wool into the round-bottom flask and the precipitate was washed with EtOAc (5 mL). The solvent was evaporated in order to afford **2a** as a pale yellow oil (3.39 g, 18.8 mmol, >99%).

Data of **2a** (EB576, MS538):



1,2-dimethoxy-4-propylbenzene (CAS: 5888-52-8)

Pale yellow oil

Spectral data are in accordance with literature[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, 1H, ^3J = 8.6 Hz, Ar*H*), 6.71-6.70 (m, 2H, Ar*H*), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 2.53 (t, 2H, ^3J = 7.5 Hz, CH_2CH$_2$CH$_3$), 1.62 (sext, 2H, ^3J = 7.5 Hz, CH$_2$CH_2CH$_3$), 0.94 (t, 3H, ^3J = 7.5 Hz, CH$_2$CH$_2$CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8 (*C*), 147.1 (*C*), 135.4 (*C*), 120.3 (*C*H), 111.9 (*C*H), 111.3 (*C*H), 56.0 (*C*H$_3$), 55.8 (*C*H$_3$), 37.7 (*C*H$_2$), 24.8 (*C*H$_2$), 13.8 (*C*H$_3$)

EI (+) (m/z): 180 (30), 165 (2), 151 (100), 107 (12)

HRMS (ESI): for $C_{11}H_{17}O_2$ $[M+H]^+$ calcd 181.1229, found 181.1229

6 Synthesis of 2b

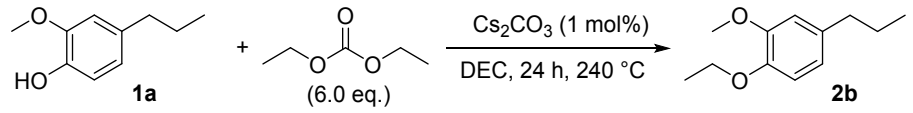


Figure S2. Ethylation of 4-propylguaiacol (**1a**) using diethyl carbonate (DEC).

Procedure (MS533):

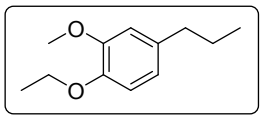
A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with 2-methoxy-4-propylphenol (**1a**, 3 mL, 18.7 mmol, 1.0 eq.) cesium carbonate (0.061 g, 0.19 mmol, 1 mol%) and diethyl carbonate (13.62 mL, 112 mmol, 6.0 eq.). The tube was sealed and the reaction mixture was heated at 240 °C for 24 h in a sand bath. Subsequently, it was cooled to room temperature, filtered and the precipitate was washed with EtOAc (4 x 3 mL). The combined organic fractions were evaporated under reduced pressure to afford the pure product **2b** as a pale yellow powder in 99% yield (3.62 g, 18.6 mmol).

Alternative procedure for reference material (EB409):

Figure S3. Ethylation of 4-propylguaiacol (**1a**) using ethyl iodide.

A 100 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 2-methoxy-4-propylphenol (**1a**, 2.00 mL, 12.5 mmol, 1.0 eq.), potassium carbonate (3.45 g, 25.0 mmol, 2.0 eq.) and DMF (10 mL). Iodoethane (3.0 mL, 37.5 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 24 h at 20 °C. The solution wad filtered, diluted with EtOAc (50 mL) and washed with an aqueous solution of saturated aq. NaCl (4 × 50 mL) and water (2 × 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure in order to afford the desired compound **2b** in >99% yield (2.41 g, 12.4 mmol).

Data of **2b** (MS533, EB409):



1-ethoxy-2-methoxy-4-propylbenzene (CAS: 41827-22-9)

Pale yellow solid

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, 1H, ^{3}J = 7.9 Hz, Ar*H*), 6.70-6.68 (m, 2H, Ar*H*), 4.07 (q, 2H, ^{3}J = 7.0 Hz, OCH_2CH_3), 3.86 (s, 3H, OCH_3), 2.52 (t, 2H, ^{3}J = 7.4 Hz, $CH_2CH_2CH_3$), 1.62 (sext, 2H, ^{3}J = 7.4 Hz, $CH_2CH_2CH_3$), 1.44 (t, 3H, ^{3}J = 7.0 Hz, OCH_2CH_3), 0.94 (t, 3H, ^{3}J = 7.4 Hz, $CH_2CH_2CH_3$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.2 (*C*), 146.4 (*C*), 135.5 (*C*), 120.3 (*C*H), 113.0 (*C*H), 112.3 (*C*H), 64.5 (CH_2), 55.9 (CH_3), 37.7 (CH_2), 24.7 (CH_2), 14.9 (CH_3), 13.8 (CH_3)

EI (+) (m/z): 194 (45), 165 (35), 137 (100), 122 (8)

HRMS (ESI): for $C_{12}H_{19}O_2$ $[M+H]^+$ calcd 195.1385, found 195.1383

Melting point: 35–38 °C (not reported in literature)

7 Synthesis of 2c

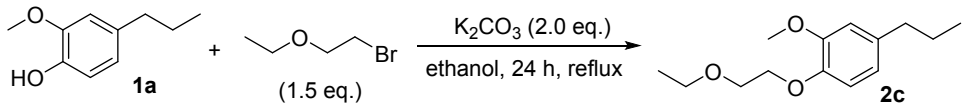
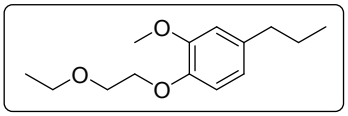


Figure S4. Synthesis of 1-(2-ethoxyethoxy)-2-methoxy-4-propylbenzene (**2c**) from 4-propylguaiacol (**1a**) and 2-bromoethyl ethyl ether.

Procedure (MS588):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 2-methoxy-4-propylphenol (**1a**, 2.08 g, 12.5 mmol, 1.0 eq.), potassium carbonate (3.46 g, 25.0 mmol, 2.0 eq.) and ethanol (10 mL). 2-bromoethyl ethyl ether (2.35 mL, 18.8 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 24 h under reflux. The reaction mixture was cooled down, filtered and solvent was evaporated. The residue was dissolved in EtOAc (10 mL) and filtered through cotton-wool. EtOAc was evaporated under reduced pressure to afford **2c** as a pale yellow oil (2.97 g, 12.5 mmol, 99%).

Data of **2c** (MS588, EB414):



1-(2-ethoxyethoxy)-2-methoxy-4-propylbenzene (no CAS number)
Pale yellow oil
Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, 1H, ^3J = 7.9 Hz, Ar*H*), 6.72−6.66 (m, 2H, Ar*H*), 4.15 (t, 2H, ^3J = 5.3 Hz), 3.84 (s, 3H, OCH_3), 3.79 (t, 2H, ^3J = 5.3 Hz), 3.59 (q, 2H, ^3J = 7.0 Hz, OCH_2CH$_3$), 2.52 (t, 2H, ^3J = 7.5 Hz, CH_2CH$_2$CH$_3$), 1.62 (sext, 2H, ^3J = 7.5 Hz, CH$_2$CH_2CH$_3$), 1.22 (t, 3H, ^3J = 7.0 Hz, OCH$_2$CH_3), 0.93 (t, 3H, ^3J = 7.5 Hz, CH$_2$CH$_2$CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6 (*C*), 146.4 (*C*), 136.2 (*C*), 120.4 (*C*H), 114.4 (*C*H), 112.6 (*C*H), 69.0 (*C*H$_2$), 68.9 (*C*H$_2$), 66.8 (*C*H$_2$), 56.0 (*C*H$_3$), 37.7 (*C*H$_2$), 24.7 (*C*H$_2$), 15.2 (*C*H$_3$), 13.8 (*C*H$_3$)

EI (+) (m/z): 238 (36), 166 (40), 137 (100), 105 (6)

HRMS (ESI): for $C_{14}H_{23}O_3$ $[M+H]^+$ calcd 239.1647, found 239.1644

8 Synthesis of 2g and 2h

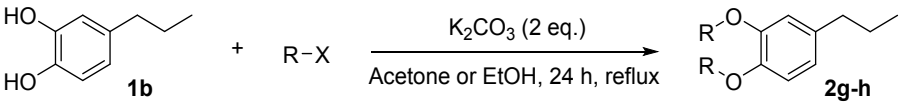
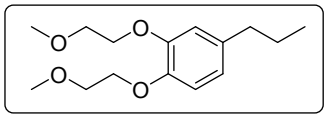


Figure S5. Alkylation of 4-propylcatechol (**1b**) using alkyl halides (R-X).

Procedure for **2g** (JBO-1356):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 4-propylbenzene-1,2-diol (**1b**, 1.07 g, 7.00 mmol, 1.0 eq.), oven dried potassium carbonate (1.94 g, 14.0 mmol, 2.0 eq.) and dry acetone (10 mL). 2-Bromoethylmethylether (1.97 mL, 21.0 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 24 h under reflux. The mixture was filtered, after which the filter was washed with acetone (20 mL). Filtrates were combined and evaporated under reduced pressure to afford **2g** (1.73 g, 6.45 mmol, 92%).

Data of **2g** (JBO-1356, EB610):



1,2-bis(2-methoxyethoxy)-4-propylbenzene (no CAS number)

Light brown oil

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, 1H, ^3J = 8.1 Hz, Ar*H*), 6.76 (s, 1H, Ar*H*), 6.71 (d, 1H, ^3J = 8.1 Hz, Ar*H*), 4.15 (t, 2H, ^3J = 4.6 Hz, OCH_2CH_2O), 4.13 (t, 2H, ^3J = 4.6 Hz, OCH_2CH_2O), 3.75 (t, 2H, ^3J = 4.6 Hz, OCH_2CH_2O), 3.74 (t, 2H, ^3J = 4.6 Hz, OCH_2CH_2O), 3.44 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 2.50 (t, 2H, ^3J = 7.4 Hz, $CH_2CH_2CH_3$), 1.60 (sext, 2H, ^3J = 7.4 Hz, $CH_2CH_2CH_3$), 0.92 (t, 3H, ^3J = 7.4 Hz, $CH_2CH_2CH_3$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.0 (*C*), 147.2 (*C*), 136.5 (*C*), 121.4 (*C*H), 115.9 (*C*H), 115.5 (*C*H), 71.3 (CH_2), 71.3 (CH_2), 69.2 (CH_2), 69.0 (CH_2), 59.2 (CH_3), 59.1 (CH_3), 37.6 (CH_2), 24.6 (CH_2), 13.8 (CH_3)

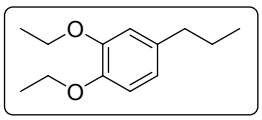
EI (+) (m/z): 268 (60), 210 (15), 178 (15), 149 (45), 123 (45), 59 (100)

HRMS (ESI): for $C_{15}H_{25}O_4$ $[M+H]^+$ calcd 269.1753, found 269.1747

Procedure for **2h** (JBO-1375):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 4-propylbenzene-1,2-diol (**1b**, 1.07 g, 7.00 mmol, 1.0 eq.), potassium carbonate (3.87 g, 28.0 mmol, 4.0 eq.) and ethanol (10 mL). Iodoethane (2.25 mL, 28.0 mmol, 4.0 eq.) was added and the reaction mixture was stirred for 24 h under reflux. The mixture was filtered and 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 concentrated under reduced pressure in order to afford **2h** (1.44 g, 6.92 moml, 99%).

Data of **2h** (JBO-1375, EB558):



1,2-diethoxy-4-propylbenzene (CAS: 497156-82-8)

Brown liquid

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, 1H, ^3J = 8.1 Hz, Ar*H*), 6.71 (d, 1H, ^4J = 1.3 Hz, Ar*H*), 6.68 (d, 1H, ^3J = 8.1 Hz, Ar*H*), 4.08 (q, 2H, ^3J = 7.0 Hz, OCH_2CH_3), 4.06 (q, 2H, ^3J = 7.0 Hz, OCH_2CH_3), 2.51 (t, 2H, ^3J = 7.5 Hz, $CH_2CH_2CH_3$), 1.61 (sext, 2H, ^3J = 7.5 Hz, $CH_2CH_2CH_3$), 1.43 (t, 3H, ^3J = 7.0 Hz, OCH_2CH_3), 1.42 (t, 3H, ^3J = 7.0 Hz, OCH_2CH_3), 0.93 (t, 3H, ^3J = 7.5 Hz, $CH_2CH_2CH_3$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.7 (*C*), 146.9 (*C*), 135.7 (*C*), 120.6 (*C*H), 114.5 (*C*H), 114.0 (*C*H), 64.8 (CH_2), 64.6 (CH_2), 37.7 (CH_2), 24.7 (CH_2), 15.0 (CH_3), 15.0 (CH_3), 13.8 (CH_3)

EI (+) (m/z): 208 (65), 179 (35), 151 (90), 123 (100), 109 (25)

HRMS (ESI): for $C_{13}H_{21}O_2$ $[M+H]^+$ calcd 209.1542, found 209.1544

9 Synthesis of 3a

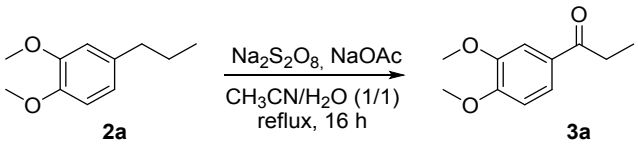


Figure S6. Benzylic oxidation of 1,2-dimethoxy-4-propylbenzene (**2a**).

Procedure (MS586):

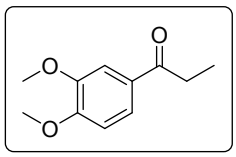
A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.6 g, 6.72 mmol, 2.0 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-dimethoxy-4-propylbenzene (**2a**, 505 mg, 2.80 mmol, 1.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred for 16 h under reflux, cooled down to room temperature and extracted with EtOAc (3×5 mL). Organic layers were combined and concentrated in order to afford a brown oil.

The crude mixture was purified with an automatic column chromatography system (column: 12 g Grace SiO_2 cartridge; eluent: gradient from 100% heptanes to 10% EtOAc in heptanes over 45 min and then 10% EtOAc in heptanes over 45 min). Fractions containing the desired product were collected and concentrated under reduced pressure. **3a** was obtained as a yellow powder (395 mg, 1.83 mmol, 73%).

Procedure with *t*BuOOH and $FeCl_3 \cdot 6H_2O$ (M. Nakanishi, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 861):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with 1,2-dimethoxy-4-propylbenzene (**2a**, 178 µL, 1.00 mmol, 1.0 eq.), $FeCl_3 \cdot 6H_2O$ (27.0 mg, 0.100 mmol, 10 mol%), *t*BuOOH 70% (412 µL, 3.00 mmol, 3.0 eq.) and pyridine (10 mL). The reaction mixture was stirred for 64 h at 85 °C, cooled down to room temperature, diluted with HCl 1M (15 mL) and extracted with EtOAc (3×15 mL). Organic layers were combined and concentrated in order to afford a brown oil. The crude mixture was analysed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard (**3e**, 0.124 mmol, 12%)

Data of **3a** (MS586, EB341):



1-(3,4-dimethoxyphenyl)propan-1-one (CAS: 1835-04-7)

Yellow powder

Spectral data are in accordance with literature[4]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, 1H, ^{3}J = 8.3 Hz, ^{4}J = 1.7 Hz, Ar*H*), 7.55 (d, 1H, ^{4}J = 1.7 Hz, Ar*H*), 6.89 (d, 1H, ^{3}J = 8.3 Hz, Ar*H*), 3.94 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 2.96 (q, 2H, ^{3}J = 7.3 Hz, CH_2CH$_3$), 1.22 (t, 3H, ^{3}J = 7.3 Hz, CH$_2$CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5 (*C*), 153.2 (*C*), 149.1 (*C*), 130.3 (*C*), 122.6 (*C*H), 110.3 (*C*H), 110.1 (*C*H), 56.1 (*C*H$_3$), 56.0 (*C*H$_3$), 31.3 (*C*H$_2$), 8.6 (*C*H$_3$)

EI (+) (m/z): 194 (25), 165 (100), 137 (10), 122 (10), 79 (10)

HRMS (ESI): for $C_{11}H_{15}O_3$ $[M+H]^+$ calcd 195.1021, found 195.1017

Melting point: 58–59 °C (in accordance with literature[4])

10 Synthesis of 4a

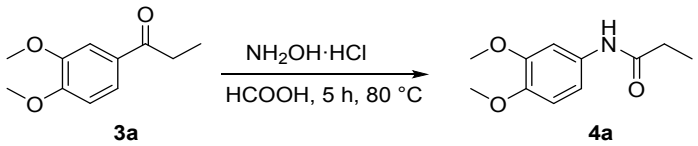


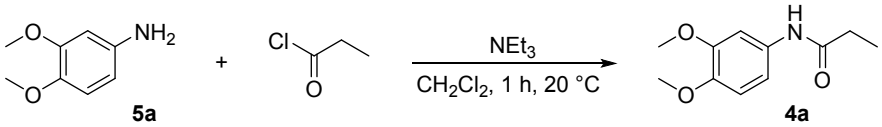
Figure S7. Beckmann rearrangement of 1-(3,4-dimethoxyphenyl)propan-1-one (**3a**).

Procedure (JBO-1350):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with **3a** (1.26 g, 6.50 mmol, 1.0 eq.), hydroxylammonium chloride (903 mg, 13.0 mmol, 2.0 eq.) and formic acid (10 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (10 mL) and extracted with MTBE (3×15 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil, which was purified with an automatic column chromatography system (column: 12 g SiO_2 cartridge; flow rate: 25 mL/min; eluent: gradient from 100% heptanes to 50% EtOAc in heptanes over 30 min, 50% EtOAc in heptanes over 10 min). Fractions containing the desired product were collected and concentrated under reduced pressure. **4a** was obtained as a white powder (1.01 g, 4.81 mmol, 74%).

Alternative procedure for reference material (EB322):

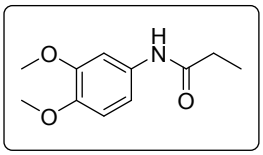
Since **4a** is not reported in literature, it was independently synthesised according to the following procedure in order to unambiguously compare it with the product obtained from **3a** following the previous procedure.



A 100 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 3,4-dimethoxyaniline (**5a**, 6.00 g, 39.2 mmol, 1.0 eq.), triethylamine (5.46 mL, 39.2 mmol, 1.0 eq.) and CH_2Cl_2 (40 mL). The reaction mixture was cooled to 0 °C using an ice bath. Propionyl chloride (3.76 mL, 43.1 mmol, 1.1 eq.) was added dropwise over 10 min at 0 °C. The reaction mixture was stirred in the ice bath reaching room temperature over ca. 1 h and was subsequently is washed with

an aqueous 1 M HCl solution (30 mL). The organic layer was filtered through 2 cm silica and concentrated under reduced pressure to afford **4a** as a purple powder (6.64 g, 31.8 mmol, 81%). **4a** can be further purified by crystallization. Therefore, the crude material was diluted with 1,4-dioxane (5 mL), heated at reflux conditions for 1 h, cooled down to 0 °C, filtered and washed with cold 1,4-dioxane (10 mL). **4a** was obtained as a light grey powder (5.74 g, 27.4 mmol, 70%).

Data of **4a** (EB322) (all analytical data were identical for the compounds obtained by the 2 different methods):



N-(3,4-dimethoxyphenyl)propanamide (CAS: 63914-26-1)

Light grey powder

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s broad, N*H*), 7.38 (d, 1H, ^4J = 1.5 Hz, Ar*H*), 6.86 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.5 Hz, Ar*H*), 6.78 (d, 1H, ^3J = 8.5 Hz, Ar*H*), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 2.37 (q, 2H, ^3J = 7.5 Hz, CH_2CH$_3$), 1.23 (t, 3H, ^3J = 7.5 Hz, CH$_2$CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1 (*C*), 149.1 (*C*), 145.8 (*C*), 131.8 (*C*), 111.8 (*C*H), 111.5 (*C*H), 105.1 (*C*H), 56.2 (*C*H$_3$), 55.9 (*C*H$_3$), 30.6 (*C*H$_2$), 9.7 (*C*H$_3$)

EI (+) (m/z): 209 (50), 153 (40), 138 (100), 125 (10), 110 (25)

HRMS (ESI): for $C_{11}H_{16}NO_3$ $[M+H]^+$ calcd 210.1130, found 210.1123

Melting point: 100–102 °C (not reported in literature)

11 Synthesis of 5a from 4a

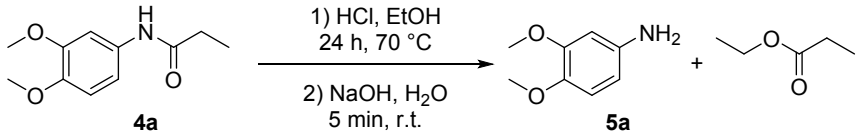
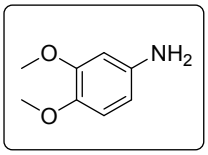


Figure S8. Alcoholysis of *N*-(3,4-dimethoxyphenyl)propanamide (**4a**).

Procedure (JBO-1360):

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with **4a** (418 mg, 2.0 mmol, 1.0 eq.) and a 1.25 M HCl solution in ethanol (1.92 mL, 2.4 mmol, 1.2 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The distillate, containing ethyl propionate and EtOH, was analysed by GC/MS and the yield of ethyl propionate was determined using a calibration curve made with a pure commercial sample of ethyl propionate. The crude mixture, containing **5a** as a hydrochloride, was diluted with water (3 mL) and washed with EtOAc (3 mL). To the aqueous layer was added solid NaOH (120 mg, 1.5 eq.) and the obtained solution was extracted with EtOAc (3 x 5 mL). The organic fractions form this extraction were combined concentrated under reduced pressure in order to afford **5a** as a light brown powder (293 mg, 1.91 mmol, 96%).

Data of **5a** (JBO-1360, EB630)



3,4-dimethoxyaniline (CAS: 6315-89-5)

Light brown powder

Spectral data are in accordance with literature[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (d, 1H, ^3J = 8.5 Hz), 6.30 (d, 1H, ^4J = 2.5 Hz), 6.23 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.5 Hz), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.45 (s broad, 2H, NH_2)

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0 (*C*), 142.3 (*C*), 140.7 (*C*), 113.3 (*C*H), 106.5 (*C*H), 100.9 (*C*H), 56.7 (CH_3), 55.8 (CH_3)

EI (+) (m/z): 153 (100), 138 (100), 125 (7), 110 (65), 95 (28)

HRMS (ESI): for $C_8H_{12}NO_2$ $[M+H]^+$ calcd 154.0868, found 154.0871

Melting point: 84–87 °C (in accordance with literature[6])

12 Synthesis of 5a from 1a

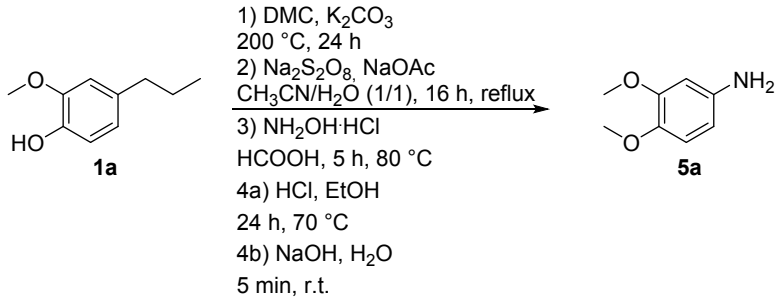


Figure S9. 4-Step approach for the transformation of 4-propylguaiacol (**1a**) into 3,4-dimethoxyaniline (**5a**).

In the following procedures, the synthesis of **5a** starting from **1a** is described, without purification of intermediates after each step.

The following procedure was used for obtaining the reaction product **5a** in the highest yield.

Step 1 (MS538):

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with potassium carbonate (26 mg, 0.19 mmol, 0.01 eq.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 3.00 mL, 18.7 mmol, 1.0 eq.) and dimethyl carbonate (10.13 g, 112 mmol, 6.0 eq.) (9.47 mL). The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to room temperature. The contents of the pressure tube was transferred with EtOAc (5 mL), filtered through cotton-wool into the round-bottom flask and the precipitate was washed with EtOAc (5 mL). The solvent was evaporated in order to afford 1,2-dimethoxy-4-propylbenzene (**2a**) as a pale yellow oil (3.37 g, 18.8 mmol, >99%).

Step 2 (JBO-1361):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-dimethoxy-4-propylbenzene (**2a**, 505 mg, 2.80 mmol, 1.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

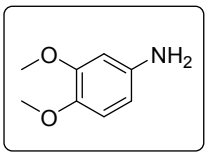
Step 3 (JBO-1362):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 2, containing 1-(3,4-dimethoxyphenyl)propan-1-one (**3a**) (around 2.08 mmol, 1.0 eq.), hydroxylammonium chloride (288 mg, 4.15 mmol, 2.0 eq.) and formic acid (3.2 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers are combined and concentrated under reduced pressure in order to afford a black oil.

Step 4 (JBO-1363):

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 3, containing *N*-(3,4-dimethoxyphenyl)propionamide (**4a**) (around 1.56 mmol, 1.0 eq.), and a 1.25 M HCl solution in ethanol (2.5 mL, 3.12 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture, containing 3,4-dimethoxyaniline (**5a**) as a hydrochloride, was diluted with water (5 mL), washed with EtOAc (5 mL) in order to remove organic by-products. To the aqueous phase was added solid NaOH (93 mg, 1.5 eq.) and the product was extracted with EtOAc (3×5 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure in order to afford **5a** as a light brown powder (224 mg, 1.46 mmol, 52% over 3 steps).

Data of **5a** (JBO-1363, EB425):



3,4-dimethoxyaniline (CAS: 6315-89-5)

Light brown powder

Spectral data are in accordance with literature[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (d, 1H, ^3J = 8.5 Hz), 6.30 (d, 1H, ^4J = 2.5 Hz), 6.23 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.5 Hz), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.45 (s broad, 2H, NH_2)

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0 (*C*), 142.3 (*C*), 140.7 (*C*), 113.3 (*C*H), 106.5 (*C*H), 100.9 (*C*H), 56.7 (CH_3), 55.8 (CH_3)

EI (+) (m/z): 153 (100), 138 (100), 125 (7), 110 (65), 95 (28)

HRMS (ESI): for $C_8H_{12}NO_2$ $[M+H]^+$ calcd 154.0868, found 154.0871

Melting point: 84–87 °C (in accordance with literature[6])

The following experimental procedure was used for the green metrics calculations.

Step 1 (MS538):

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with potassium carbonate (26 mg, 0.19 mmol, 0.01 eq.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 3.00 mL, 18.7 mmol, 1.0 eq.) and dimethyl carbonate (10.13 g, 112 mmol, 6.0 eq.) (9.47 mL). The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to room temperature. The contents of the pressure tube was transferred with EtOAc (5 mL), filtered through cotton-wool into the round-bottom flask and the precipitate was washed with EtOAc (5 mL). The solvent was evaporated in order to afford 1,2-dimethoxy-4-propylbenzene (**2a)** as a pale yellow oil (3.37 g, 18.8 mmol, >99%).

Step 2 (JBO-1364):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-dimethoxy-4-propylbenzene (**2a**, 505 mg, 2.80 mmol, 1.0 eq.), CH_3CN (12 mL) and H_2O (12 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

Step 3 (JBO-1365):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 2, containing 1-(3,4-dimethoxyphenyl)propan-1-one (**3a**) (around 1.68 mmol, 1.0 eq.), hydroxylammonium chloride (233 mg, 3.36 mmol, 2.0 eq.) and formic acid (2.5 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a black oil.

Step 4 (JBO-1366):

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 3, containing *N*-(3,4-dimethoxyphenyl)propionamide (**4a**) (around 1.26 mmol, 1.0 eq.), and a 1.25 M HCl solution in ethanol (2.0 mL, 2.50 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture, containing 3,4-dimethoxyaniline (**5a**) as a hydrochloride, was diluted with water (5 mL), washed with EtOAc (5 mL) in order to remove organic by-products. To the aqueous phase was added solid NaOH (75 mg, 1.5 eq.) and the product was extracted with EtOAc (3×5 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure in order to afford **5a** as a light brown powder (177 mg, 1.16 mmol, 41% over 4 steps). The obtained spectral data are in accordance with those obtained before.

13 Synthesis of 5b-c from 1a

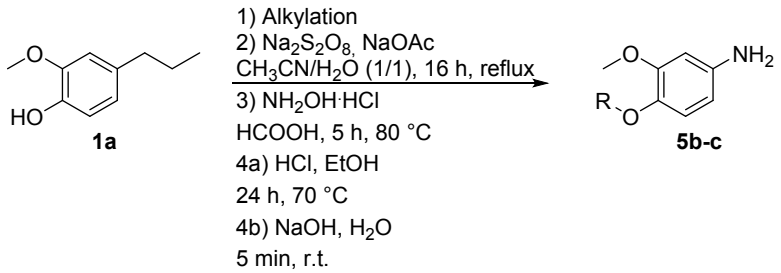


Figure S10. 4-Step approach for the transformation of 4-propylguaiacol (**1a**) into 3-methoxy-4-alkoxyanilines **5b-c**.

Procedure for **5b** :

Step 1 (MS533):

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with 2-methoxy-4-propylphenol (**1a**, 3 mL, 18.7 mmol, 1.0 eq.), cesium carbonate (0.061 g, 0.19 mmol, 1 mol%) and diethyl carbonate (13.62 mL, 112 mmol, 6.0 eq.). The tube was sealed and the reaction mixture was heated at 240 °C for 24 h in a sand bath. Subsequently, it was cooled to room temperature, filtered and the precipitate was washed with EtOAc (4 x 3 mL). The combined organic fractions were evaporated under reduced pressure to afford the pure product **2b** as a pale yellow powder in 99% yield (3.62 g, 18.63 mmol).

Step 2 (MS592):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1-ethoxy-2-methoxy-4-propylbenzene (**2b**, 544 mg, 2.80 mmol, 1.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

Step 3 (MS598):

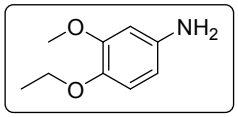
A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 2, containing 1-(4-ethoxy-3-

methoxyphenyl)propan-1-one (**3b**), hydroxylammonium chloride (378 mg, 5.44 mmol, 2.0 eq.) and formic acid (4.2 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers are combined and concentrated under reduced pressure in order to afford a black oil.

Step 4 (MS603):

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 3, containing *N*-(4-ethoxy-3-methoxyphenyl)propionamide (**4b**), and a 1.25 M HCl solution in ethanol (9.6 mL, 12.0 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture, containing 3,4-dimethoxyaniline (**5a**) as a hydrochloride, was diluted with water (5 mL), washed with EtOAc (5 mL) in order to remove organic by-products. To the aqueous phase was added solid NaOH (179 mg, 1.5 eq.) and the product was extracted with EtOAc (3×5 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure in order to afford **5b** as a light brown powder (303 mg, 1.81 mmol, 65% over 4 steps).

Data of **5b** (EB419, MS603):



4-ethoxy-3-methoxyaniline (CAS: 19782-77-5)

Brown solid

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (d, 1H, ^3J = 8.4 Hz, Ar*H*), 6.29 (d, 1H, ^4J = 2.2 Hz, Ar*H*), 6.20 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.2 Hz, Ar*H*), 3.99 (q, 2H, ^3J = 7.0 Hz, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 3.45 (s broad, 2H, NH_2), 1.39 (t, 3H, ^3J = 7.0 Hz, OCH_2CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.6 (*C*), 141.3 (*C*), 141.0 (*C*), 115.7 (*C*H), 106.6 (*C*H), 101.0 (*C*H), 65.5 (CH_2), 55.8 (CH_3), 15.0 (CH_3)

EI (+) (m/z): 167 (75), 138 (100), 124 (12), 110 (50), 96 (20)

HRMS (ESI): for $C_9H_{14}NO_2$ $[M+H]^+$ calcd 168.1025, found 168.1017

Melting point: 59–61 °C (not reported in literature)

Procedure for **5c** :

Step 1 (MS588):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 2-methoxy-4-propylphenol (**1a**, 2.87 g, 2.35 mL, 12.5 mmol, 1.0 eq.), potassium carbonate (3.46 g, 25.0 mmol, 2.0 eq.) and ethanol (10 mL). 2-bromoethyl ethyl ether (2.87 g, 2.35 mL, 18.7 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 24 h under reflux. The reaction mixture was cooled down, filtered and solvent was evaporated. The residue was dissolved in EtOAc (10 mL) and filtered through cotton-wool. EtOAc was evaporated under reduced pressure to afford **2c** as a pale yellow oil (2.97 g, 12.7 mmol, 99%).

Step 2 (MS593):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1-(2-ethoxyethoxy)-3-methoxy-4-propylbenzene (**2c**, 667 mg, 2.80 mmol, 1.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

Step 3 (MS599):

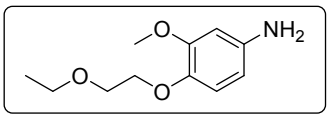
A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 2, containing 1-(4-(2-ethoxyethoxy)-3-methoxyphenyl)propan-1-one (**3c**), hydroxylammonium chloride (385 mg, 5.54 mmol, 2.1 eq.) and formic acid (4.3 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers are combined and concentrated under reduced pressure in order to afford a black oil.

Step 4 (MS604):

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 3, containing *N*-(4-(2-ethoxyethoxy)-3-methoxyphenyl)propionamide (**4c**), and a 1.25 M HCl solution in ethanol (9.6 mL, 12.0 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and

concentrated under reduced pressure. The crude mixture, containing 3,4-dimethoxyaniline (**5c**) as a hydrochloride, was diluted with water (5 mL), washed with EtOAc (5 mL) in order to remove organic by-products. To the aqueous phase was added solid NaOH (180 mg, 1.5 eq.) and the product was extracted with EtOAc (3×5 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure in order to afford **5c** as a light brown powder (360 mg, 1.70 mmol, 61% over 4 steps).

Data of **5c** (EB439, MS604):



4-(2-ethoxyethoxy)-3-methoxyaniline (CAS: 1250195-73-3)

Dark brown oil

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, 1H, ^3J = 8.4 Hz, Ar*H*), 6.28 (d, 1H, ^4J = 2.3 Hz, Ar*H*), 6.19 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.3 Hz, Ar*H*), 4.07 (t, 2H, ^3J = 5.4 Hz, OCH_2CH_2O), 3.79 (s, 3H, OCH_3), 3.74 (t, 2H, ^3J = 5.4 Hz, OCH_2CH_2O), 3.58 (q, 2H, ^3J = 7.0 Hz, OCH_2CH_3), 3.50 (s broad, 2H, NH_2), 1.22 (t, 3H, ^3J = 7.0 Hz, OCH_2CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.0 (*C*), 141.7 (*C*), 141.2 (*C*), 117.3 (*C*H), 106.7 (*C*H), 101.0 (*C*H), 70.0 (CH_2), 69.2 (CH_2), 66.7 (CH_2), 55.8 (CH_3), 15.2 (CH_3)

EI (+) (m/z): 211 (60), 139 (100), 124 (35), 110 (30), 96 (15), 80 (12)

HRMS (ESI): for $C_{11}H_{18}NO_3$ $[M+H]^+$ calcd 212.1287, found 212.1283

14 Synthesis of 5g-h from 1b

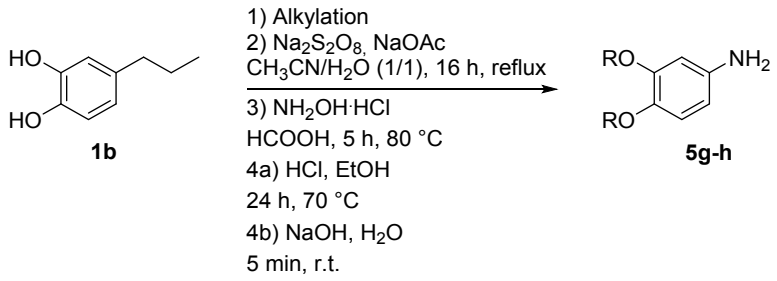


Figure S11. 4-Step approach for the transformation of 4-propylcatechol (**1b**) into 3,4-dialkoxyanilines **5g-h**.

Procedure for **5h**:

Step 1 (JBO-1375):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 4-propylbenzene-1,2-diol (**1b**, 1.07 g, 7.00 mmol, 1.0 eq.), potassium carbonate (3.87 g, 28.0 mmol, 4.0 eq.) and ethanol (10 mL). Iodoethane (2.25 mL, 28.0 mmol, 4.0 eq.) was added and the reaction mixture was stirred for 24 h under reflux. The mixture was filtered and 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 concentrated under reduced pressure in order to afford **2h** (1.44 g, 6.92 moml, 99%).

Step 2 (MS597):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.6 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-diethoxy-4-propylbenzene (**2h**, 583 mg, 2.80 mmol, 1 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). The organic layers are combined and concentrated in order to afford a brown oil.

Step 3 (MS602):

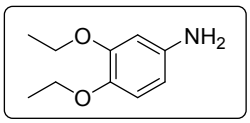
A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with previous crude mixture containing 1-(3,4-dimethoxyphenyl)propan-1-one (**3h**),

hydroxylammonium chloride (380 mg, 5.46 mmol, 2 eq.) and formic acid (4.43 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a black oil.

Step 4 (MS607):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, is charged with previous crude mixture containing *N*-(3,4-dimethoxyphenyl)propionamide (**4h**), and a 1.25 M HCl solution in ethanol (12 mL, 14.9 mmol, 4 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. Crude mixture containing 3,4-diethoxyaniline (**5h**) as a hydrochloride was diluted with water (4 mL), washed with EtOAc (3 mL) in order to remove organic by-products, basified with NaOH (223 mg, 5.58 mmol, 1.5 equiv.) and extracted with EtOAc (3×5 mL). The organic layers were concentrated in order to afford pure 3,4-diethoxyaniline (**5h**) as a dark brown solid (274 mg, 1.51 mmol, 54% over 4 steps).

Data of **5h** (MS607, EB589):



3,4-diethoxyaniline (CAS: 39052-12-5)

Dark brown solid

^{1}H spectral data are in accordance with literature;[7] ^{13}C spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, 1H, ^3J = 8.4 Hz, Ar*H*), 6.30 (d, 1H, ^4J = 2.4 Hz, Ar*H*), 6.20 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.4 Hz, Ar*H*), 4.02 (q, 2H, ^3J = 7.0 Hz, OCH_2CH_3), 3.99 (q, 2H, ^3J = 7.0 Hz, OCH_2CH_3), 3.44 (s broad, 2H, NH_2), 1.41 (t, 3H, ^3J = 7.0 Hz, OCH_2CH_3), 1.37 (t, 3H, ^3J = 7.0 Hz, OCH_2CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.2 (*C*), 141.7 (*C*), 141.2 (*C*), 116.9 (*C*H), 106.9 (*C*H), 102.6 (*C*H), 66.0 (CH_2), 64.4 (CH_2), 15.1 (CH_3), 14.9 (CH_3)

EI (+) (m/z): 181 (60), 152 (40), 136 (5), 124 (100), 96 (60)

HRMS (ESI): for $C_{10}H_{16}NO_2$ $[M+H]^+$ calcd 182.1181, found 182.1185

Melting point: 40–42 °C (not reported in literature)

Procedure for **5g**:

Step 1 (JBO-1356):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 4-propylbenzene-1,2-diol (**1b**, 1.07 g, 7.00 mmol, 1.0 eq.), oven dried potassium carbonate (1.94 g, 14.0 mmol, 2.0 eq.) and dry acetone (10 mL). 2-Bromoethylmethylether (1.97 mL, 21.0 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 24 h under reflux. The mixture was filtered, after which the filter was washed with acetone (20 mL). Filtrates were combined and evaporated under reduced pressure to afford **2g** (1.73 g, 6.45 mmol, 92%).

Step 2 (MS596)

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.6 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-bis(2-methoxyethoxy)-4-propylbenzene (**2g**, 751 mg, 2.80 mmol, 1.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). The organic layers are combined and concentrated in order to afford a brown oil.

Step 3 (MS601):

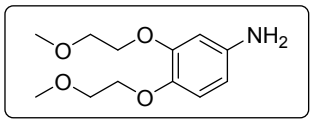
A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with previous crude mixture containing 1-(3,4-bis(2-methoxyethoxy)phenyl)propan-1-one (**3g**), hydroxylammonium chloride (356 mg, 5.12 mmol, 2.0 eq.) and formic acid (4.15 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a black oil.

Step 4 (MS606):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, is charged with previous crude mixture containing *N*-(3,4-bis(2-methoxyethoxy)phenyl)propionamide (**4g**), and a 1.25 M HCl solution in ethanol (10.6 mL, 13.22 mmol, 4.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. Crude mixture containing 3,4-bis(2-methoxyethoxy)aniline (**5g**) as a hydrochloride was

diluted with water (4 mL), washed with EtOAc (3 mL) in order to remove organic by-products, basified with NaOH (198 mg, 4.96 mmol, 1.5 equiv.) and extracted with EtOAc (3×5 mL). The organic layers were concentrated in order to afford pure 3,4-bis(2-methoxyethoxy)aniline (**5g**) as a dark brown solid (317 mg, 1.31 mmol, 47% over 4 steps).

Data of **5g** (MS606, EB615):



3,4-bis(2-methoxyethoxy)aniline (CAS: 577780-97-3)

Dark brown oil

Spectral data are in accordance with literature[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, 1H, ^3J = 8.4 Hz, Ar*H*), 6.32 (d, 1H, ^4J = 2.2 Hz, Ar*H*), 6.22 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.2 Hz, Ar*H*), 4.10 (t, 2H, ^3J = 4.9 Hz, OCH_2CH_2O), 4.06 (t, 2H, ^3J = 4.9 Hz, OCH_2CH_2O), 3.74 (t, 2H, ^3J = 4.9 Hz, OCH_2CH_2O), 3.69 (t, 2H, ^3J = 4.9 Hz, OCH_2CH_2O), 3.47 (s broad, 2H, NH_2), 3.43 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.5 (*C*), 142.0 (*C*), 141.8 (*C*), 118.6 (*C*H), 107.7 (*C*H), 103.5 (*C*H), 71.4 (CH_2), 71.2 (CH_2), 70.4 (CH_2), 68.7 (CH_2), 59.1 (CH_3), 59.0 (CH_3)

EI (+) (m/z): 241 (90), 183 (15), 151 (20), 136 (8), 124 (100), 96 (20)

HRMS (ESI): for $C_{12}H_{20}NO_4$ $[M+H]^+$ calcd 242.1392, found 242.1383

15 Synthesis of 5d from 1a

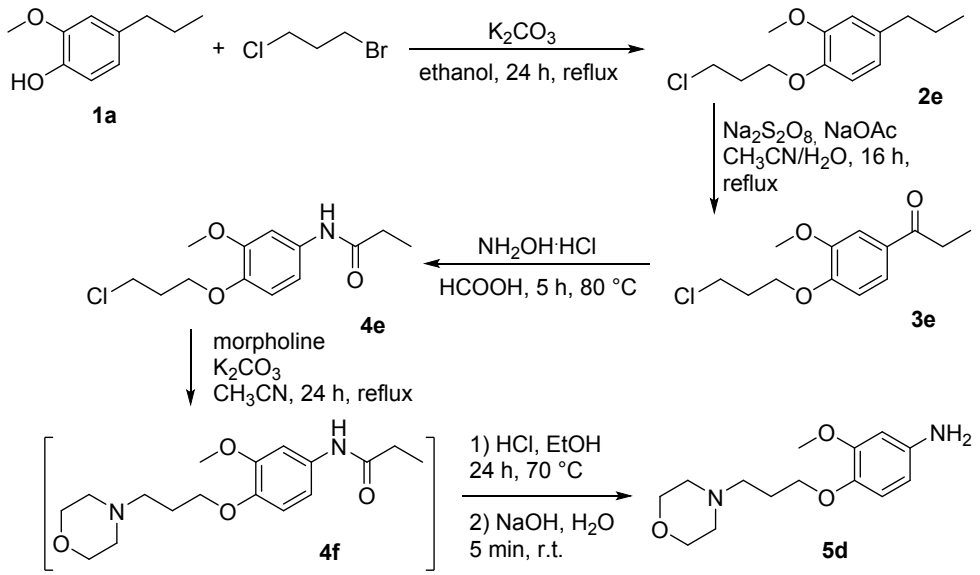
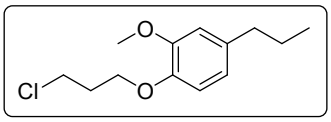


Figure S12. 5-Step approach for the transformation of 4-propylguaiacol (**1a**) into 3-methoxy-4-[3-(morpholin-4-yl)propoxy]aniline (**5d**).

Procedure for **2e** (MS594):

A 25 mL round bottomed flask, equipped with a magnetic stirring bar, was charged with 2-methoxy-4-propylphenol (**1a**, 2.08 g, 12.5 mmol, 1.0 eq.), potassium carbonate (3.46 g, 25.0 mmol, 2.0 eq.) and ethanol (10 mL). 1-Bromo-3-chloropropane (5.90 g, 3.71 mL, 37.5 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 24 h under reflux. The reaction mixture was cooled down and filtered. Ethanol was evaporated on the rotary evaporator and EtOAc (10 mL) was added to the formed oil. The solution was filtered through a cotton-wool, and the solvent was evaporated. under reduced pressure. **2e** was obtained as a colorless oil (3.04 g, 12.5 mmol, > 99%).

Data of **2e** (MS594, EB518):



1-(3-chloropropoxy)-2-methoxy-4-propylbenzene (CAS: 1260505-96-1)

Colorless oil

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (d, 1H, ^3J = 8.0 Hz, Ar*H*), 6.72−6.66 (m, 2H, Ar*H*), 4.12 (t, 2H, ^3J = 6.2 Hz), 3.83 (s, 3H, OCH_3), 3.75 (t, 2H, ^3J = 6.2 Hz), 2.52 (t, 2H, ^3J = 7.5 Hz), 2.24 (quint, 2H, ^3J = 6.2 Hz), 1.62 (sext, 2H, ^3J = 7.5 Hz, $CH_2CH_2CH_3$), 0.94 (t, 3H, ^3J = 7.5 Hz, $CH_2CH_2CH_3$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6 (*C*), 146.3 (*C*), 136.2 (*C*), 120.4 (*C*H), 114.1 (*C*H), 112.6 (*C*H), 66.1 (CH_2), 55.9 (CH_3), 41.7 (CH_2), 37.7 (CH_2), 32.5 (CH_2), 24.7 (CH_2), 13.8 (CH_3)

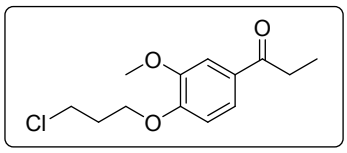
EI (+) (m/z): 242 (25), 213 (15), 165 (8), 137 (100)

HRMS (ESI): for $C_{13}H_{20}O_2Cl$ $[M+H]^+$ calcd 243.1152, found 243.1149

Procedure for **3e** (MS595):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with **2e** (0.680 mg, 2.80 mmol, 1.0 eq.), sodium persulfate (1.6 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). Organic layers were combined and concentrated under reduced pressure. The crude mixture was purified with an automatic column chromatography system (column: 12 g SiO_2 cartridge; eluent: gradient from 100% heptanes to 20% EtOAc in heptanes over 20 min and then from 20% EtOAc in heptanes to 36 % EtOAc in heptanes 2 min). Fractions containing the desired product were collected and concentrated under reduced pressure. **3e** was obtained as a yellow oil (376 mg, 1.47 mmol, 52%).

Data of **3e** (MS595, EB564):



1-[4-(3-chloropropoxy)-3-methoxyphenyl]propan-1-one (no CAS number)

Yellow oil

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.52 (m, 2H, Ar*H*), 6.91 (d, 1H, ^3J = 8.2 Hz, Ar*H*), 4.23 (t, 2H, ^3J = 6.0 Hz), 3.91 (s, 3H), 3.77 (t, 2H, ^3J = 6.0 Hz), 2.96 (q, 2H, ^3J = 7.3 Hz), 2.31 (quint, 2H, ^3J = 6.0 Hz), 1.22 (t, 3H, ^3J = 7.3 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5 (*C*), 152.4 (*C*), 149.4 (*C*), 130.5 (*C*), 122.5 (*C*H), 111.7 (*C*H), 110.8 (*C*H), 65.5 (CH_2), 56.0 (CH_3), 41.4 (CH_2), 32.1 (CH_2), 31.3 (CH_2), 8.6 (CH_3)

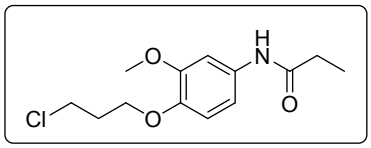
EI (+) (m/z): 256 (30), 227 (100), 151 (90), 123 (15)

HRMS (ESI): for $C_{13}H_{18}O_3Cl$ $[M+H]^+$ calcd 257.0944, found 257.0939

Procedure for **4e** (MS600):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with **3e** (374 mg, 1.46 mmol, 1.0 eq.), hydroxylammonium chloride (202 mg, 2.91 mmol, 2.0 eq.) and formic acid (2.36 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled down to room temperature, diluted with H_2O (8 mL) and extracted with MTBE (3×10 mL). Organic layers were combined and concentrated under reduced pressure. Crude mixture was purified with an automatic column chromatography system (column: 12 g SiO_2 cartridge; eluent: gradient from 100% heptanes to 20% EtOAc in heptanes over 20 min and then 20% EtOAc in heptanes to 100% EtOAc over 20 min). Fractions containing desired product were collected and concentrated under reduced pressure. **4e** was obtained as a white solid (286 mg, 1.05 mmol, 72%).

Data of **4e** (MS600, EB572):



N-[4-(3-chloropropoxy)-3-methoxyphenyl]propanamide (no CAS number)

White solid

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 1H, ^4J = 1.7 Hz, Ar*H*), 7.16 (s broad, 1H, N*H*), 6.84 (d, 1H, ^3J = 8.5 Hz, Ar*H*), 6.80 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.7 Hz, Ar*H*), 4.13 (t, 2H, ^3J = 6.3 Hz), 3.85 (s, 3H, OCH_3), 3.76 (t, 2H, ^3J = 6.3 Hz), 2.37 (q, 2H, ^3J = 7.5 Hz), 2.25 (quint, 2H, ^3J = 6.0 Hz), 1.24 (t, 3H, ^3J = 7.5 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9 (*C*), 150.0 (*C*), 144.9 (*C*), 132.4 (*C*), 114.5 (*C*H), 111.7 (*C*H), 105.4 (*C*H), 66.4 (CH_2), 56.0 (CH_3), 41.7 (CH_2), 32.4 (CH_2), 30.7 (CH_2), 9.7 (CH_3)

EI (+) (m/z): 271 (30), 215 (15), 194 (10), 138 (100)

HRMS (ESI): for $C_{13}H_{19}NO_3Cl$ $[M+H]^+$ calcd 272.1053, found 272.1060

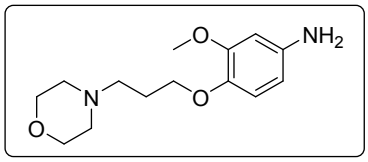
Melting point: 97–100 °C (not reported in literature)

Procedure for **5d** (MS605):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with **4e** (285 mg, 1.05 mmol, 1.0 eq.), potassium carbonate (290 mg, 2.10 mmol, 2 eq.), morpholine (365 mg, 4.20 mmol, 4.0 eq.) and CH_3CN (5 mL). The reaction mixture was stirred under reflux for 24 h, cooled down to room temperature, filtrated and concentrated under reduced pressure. The crude mixture, containing **4f**, was directly used in the following step without purification.

A 50 mL round bottom flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture, containing **4f** and a 1.25 M HCl solution in ethanol (4.28 mL, 5.35 mmol, 5.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture, containing **5d** as a hydrochloride, was diluted with water (4 mL), washed with EtOAc (3 mL) in order to remove organic by-products., basified with NaOH (107 mg, 2.68 mmol, 2.5 equiv.) and extracted with EtOAc (3×5 mL). Organic layers were concentrated in order to afford **5d** as an off-white solid (275 mg, 1.03 mmol, 98% starting from **4e**).

Data of **5d** (MS608, EB597):



3-methoxy-4-[3-(morpholin-4-yl)propoxy]aniline (CAS: 700804-30-4)

Off-white solid

Spectral data are in accordance with literature[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, 1H, ^3J = 8.4 Hz, Ar*H*), 6.30 (d, 1H, ^4J = 2.5 Hz, Ar*H*), 6.20 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.5 Hz, Ar*H*), 3.98 (t, 2H, ^3J = 7.0 Hz), 3.80 (s, 3H, OCH_3), 3.71 (t, 4H, ^3J = 4.6 Hz), 3.24 (s broad, 2H, NH_2), 2.51 (t, 2H, ^3J = 7.0 Hz), 2.45 (t, 4H, ^3J = 4.6 Hz), 1.95 (quint, 2H, ^3J = 7.0 Hz)

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.8 (*C*), 141.4 (*C*), 141.2 (*C*), 116.4 (*C*H), 106.6 (*C*H), 101.1 (*C*H), 68.8 (CH_2), 67.0 (CH_2), 55.8 (CH_3), 55.6 (CH_2), 53.7 (CH_2), 26.6 (CH_2)

EI (+) (m/z): 266 (5), 138 (5), 128 (100), 110 (5), 100 (70)

HRMS (ESI): for $C_{14}H_{23}N_2O_3$ $[M+H]^+$ calcd 267.1709, found 267.1710

Melting point: 96–99 °C (not reported in literature)

16 Synthesis of 7 from 1a

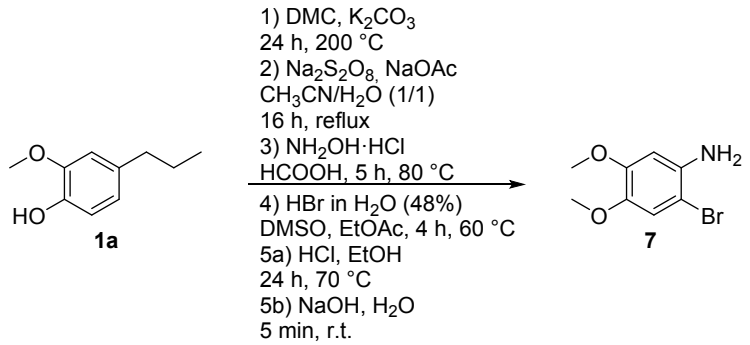


Figure S13. 5-Step approach for the transformation of 4-propylguaiacol (**1a**) into 2-bromo-4,5-dimethoxyaniline (**7**).

The following procedure was used for obtaining the reaction product **7** in the highest yield:

Step 1 (MS538):

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with potassium carbonate (26 mg, 0.19 mmol, 0.01 eq.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 3.00 mL, 18.8 mmol, 1.0 eq.) and dimethyl carbonate (10.13 g, 112 mmol, 6.0 eq.) (9.47 mL). The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to room temperature. The contents of the pressure tube was transferred with EtOAc (5 mL), filtered through cotton-wool into the round-bottom flask and the precipitate was washed with EtOAc (5 mL). The solvent was evaporated in order to afford 1,2-dimethoxy-4-propylbenzene (**2a**) as a pale yellow oil (3.39 g, 18.8 mmol, >99%).

Step 2 (JBO-1367):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), the crude mixture from Step 1 containing 1,2-dimethoxy-4-propylbenzene (**2a**, 505 mg, 2.80 mmol, 1.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature, and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

Step 3 (JBO-1368):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 2 containing 1-(3,4-dimethoxyphenyl)propan-1-one (**3a**, around 2.08 mmol, 1.0 eq.), hydroxylammonium chloride (288 mg, 4.15 mmol, 2.0 eq.) and formic acid (3.2 mL). The reaction mixture was stirred at 80 °C for 6 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a black oil.

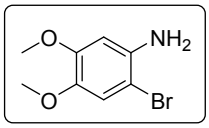
Step 4 (JBO-1369):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 3 containing *N*-(3,4-dimethoxyphenyl)propionamide (**4a**, around 1.56 mmol, 1.0 eq.), DMSO (122 µL, 1.71 mmol, 1.1 eq.), aqueous solution of HBr 48% (193 µL, 1.71 mmol, 1.1 eq.) and EtOAc (5 mL). The reaction mixture was stirred at 60 °C for 4h, cooled down to room temperature and washed with water (3×5 mL). The organic layer is dried with $MgSO_4$, filtered and concentrated under reduced pressure in order to afford a black oil.

Step 5 (JBO-1370):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 4 containing *N*-(2-bromo-4,5-dimethoxyphenyl)propionamide (**10**, around 1.47 mmol, 1.0 eq.) and a 1.25 M HCl solution in ethanol (2.34 mL, 2.93 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture containing 2-bromo-3,4-dimethoxyaniline as a hydrochloride (**7**·HCl) was diluted with H_2O (3 mL), washed with EtOAc (3 mL) in order to remove organic by-products. NaOH (88 mg, 2.20 mmol, 1.5 eq.) was added to the aqueous layer and this layer was extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford 2-bromo-4,5-dimethoxyaniline (**7**) as a brown powder (209 mg, 0.90 mmol, 32% over 5 steps).

Data of **7** (JBO-1370, EB486):



2-bromo-4,5-dimethoxyaniline (CAS: 16791-41-6)

Brown solid

Spectral data are in accordance with literature[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (s, 1H, Ar*H*), 6.34 (s, 1H, Ar*H*), 3.83 (s broad, 2H, NH_2), 3.77 (s, 6H, OCH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6 (*C*), 142.3 (*C*), 138.2 (*C*), 116.1 (*C*H), 100.7 (*C*H), 98.5 (*C*), 56.8 (CH_3), 55.9 (CH_3)

EI (+) (m/z): 233 (80), 231 (80), 218 (100), 216 (100), 190 (40), 188 (40), 175 (12), 173 (12), 160 (12), 158 (12), 109 (40), 94 (40)

HRMS (ESI): for $C_8H_{11}NO_2Br$ $[M+H]^+$ calcd 231.9973, found 231.9964

Melting point: 53–55 °C (in accordance with literature[10])

The following experimental procedure was used for the green metrics calculations.

Step 1 (MS538):

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with potassium carbonate (26 mg, 0.189 mmol, 0.01 eq.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 3.00 mL, 18.8 mmol, 1.0 eq.) and dimethyl carbonate (10.13 g, 9.47 mL, 112 mmol, 6.0 eq.). The tube was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to room temperature. The contents of the pressure tube was transferred with EtOAc (5 mL), filtered through cotton-wool into the round-bottom flask and the precipitate was washed with EtOAc (5 mL). The solvent was evaporated in order to afford 1,2-dimethoxy-4-propylbenzene (**2a)** as a pale yellow oil (3.39 g, 18.8 mmol, >99%).

Step 2 (JBO-1371):

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-dimethoxy-4-propylbenzene (**2a**, 505 mg, 2.80 mmol, 1.0 eq.), CH_3CN (12 mL) and H_2O (12 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature, and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

Step 3 (JBO-1372):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 2 containing 1-(3,4-dimethoxyphenyl)propan-1-one (**3a**, around 1.68 mmol, 1.0 eq.), hydroxylammonium chloride (234 mg, 3.37 mmol, 2.0 eq.) and formic acid (2.6 mL). The reaction mixture was stirred at 80 °C for 6 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a black oil.

Step 4 (JBO-1373):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 3 containing *N*-(3,4-dimethoxyphenyl)propionamide (**4a**, around 1.26 mmol, 1.0 eq.), DMSO (99 µL, 1.39 mmol, 1.1 eq.), aqueous solution of HBr 48% (156 µL, 1.39 mmol, 1.1 eq.) and EtOAc (5 mL). The reaction mixture was stirred at 60 °C for 4 h, cooled down to room temperature and washed with water (3×5 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure in order to afford a black oil.

Step 5 (JBO-1374):

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 4 containing *N*-(2-bromo-4,5-dimethoxyphenyl)propionamide (**10**, around 1.32 mmol, 1.0 eq.) and a 1.25 M HCl solution in ethanol (1.90 mL, 2.37 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture containing 2-bromo-3,4-dimethoxyaniline as a hydrochloride (**7**·HCl) was diluted with H_2O (3 mL), washed with EtOAc (3 mL) in order to remove organic by-products. NaOH (71 mg, 1.78 mol, 1.5 eq.) was added to the aqueous layer and it was extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford 2-bromo-4,5-dimethoxyaniline (**7**) as a brown powder (169 mg, 0.728 mmol, 26% over 5 steps). The obtained spectral data correspond to those reported before.

17 Synthesis of 8 from 2a

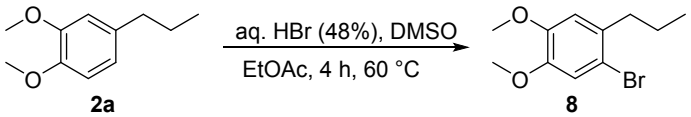


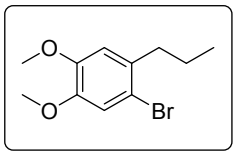
Figure S14. Bromination of 3,4-dimethoxy-4-propylbenzene (**2a**).

Procedure:

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with 1,2-dimethoxy-4-propylbenzene (**2a**, 5.62 g, 31.2 mmol, 1.0 eq.), DMSO (2.44 mL, 34.3 mmol, 1.1 eq.), a 48% aqueous HBr solution (3.9 mL, 34.3 mmol, 1.1 eq.) and EtOAc (25 mL). The reaction mixture was stirred at 60 °C for 4 h, cooled down to room temperature and washed with water (3×15 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure in order to afford a yellow oil (85%, yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard).

The crude mixture was purified with an automatic column chromatography system (column: 80 g SiO_2 cartridge; eluent: gradient from 100% heptanes to 2% EtOAc in heptanes over 60 min). Separation was found difficult; fractions containing only the pure desired product are collected and concentrated under reduced pressure in order to afford a colorless oil (3.89 g, 15.0 mmol, 48%).

Data of **8** (EB310):



1-bromo-4,5-dimethoxy-2-propylbenzene (CAS: 883239-02-9)

Colorless oil

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 1H, Ar*H*), 6.71 (s, 1H, Ar*H*), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.63 (t, 2H, ^3J = 7.5 Hz, CH_2CH$_2$CH$_3$), 1.62 (sext, 2H, ^3J = 7.5 Hz, CH$_2$CH_2CH$_3$), 0.97 (t, 3H, ^3J = 7.5 Hz, CH$_2$CH$_2$CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.3 (*C*), 147.8 (*C*), 134.0 (*C*), 115.6 (*C*H), 114.1 (*C*), 113.1 (*C*H), 56.2 (*C*H$_3$), 56.0 (*C*H$_3$), 37.8 (*C*H$_2$), 23.4 (*C*H$_2$), 13.8 (*C*H$_3$)

EI (+) (m/z): 260 (36), 258 (36), 231 (100), 229 (100), 215 (3), 185 (7), 157 (5), 107 (9), 91 (7), 77 (9)

HRMS (ESI): for $C_{11}H_{16}O_2Br$ $[M+H]^+$ calcd 259.0334, found 259.0326

18 Synthesis of 9 from 8

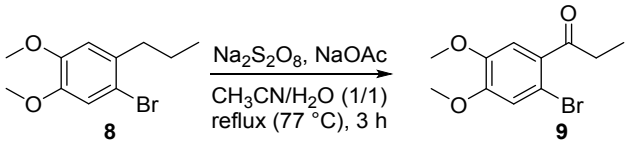
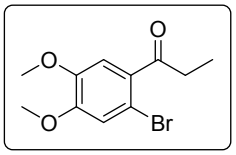


Figure S15. Benzylic oxidation of 1-bromo-4,5-dimethoxy-2-propylbenzene (**8**).

Procedure:

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with 1-bromo-4,5-dimethoxy-2-propylbenzene (**8**, 518 mg, 2.0 mmol, 1.0 eq.), sodium persulfate (950 mg, 4.0 mmol, 2.0 eq.), sodium acetate (328 mg, 4.0 mmol, 2.0 eq.), CH_3CN (25 mL) and H_2O (25 mL). The reaction mixture was stirred for 3 h at 80 °C, cooled down to room temperature, diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The organic layers were combined and concentrated under reduced pressure in order to afford brown oil, that was purified with an automatic column chromatography system (column: 40 g SiO_2 cartridge; eluent: gradient from 100% heptanes to 10% EtOAc in heptanes over 40 min). **9** is obtained as a colorless oil (165 mg, 0.67 mmol, 34%).

Data of **9** (EB622):



1-(2-bromo-4,5-dimethoxyphenyl)propan-1-one (CAS: 125575-56-6)

Colorless oil

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H, Ar*H*), 7.03 (s, 1H, Ar*H*), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.99 (q, 2H, ^3J = 7.5 Hz, CH_2CH$_3$), 1.21 (t, 3H, ^3J = 7.5 Hz, CH$_2$CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.4 (*C*), 151.3 (*C*), 148.3 (*C*), 133.3 (*C*), 116.4 (*C*H), 112.2 (*C*H), 110.8 (*C*), 56.3 (CH_3), 56.2 (CH_3), 35.7 (CH_2), 8.5 (CH_3)

EI (+) (m/z): 274 (20), 272 (20), 245 (100), 243 (100), 217 (5), 215 (5), 202 (8), 200 (8)

HRMS (ESI): for $C_{11}H_{14}O_3Br$ $[M+H]^+$ calcd 273.0126, found 273.0120

19 Synthesis of 10 from 4a

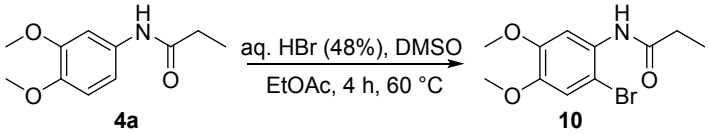
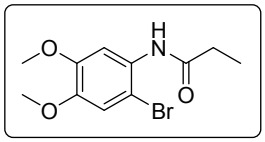


Figure S16. Bromination of *N*-(3,4-dimethoxyphenyl)propionamide (**4a**).

Procedure (MS559):

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with *N*-(3,4-dimethoxyphenyl)propionamide (**4a**, 362 mg, 1.73 mmol, 1.0 eq.), DMSO (135 µL, 1.90 mmol, 1.1 eq.), a 48% aqueous HBr solution 48% (215 µL, 1.90 mmol, 1.1 eq.) and EtOAc (5 mL). The reaction mixture was stirred at 60 °C for 4 h, cooled down to room temperature and washed with water (3×5 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure in order to afford a pink powder. The crude mixture was purified with an automatic column chromatography system (column: 12 g SiO_2 cartridge; eluent: gradient 100% heptanes to 81% EtOAc in heptanes over 16 min). Fractions containing the desired product were combined and concentrated under reduced pressure in order to afford a pink powder (431 mg, 1.50 mmol, 86%).

Data of **10** (EB568):



N-(2-bromo-4,5-dimethoxyphenyl)propanamide (no CAS number)

Pink powder

Spectral data are not reported in literature

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H, Ar*H*), 7.45 (s broad, 1H, N*H*), 6.98 (s, 1H, Ar*H*), 3.89 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 2.46 (q, 2H, ^3J = 7.4 Hz, CH_2CH$_3$), 1.28 (t, 3H, ^3J = 7.4 Hz, CH$_2$CH_3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9 (*C*), 148.7 (*C*), 145.9 (*C*), 129.5 (*C*), 114.6 (*C*H), 105.8 (*C*H), 102.7 (*C*), 56.4 (*C*H$_3$), 56.1 (*C*H$_3$), 30.9 (*C*H$_2$), 9.5 (*C*H$_3$)

EI (+) (m/z): 289 (20), 287 (20), 233 (20), 231 (20), 218 (45), 216 (45), 208 (100), 190 (10), 188 (10)

HRMS (ESI): for $C_{11}H_{15}NO_3Br$ $[M+H]^+$ calcd 288.0235, found 288.0234

Melting point: 102 °C

20 Evaluation of the green credentials for the synthesis of 3,4-dimethoxyaniline (5a) and 2-bromo-4,5-dimethoxyaniline (7)

20.1 Introduction

In order to evaluate the "greenness" of the developed approach for the synthesis of dimethoxyanilines from biorenewable 4-propylguaicol, the different synthetic steps involved were evaluated using the CHEM21 Green Metrics Toolkit, developed by Clark in the framework of a European project.[11] This assessment of the so-called "green metrics" is a relative concept. Therefore, the same assessment of a classical synthesis route for the same compounds, obtained from literature data starting from a petrochemical resource, needs to be performed as well. This way, we were able to compare the newly developed route with existing pathway(s) with respect to greenness.

In this paper, we specifically looked at reducing the amount of solvents, the solvent type selection (preferred, problematic of hazardous according to the CHEM21 Solvent Selection Guide)[12] and the applied work-up method in order to maximize greenness. In our synthesis route, the goal was to obtain pure reaction products, dimethoxyanilines, rather than having a purified intermediate after each synthetic step (we used crude material with small impurities in the next step). We are aware of the fact that the compounds we consider as intermediate in the classical sequence towards dimethoxyanilines were rigorously purified; solvents used for work-up (type and amount) is not optimized and column chromatography is typically the standard work-up on small scale. 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 idea 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.

20.2 The CHEM21 Green Metrics Toolkit

The CHEM21 Green Metrics Toolkit is split into four *passes* with increasing complexity.[11] 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 (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.[13]

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.

20.2.1 Quantitative parameters

For evaluated every reaction step, *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 formulas in Equation S1.

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

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

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

Equation S1. Formulas for calculation of yield, conversion and selectivity

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 reactions 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 defined incorporating the stoichiometry of the reaction. Important to mention is that both do not incorporate reagents or catalysts. The formulas are given in **Equation S2**.

$$\mathrm{AE}\ (\%) = \frac{\mathrm{MW_{product}}}{\sum \mathrm{MW_{reactants}}} * 100\% \qquad \mathrm{RME}\ (\%) = \frac{\text{mass of isolated product}}{\sum \text{mass of reactants}} * 100\%$$

Equation S2. Formulas for calculation of Atom Economy (AE) and Reaction Mass Efficiency (RME).

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 workup. It is defined as "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, as shown in **Equation S3**.

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

Equation S3. Formula for calculation of Process Mass Intensity (PMI).

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 solvents; *PMI Work-up* (PMI WU), in which only the work-up (both auxiliary materials for purification and solvents) of a certain reaction is considered (**Equation S4**). As already stated earlier, the latter sub category is of less relevance for discovery research.

$$\text{PMI RRC}\left(\text{g}\cdot\text{g}^{-1}\right) = \frac{\text{m}_{\text{reactants}} + \text{m}_{\text{reagents}} + \text{m}_{\text{catalysts}}}{\text{mass of the isolated product}}$$

$$\text{PMI Rxn}\left(\text{g}\cdot\text{g}^{-1}\right) = \frac{\text{m}_{\text{reactants}} + \text{m}_{\text{reagents}} + \text{m}_{\text{catalysts}} + \text{m}_{\text{reaction solvent}}}{\text{mass of the isolated product}}$$

$$\text{PMI WU}\left(\text{g}\cdot\text{g}^{-1}\right) = \frac{\text{m}_{\text{work - up chemical}} + \text{m}_{\text{work - up solvents}}}{\text{mass of the isolated product}}$$

Equation S4. Formulas for different categories of PMI.

All previous equations are meant to be used for reactions consisting of one single step. However, since the synthesis routes under study here consist of several linear steps, the equations need to be adapted. In these equations, the PMI obtained in the previous step is incorporated in the next step of the sequence. To illustrate this concept, the following two step reaction was considered: product $\boldsymbol{E}$ was made from products $\boldsymbol{C}$ and $\boldsymbol{D}$ of which product $\boldsymbol{C}$ was also made from $\boldsymbol{A}$ and $\boldsymbol{B}$. Formulas are given in Equation S5.

$$\textbf{Step 1}: \boldsymbol{A} + \boldsymbol{B} \rightarrow \boldsymbol{C}$$
$$\textbf{Step 2}: \boldsymbol{C} + \boldsymbol{D} \rightarrow \boldsymbol{E}$$

$$\text{AE}_{E,\text{cumulative}}\,(\%) = \frac{\text{MW}_E}{\frac{\text{MW}_C * 100}{\text{AE}_C} + \text{MW}_D} * 100\%$$

$$\text{Yield}_{E,\text{cumulative}} = \text{Yield}_{C,\text{Step 1}} * \text{Yield}_{E,\text{Step 2}}$$

$$\text{RME}_{E,\text{cumulative}}\,(\%) = \frac{\text{m}_E}{\frac{\text{m}_C * 100}{\text{RME}_C} + \text{m}_D} * 100\%$$

$$\text{PMI}_{E,\text{cumulative}}\left(\text{g}\cdot\text{g}^{-1}\right) = \frac{\text{m}_C * \text{PMI}_{C,\text{Step 1}} + \text{m}_D + \text{m}_{\text{other chemicals in Step 2}}}{\text{m}_E}$$

Equation S5. Formulas for calculation of Yield, AE, RME and PMI of a two-step process.

20.2.2 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 S5, a brief overview is given on how the flags are determined for each item (except solvents).

Table S5. 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	
S17Critical 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	H200, H201, H202, H203, H230, H240, H250, H300, H310, H330, H340, H350, H360, H370, H372, H400, H410, H411, H420	H205, H220, H224, H241, H301, H311, H331, H341, H351, H361, H371, H373, H401, H412	

For solvent use, one can make use of the open access CHEM21 Solvent Selection Guide.[12] In Table S6, 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 S6. CHEM21 solvent selection guide of classical solvents.[12]

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-pryrrolidone (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)

20.3 Selection of a classical reference synthesis route for 3,4-dimethoxyaniline (5a) and 2-bromo-4,5-dimethoxyaniline (7) synthesis

The greenness of a new reaction pathway can only be evaluated when compared to an existing "classical" route. Therefore, literature procedures for the different reaction products in this paper were searched for. For 3,4-Dimethoxyaniline (**5a**) and 2-bromo-4,5-dimethoxyaniline (**7**) a well-described synthetic procedure was found. The selected synthetic routes and individual steps are shown in Figure S17 and Figure S18 (reactions in black). For some steps, different publications or patens featuring different reaction conditions were found. We selected those conditions with well-described and detailed experimental procedures making use of industrially acceptable chemicals.

For the classical route, we decided to start from benzene obtained by petroleum refinery. This matches with the new approach starting from 4-propylguaicol (**1a**) obtained via a biorefinery.[14] Cumene can be made from benzene via reaction with propylene (Step 1, Figure S18).[15] Phenol is industrially produced from cumene over two steps.[16] This involves in a first stage the oxidation of cumene to cumene hydroperoxide in the presence of air as oxidant (Step 2).[17] Conversion of cumene to 19.4%, with a known amount of air, and recycling of the remaining substrate finally

yields 93.7% of the desired product (relative to cumene). Treatment of the obtained cumene hydroperoxide with HOAc and $HClO_4$ led to the desired phenol in 95% yield via Hock rearrangement (Step 3).[18] Catechol is generally produced from phenol via direct hydroxylation using H_2O_2 in the presence of a(n) (acidic) catalyst (Step 4). Ube Industries adds additional methyl isopropyl ketone (MIBK) to enhance catechol selectivity and suppress hydroquinone formation.[19-20] Unfortunately, *para*-hydroxylation cannot be avoided and in the best case, a selectivity of 54% for catechol (*ortho*-hydroxylation) was obtained. The concentration of H_2O_2 is kept low, so more than 95% of the used phenol is not converted and recycled afterwards.

Transformation of catechol into 3,4-dimethoxyaniline (**5a**) can be performed in a sequence of three steps: double *O*-methylation (Step 5), nitration (Step 6) and nitro reduction (Step 7). *O*-Methylation of catechol is described using dimethylcarbonate as carbon source delivering veratrole in almost quantitative yield in the presence of DBU in a closed vessel at 170 °C (Step 5).[21] Selective *para*-nitration versus a methoxy group was achieved in 83% by using aqueous HNO_3 (Step 6),[22] after which a reduction of the nitro group was achieved through treatment with Pd/C and H_2 gas (Step 7).[23] The obtained 3,4-dimethoxyaniline (**5a**) can be converted into the desired 2-bromo-4,5-dimethoxyaniline (**7**) by treatment with Bu_4NBr_3 applying a modified literature procedure of Lopez-Tapia (Step 8).[10, 24]

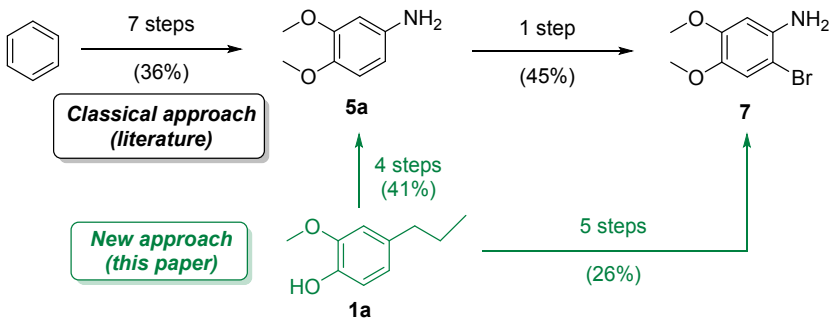


Figure S17. Number of steps required in the classical (black) versus new approach (green) towards 3,4-dimethoxyaniline (**5a**) and 2-bromo-4,5-dimethoxyaniline (**7**).

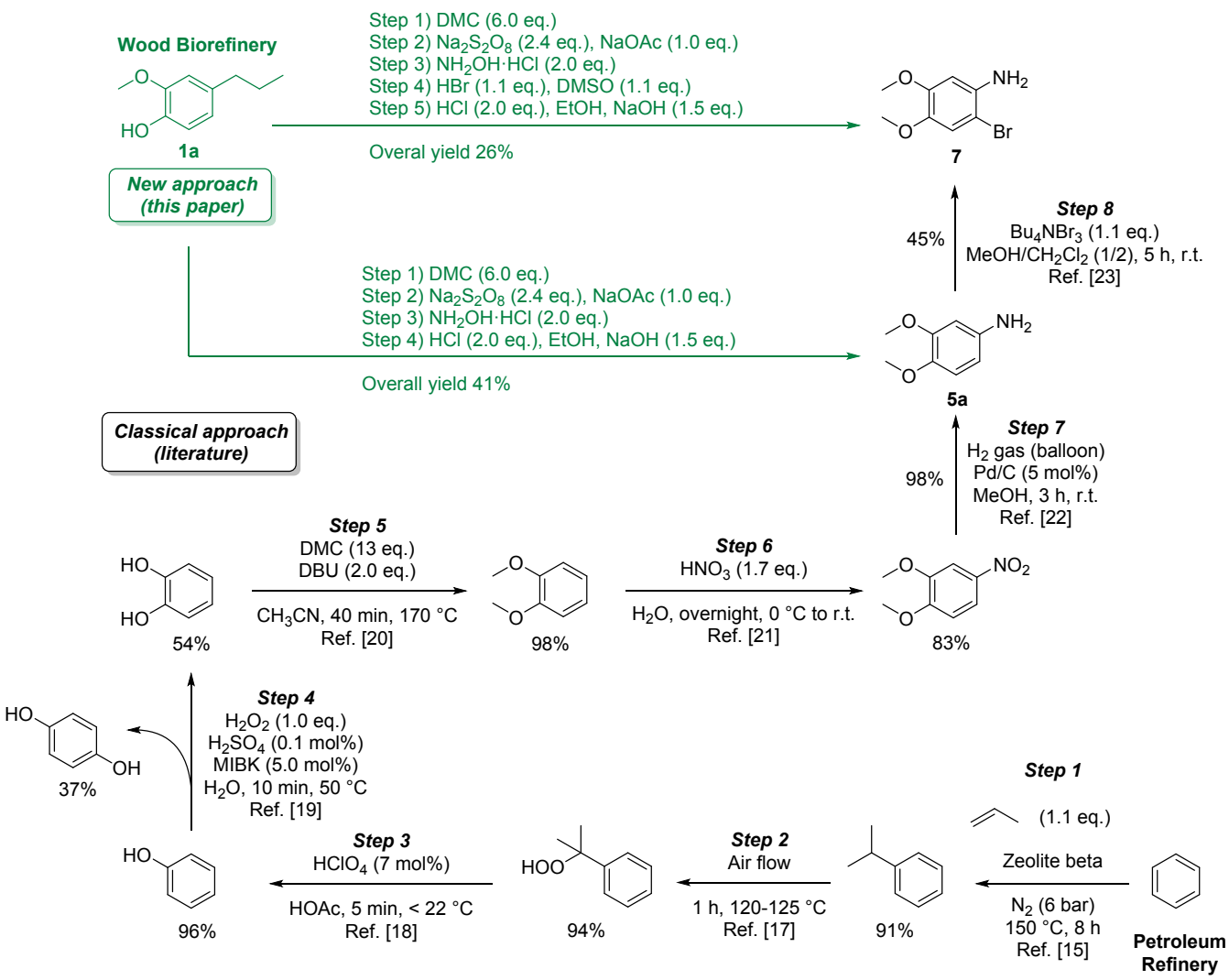


Figure S18. Synthesis of 3,4-dimethoxyaniline (**5a**) and 2-bromo-4,5-dimethoxyaniline (**7**) via a classical route (black) starting from benzene versus a new route (green) based on 4-propylguaiacol (**1a**).

20.4 Comments regarding the metrics calculations

Before starting the assessment of the different metrics for the new and classical approaches, some assumptions had to be made:

- For the new route, we described different experimental procedures and for the green metrics calculations, we used the procedures described in Sections 12 and 16 of this SI. In these procedures, the desired anilines were obtained from 4-propylguaiacol in four or five steps without intermediate purification, leading to the lowest PMI possible. In these experimental procedures without work-up, we did not to want to use too large amounts

of chemicals in the next step of the sequence and therefore we did not consider the crude product as 100% pure but took into account the actual yield, obtained in experiments where isolation for that step was performed and a "real" isolated yield available. Based on those yields, the required amount of chemicals for the next step was calculated.

- For the methylation of 4-propylguaiacol (**1a**) using dimethyl carbonate (DMC) (Step 1), this compound was both used as reactant as well as solvent. For the assessment of this reaction, the theoretically required 1.0 eq. was considered as reactant and the remaining amount as reaction solvent, so that the total amount in the calculations corresponds to what was written down in the experimental procedure. The classical route also involves a methylation of catechol with DMC (Step 5), for which we made the same assumption (the theoretically required 2.0 eq. as reactant since two methylations are involved and the remaining as solvent). This assumption influences the obtained value for PMI RRC, which only includes the amount of reactants, reagents and catalysts. For the PMI Rxn, the obtained value obviously does not change as long as the total amount of solvent is incorporated, irrespective whether it is considered as reactant or as solvent.

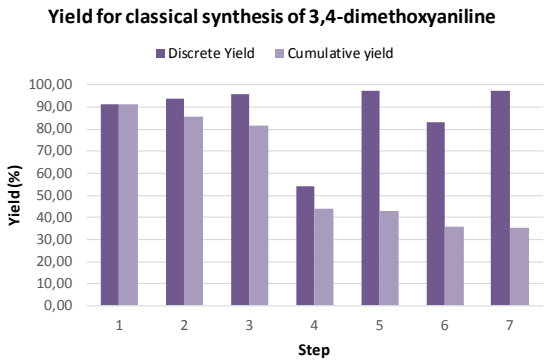
- The last step in the new procedures towards both **5a** and **7** consists of the cleavage of an aromatic amide with the formation of the corresponding aniline under acidic conditions (HCl). Concomitantly, ethyl propionate is formed as by-product with ethanol present as reactant and solvent. During the ethanolysis, the HCl salt of the aniline is formed from which the remaining alcohol and the formed ester are easily removed by evaporation. Washing the crude product with organic solvent then allowed to remove organic (i.e. non HCl salt) impurities. Subsequently, dissolving the residue in water and addition of solid NaOH (1.5 eq.) followed by extraction with an organic solvent (preferably EtOAc) and evaporation enabled us to obtain the pure desired aniline without making use of column chromatography (as in any of the other steps starting from **1a**). Therefore, the used amounts of NaOH and H_2O were considered as reagent and reaction solvent rather than including them in the work-up procedure. The by-product ethyl propionate is treated as waste in our calculations, though it is an industrial valuable compound.[25]

- For three reactions in the classical method recycling of the substrate was involved. The recycling was taken into account for obtaining "realistic" results in the green metrics analysis. Otherwise, if recycling is neglected, the PMI would rise incredibly which does not reflect reality. In contrast, the original CHEM21 Metrics Toolkit does not take this aspect into account. For the hydroxylation of phenol (Step 4), more than 95% of the substrate is not converted in one single reaction under the given conditions. For this reason, the amount of phenol which was not converted (and therefore recycled in a next run) was not taken into account as reactant. For the specific example, 1852 grams of phenol (19.68 mol) were used as substrate, together with 33.48 grams H_2O_2 (0.98 mol). This way, 57 grams of catechol (0.52 mol) and 38 grams of hydroquinone (0.35 mol) were obtained and 1762 grams of phenol were recycled. This way, only 90 grams of phenol reacted and this is the amount of reactant that was used in the calculations. Next, the first reaction of the classical route consists of the formation of cumene from benzene with propylene. In one run, 13% of the substrate was converted to the desired reaction product. In order to obtain cumene with a yield of 91.3% (mentioned by the authors), this specific run has to be repeated seven times, so the amount of propylene required in one run was multiplied by a factor seven in the green metrics calculations. The zeolite catalyst used could be re-used several times so there was no need to multiply its amount. A similar situation was found for the oxidation of cumene to its hydroperoxide (Step 2), in which 19.4% yield is obtained after a reaction time of one hour. Therefore, the amount of the air which is required to obtain 93.7% yield, is 4.83 times (93.7 divided by 19.4) more than what is reported in the procedure. The air used during this reaction was split into two parts: the oxygen (for oxidation) as oxidant being the reactant and the nitrogen (for providing a good flow) as diluent being the solvent. For the ease of the calculations, air was considered as a 20/80 mixture (mole ratio) of O_2 and N_2 gases. The side compound hydroquinone is an industrially valuable chemical but in our sequence undesired and therefore treated as waste in the calculations.

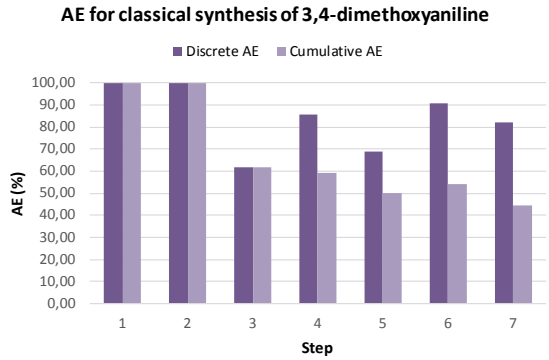
- The amount of H_2 gas (atmospheric pressure) in the fourth step of the literature procedure was estimated by the volume of a standard balloon, about 4 liters and H_2 was considered an ideal gas, allowing to use the ideal gas law.

20.5 Comparison of the green metrics for classical versus new route for 3,4-dimethoxyaniline (5a) and 2-bromo-4,5-dimethoxyaniline (7) synthesis

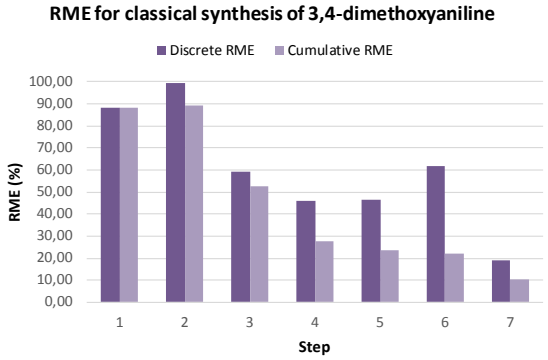
Underneath in Figure S19, Figure S20, Figure S21, and Figure S22 a graphical representation of the qualitative metrics for both the classical and new synthesis of 3,4-dimethoxyaniline (**5a**) and 2-bromo-4,5-dimethoxyaniline (**7**) can be found. For each parameter, a value for the individual step and the cumulative one including that step is shown. The discussion of the data is included in the manuscript.



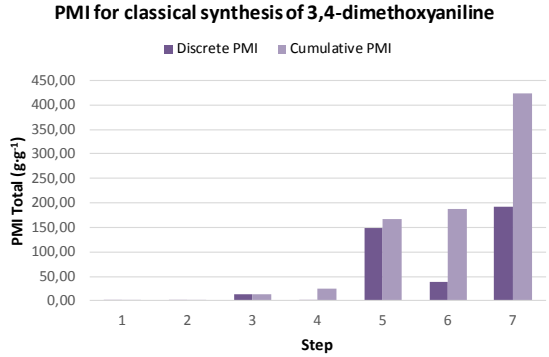
(a)



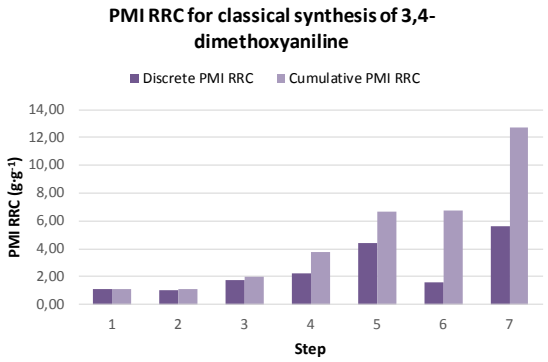
(b)



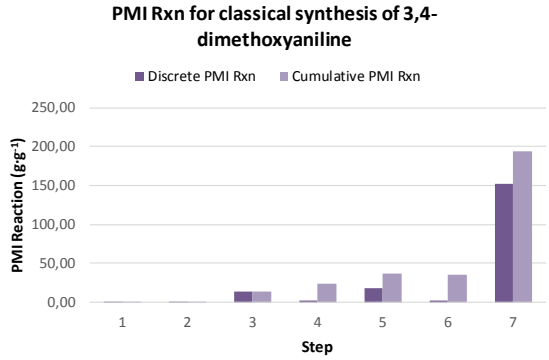
(c)



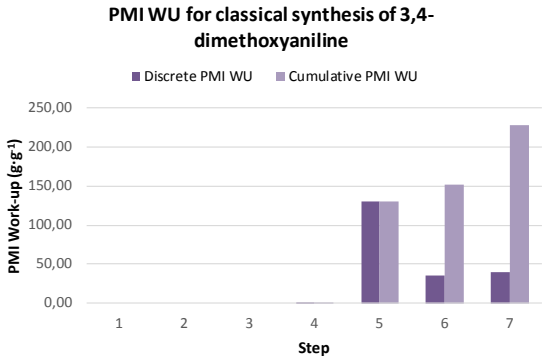
(d)



(e)

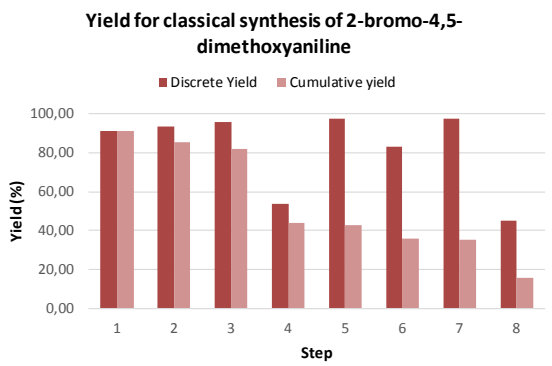


(f)

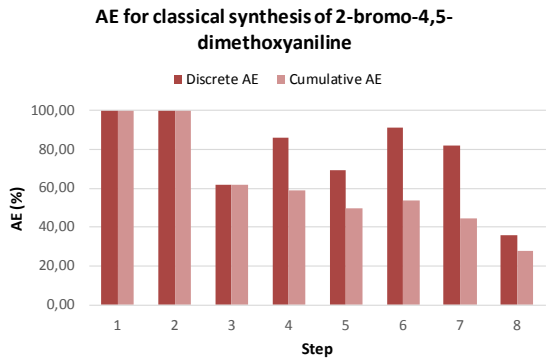


(g)

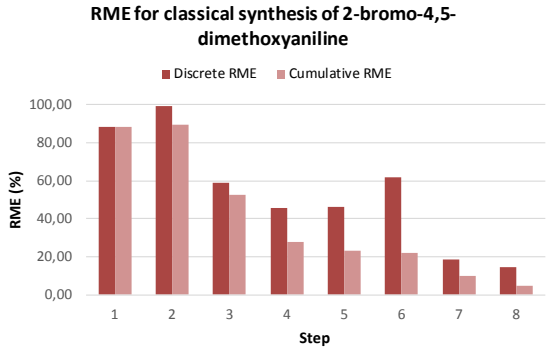
Figure S19. Yield, AE, RME, PMI, PMI RRC, PMI Rxn and PMI WU for the classical synthesis of 3,4-dimethoxyaniline (**5a**).



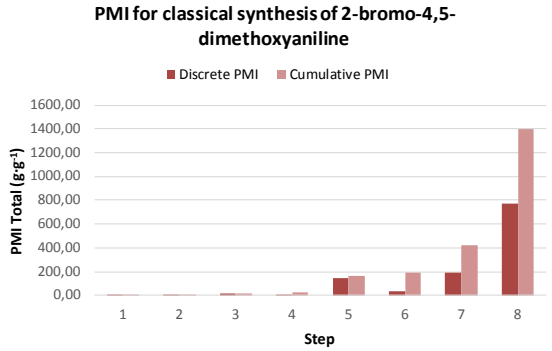
(a)



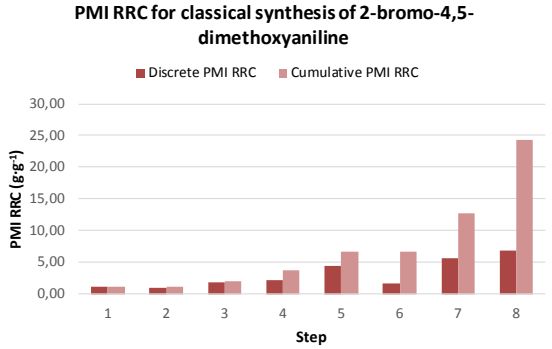
(b)



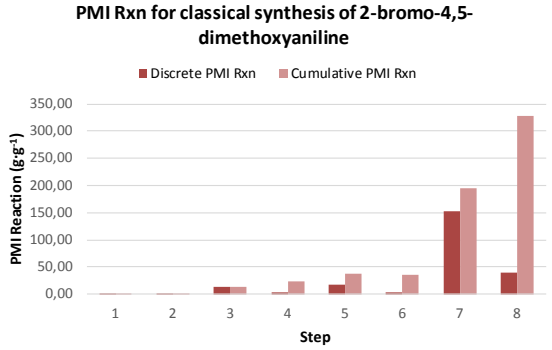
(c)



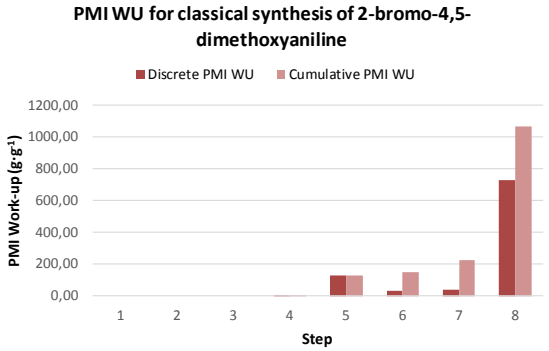
(d)



(e)



(f)



(g)

Figure S20. Yield, AE, RME, PMI, PMI RRC, PMI Rxn and PMI WU for the classical synthesis of 2-bromo-4,5-dimethoxyaniline (**7**).

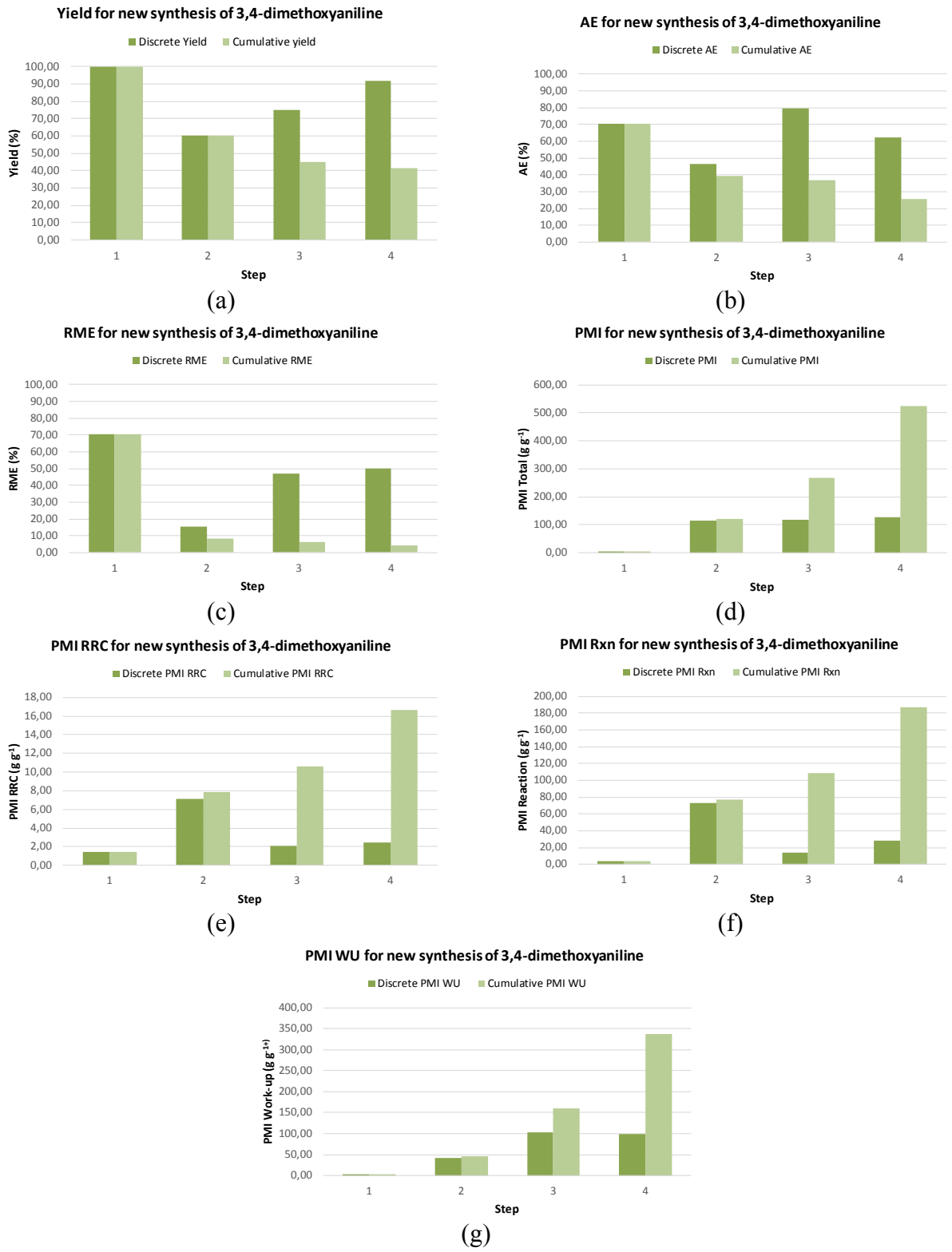
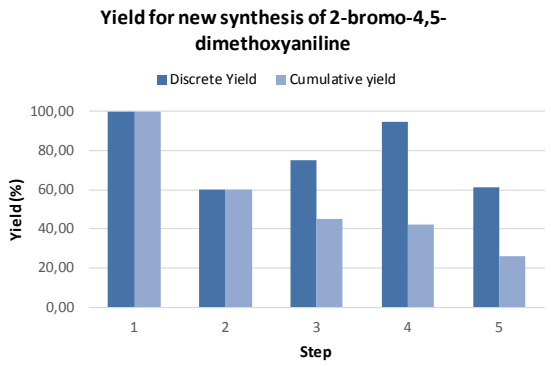
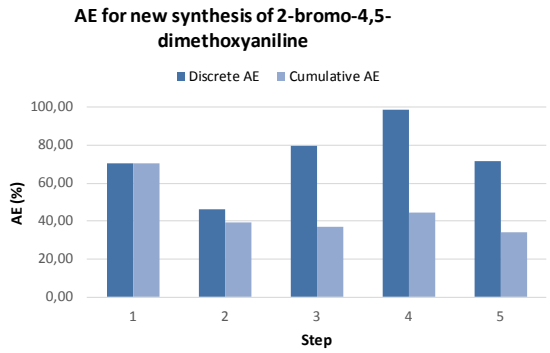


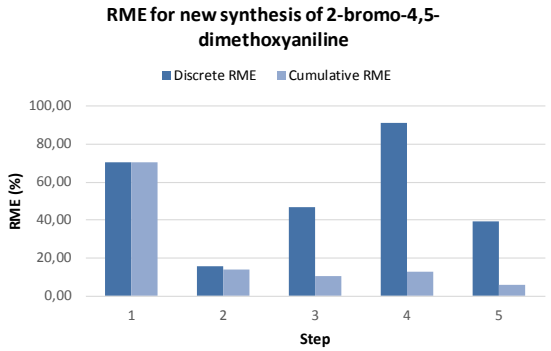
Figure S21. Yield, AE, RME, PMI, PMI RRC, PMI Rxn and PMI WU for the new synthesis of 3,4-dimethoxyaniline (**5a**).



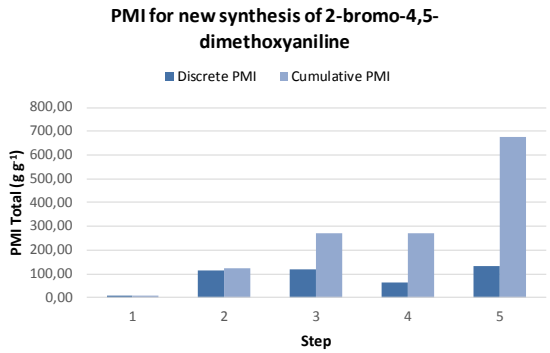
(a)



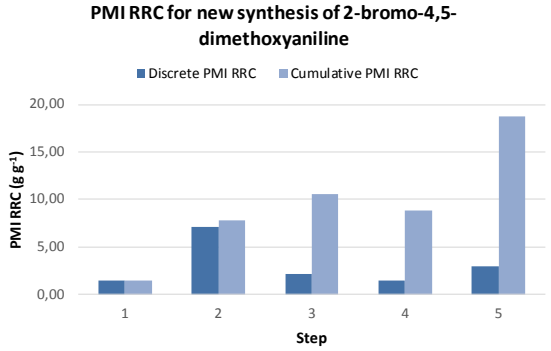
(b)



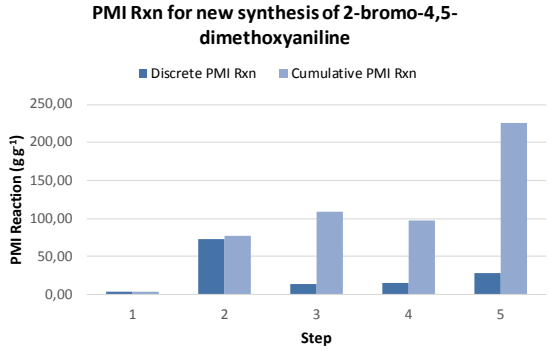
(c)



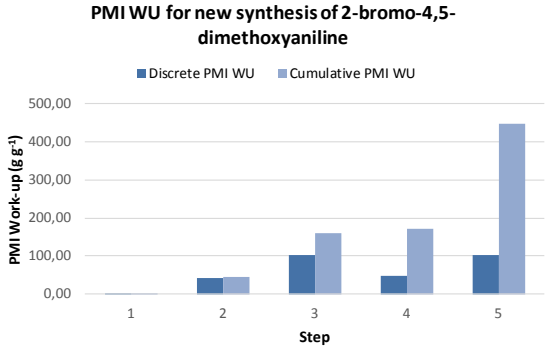
(d)



(e)



(f)



(g)

Figure S22. Yield, AE, RME, PMI, PMI RRC, PMI Rxn and PMI WU for the new synthesis of 2-bromo-4,5-dimethoxyaniline (**7**).

20.6 Ethylation of 4-propylguaiacol (1a) with diethylcarbonate

Ethylation of phenolic compounds is typically performed by using an excess of ethyl iodide in the presence of a base in DMF as solvent. This methodology enabled us to obtain the desired 1-ethoxy-2-methoxy-4-propylbenzene (**2b**) in 99% yield (Method A in Figure S23). However, since DMF is considered as a Substance of Very High Concern by ChemSec,[26] its use needs to be avoided. Also, the used excesses of reactant (ethyl iodide) and reagent (K_2CO_3) have a negative impact on the greenness of the approach, both quantitatively and qualitatively. Therefore, a new approach was developed similar to the earlier described methylation with dimethyl carbonate (see Sections 5 and 6, and Figure S18 Step 1 *New Approach* of this SI).[27] Treating the substrate **1a**, with a catalytic amount of base and 6.0 eq. of diethyl carbonate (which is also used as solvent) at 240 °C delivered the desired product **2b** in quantitative yield (Method B in Figure S23).

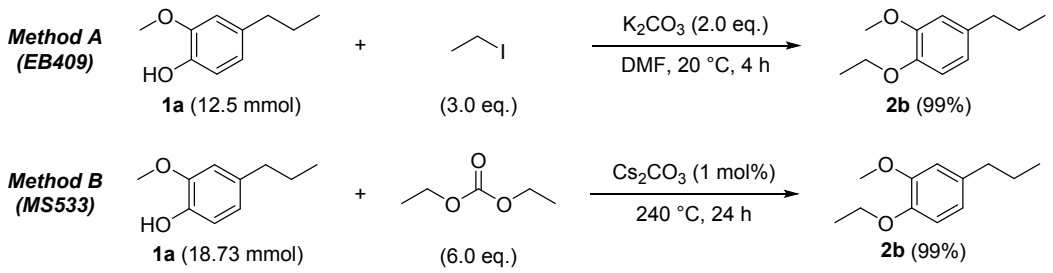


Figure S23. Synthesis of 1-ethoxy-2-methoxy-4-propylbenzene (**2b**) with ethyl iodide (A) and diethyl carbonate (B).

The green credentials were also evaluated using the CHEM21 Green Metrics Toolkit. The results are reported in Table S7 and Table S8. Since diethyl carbonate (DEC) is used both as reactant and as solvent in Method B, the theoretical value of 1.0 eq. was considered as reactant and the remaining 5.0 eq. as solvent. When looking at the data for the quantitative metrics analysis (Table S7), it is clear that the method involving DEC scores better than the traditional method with ethyl iodide (EtI). The PMI RCC and PMI Rxn, with our without including solvent, could be decreased to half of the original value (8.64 to 4.42 and 4.72 to 2.04, respectively). While yield and AE are similar for both approaches, RME is higher for method B. An explanation for the rather low AE in both reactions can be found in the structures of the ethylating reactants, since both ethyl iodide and diethyl carbonate possess a leaving group which contributes to more than 75% of the molecular weight of the compound. In the assessment of the qualitative metrics, the difference between the two methods is also remarkable. Both for Health & Safety and the amount of reagent used, the red

flag could be transformed into a green flag. This improvement in metrics is also seen for the used solvent. DEC is unfortunately not present in the CHEM21 Solvent Guide. Therefore, a full analysis as described in this Guide, taking into account physical properties, H statements and REACH registration, was required leading to a classification as "recommended" and therefore another green flag.[12] Only for the required temperature, diethyl carbonate scores a red flag in comparison to ethyl iodide. This is inherent to the reactant properties requiring a high temperature for use as alkylating agent.

Table S7. Quantitative metrics for the synthesis of 1-ethoxy-2-methoxy-4-propylbenzene (**2b**).

Method	Yield (%)	AE (%)	RME (%)	PMI ($g \cdot g^{-1}$)	PMI RRC [a] ($g \cdot g^{-1}$)	PMI Rxn [b] ($g \cdot g^{-1}$)	PMI WU [c] ($g \cdot g^{-1}$)
A (EtI)	99	60	30	187	4.72	8.64	178
B (DEC)	99	68	49	6.85	2.04	4.42	2.42

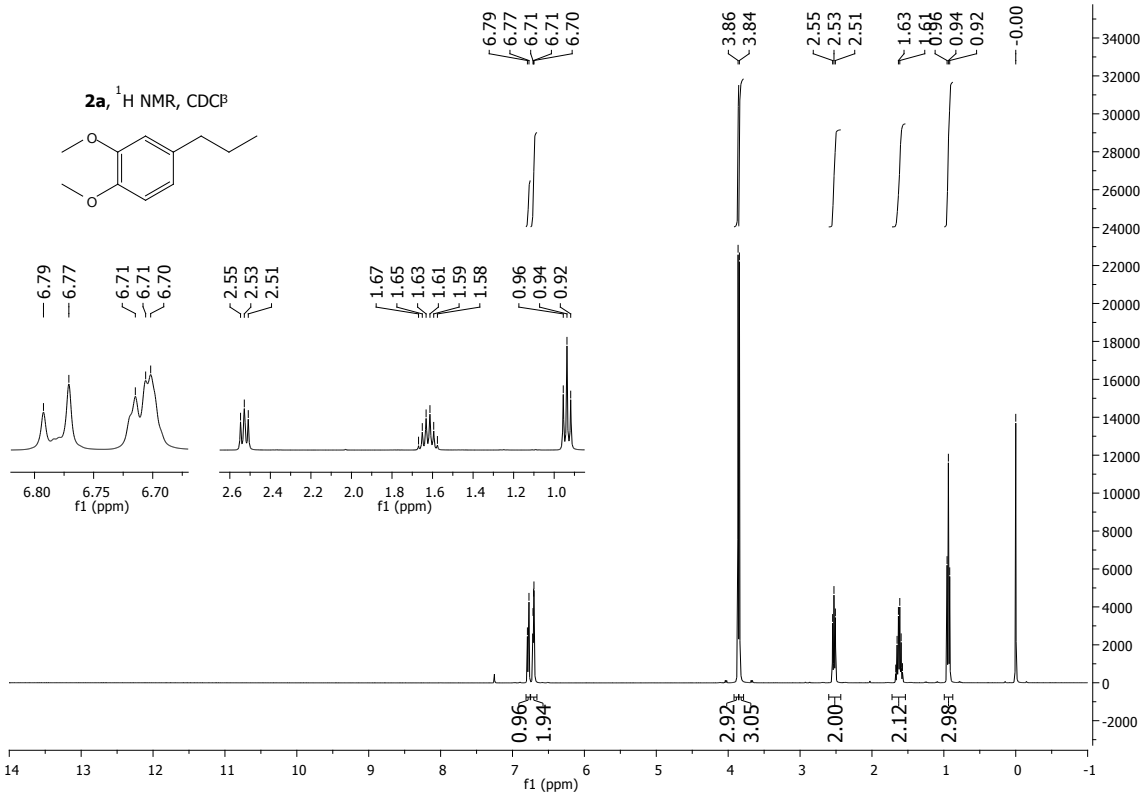
[a] RRC: Reactants, Reagents, Catalysts. [b] Rxn: Reaction. [c] WU: Work-up.

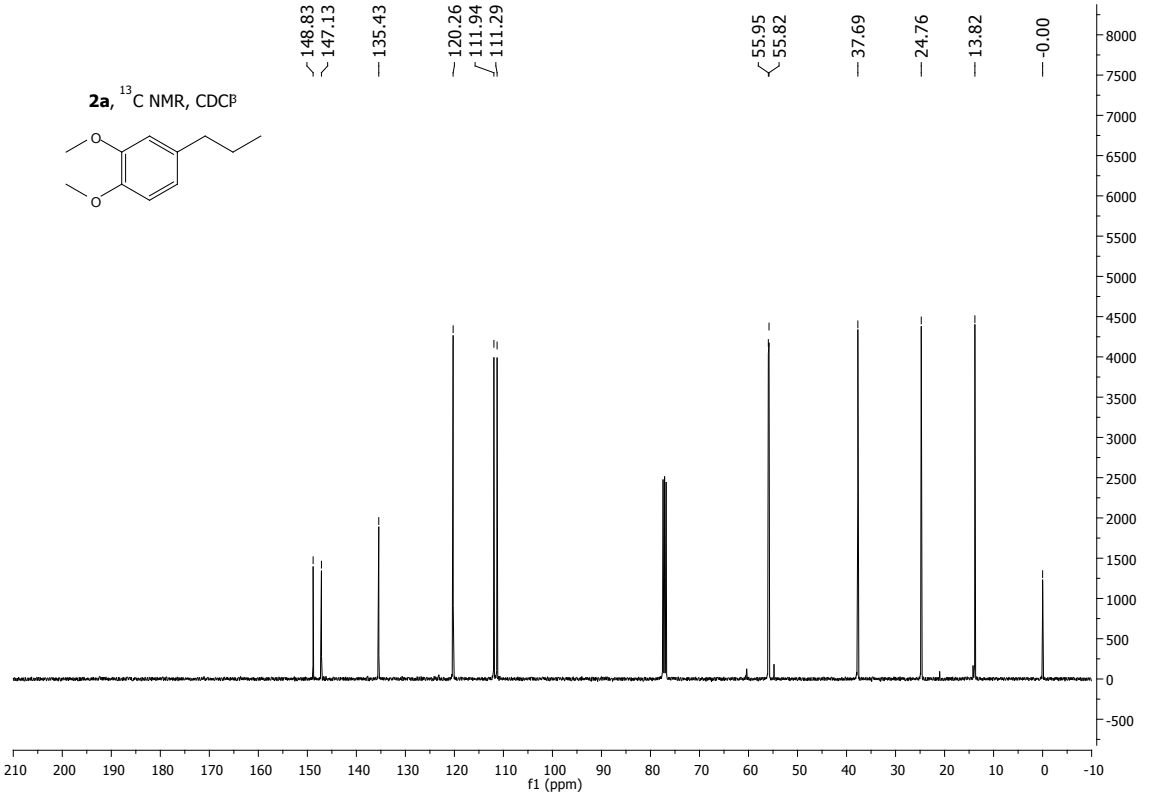
Table S8. Qualitative appraisal of solvent use, inherent hazards of used chemicals, catalyst/reagent use, energy and work-up methods for the synthesis of 1-ethoxy-2-methoxy-4-propylbenzene (**2b**).

Method	Solvents	Flag	Critical elements	Flag	Health and Safety	Flag	Reagent used	Flag	Energy	Flag	Work-up	Flag
A (EtI)	DMF		I		DMF: H360 [a]		Excess		20 °C		Extraction	
B (DEC)	DEC		-		- [a]		Catalyst		240 °C		Filtration	

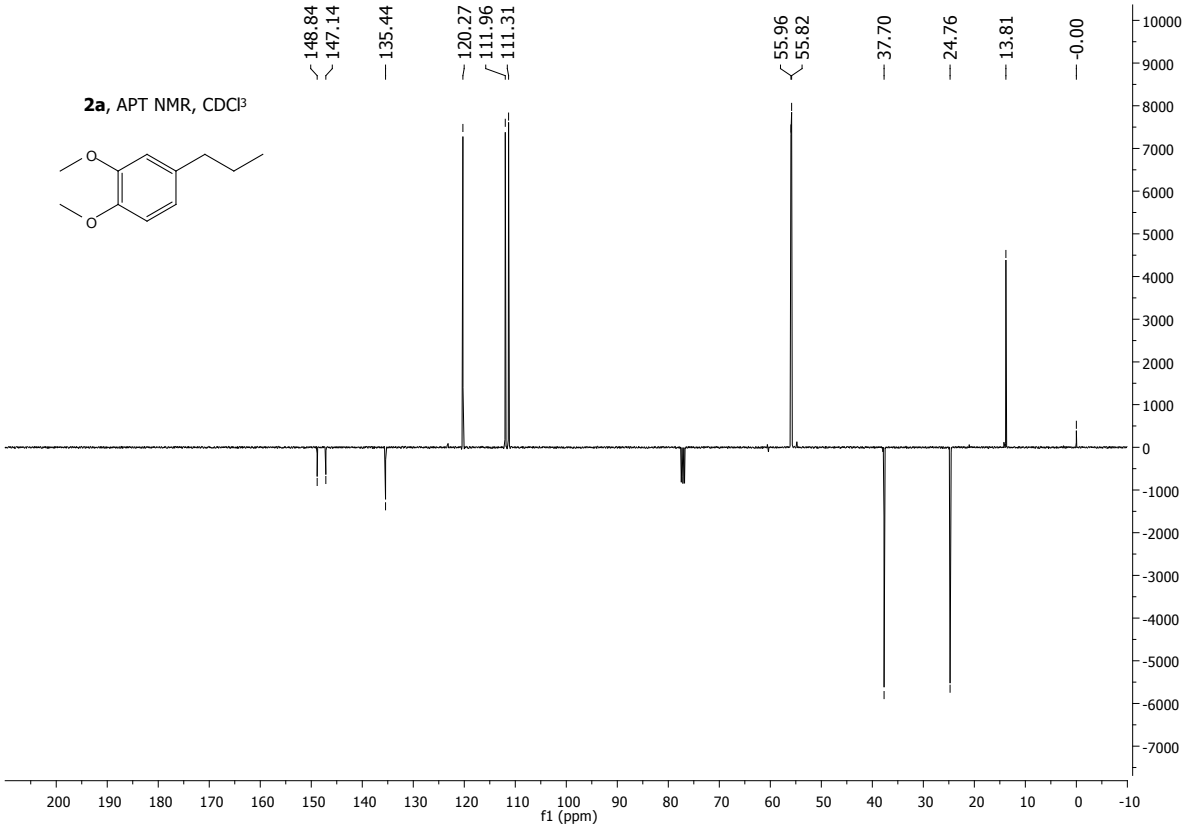
[a]: The substrate, 4-propylguaiacol (**1a**) is toxic in contact with skin (H311), which leads to a yellow flag for "Health & Safety". However, it is the starting material for both approaches and therefore not included.

21 NMR spectra

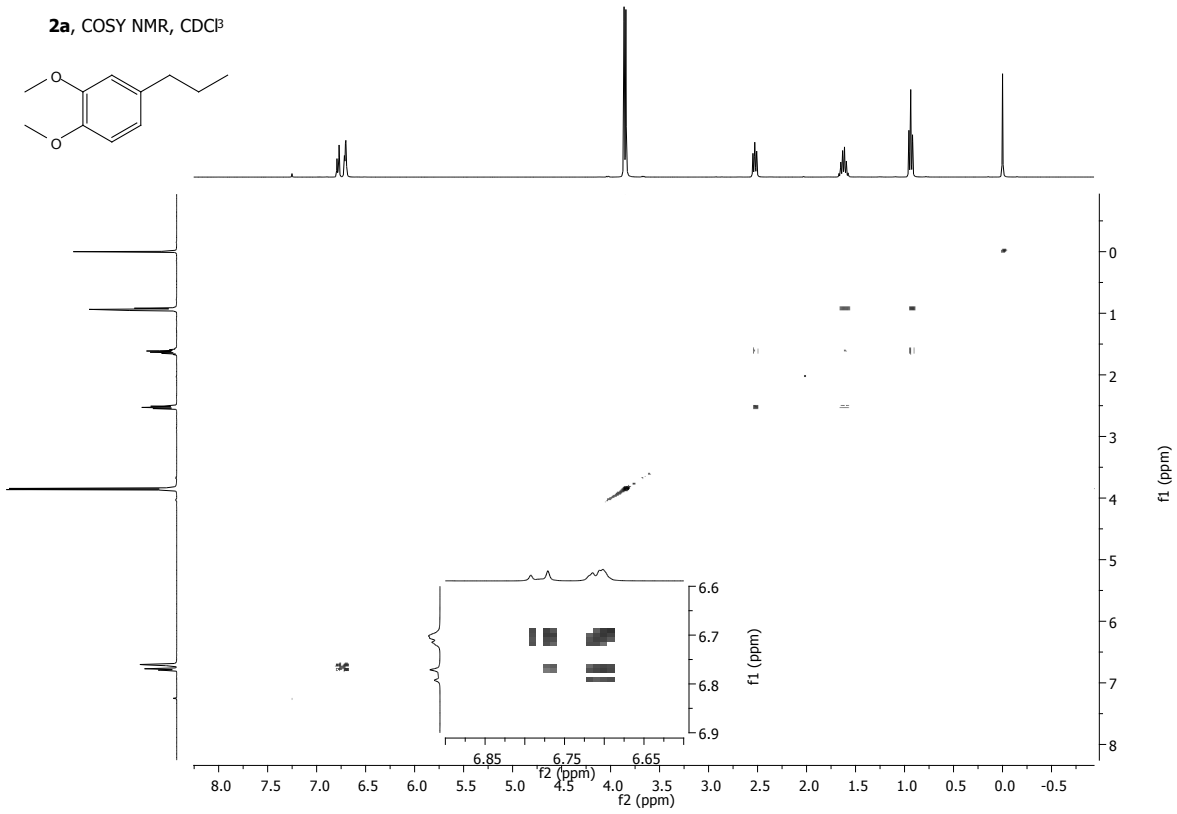


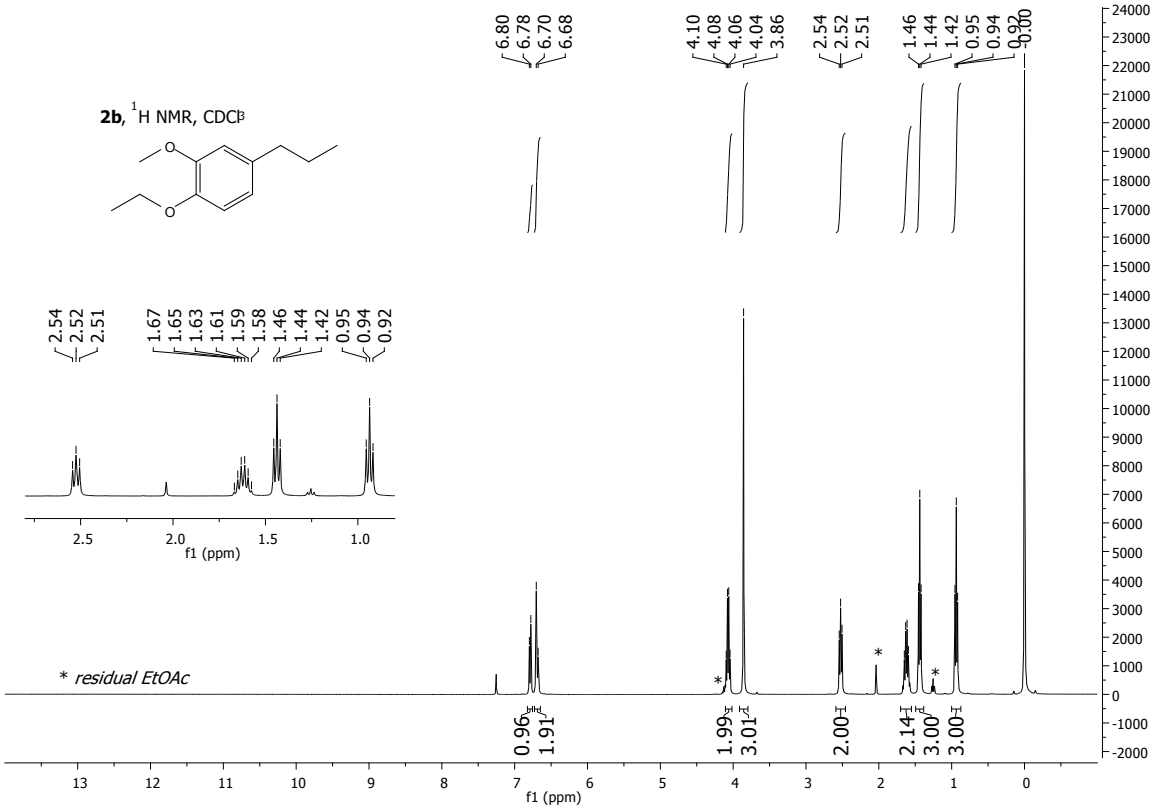


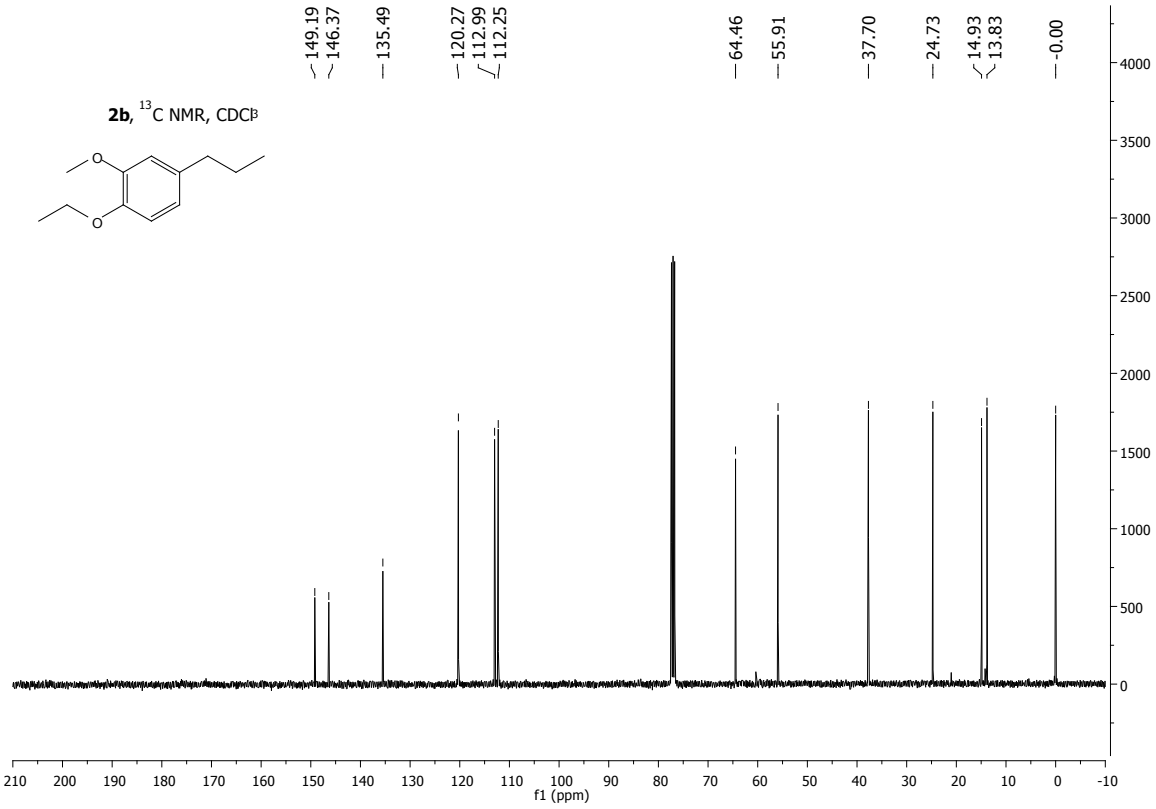
2a, APT NMR, $CDCl_3$



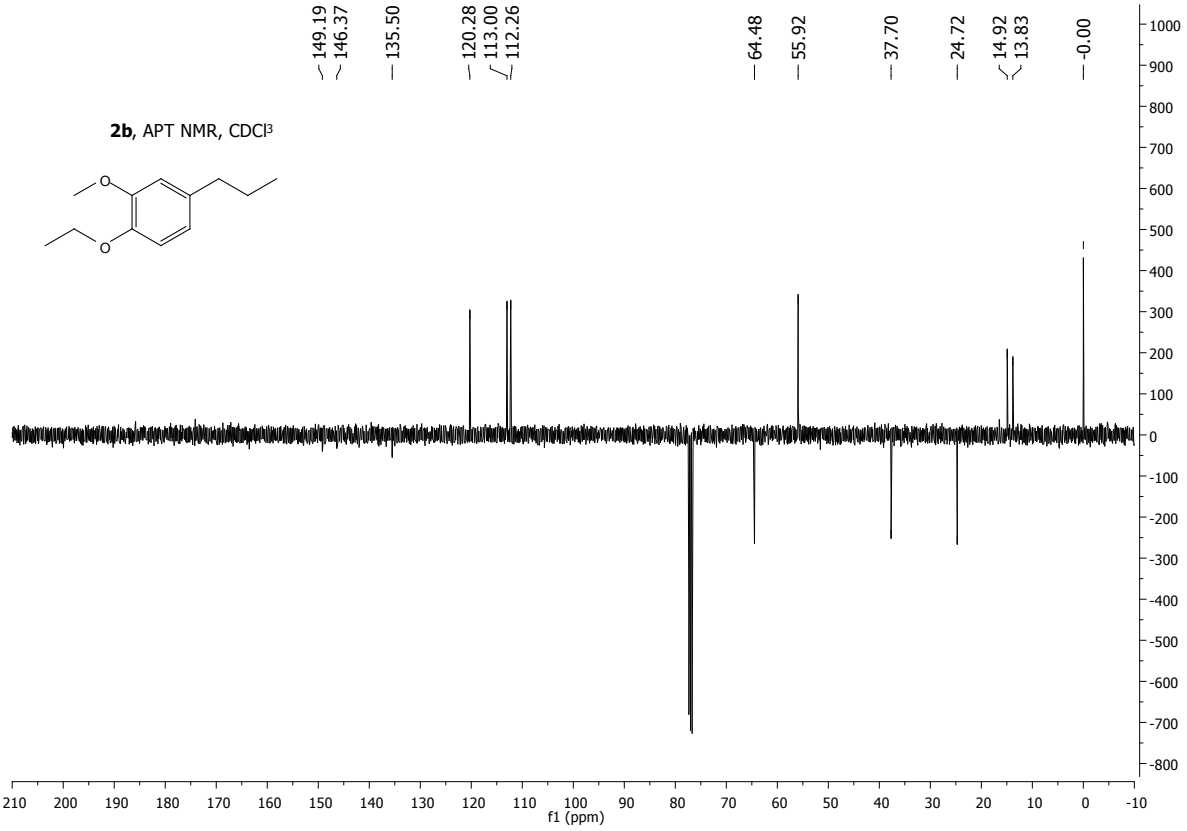
2a, COSY NMR, $CDCl_3$



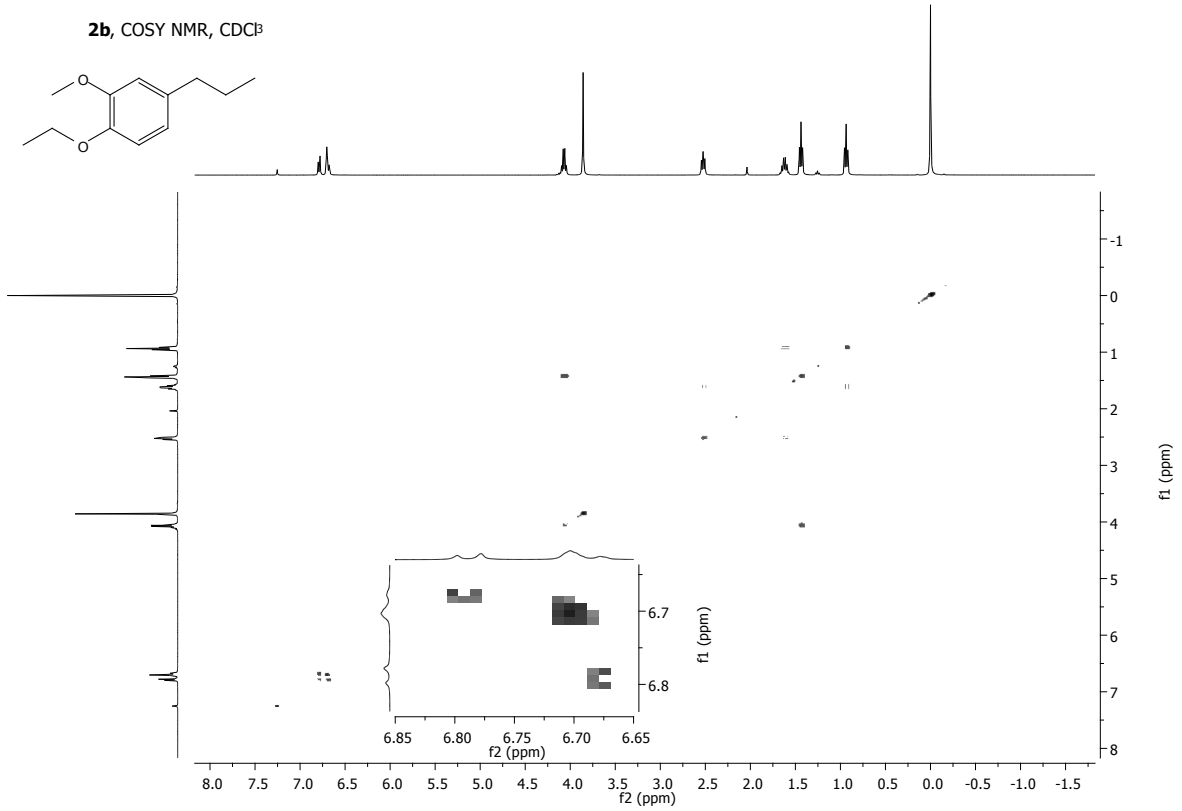

2b, 1H NMR, CDCl3
6.80
6.78
6.70
6.68
4.10
4.08
4.06
4.04
3.86
2.54
2.52
2.51
1.46
1.44
1.42
0.95
0.94
0.92
0.00
2.54
2.52
2.51
1.67
1.65
1.63
1.61
1.59
1.58
1.46
1.44
1.42
0.95
0.94
0.92
2.5
2.0
1.5
1.0
f1 (ppm)
* residual EtOAc
0.96
1.91
1.99
3.01
2.00
2.14
3.00
3.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

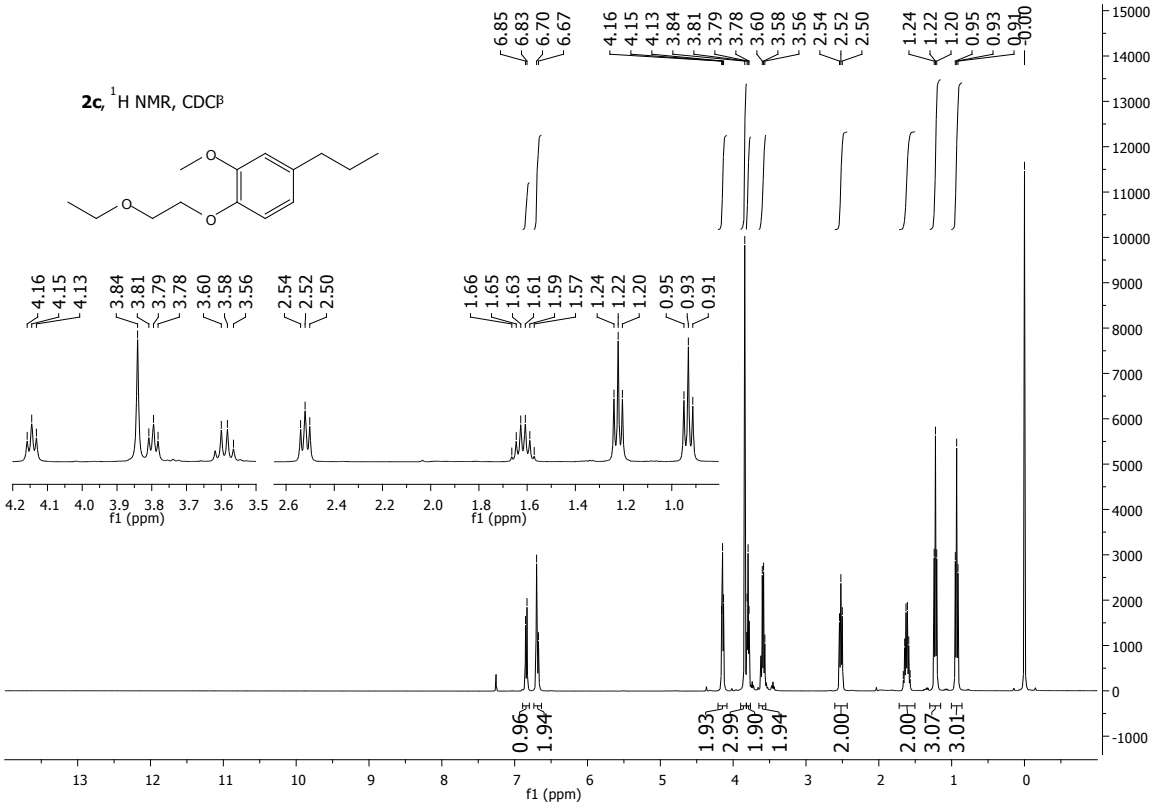

149.19
146.37
135.49
120.27
112.99
112.25
64.46
55.91
37.70
24.73
14.93
13.83
-0.00
2b, 13C NMR, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

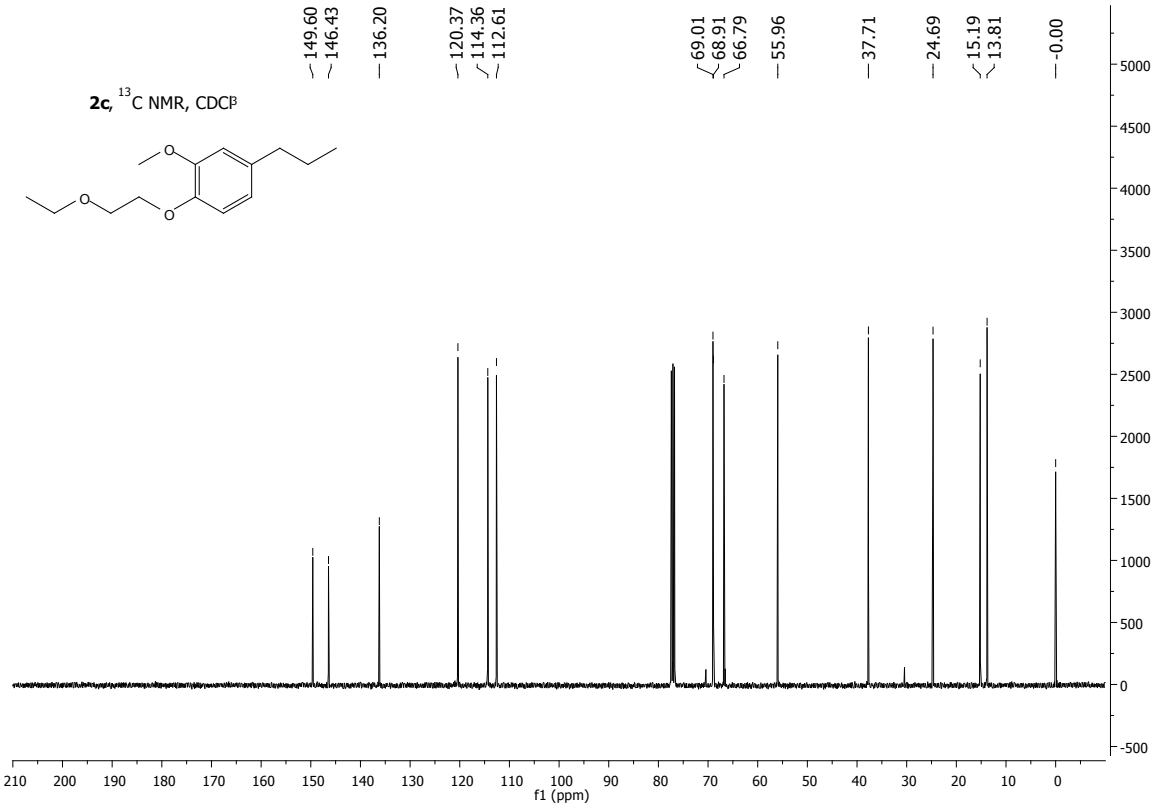
2b, APT NMR, $CDCl_3$

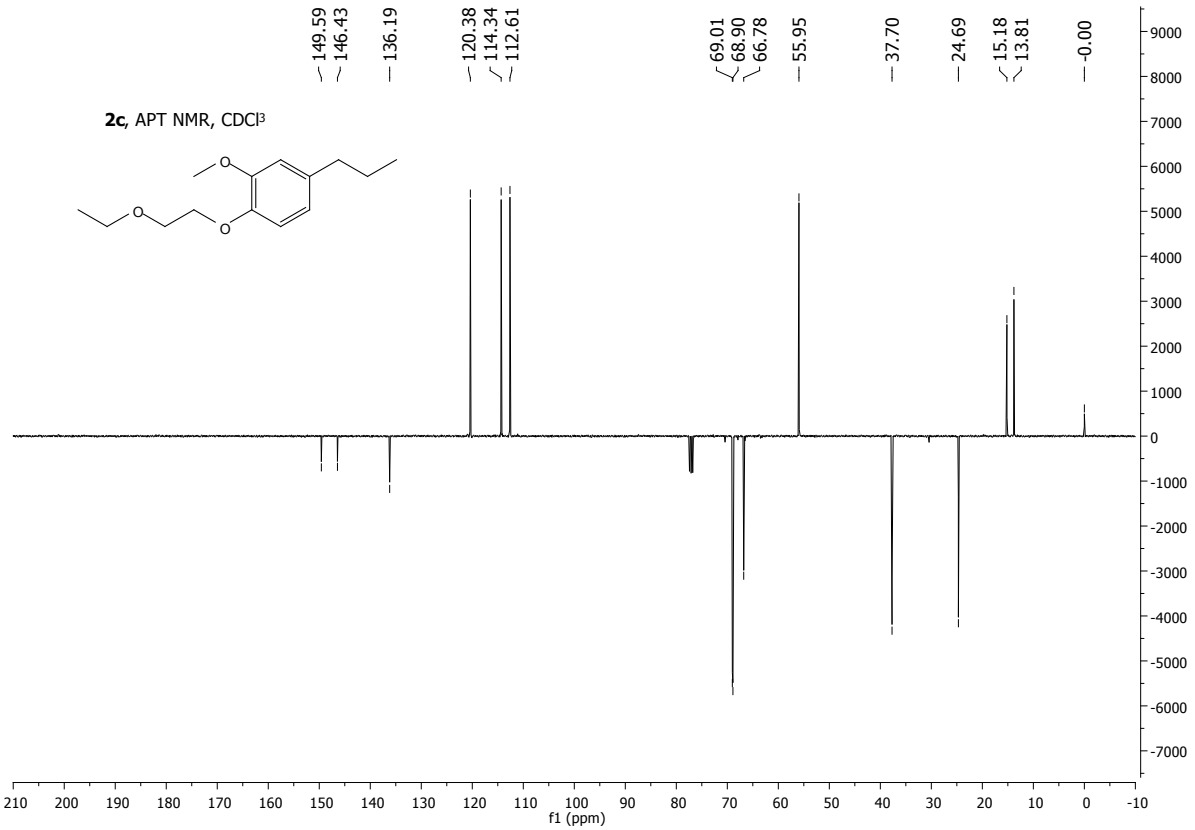


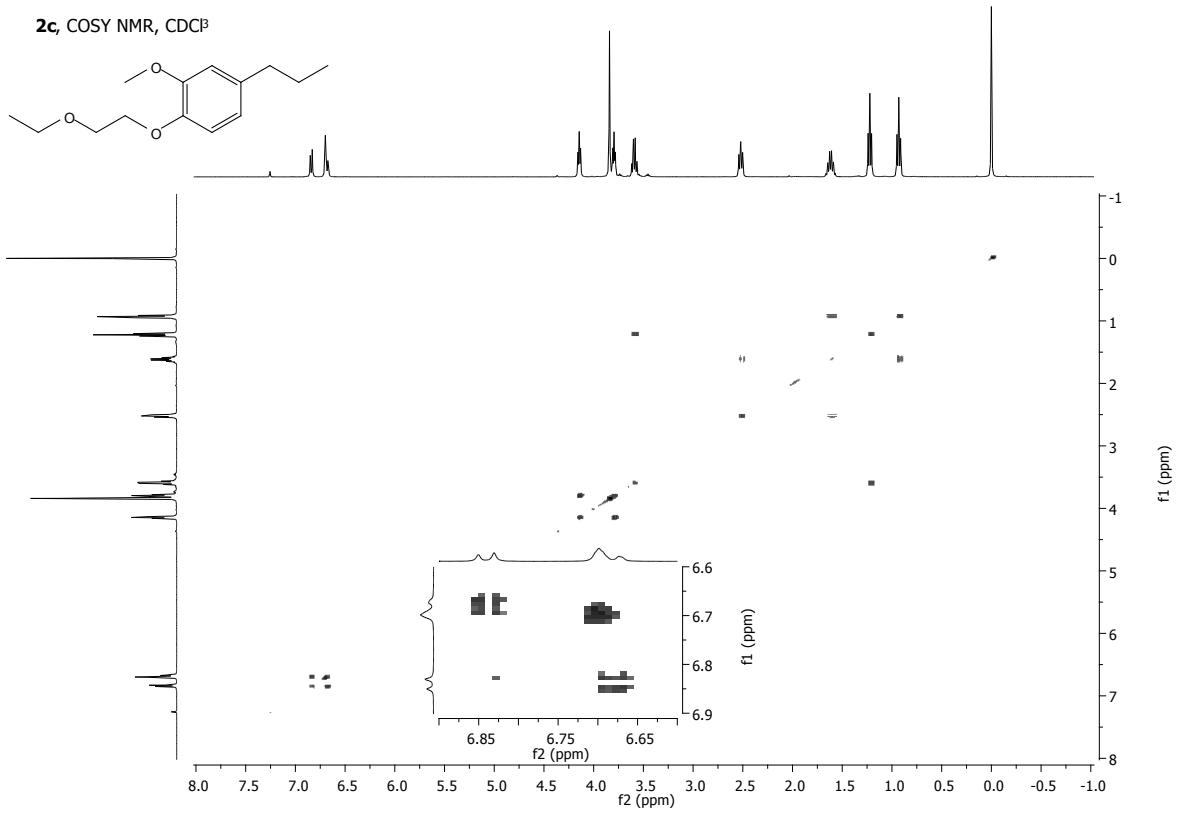
2b, COSY NMR, $CDCl_3$

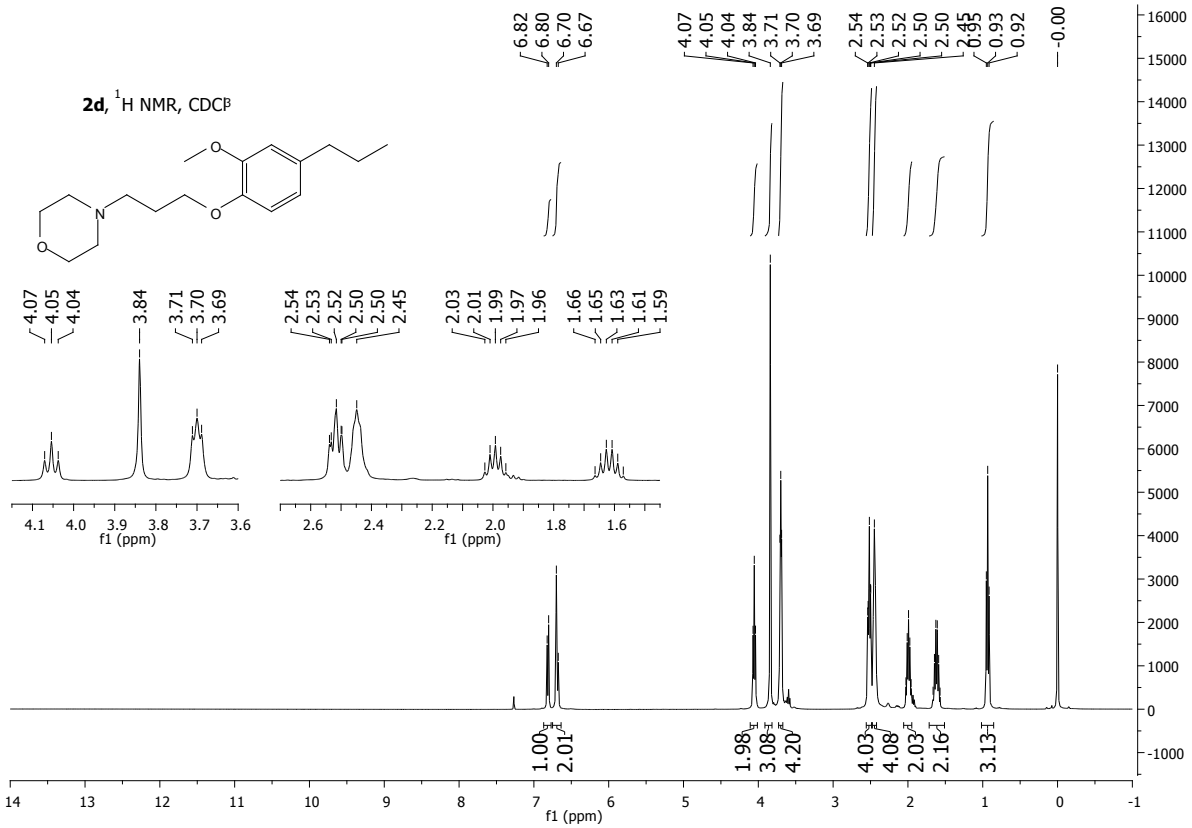


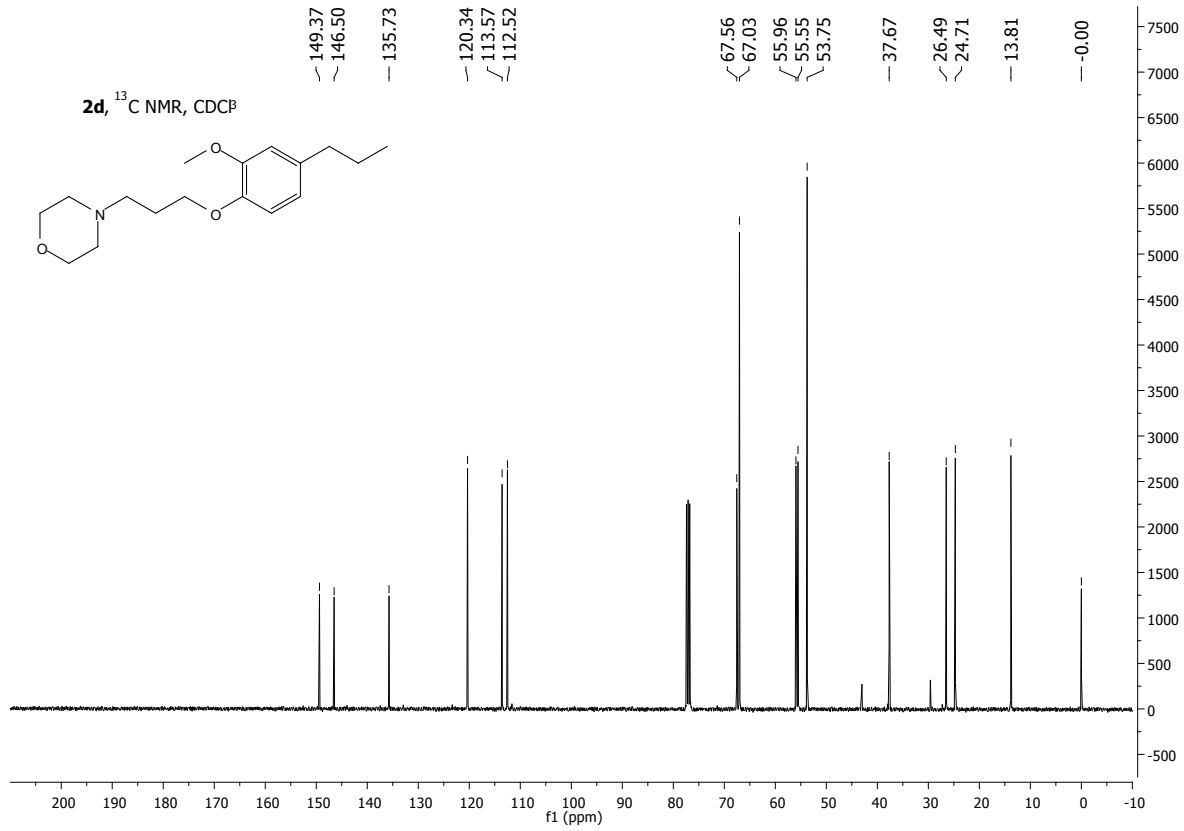

2c, 1H NMR, CDCl3
6.85
6.83
6.70
6.67
4.16
4.15
4.13
3.84
3.81
3.79
3.78
3.60
3.58
3.56
2.54
2.52
2.50
1.24
1.22
1.20
0.95
0.93
0.91
0.00
1.66
1.65
1.63
1.61
1.59
1.57
0.96
1.94
1.93
2.99
1.90
1.94
2.00
2.00
3.07
3.01
f1 (ppm)


2c, 13C NMR, CDCl3
149.60
146.43
136.20
120.37
114.36
112.61
69.01
68.91
66.79
55.96
37.71
24.69
15.19
13.81
-0.00
f1 (ppm)

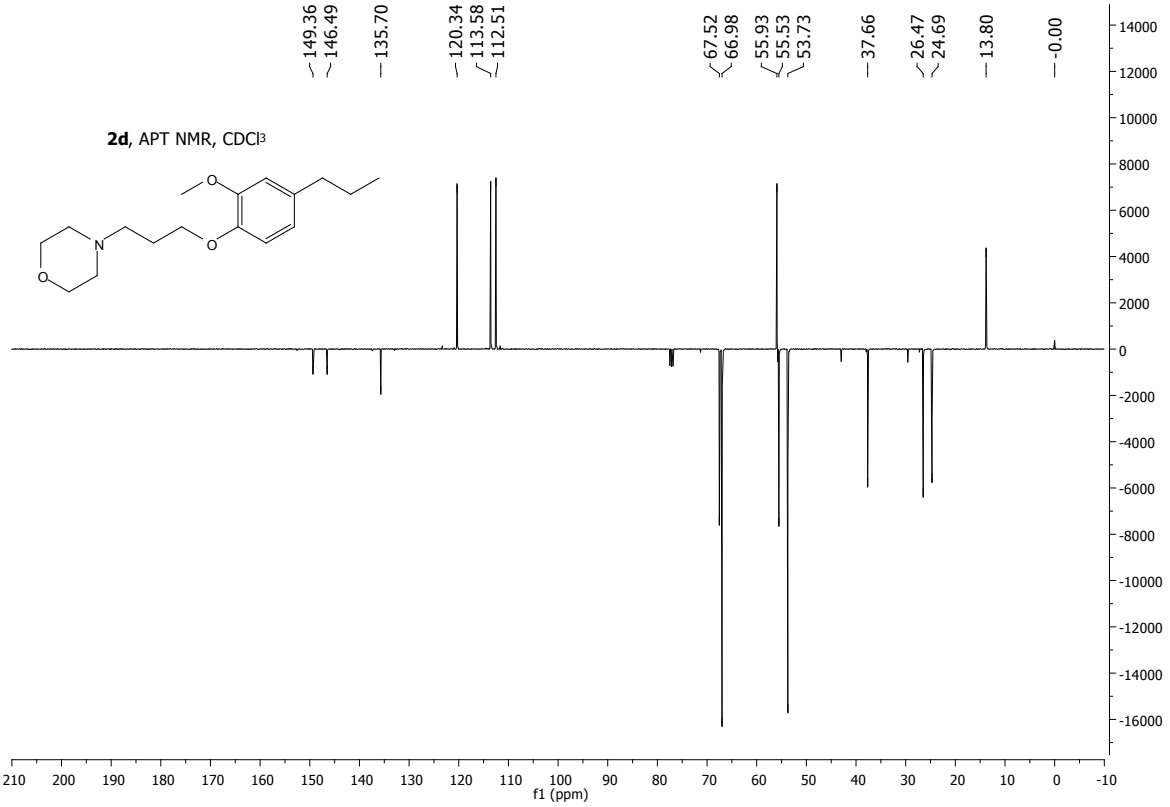

2c, APT NMR, CDCl3
149.59
146.43
136.19
120.38
114.34
112.61
69.01
68.90
66.78
55.95
37.70
24.69
15.18
13.81
-0.00
f1 (ppm)


2c, COSY NMR, CDCl3
f1 (ppm)
f2 (ppm)

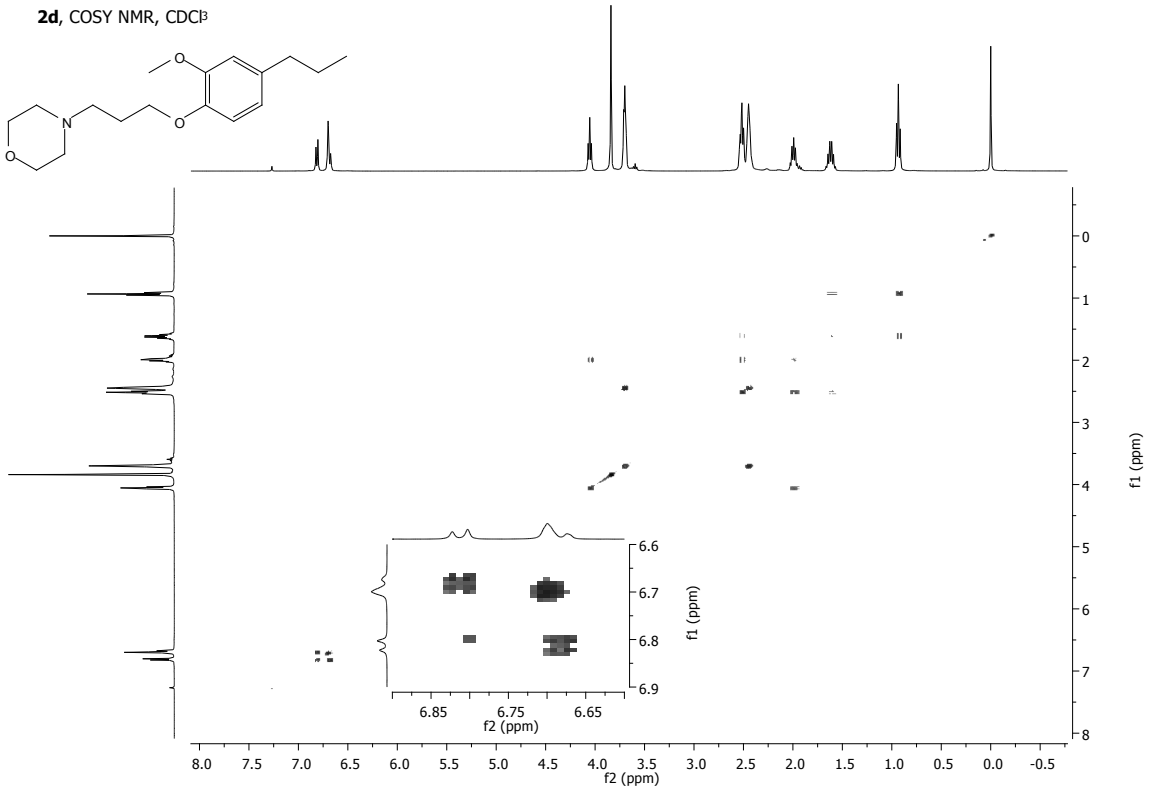

2d, 1H NMR, CDCl3
6.82
6.80
6.70
6.67
4.07
4.05
4.04
3.84
3.71
3.70
3.69
2.54
2.53
2.52
2.50
2.50
2.45
0.95
0.93
0.92
-0.00
2.03
2.01
1.99
1.97
1.96
1.66
1.65
1.63
1.61
1.59
1.00
2.01
1.98
3.08
4.20
4.03
4.08
2.03
2.16
3.13
f1 (ppm)

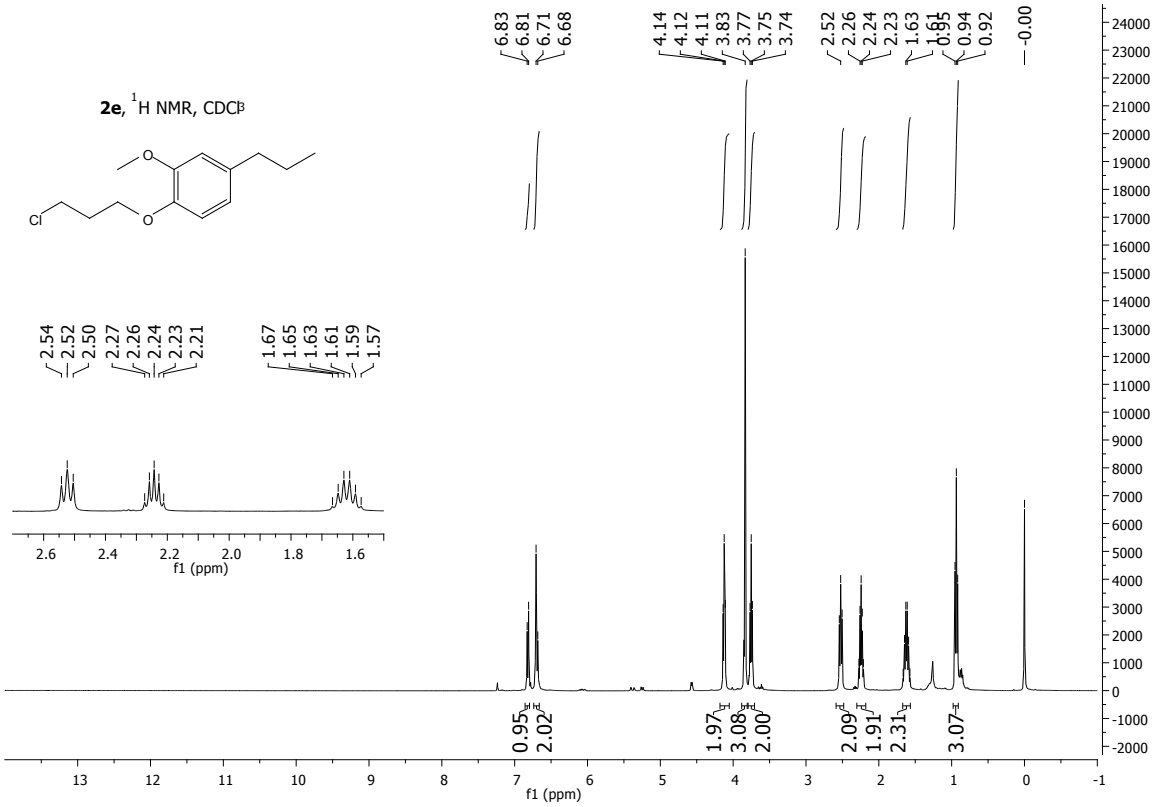

2d, 13C NMR, CDCl3
149.37
146.50
135.73
120.34
113.57
112.52
67.56
67.03
55.96
55.55
53.75
37.67
26.49
24.71
13.81
-0.00
f1 (ppm)

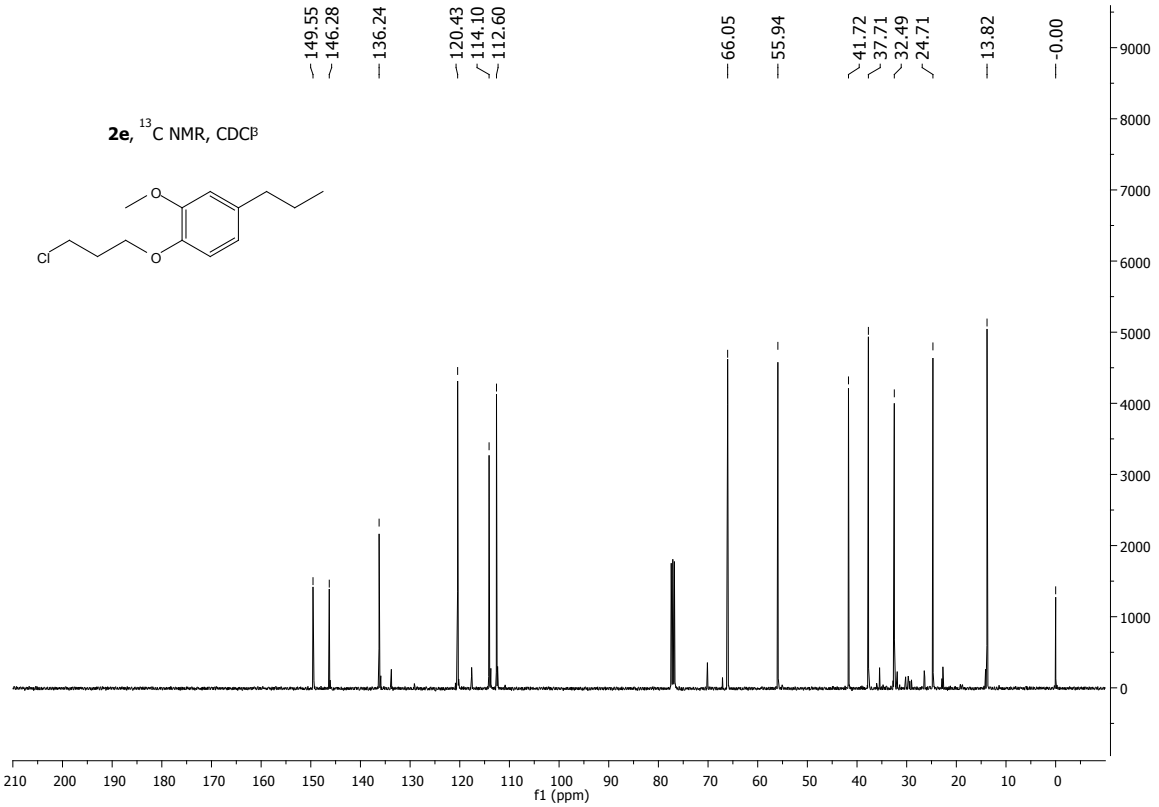
2d, APT NMR, $CDCl_3$

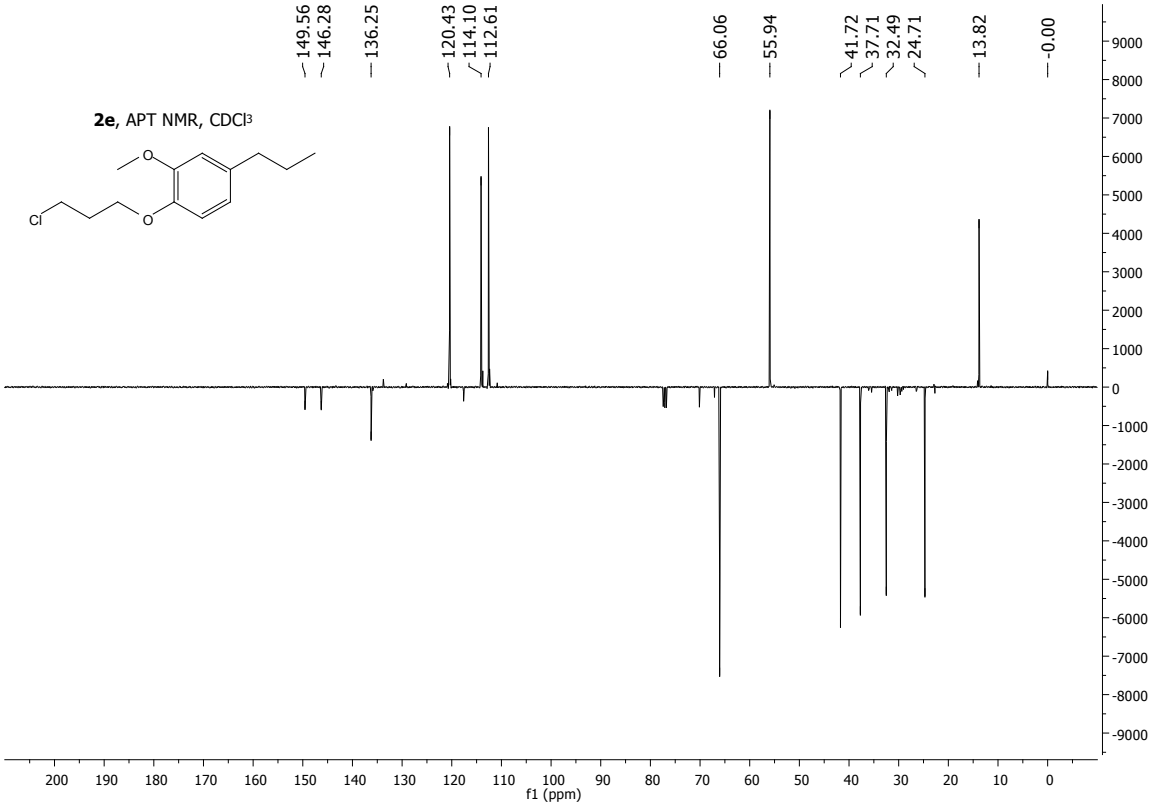


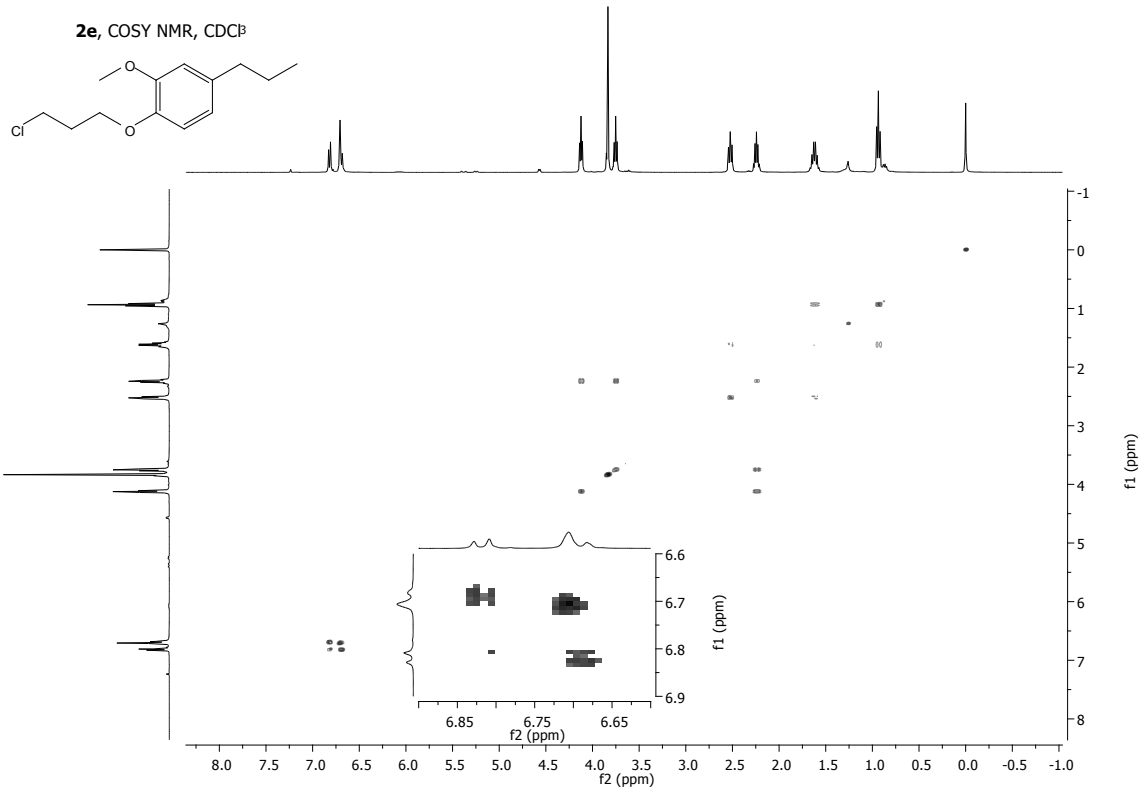
2d, COSY NMR, $CDCl_3$



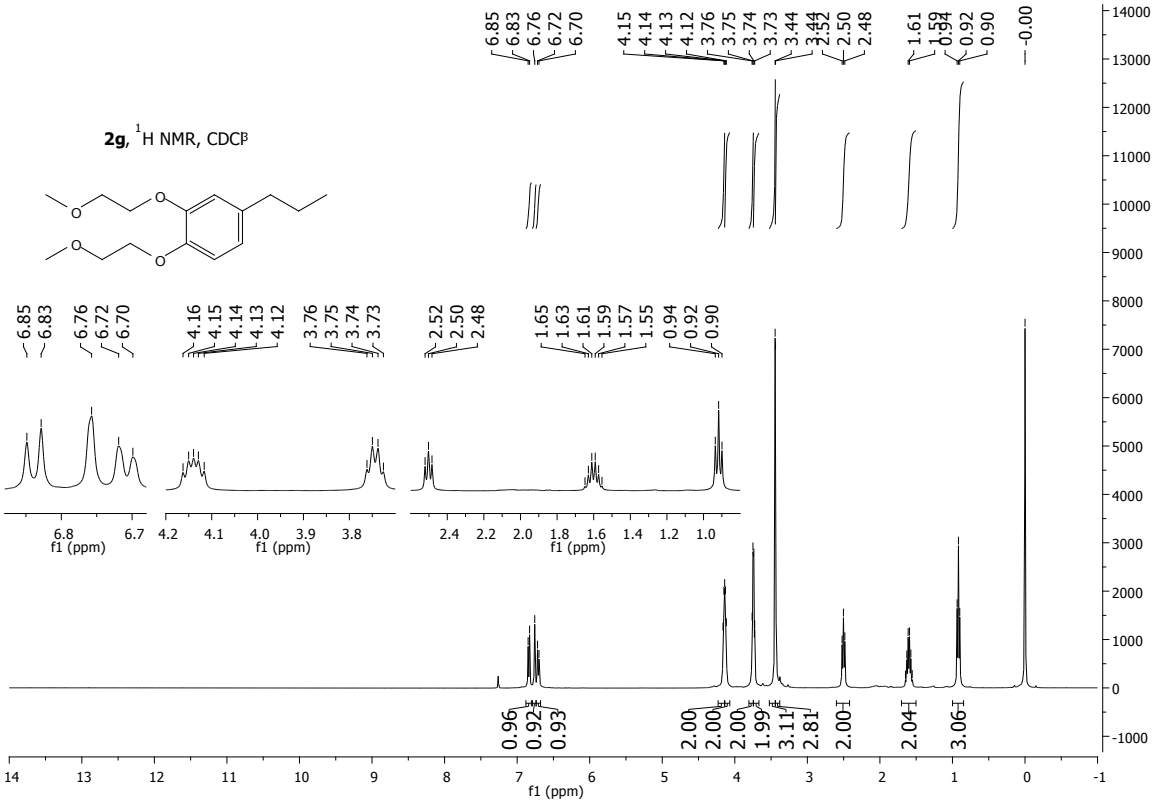

2e, 1H NMR, CDCl3
6.83
6.81
6.71
6.68
4.14
4.12
4.11
3.83
3.77
3.75
3.74
2.52
2.26
2.24
2.23
1.63
1.61
0.95
0.94
0.92
-0.00
2.54
2.52
2.50
2.27
2.26
2.24
2.23
2.21
1.67
1.65
1.63
1.61
1.59
1.57
0.95
2.02
1.97
3.08
2.00
2.09
1.91
2.31
3.07
f1 (ppm)


2e, 13C NMR, CDCl3
149.55
146.28
136.24
120.43
114.10
112.60
66.05
55.94
41.72
37.71
32.49
24.71
13.82
-0.00
f1 (ppm)

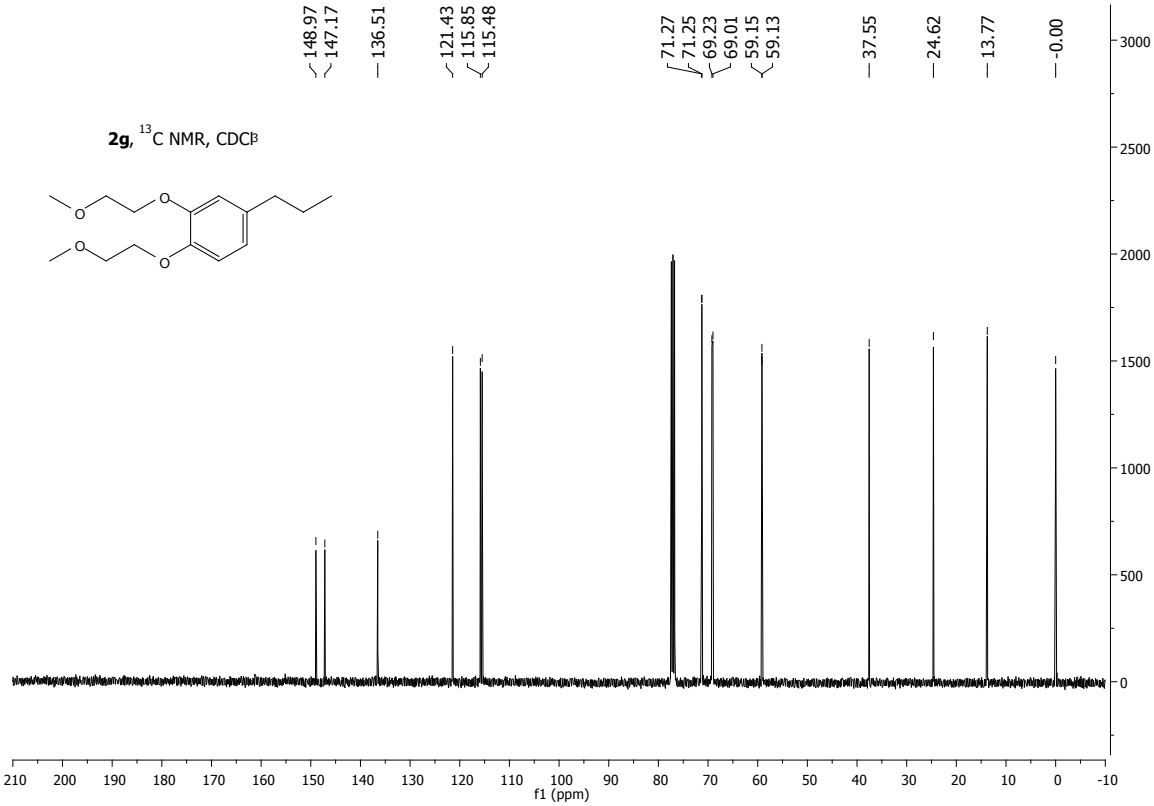

2e, APT NMR, CDCl3
149.56
146.28
136.25
120.43
114.10
112.61
66.06
55.94
41.72
37.71
32.49
24.71
13.82
-0.00
f1 (ppm)

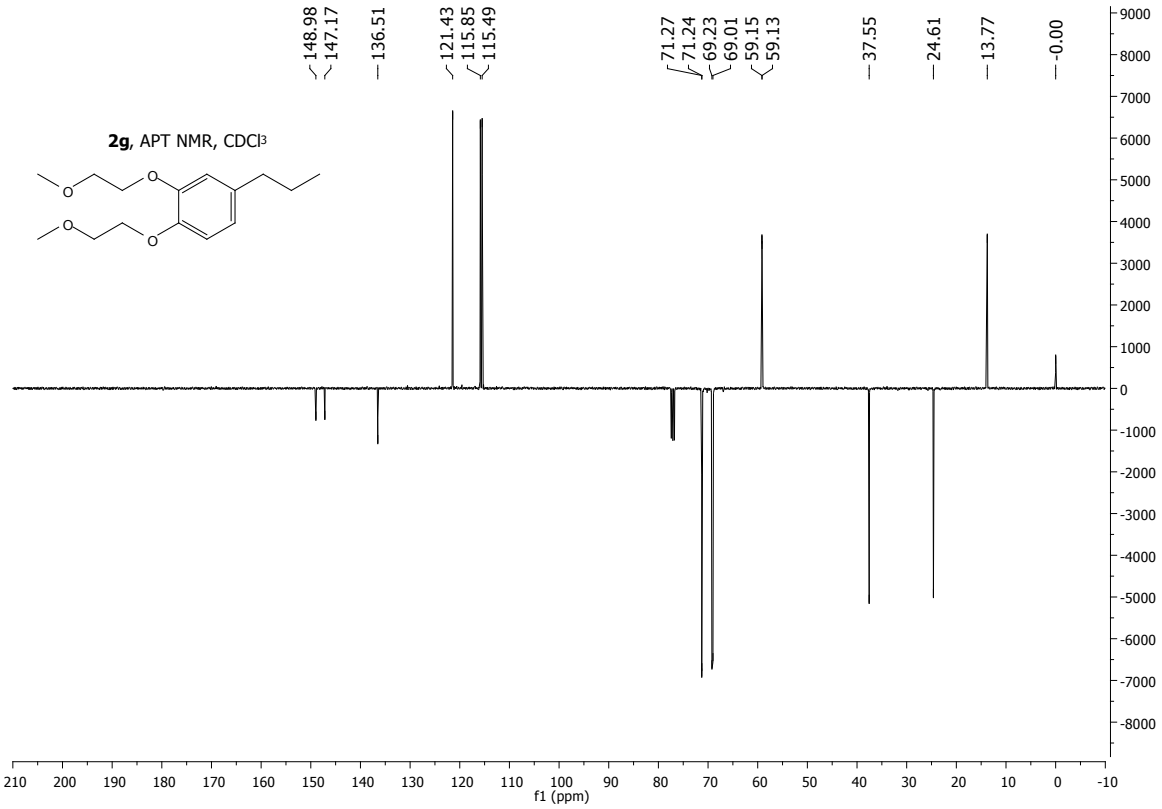

2e, COSY NMR, CDCl3
f1 (ppm)
f2 (ppm)

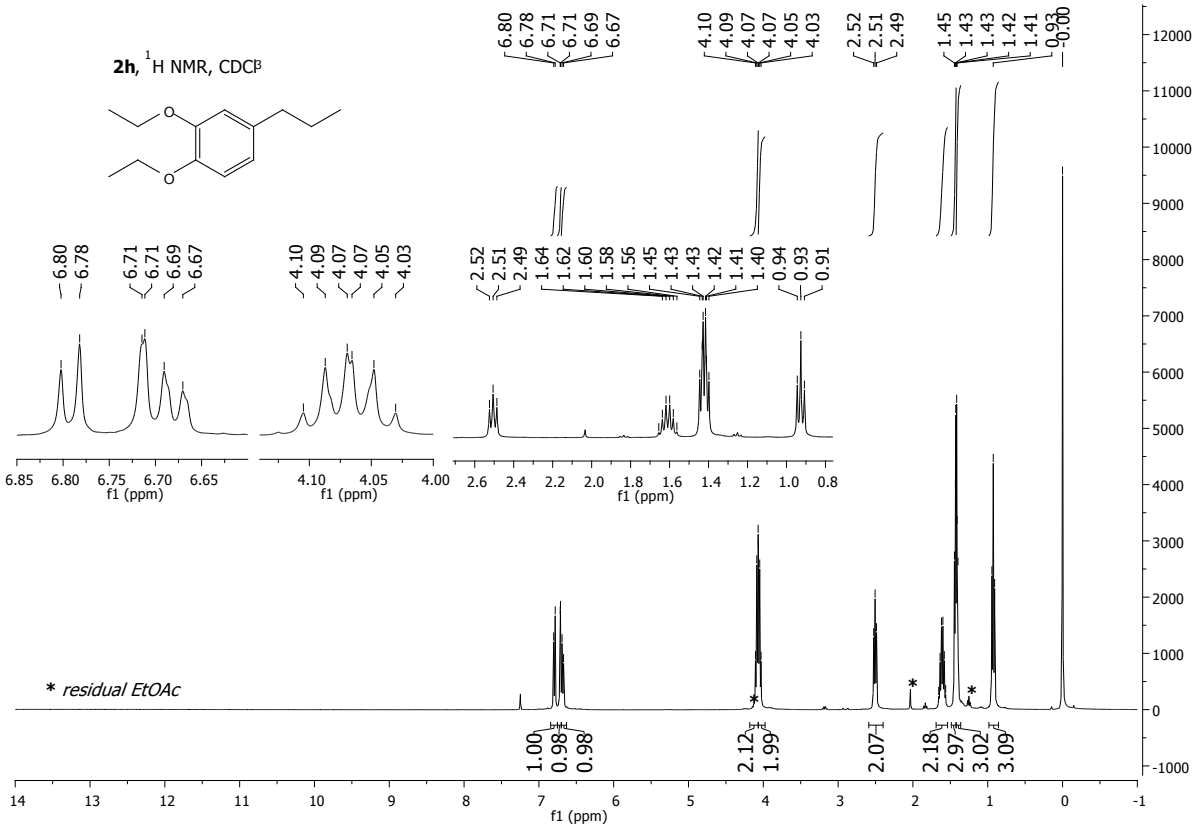
2g, ^{1}H NMR, $CDCl_3$

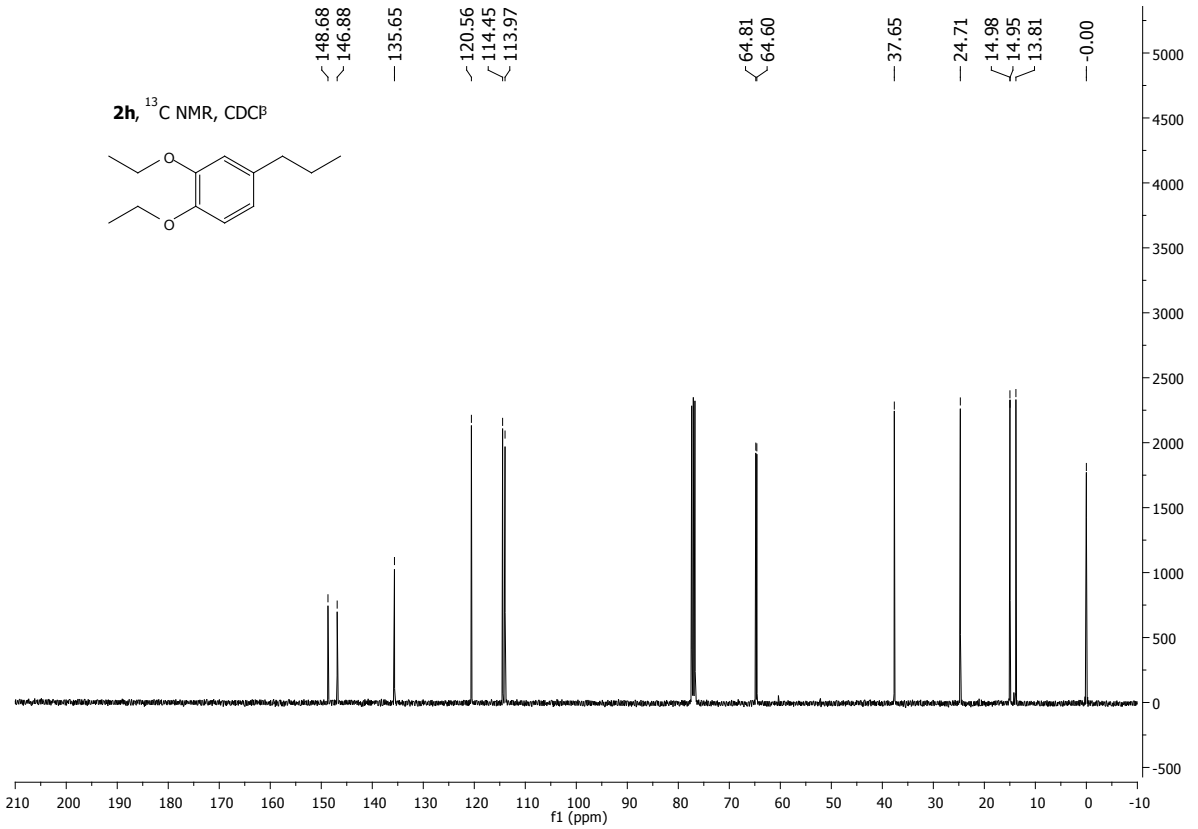


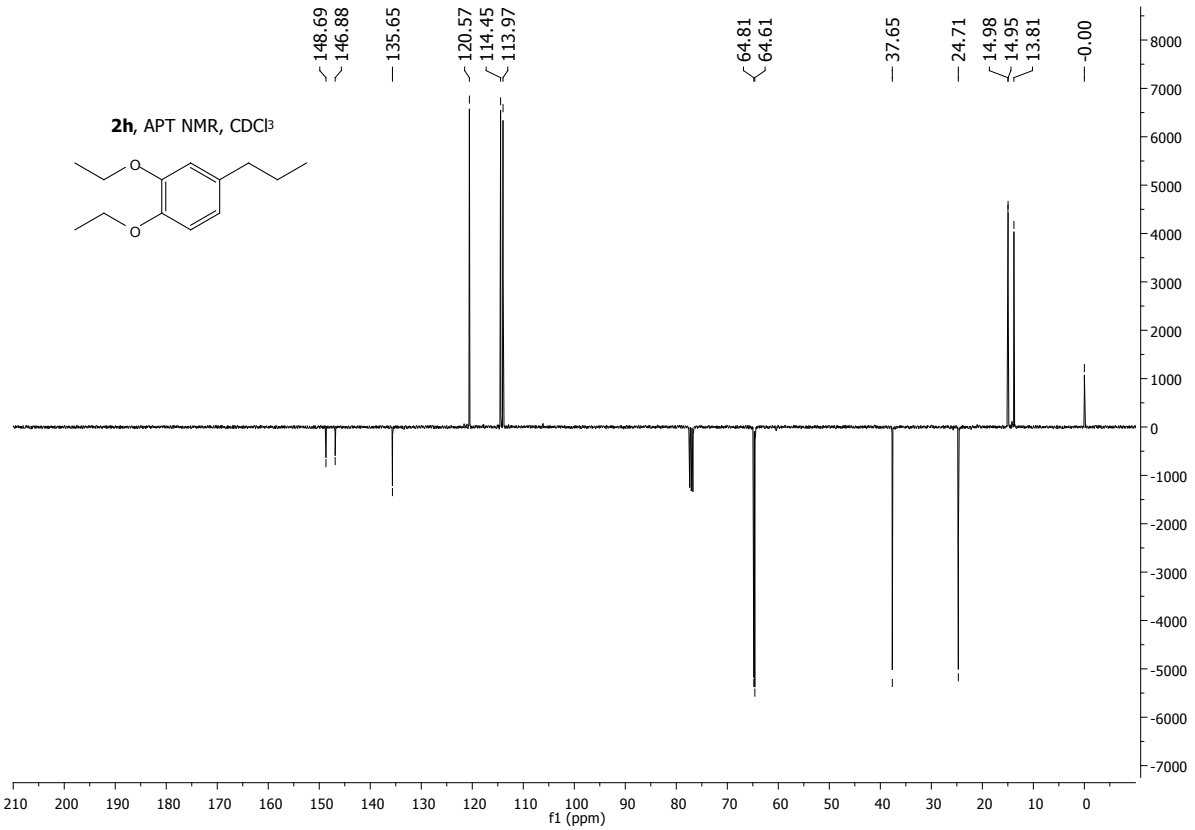
2g, ^{13}C NMR, $CDCl_3$

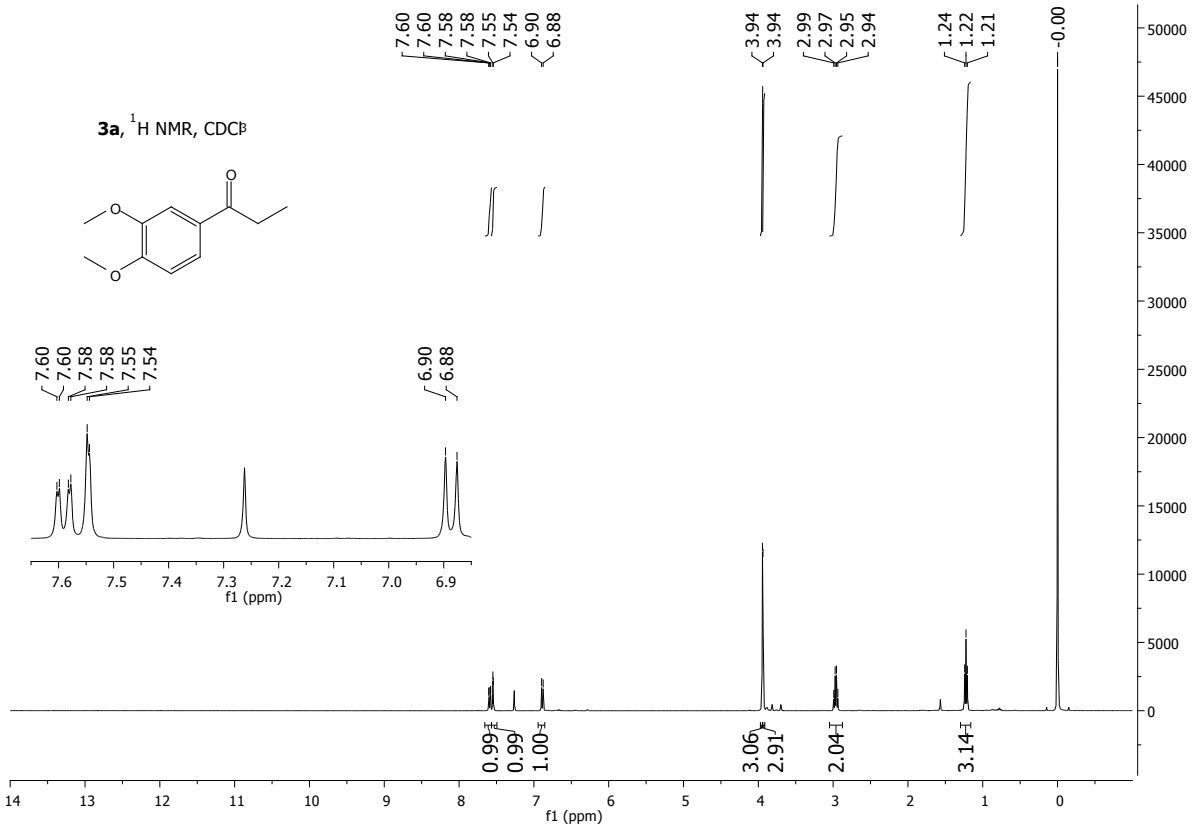


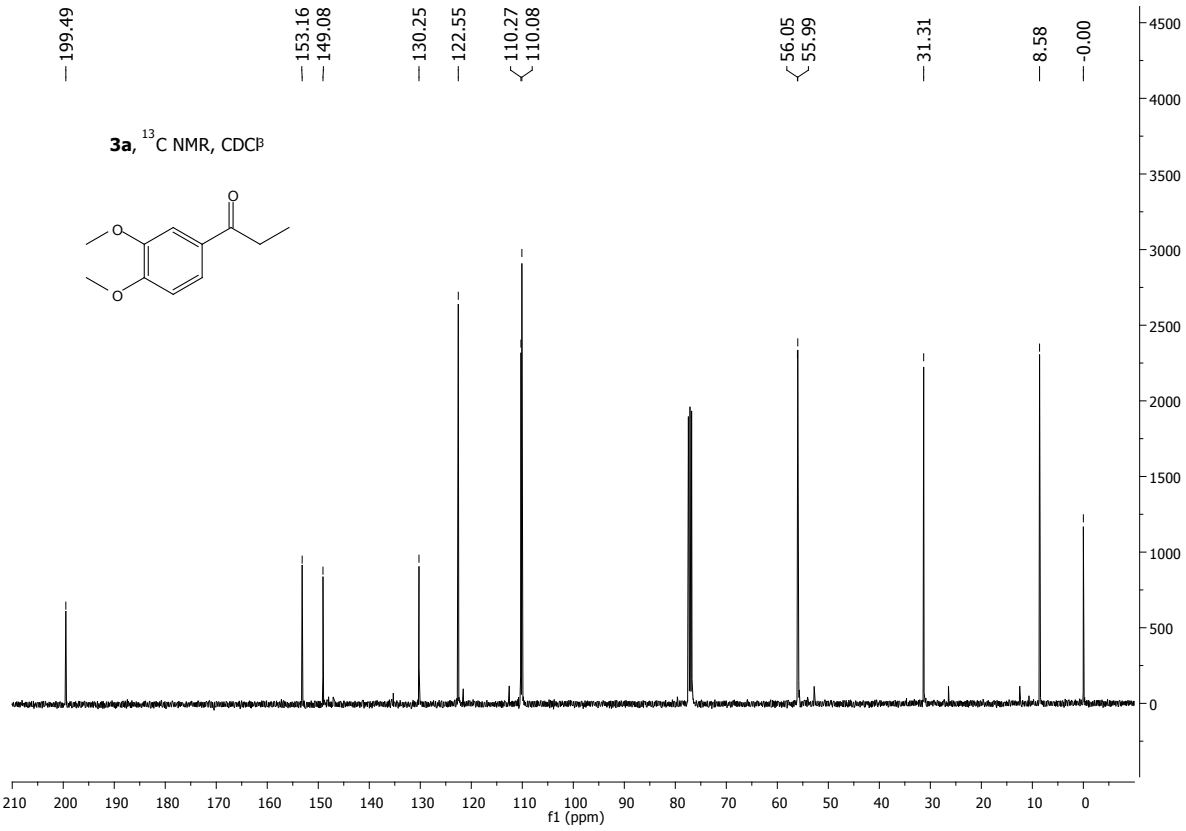

148.98
147.17
136.51
121.43
115.85
115.49
71.27
71.24
69.23
69.01
59.15
59.13
37.55
24.61
13.77
-0.00
2g, APT NMR, CDCl3
f1 (ppm)

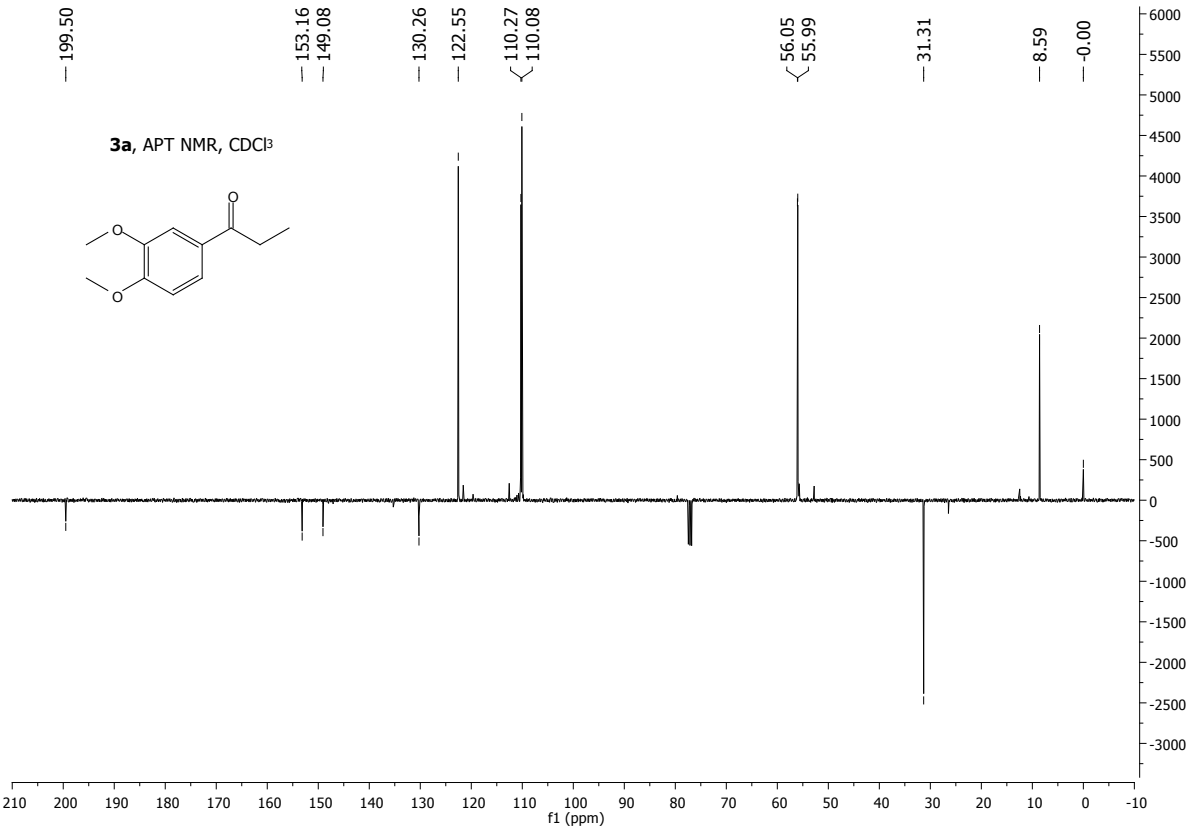

2h, 1H NMR, CDCl3
* residual EtOAc
f1 (ppm)

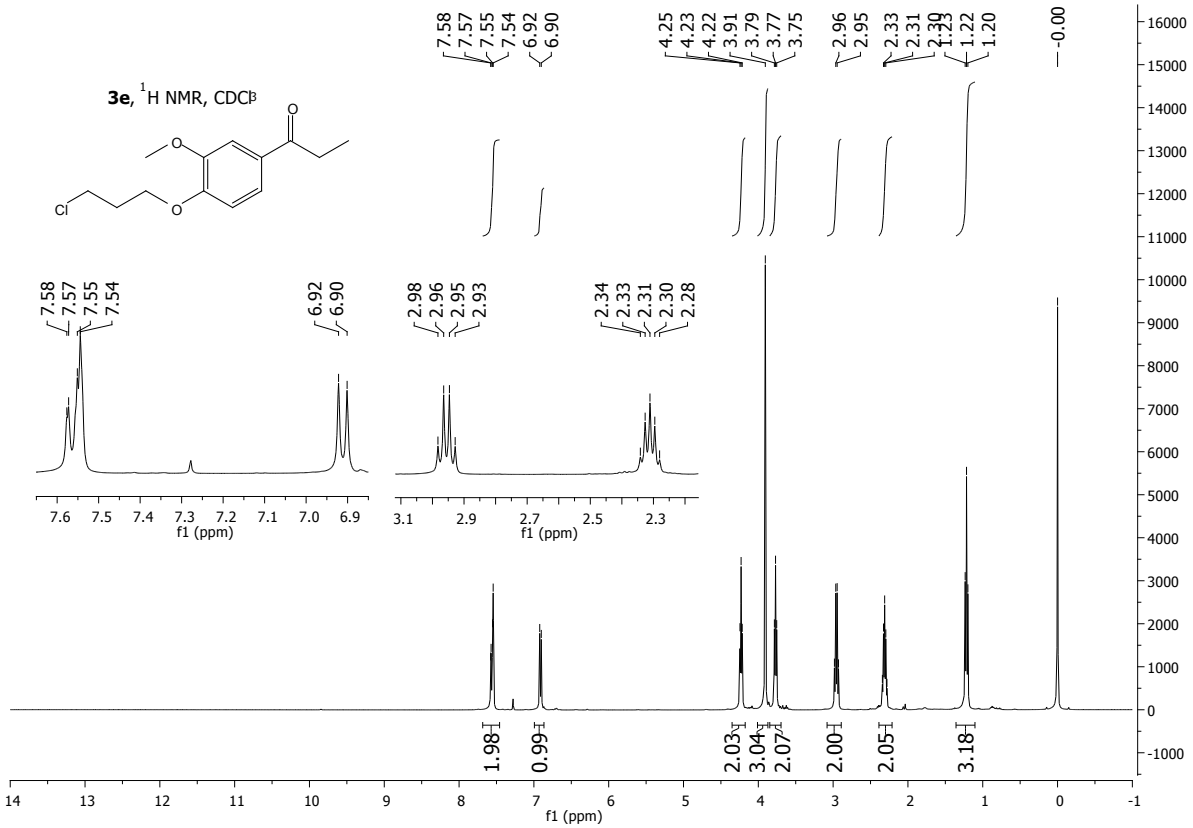

2h, 13C NMR, CDCl3
f1 (ppm)

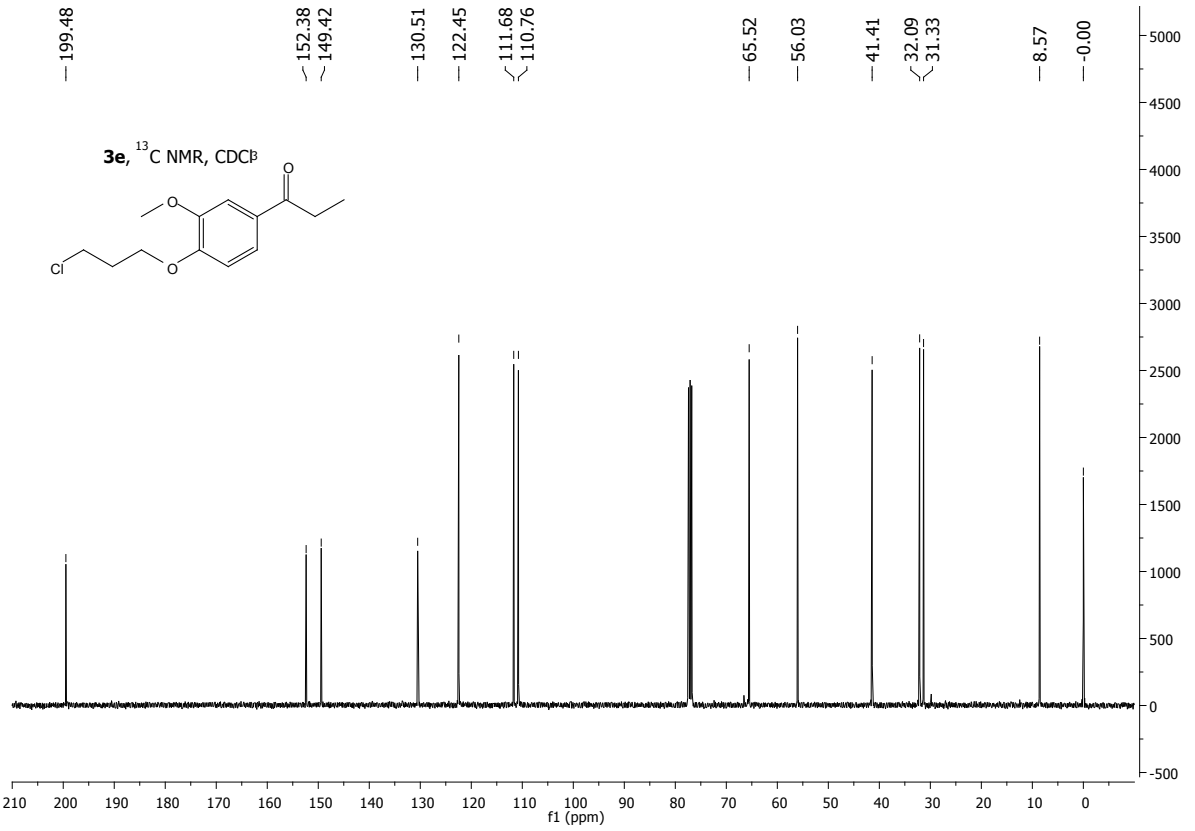

2h, APT NMR, CDCl3
148.69
146.88
135.65
120.57
114.45
113.97
64.81
64.61
37.65
24.71
14.98
14.95
13.81
-0.00
f1 (ppm)

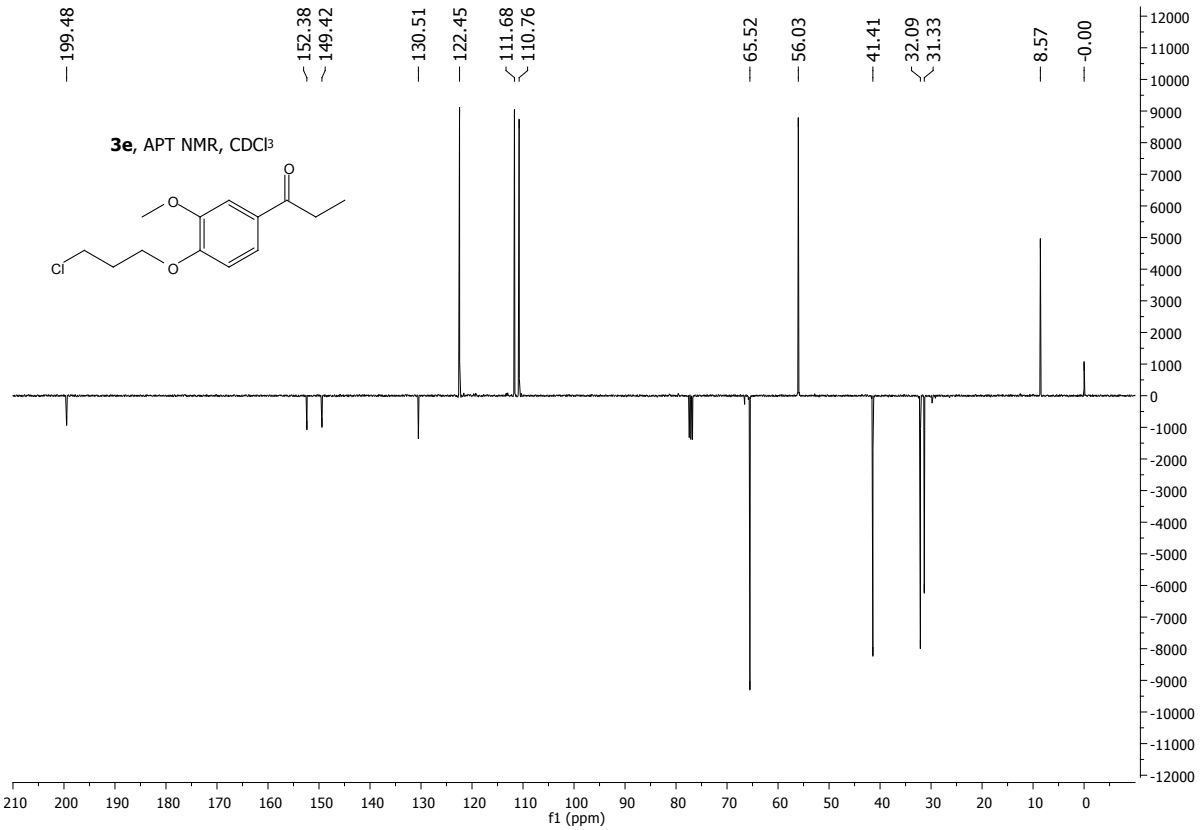

3a, 1H NMR, CDCl3
7.60
7.60
7.58
7.58
7.55
7.54
6.90
6.88
3.94
3.94
2.99
2.97
2.95
2.94
1.24
1.22
1.21
-0.00
0.99
0.99
1.00
3.06
2.91
2.04
3.14
f1 (ppm)

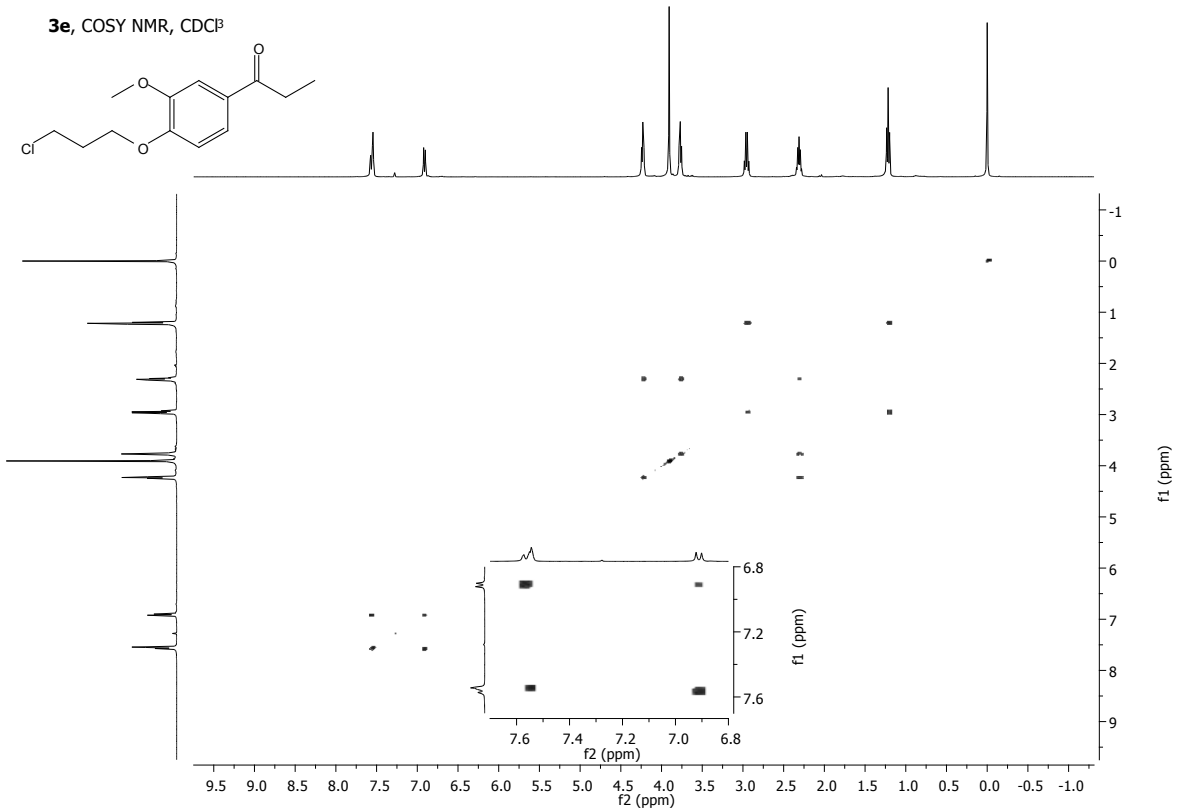

3a, 13C NMR, CDCl3
199.49
153.16
149.08
130.25
122.55
110.27
110.08
56.05
55.99
31.31
8.58
-0.00
f1 (ppm)

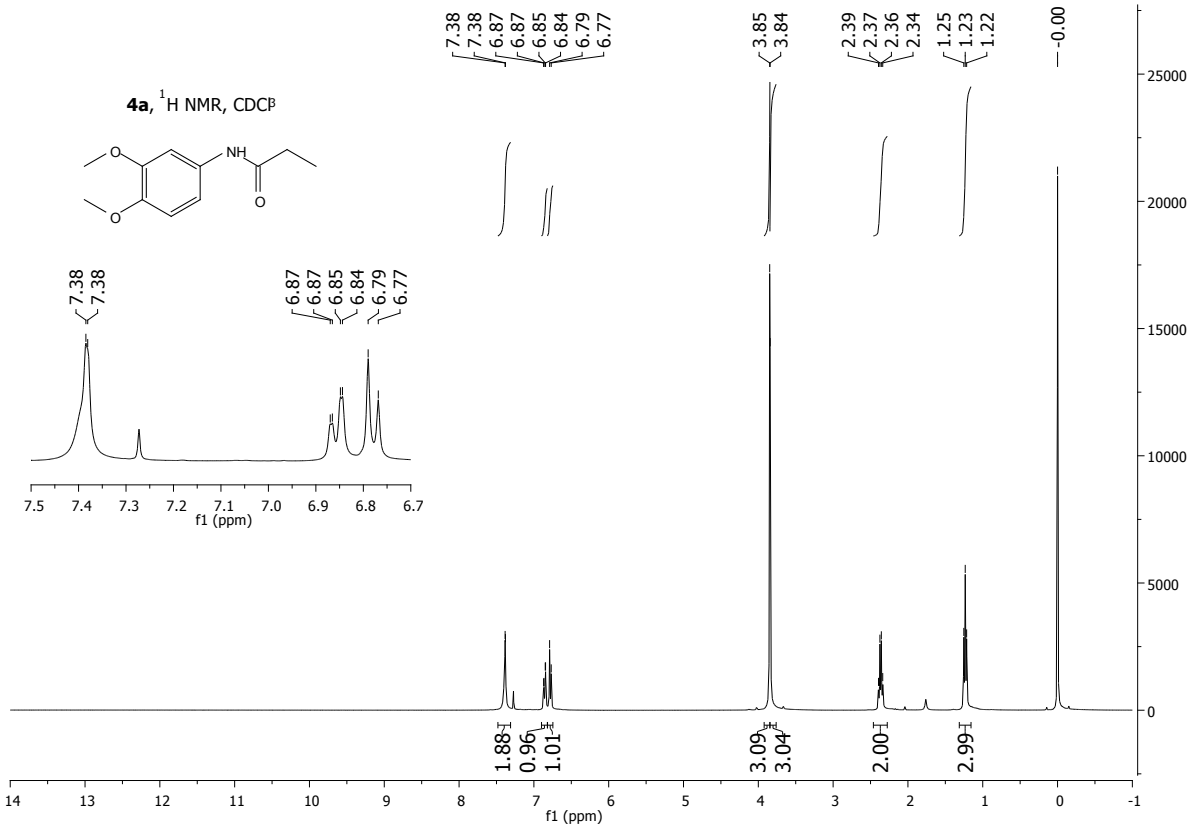

199.50
153.16
149.08
130.26
122.55
110.27
110.08
56.05
55.99
31.31
8.59
-0.00
3a, APT NMR, CDCl3
O
O
O
f1 (ppm)

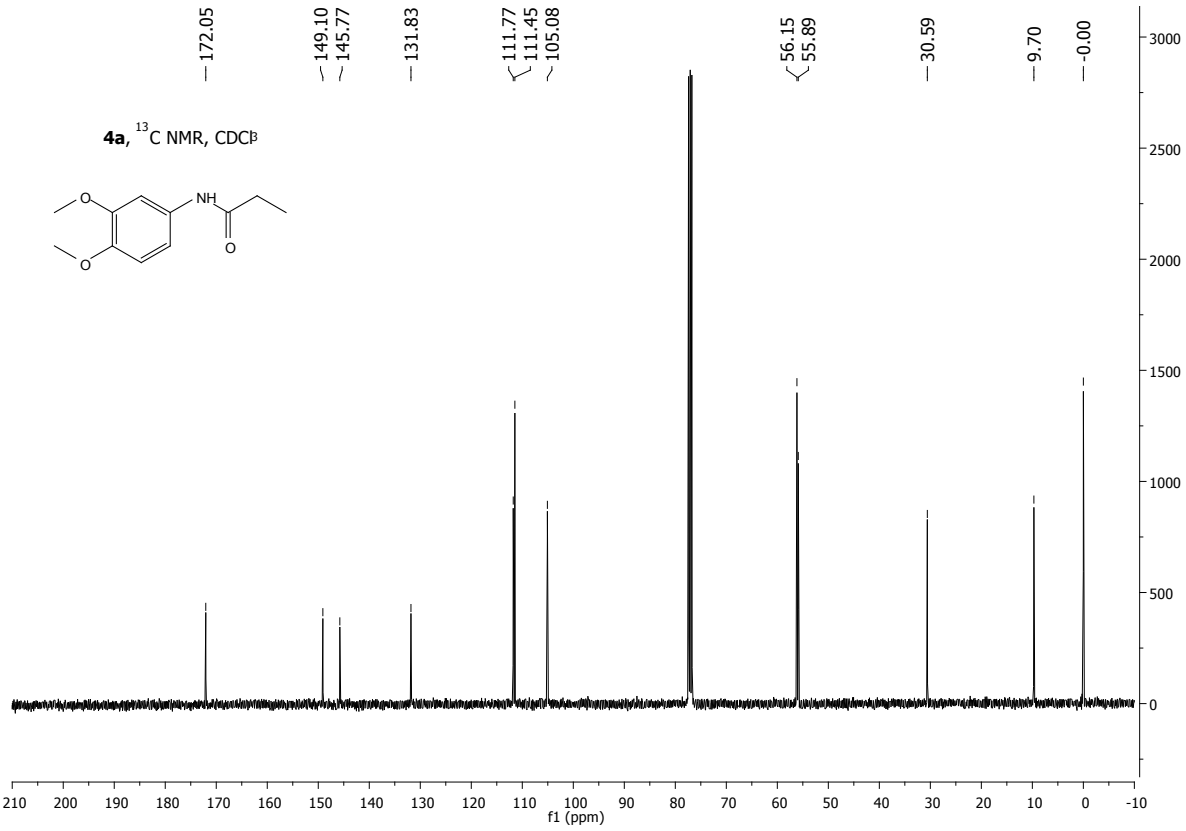

3e, 1H NMR, CDCl3
7.58
7.57
7.55
7.54
6.92
6.90
4.25
4.23
4.22
3.91
3.79
3.77
3.75
2.96
2.95
2.33
2.31
1.22
1.20
-0.00
2.98
2.96
2.95
2.93
2.34
2.33
2.31
2.30
2.28
1.98
0.99
2.03
3.04
2.07
2.00
2.05
3.18
f1 (ppm)

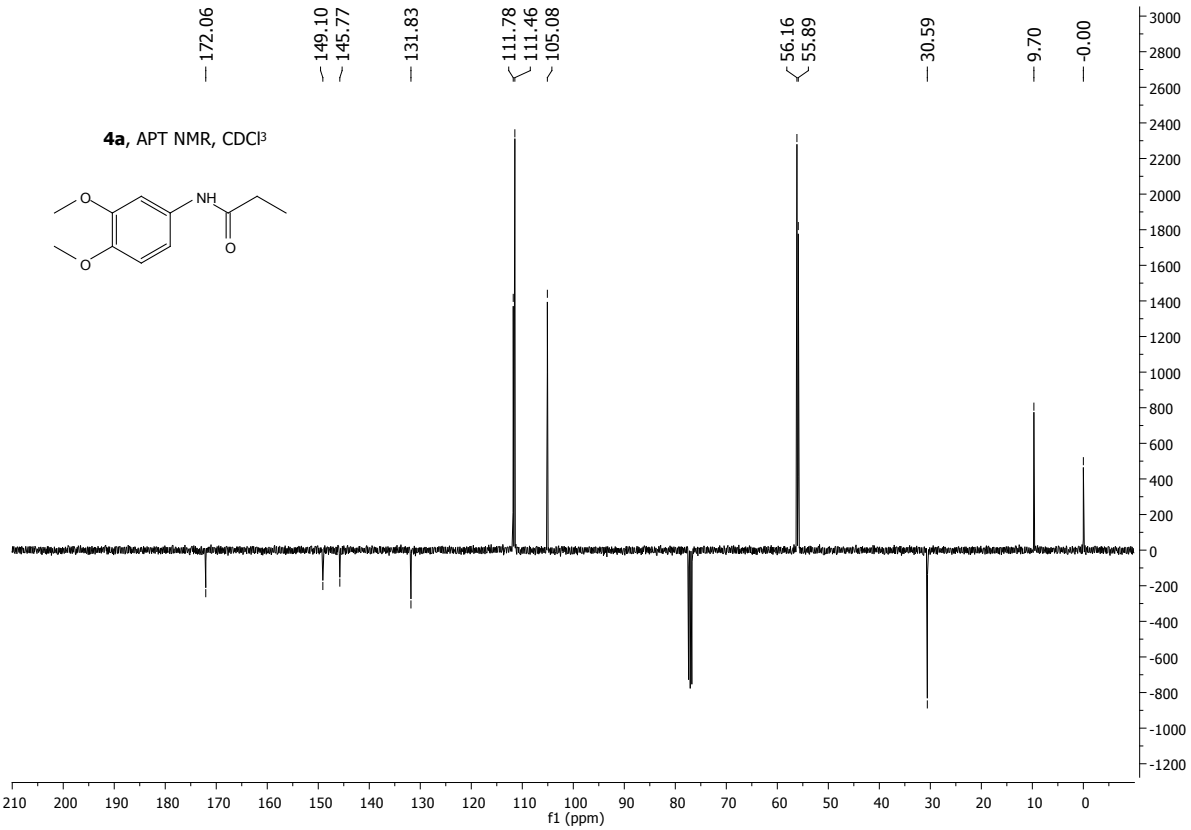

3e, 13C NMR, CDCl3
199.48
152.38
149.42
130.51
122.45
111.68
110.76
65.52
56.03
41.41
32.09
31.33
8.57
-0.00
f1 (ppm)

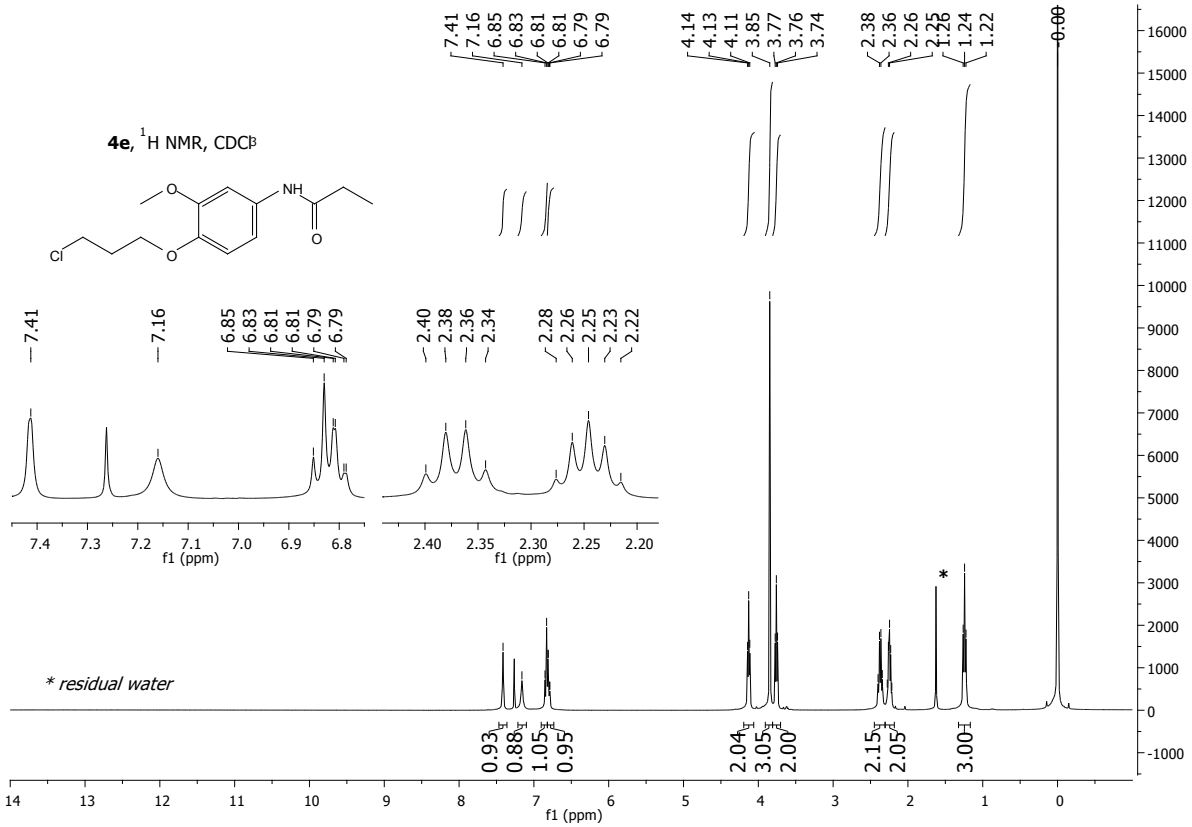

3e, APT NMR, CDCl3
199.48
152.38
149.42
130.51
122.45
111.68
110.76
65.52
56.03
41.41
32.09
31.33
8.57
-0.00
f1 (ppm)

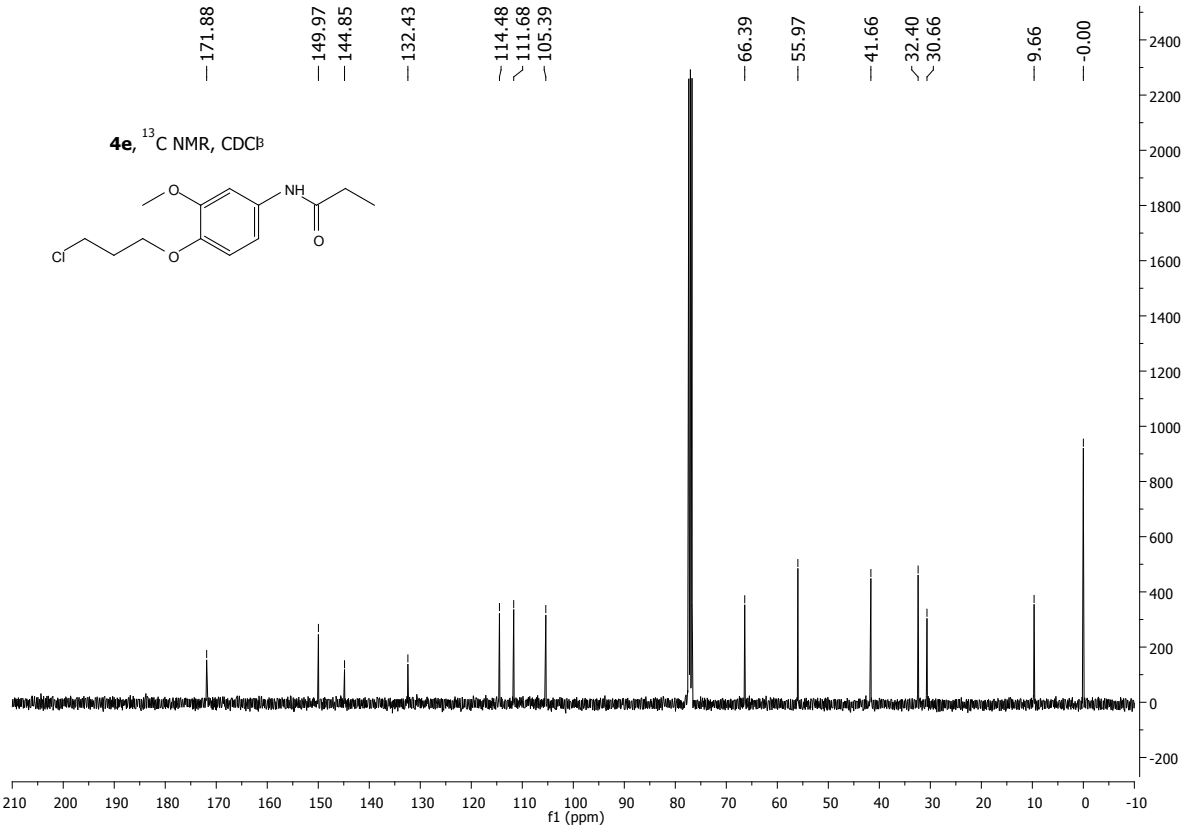

3e, COSY NMR, CDCl3
f1 (ppm)
f2 (ppm)

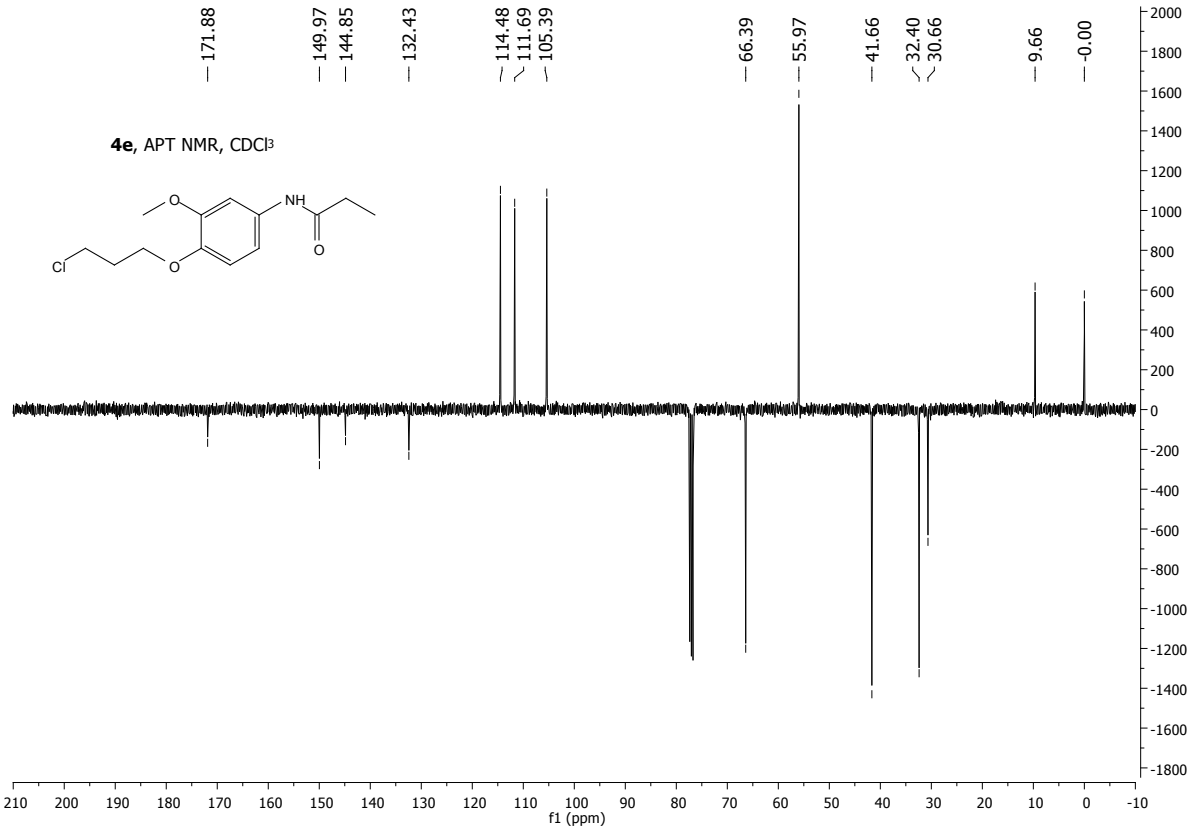

4a, 1H NMR, CDCl3
7.38
7.38
6.87
6.87
6.85
6.84
6.79
6.77
3.85
3.84
2.39
2.37
2.36
2.34
1.25
1.23
1.22
-0.00
1.88
0.96
1.01
3.09
3.04
2.00
2.99
f1 (ppm)


4a, 13C NMR, CDCl3
172.05
149.10
145.77
131.83
111.77
111.45
105.08
56.15
55.89
30.59
9.70
-0.00
f1 (ppm)

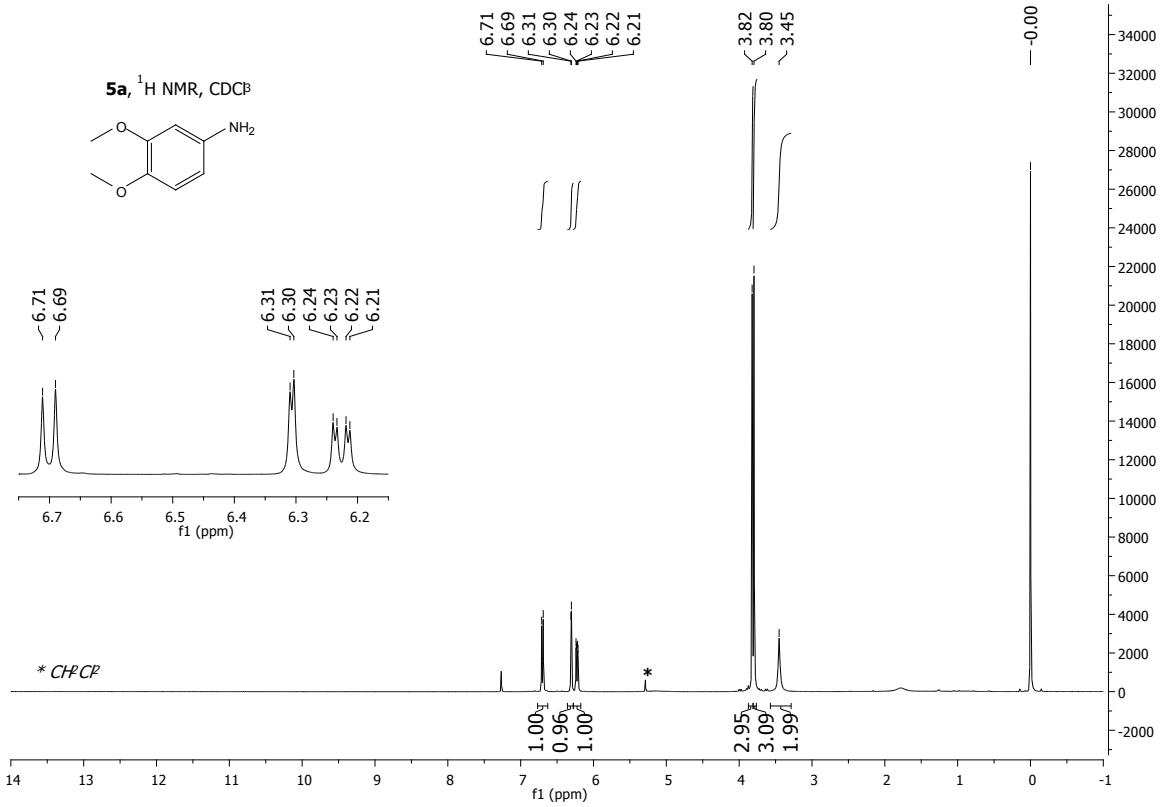

172.06
149.10
145.77
131.83
111.78
111.46
105.08
56.16
55.89
30.59
9.70
-0.00
4a, APT NMR, CDCl3
NH
O
O
O
f1 (ppm)


4e, 1H NMR, CDCl3
* residual water
f1 (ppm)

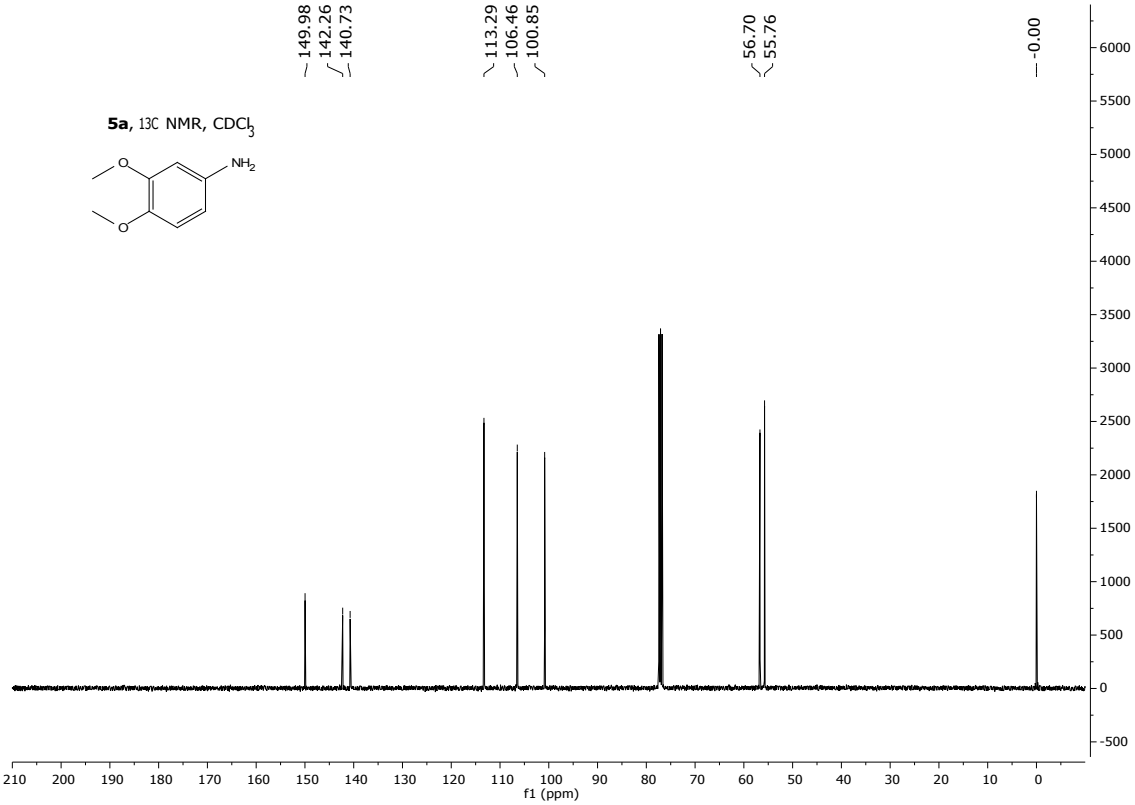

4e, 13C NMR, CDCl3
f1 (ppm)

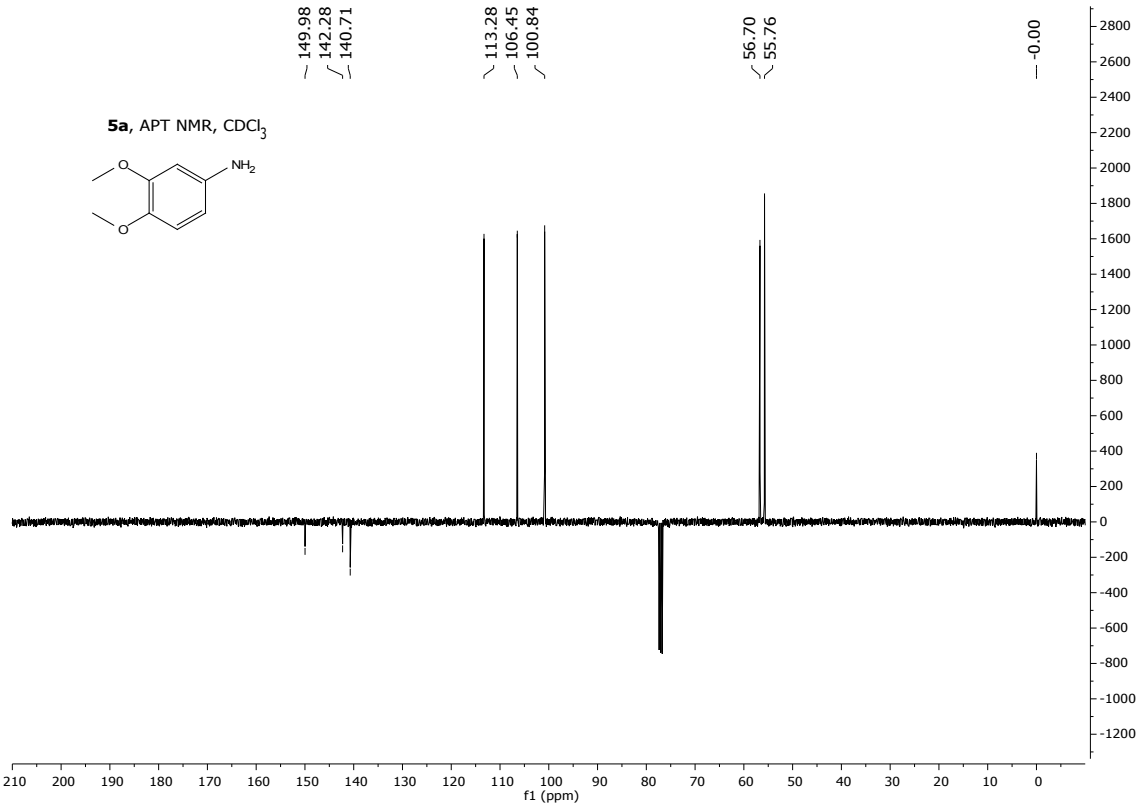

171.88
149.97
144.85
132.43
114.48
111.69
105.39
66.39
55.97
41.66
32.40
30.66
9.66
-0.00
4e, APT NMR, CDCl3
NH
O
O
O
Cl
f1 (ppm)

5a, ^{1}H NMR, $CDCl_3$

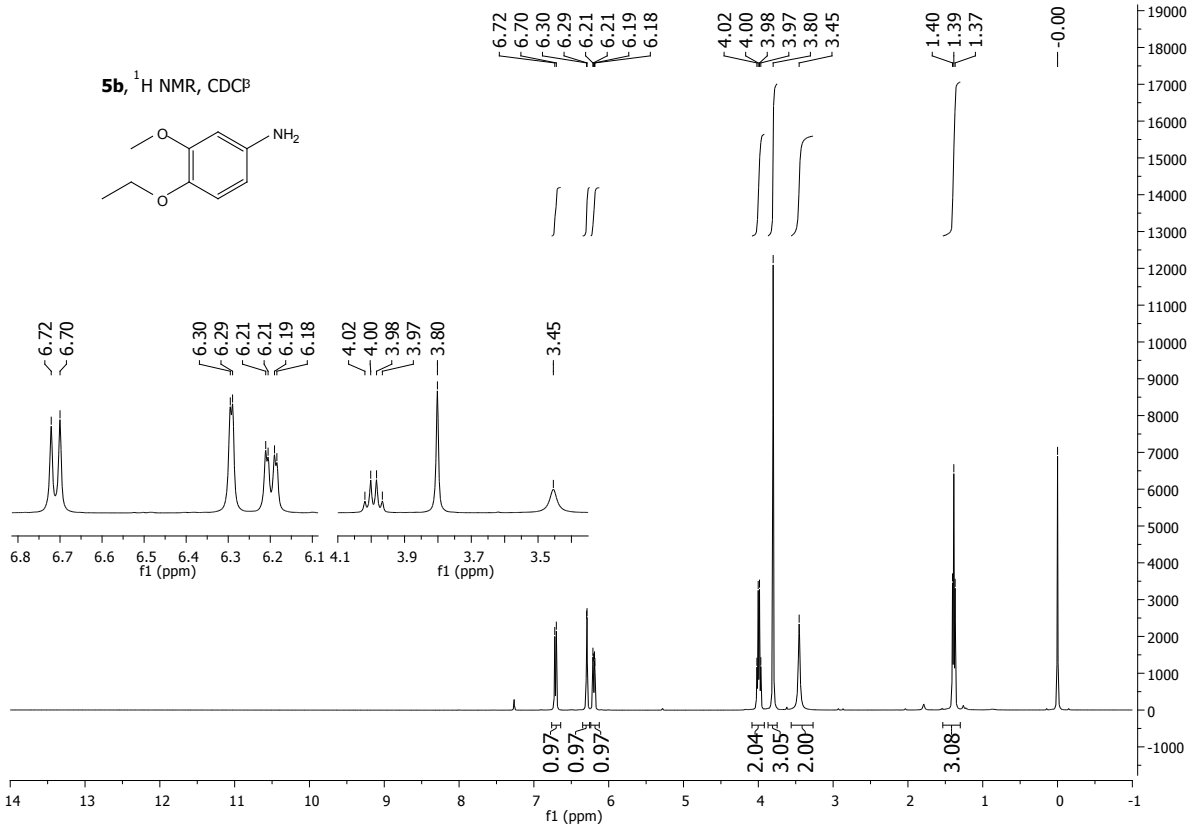


5a, ^{13}C NMR, $CDCl_3$

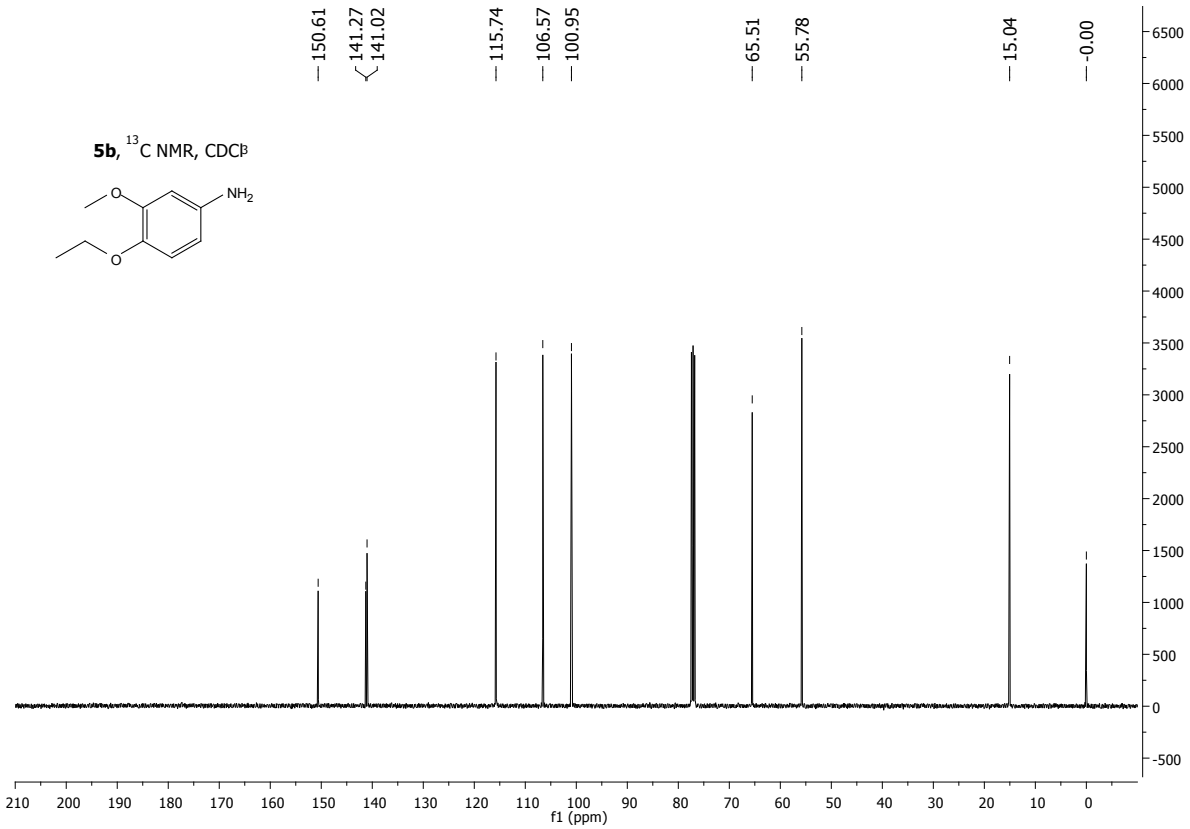


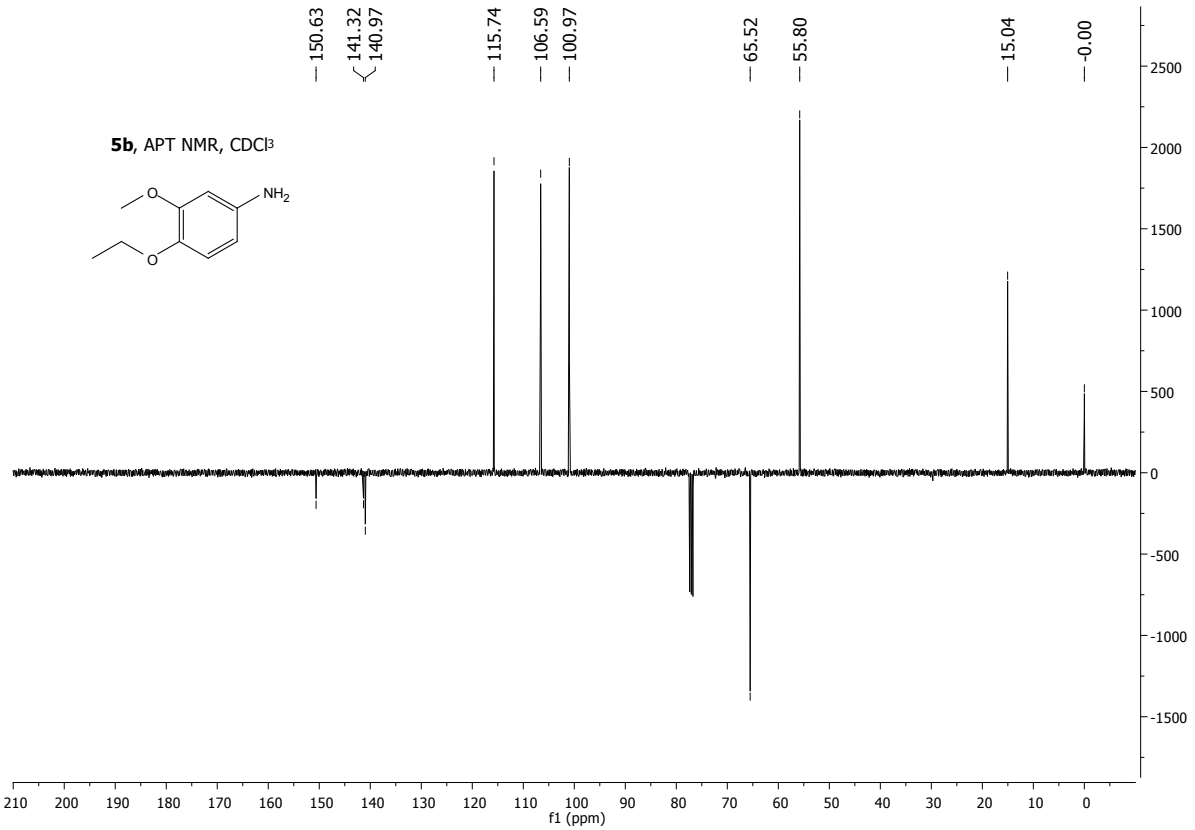

149.98
142.28
140.71
113.28
106.45
100.84
56.70
55.76
-0.00
5a, APT NMR, CDCl3
NH2
O
O
f1 (ppm)

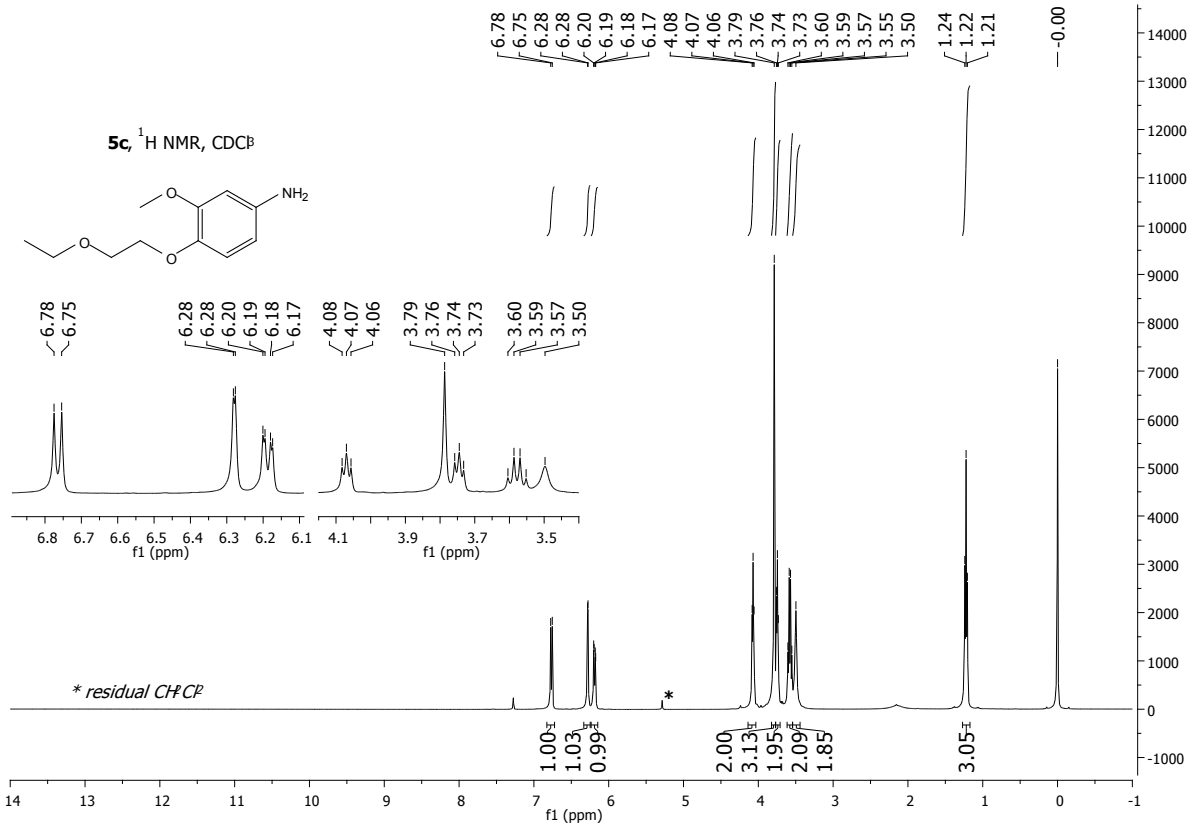
5b, ^{1}H NMR, $CDCl_3$

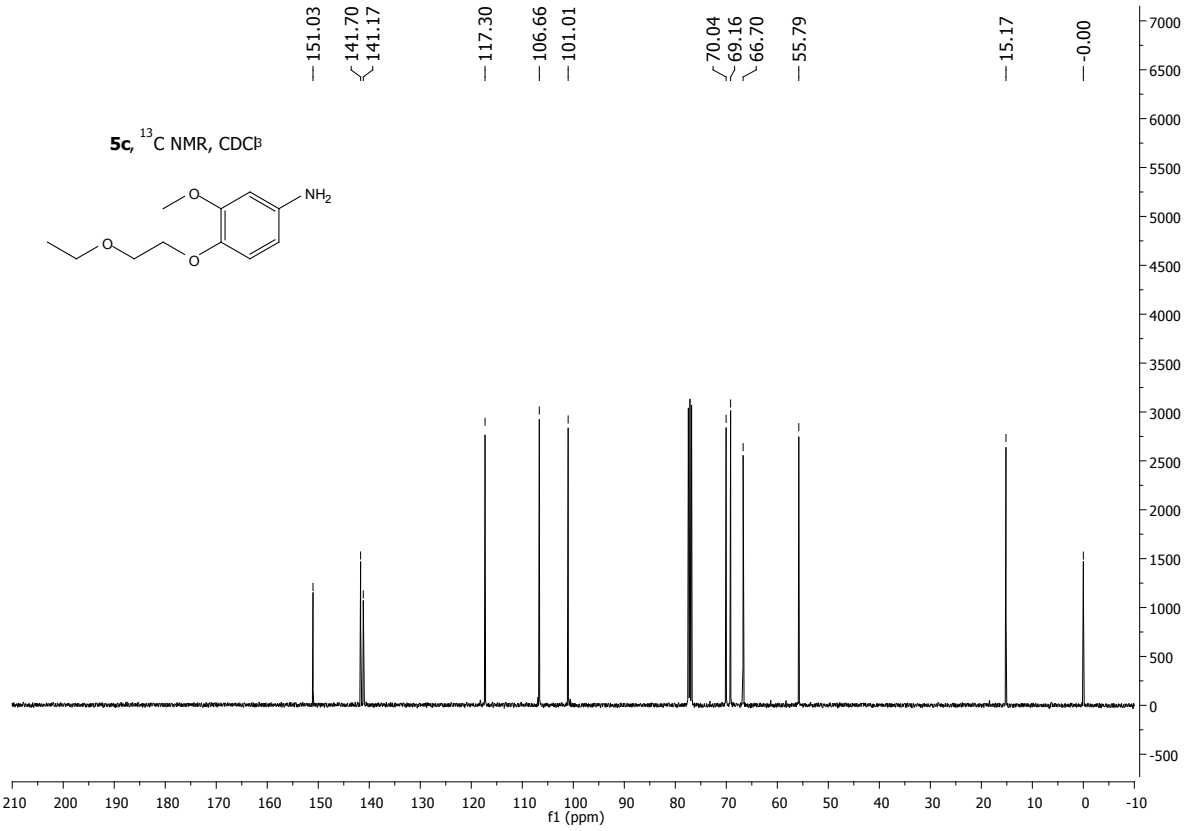


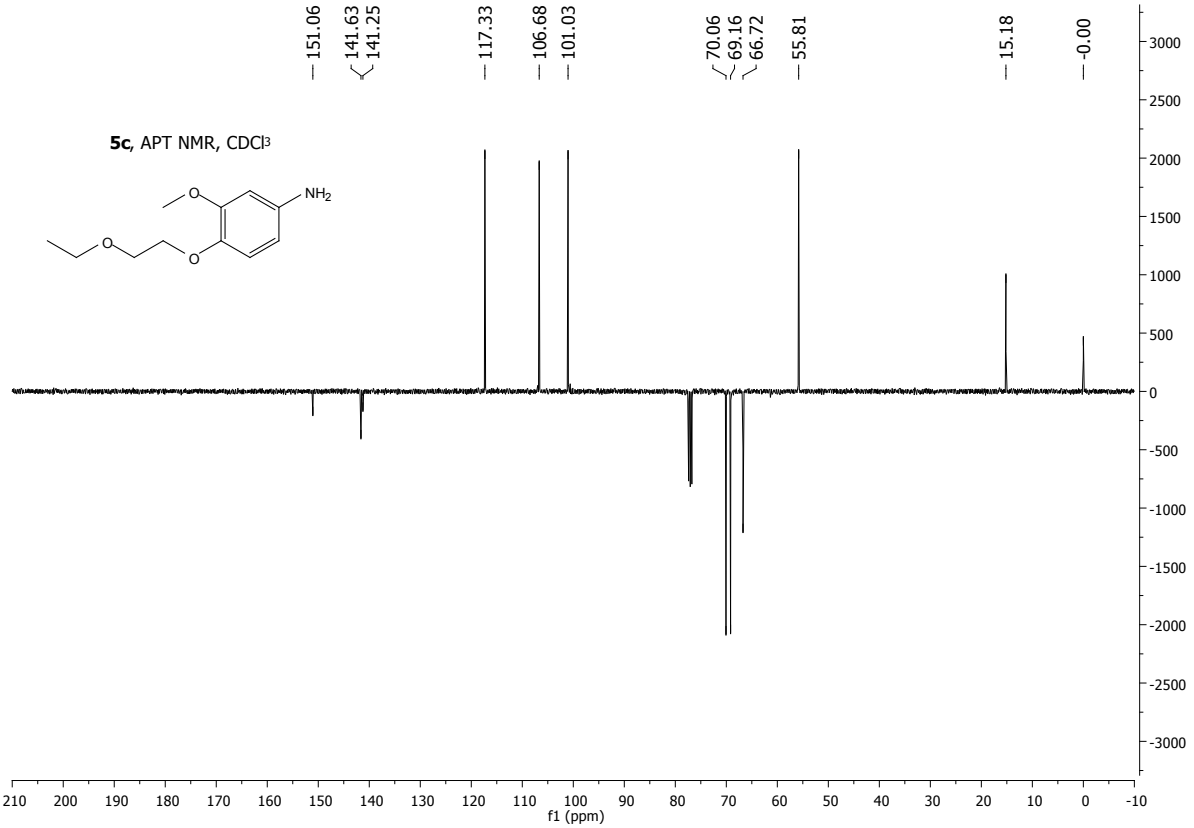
5b, ^{13}C NMR, $CDCl_3$

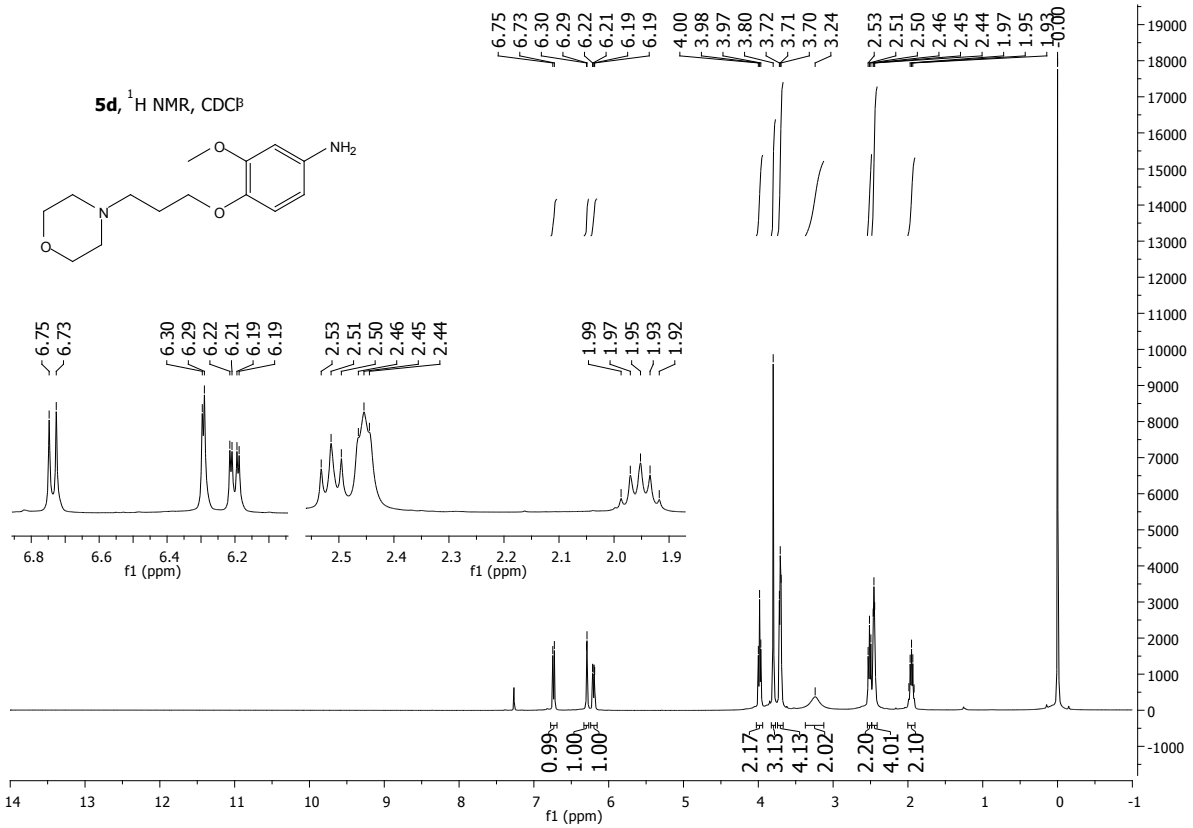


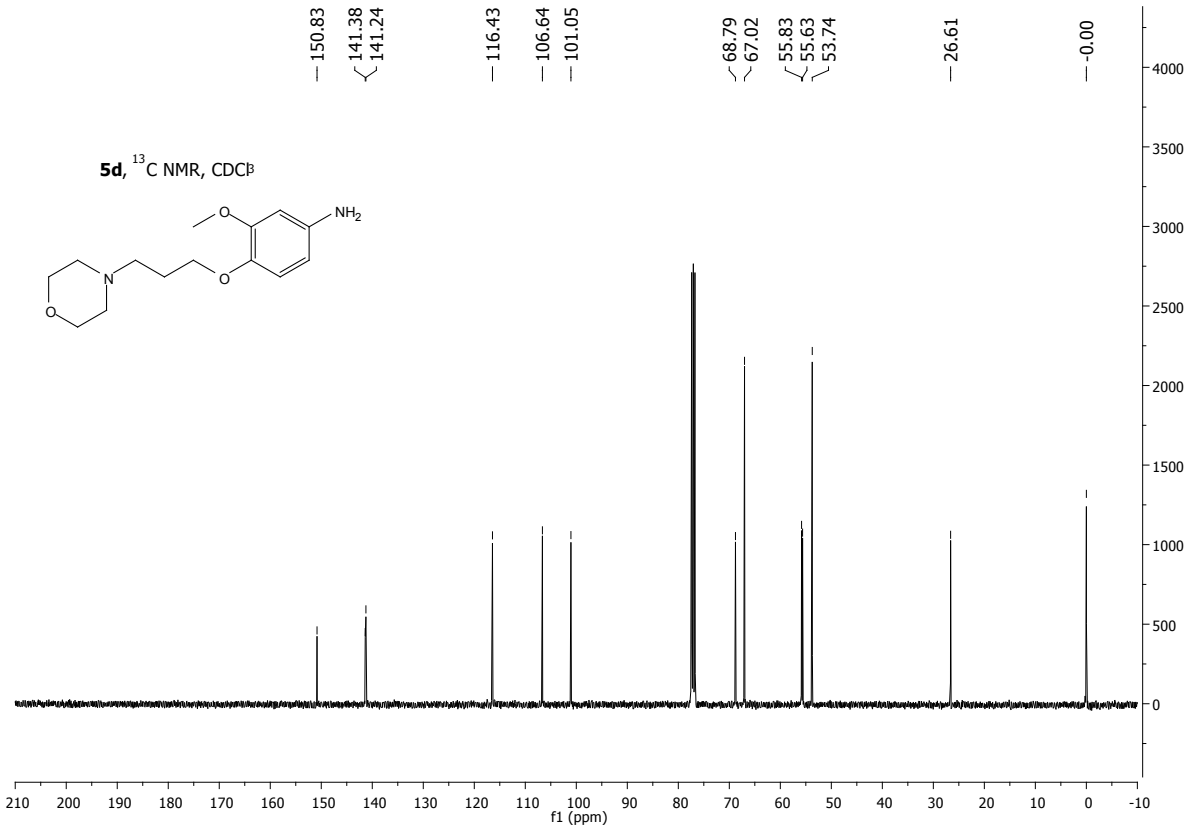

150.63
141.32
140.97
115.74
106.59
100.97
65.52
55.80
15.04
-0.00
5b, APT NMR, CDCl3
NH2
O
O
2500
2000
1500
1000
500
0
-500
-1000
-1500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

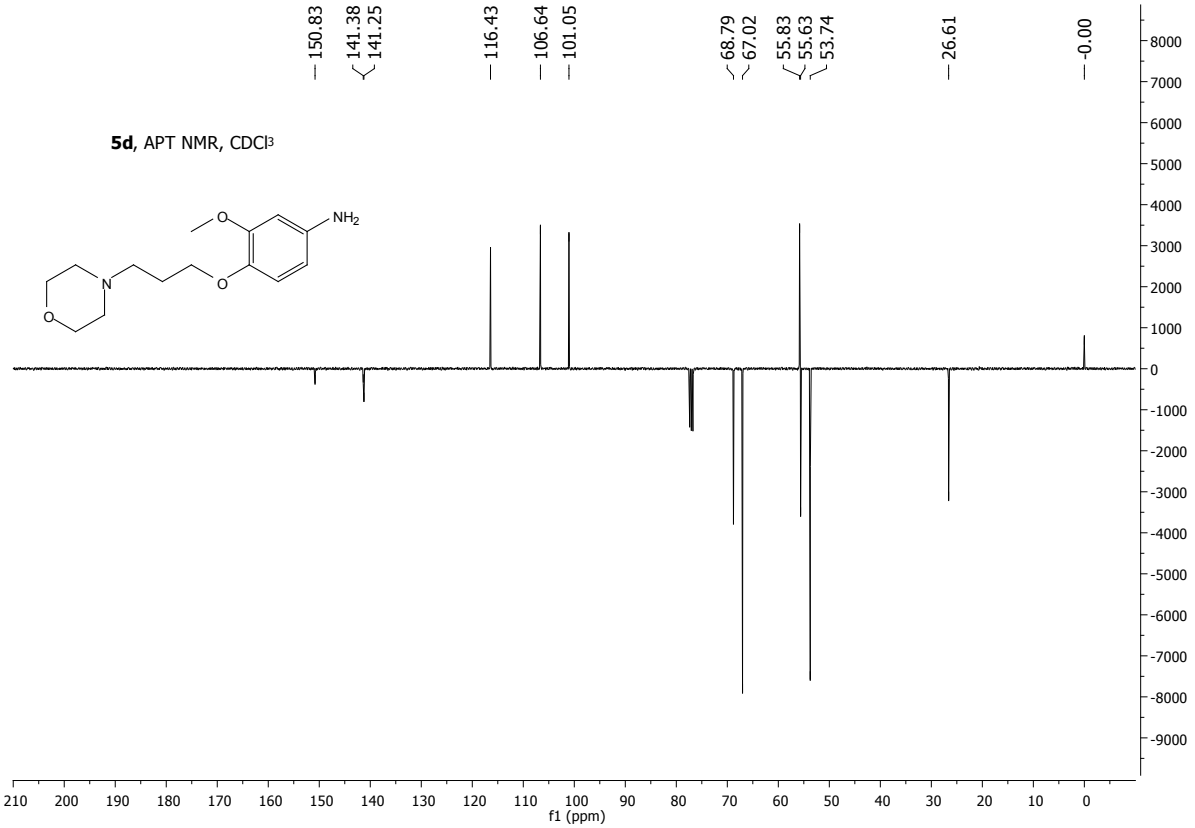

5c, 1H NMR, CDCl3
NH2
O
O
O
6.78
6.75
6.28
6.28
6.20
6.19
6.18
6.17
4.08
4.07
4.06
3.79
3.76
3.74
3.73
3.60
3.59
3.57
3.50
1.24
1.22
1.21
-0.00
* residual CH2Cl2
1.00
1.03
0.99
2.00
3.13
1.95
2.09
1.85
3.05
f1 (ppm)

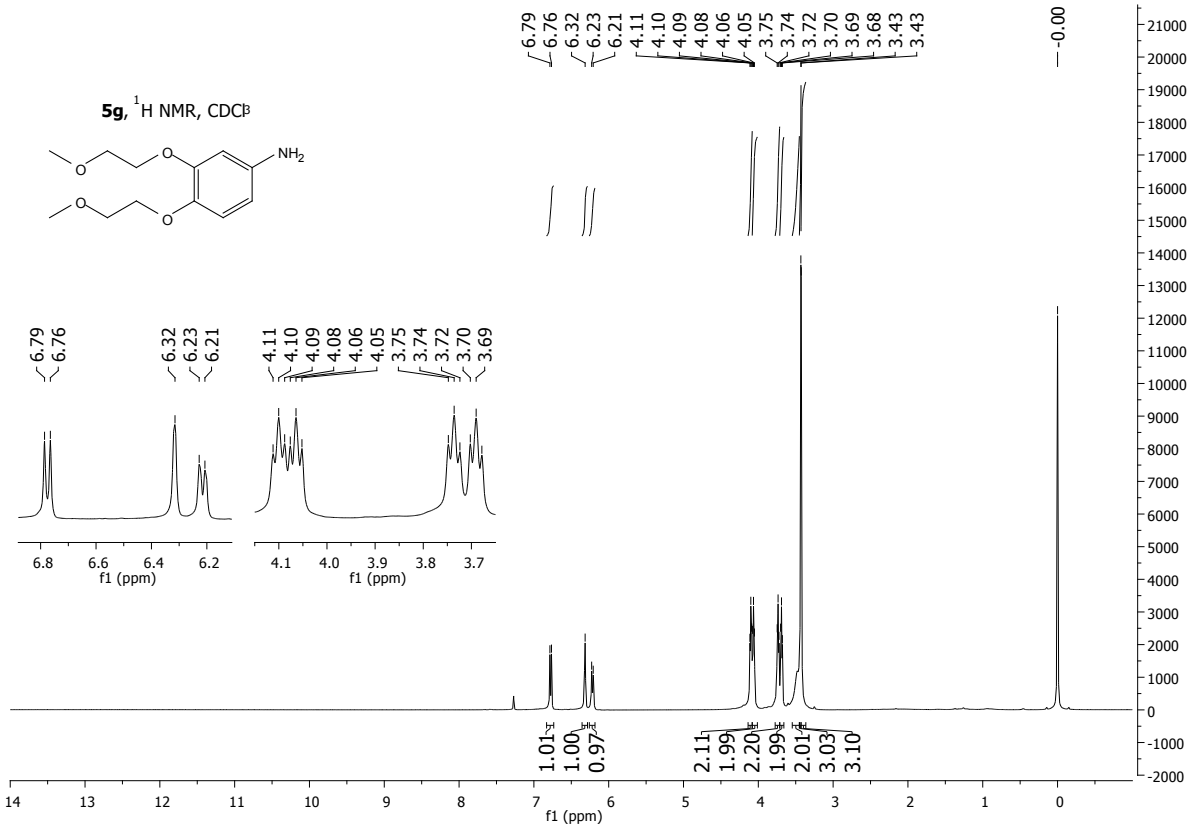

5c, 13C NMR, CDCl3
NH2
O
O
O
151.03
141.70
141.17
117.30
106.66
101.01
70.04
69.16
66.70
55.79
15.17
-0.00
f1 (ppm)

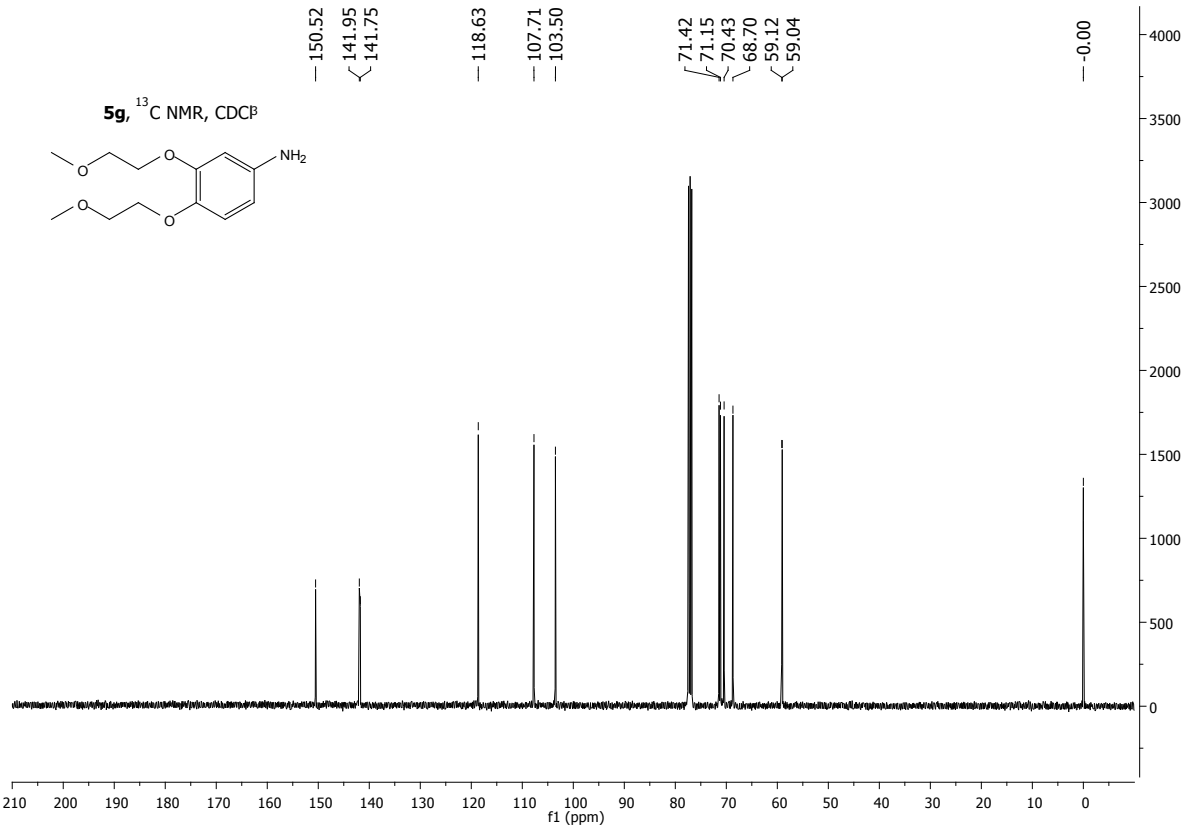

5c, APT NMR, CDCl3
NH2
151.06
141.63
141.25
117.33
106.68
101.03
70.06
69.16
66.72
55.81
15.18
-0.00
f1 (ppm)

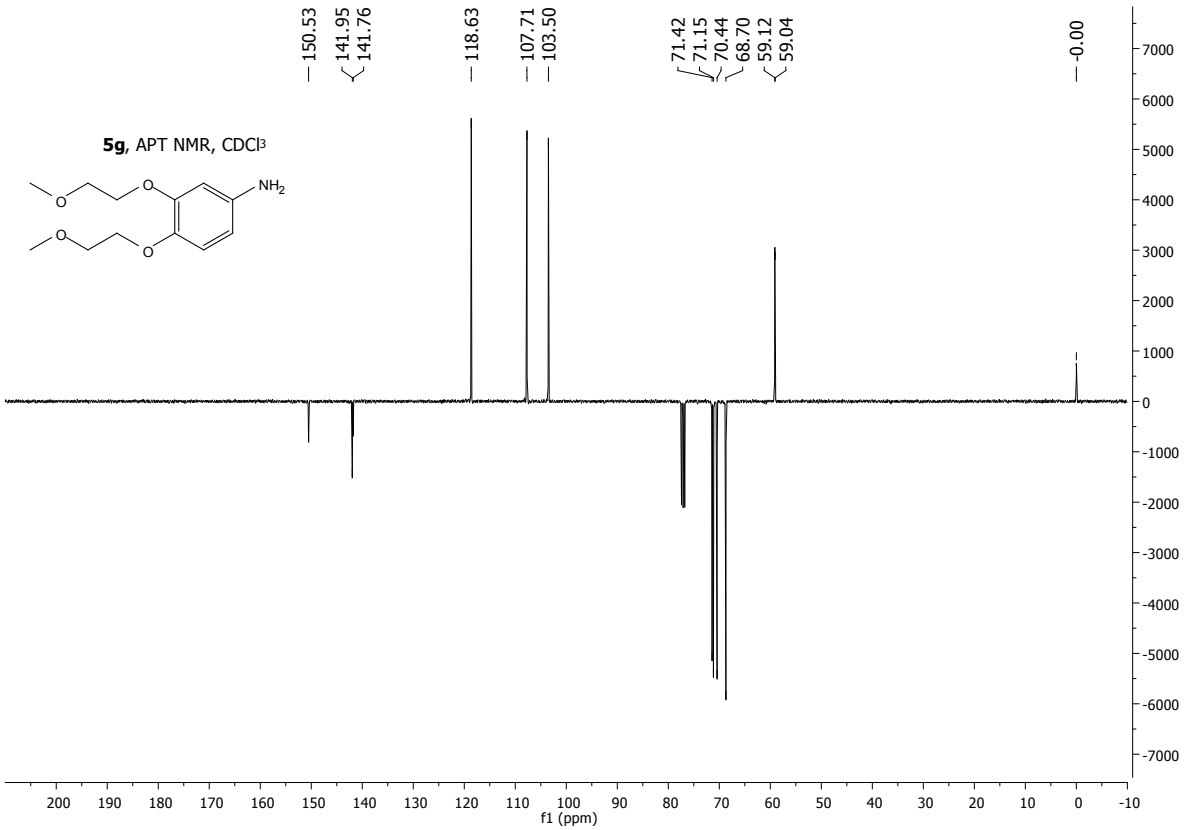

5d, 1H NMR, CDCl3
NH2
O
N
f1 (ppm)


5d, 13C NMR, CDCl3
NH2
O
N
f1 (ppm)


150.83
141.38
141.25
116.43
106.64
101.05
68.79
67.02
55.83
55.63
53.74
26.61
-0.00
5d, APT NMR, CDCl3
NH2
O
N
O
O
f1 (ppm)

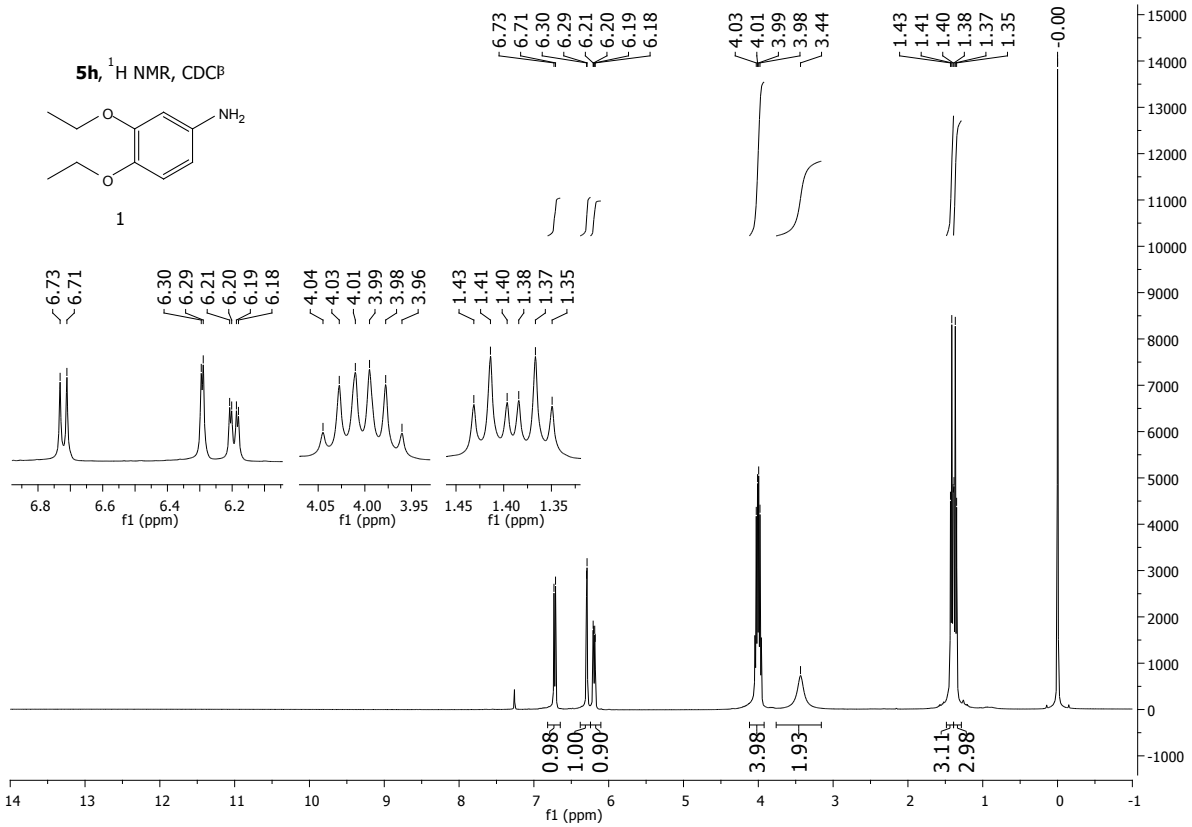

5g, 1H NMR, CDCl3
NH2
6.79
6.76
6.32
6.23
6.21
4.11
4.10
4.09
4.08
4.06
4.05
3.75
3.74
3.72
3.70
3.69
3.68
3.43
3.43
-0.00
1.01
1.00
0.97
2.11
1.99
2.20
1.99
2.01
3.03
3.10
f1 (ppm)


5g, 13C NMR, CDCl3
NH2
150.52
141.95
141.75
118.63
107.71
103.50
71.42
71.15
70.43
68.70
59.12
59.04
-0.00
f1 (ppm)

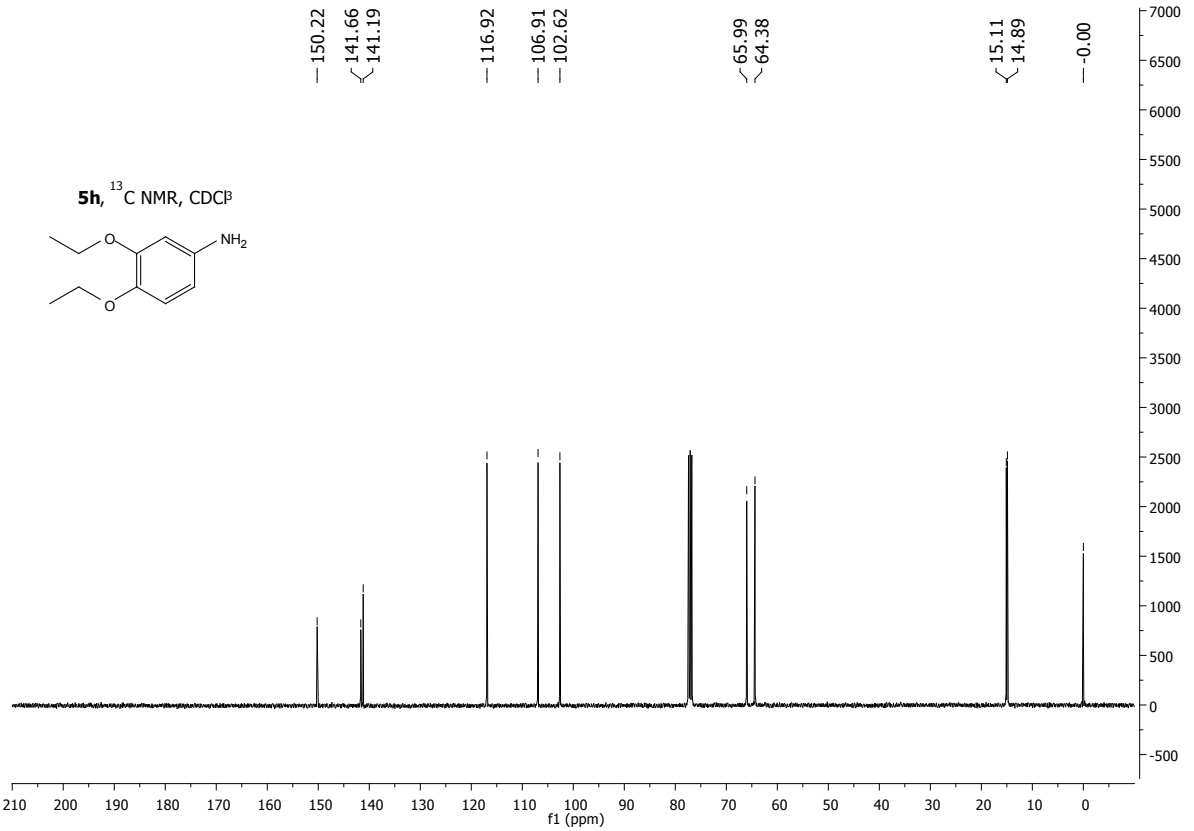

5g, APT NMR, CDCl3
NH2
O
150.53
141.95
141.76
118.63
107.71
103.50
71.42
71.15
70.44
68.70
59.12
59.04
-0.00
f1 (ppm)

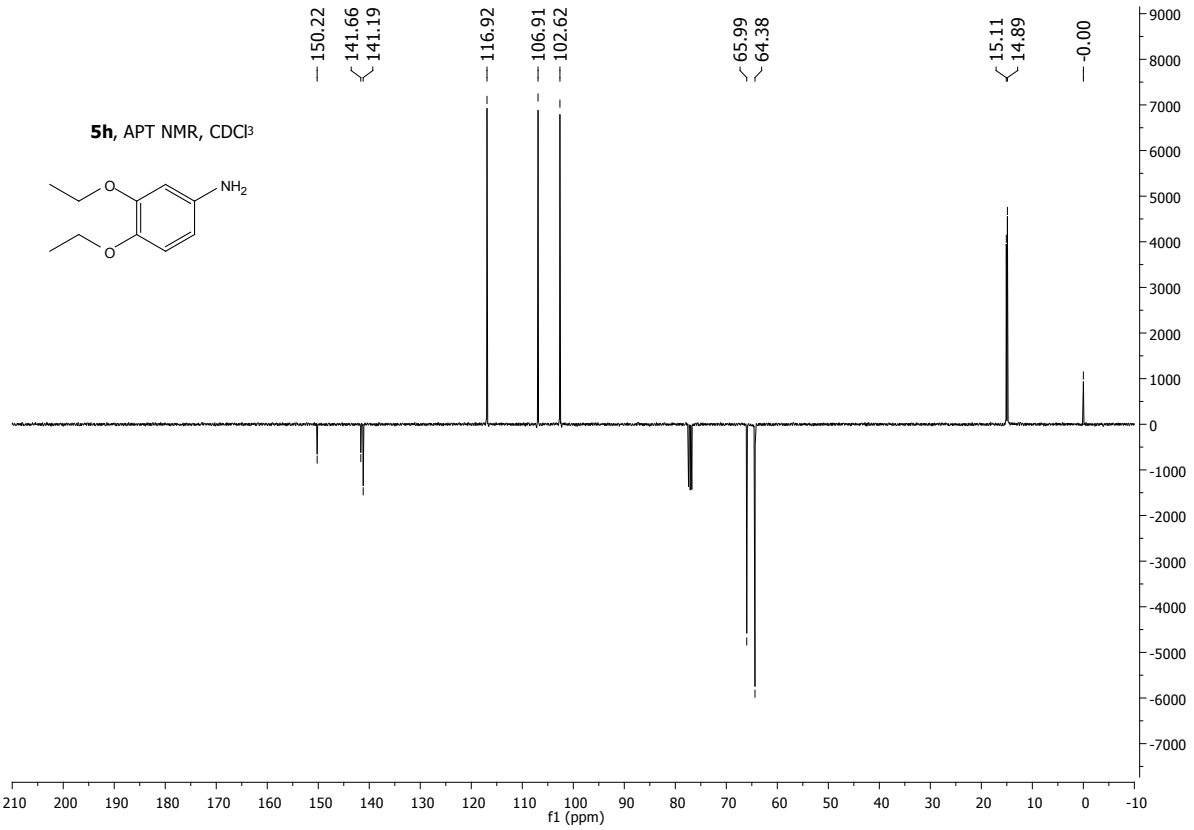
5h, ^{1}H NMR, $CDCl_3$

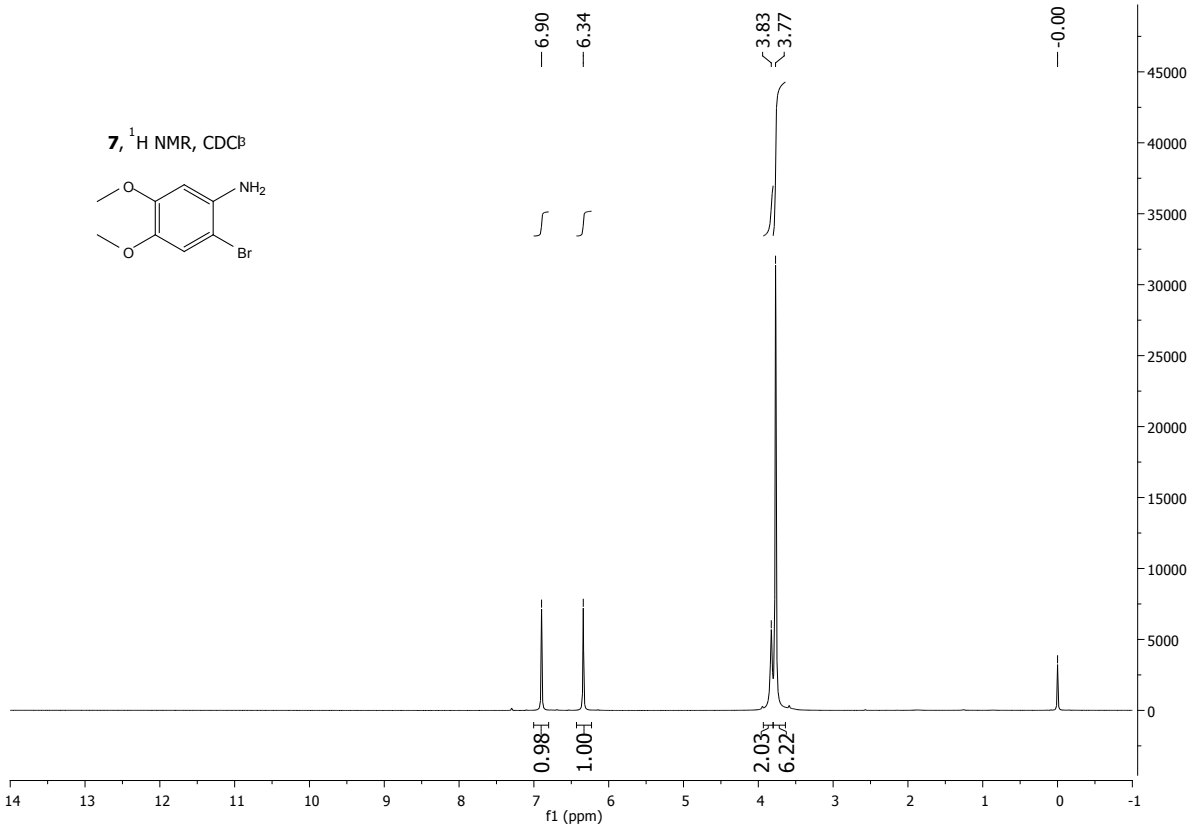
1

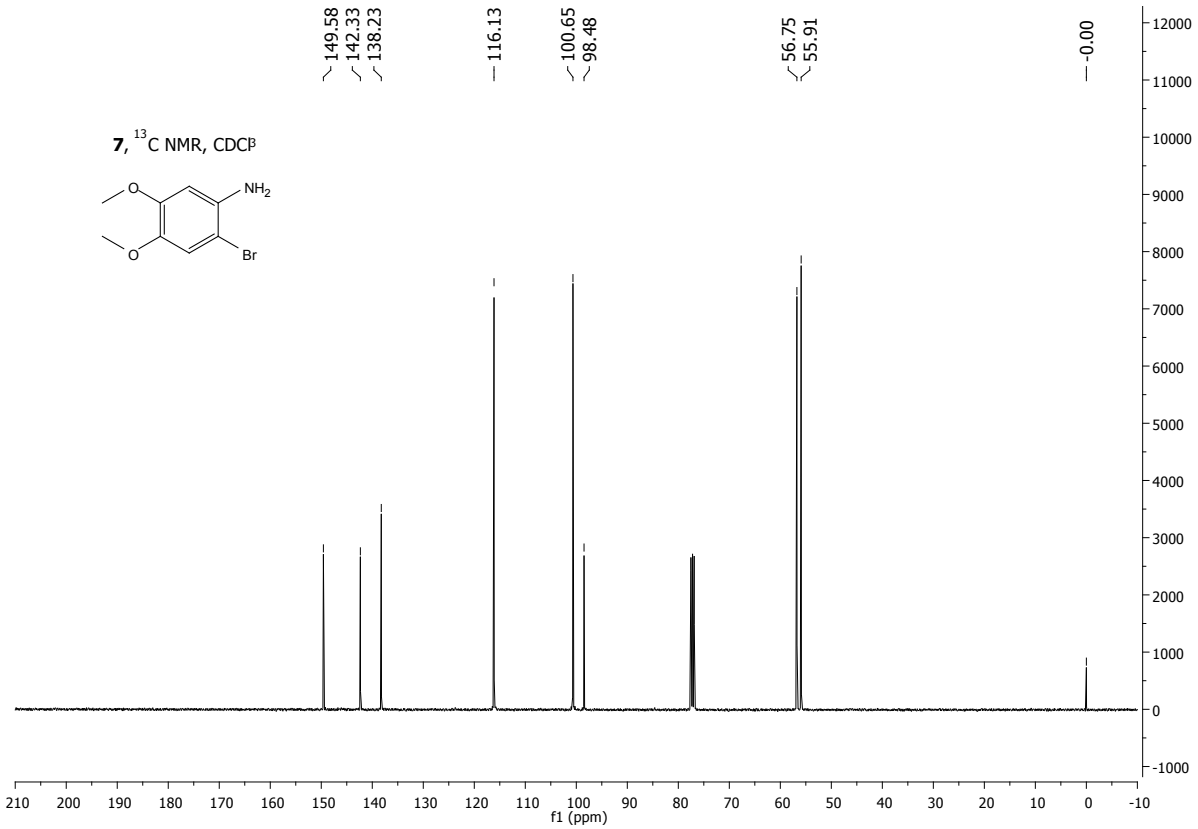


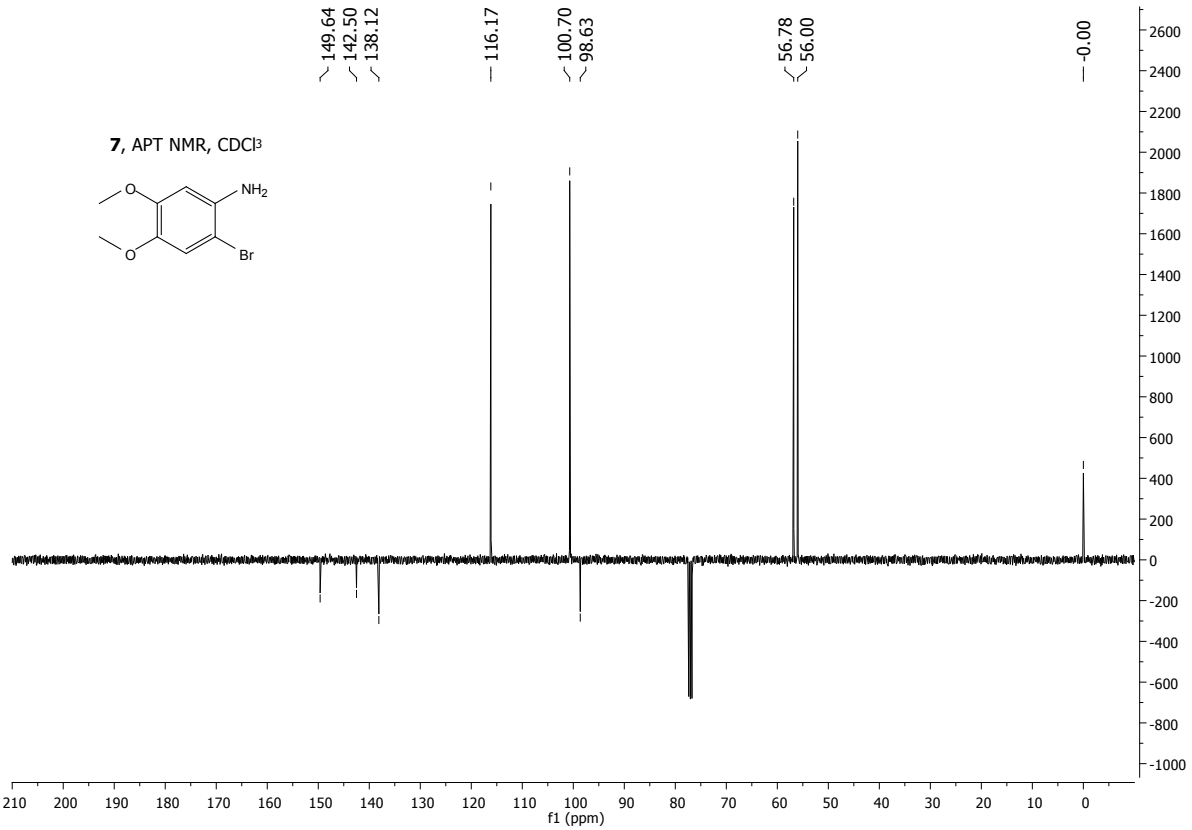
5h, ^{13}C NMR, $CDCl_3$

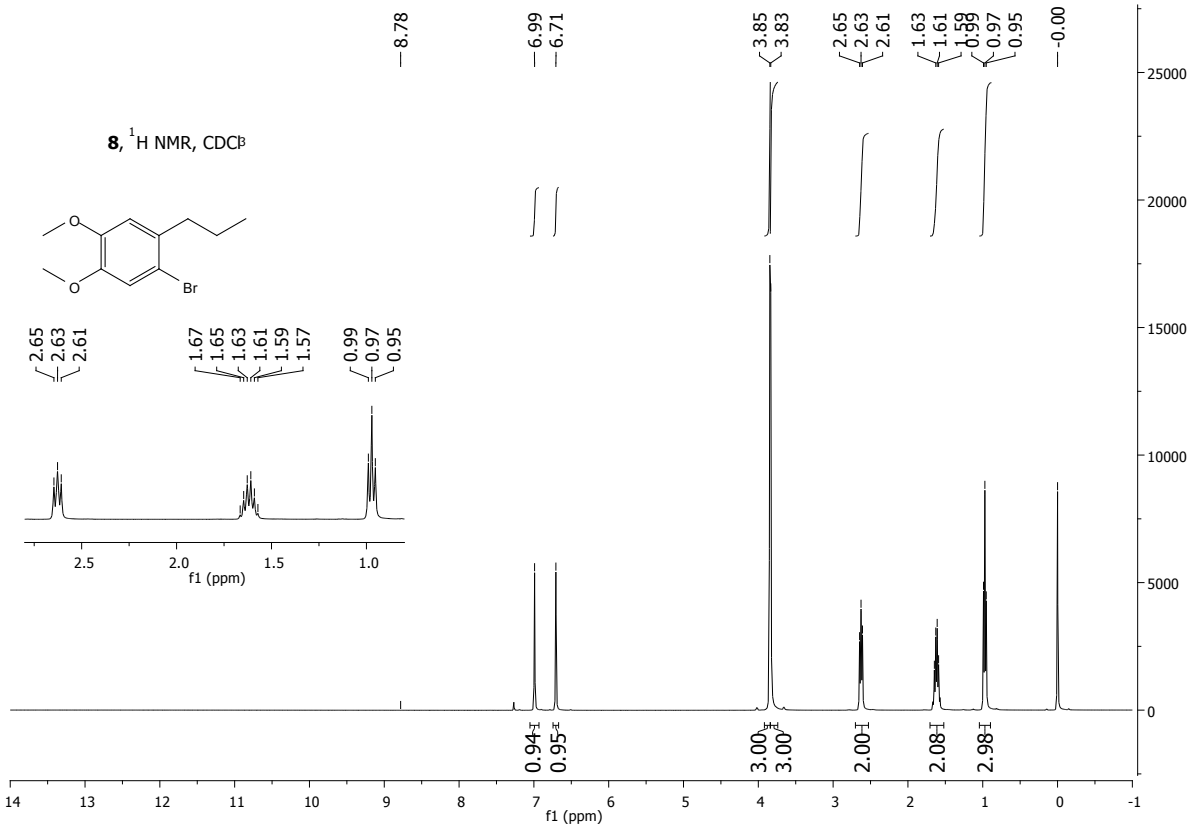


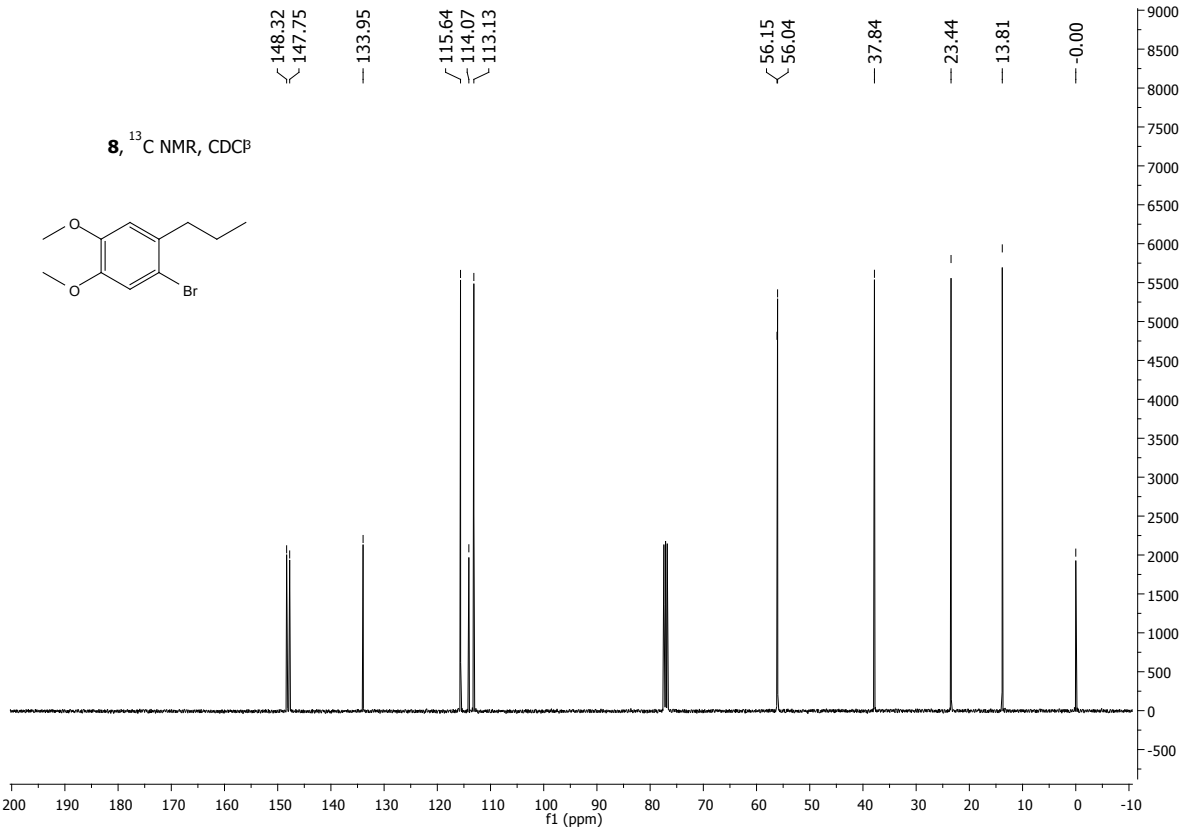

5h, APT NMR, CDCl3
NH2
O
O
150.22
141.66
141.19
116.92
106.91
102.62
65.99
64.38
15.11
14.89
-0.00
f1 (ppm)

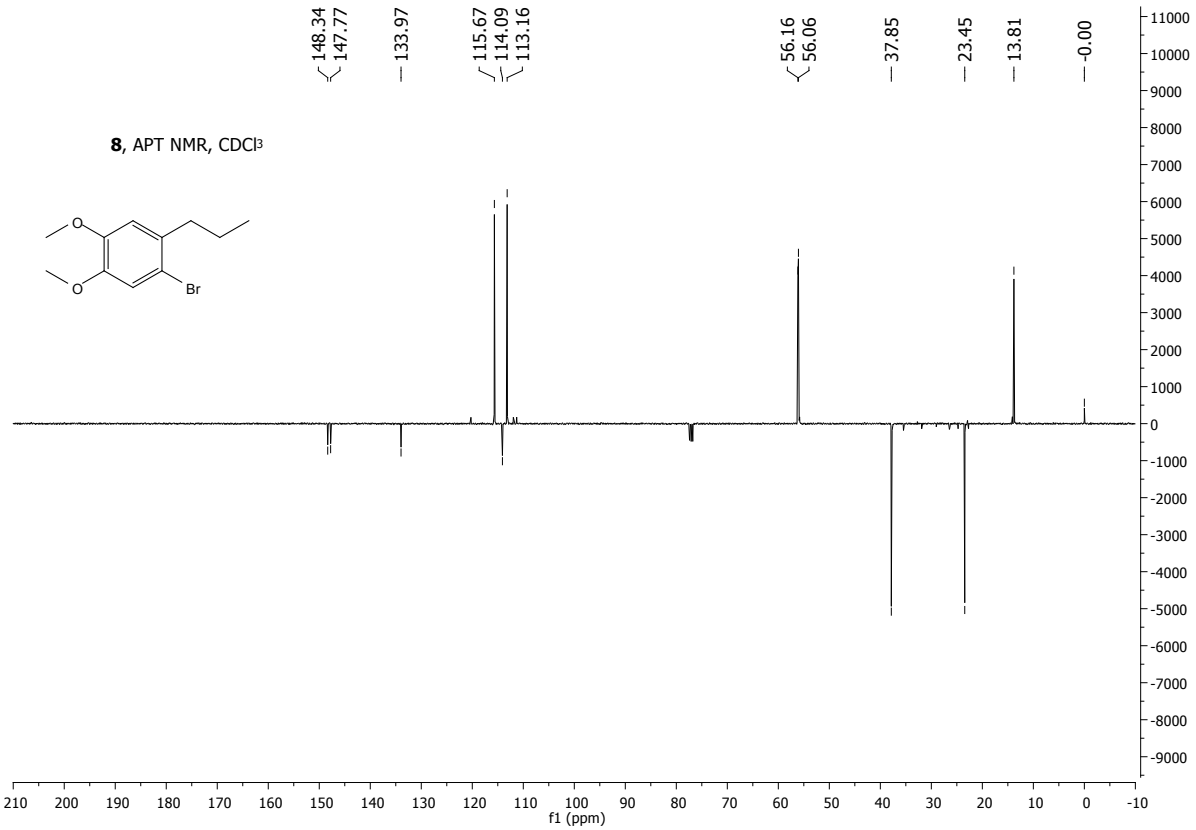

7, 1H NMR, CDCl3
NH2
Br
6.90
6.34
3.83
3.77
-0.00
0.98
1.00
2.03
6.22
f1 (ppm)

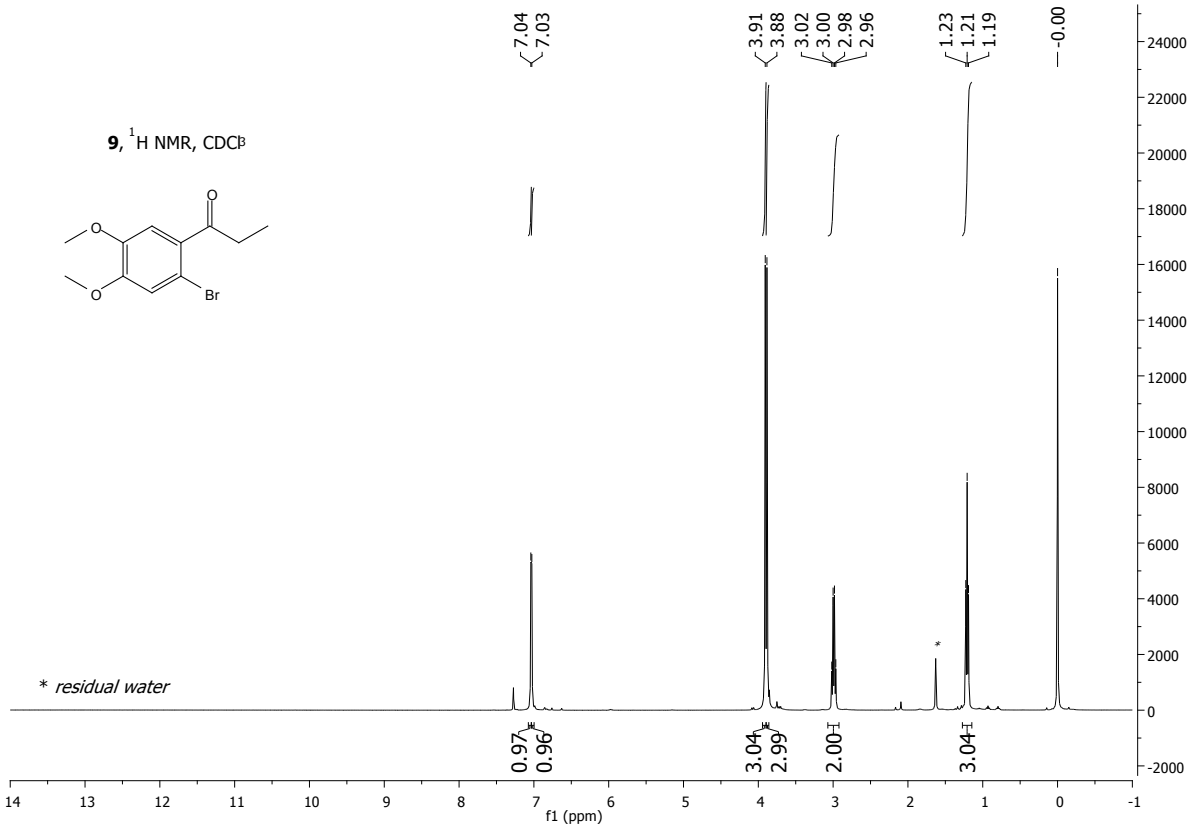

7, 13C NMR, CDCl3
NH2
Br
149.58
142.33
138.23
116.13
100.65
98.48
56.75
55.91
-0.00
f1 (ppm)

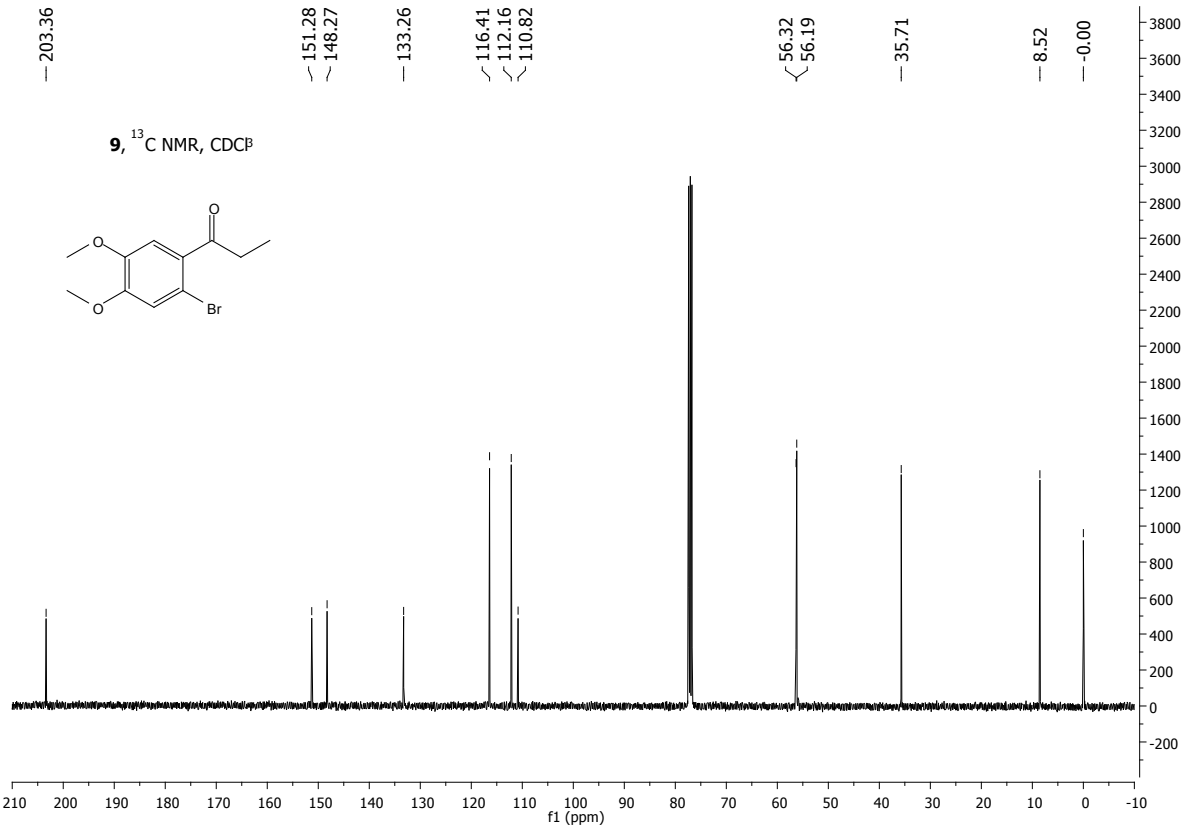

7, APT NMR, CDCl3
NH2
Br
O
O
149.64
142.50
138.12
116.17
100.70
98.63
56.78
56.00
-0.00
f1 (ppm)

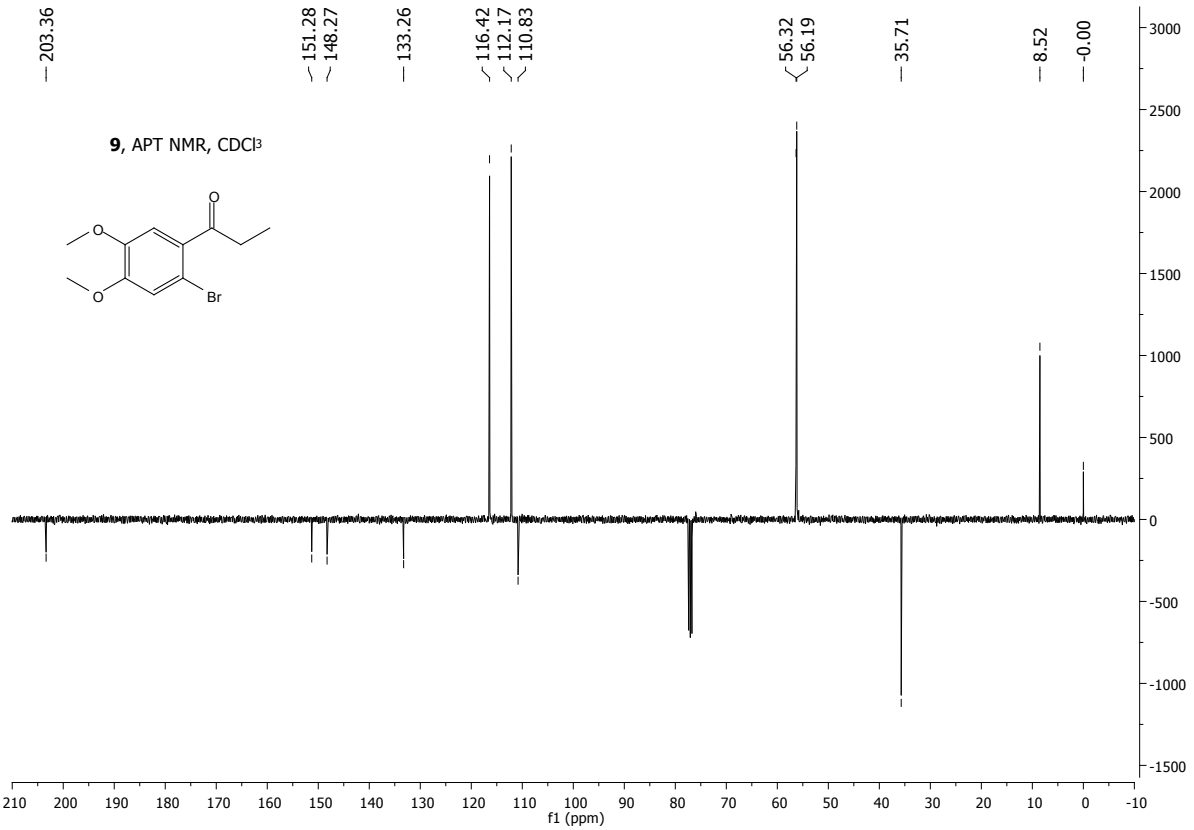

8, 1H NMR, CDCl3
8.78
6.99
6.71
3.85
3.83
2.65
2.63
2.61
1.63
1.61
1.59
0.99
0.97
0.95
-0.00
0.94
0.95
3.00
3.00
2.00
2.08
2.98
f1 (ppm)


8, 13C NMR, CDCl3
148.32
147.75
133.95
115.64
114.07
113.13
56.15
56.04
37.84
23.44
13.81
-0.00
f1 (ppm)

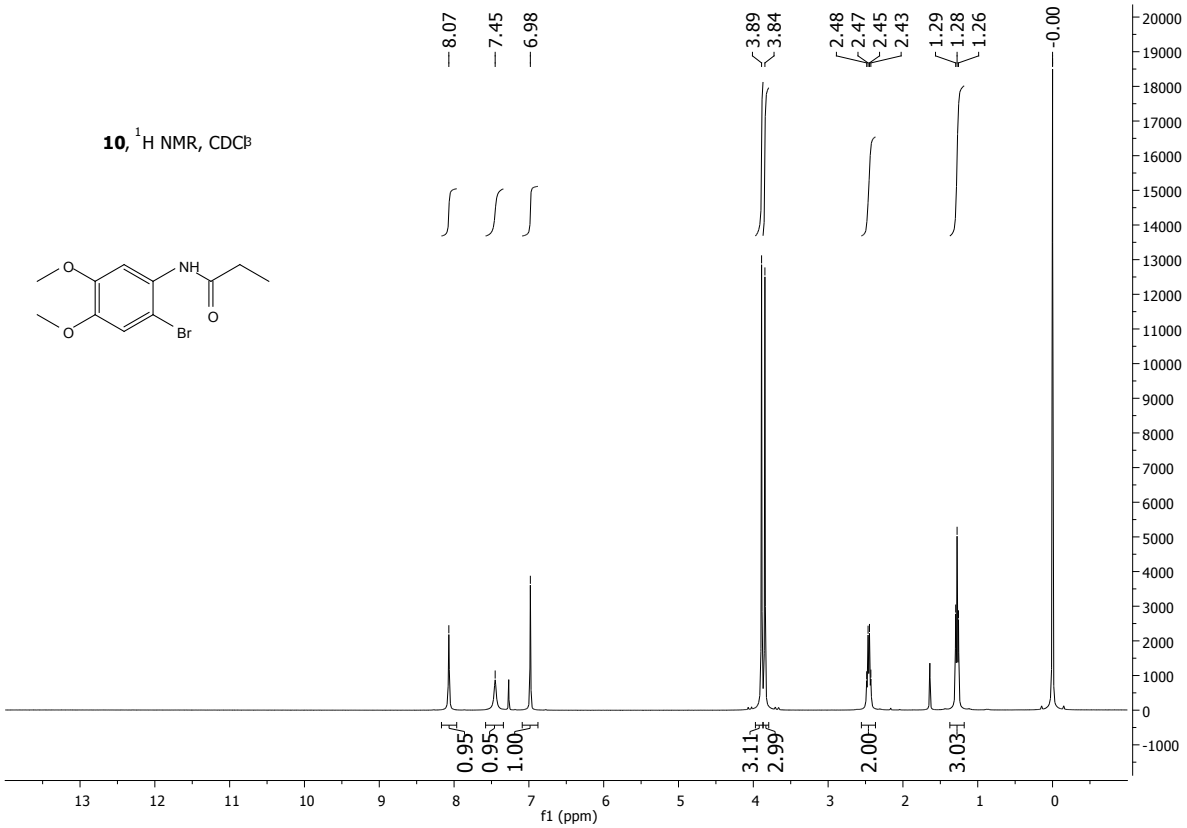

148.34
147.77
133.97
115.67
114.09
113.16
56.16
56.06
37.85
23.45
13.81
-0.00
8, APT NMR, CDCl3
O
O
Br
f1 (ppm)


9, 1H NMR, CDCl3
O
O
O
Br
7.04
7.03
3.91
3.88
3.02
3.00
2.98
2.96
1.23
1.21
1.19
-0.00
* residual water
0.97
0.96
3.04
2.99
2.00
3.04
f1 (ppm)

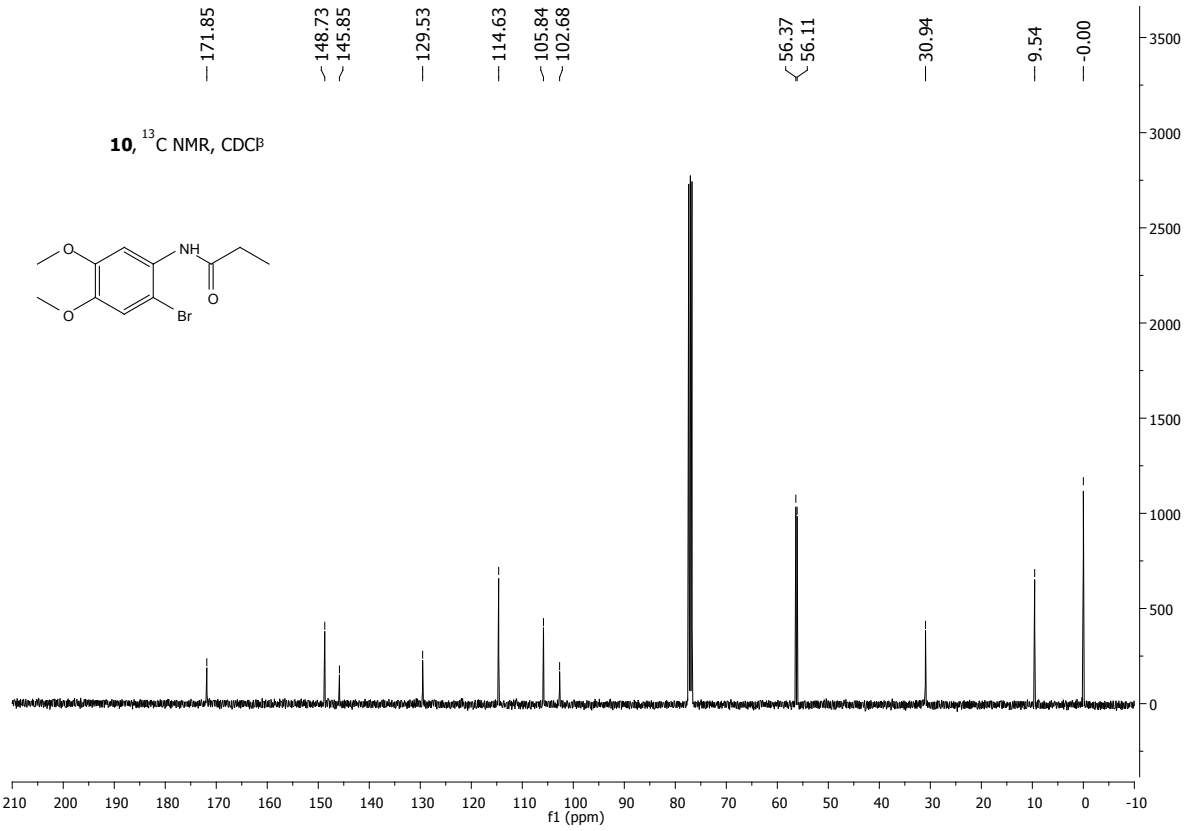

9, 13C NMR, CDCl3
O
O
O
Br
203.36
151.28
148.27
133.26
116.41
112.16
110.82
56.32
56.19
35.71
8.52
-0.00
f1 (ppm)

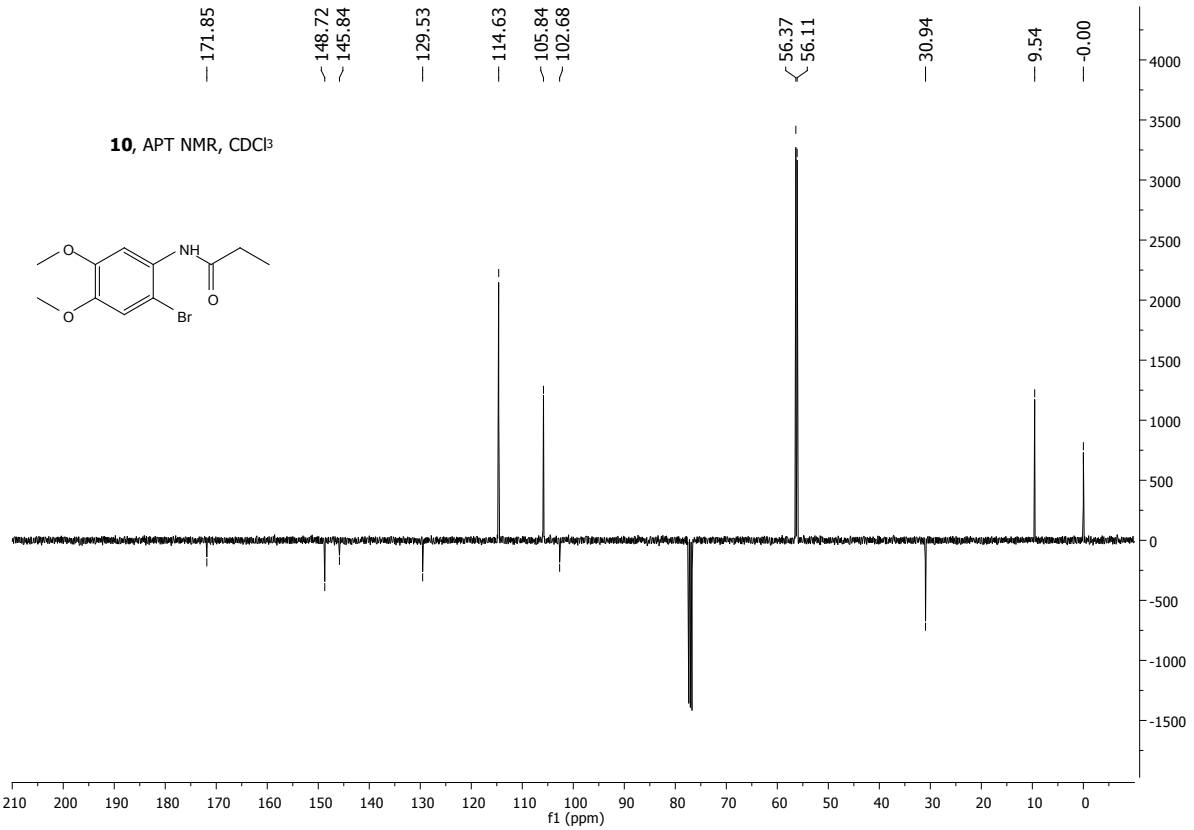

203.36
151.28
148.27
133.26
116.42
112.17
110.83
56.32
56.19
35.71
8.52
-0.00
9, APT NMR, CDCl3
O
O
O
Br
f1 (ppm)

10, ^{1}H NMR, $CDCl_3$



10, ^{13}C NMR, $CDCl_3$




171.85
148.72
145.84
129.53
114.63
105.84
102.68
56.37
56.11
30.94
9.54
-0.00
10, APT NMR, CDCl3
NH
O
O
O
Br
f1 (ppm)

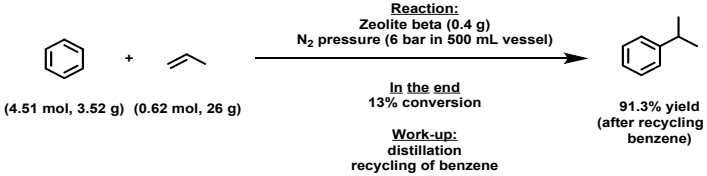
22 Copies of the Excel Sheets used for Green Metrics calculations

22.1 Classical synthesis of 3,4-dimethoxyaniline (5a)

- Step 1

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)
Benzene	352,00	78,11	4,51	Zeoite beta	0,40			N_2			3,39						
Propylene	208,00	42,08	4,94														
			#DIV/0!														
			#DIV/0!														
			#DIV/0!														
			#DIV/0!														
			#DIV/0!														
Total	560,00	120,19			0,40		0,00				3,39		0,00				0,00



	STEP	CUMULATIVE
Yield (%)	91,30	91,30
Conversion (%)	100,00	/
Selectivity (%)	91,30	/
AE (%)	99,92	99,92
RME (%)	88,23	88,23
PMI total ($g \cdot g^{-1}$)	1,14	1,14
PMI Reaction ($g \cdot g^{-1}$)	1,14	1,14
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	1,13	1,13

	Mass	MW	Mol
Product	4,94E+02	120,09	4,11E+00
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
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	

Experimental:

G. Spano, S. Ramello, G. Girotti, F. Rivetti, A. Carati *Polimeri Europa S.p.A., Italy; Enitecnologie S.p.A.* . **2006**, WO2006002805A1.

5 :Example nr. 5; 0.4 g of beta zeolite prepared according to what is described in example l, previously dried to 120°C for 16 hours, are charged into an electrically heated autoclave with an internal volume equal to 0.5 litres, equipped with a mechanical stirrer and with all the necessary devices forthe feeding of the benzene and propylene reagents.The autoclave is closed, put under vacuum by suction with a pump connected externally, and 352 g of benzene are .bul. then charged by suction. The autoclave is pressurized with nitrogen until a pressure of about 6 bar is reached and the heating is initiated to the programmed temperature of 150°C. When the temperature inside the autoclave has stably reached the pre-selected value, 26 g of propylene are rap-idly fed, by means of a pressure tank, and the mixture i s left to react for a time of exactly l hour, calculated starting from the end of the propylene feeding.At the end of the reaction, the product is discharged and analyzed by gas chromatography. The following products are present in the mixture at the end of the reaction: benzene, cumene, C_6 and C_9 ofligomers of propylene, diisopropyl benzenes, other diisopropyl benzene isomers (C_6-phenyl = aromatic products generally indicated with the formula $C_{12}H_{18}$) / triisopropyl benzenes, other triisopropyl benzene isomers (C_9-phenyl = aromatic products generally indicated with the formula $C_{18}H_{30}$) , polyalkylated products with a mo-lecular weight higher than triisopropyl benzene (heavy polyalkylated products).The propylene conversion proves to be higher than97.0percent, the selectivity to mono-alkylated product (cumene)with respect to the converted propylene is equal to 91.3percentand the selectivity to (cumene + diisopropyl benzenes + triisopropyl benzenes) with respect to the converted pro-pylene is equal to 97.5percent.The weight ratio, called R, between the sum of (diisopropyl benzenes + triisopropyl benzenes + C_6-phenyl + C_9-phenyl + heavy polyalkylated products) and the sum of (cumene + diisopropyl benzenes + triisopropyl benzenes + C_6-phenyl + C_9-phenyl + heavy polyalkylated products) proves to be equal to 0.052.This ratio R is a measurement of the total quantity ofthe polyalkylated by-products alone with respect to the to- tal products and alkylated by-products formed during thereaction.

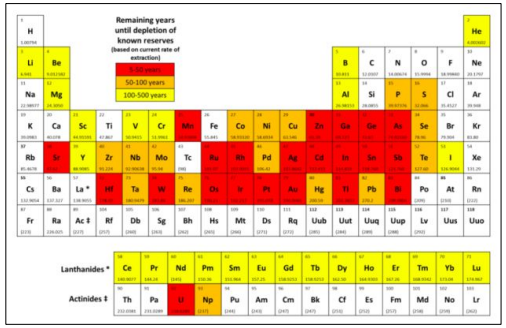
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any**	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	Al
+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	
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 pressure)	Green Flag	X
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

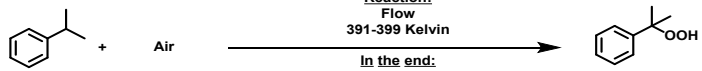
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Propylene: H220	
Explosive thermal runaway	H230, H240, H250	H241				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

- Step 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 (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Cumene	2,68E+07	120,09	2,23E+05					N_2 from air			1,57E+07						
O_2 from air	5,22E+06	31,99	1,63E+05														
Total	3,20E+07	152,08			0,00		0,00				1,57E+07		0,00				0,00



(26770 kg/h) (4330 kg/h)

Reaction:
Flow
391-399 Kelvin

In the end:
24000 kg/h at 386 K
desired product 19.4 w-%

Work-up:
condensation
distillation
recycling of cumene

93.7% yield
(after recycling of cumene)

	STEP	CUMULATIVE
Yield (%)	93,70	85,55
Conversion (%)	100,00	/
Selectivity (%)	93,70	/
AE (%)	100,00	99,94
RME (%)	99,30	89,33
PMI total ($g \cdot g^{-1}$)	1,50	1,62
PMI Reaction ($g \cdot g^{-1}$)	1,50	1,62
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	1,01	1,12

	Mass	MW	Mol
Product	3,18E+07	152,08	2,09E+05
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
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	

Experimental:

H. Bartkowiak, B. Haase, R. Hofmann, H. J. Naumann, B. Raue *VEB Leuna-Werke "Walter Ulbricht", Ger. Dem. Rep.* **1988**, DD258531A3.

Beispiel 1

Die Oxidation des Cumens zu Cumenhydroperoxid erfolgt in einem stehenden 62 m^3 großen Reaktor, der durch Siebbodenelemente in vier Reaktionsabschnitte geteilt ist, deren Reaktionsvolumen von oben nach unten 21, 21, 13 und 7 m^3 beinhalten. Dem Reaktor werden stündlich 26770 kg Cumen mit einer Temperatur von 388 K, das 1,8 Ma.-% Cumenhydroperoxid enthält, zugeführt. Unten werden 4330 kg/h Luft mit einer Temperatur von 298 K in den Reaktor eingeleitet. Oben verlassen den Reaktor 7100 kg/h Abgas, bestehend aus Stickstoff, Sauerstoff, Cumen und Cumenhydroperoxid mit einer Temperatur von 398 K. Mittels eines Kühlkreislaufes werden die Temperaturen in den einzelnen Reaktionsstufen zwischen 399 K oben und 391 K unten gehalten. Den Reaktor verlassen 24000 kg/h Oxidat mit einer Temperatur von 386 K und einem Gehalt an Cumenhydroperoxid von 19,4 Ma.-%. Das im Abgas enthaltene Cumen und Cumenhydroperoxid wird mittels Kühlwasser auskondensiert. Gleichfalls mittels Kühlwasser wird dem Kühlkreislauf die im Reaktor aufgenommene Wärme entzogen. Die Erwärmung des Cumens auf die Eintrittstemperatur von 388 K erfolgt zunächst in einem Wärmeaustauschapparat mittels des den Reaktor verlassenden Oxidats, wobei sich das Cumen von 303 K auf 349 K erwärmt und dann in einem weiteren Wärmeaustauscher mittels Heizdampf. Das Oxidat wird dabei innerhalb von 15 Minuten auf eine Temperatur von 346 K abgekühlt und gelangt danach in eine unterteilte, bei Drücken von 4 kPa und 1 kPa arbeitende Verdampferstufe, in der das Oxidat auf 89 Ma.-% Cumenhydroperoxid aufkonzentriert wird. Die Ausbeute an nutzbarem Cumenhydroperoxid beträgt bezüglich Cumen 93,7 Ma.-%. Der Verbrauch an Heizdampf zur Erzeugung des 89%igen Cumenhydroperoxids beträgt 4970 kg/h.

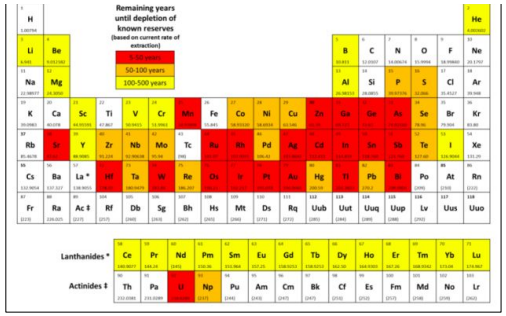
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any**	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	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	X
Batch	Amber Flag	

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

Health & safety

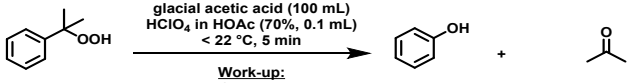
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			air
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, 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		Cumene (H411)		

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	

- Step 3

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)
Cumene hydroperoxide	15,20	152,08	0,0999	$HClO_4$	0,74			HOAc	100,00	1,05	104,92						
								HOAc	0,10	1,05	0,10						
Total	15,20	152,08			0,74		0,00				105,02		0,00				0,00



(15.2 g, 0.1 mol) (9.0 g, 95%) (estimated by means of its dinitrophenylhydrazone)

	STEP	CUMULATIVE
Yield (%)	95,69	81,85
Conversion (%)	100,00	/
Selectivity (%)	95,69	/
AE (%)	61,88	61,84
RME (%)	59,21	52,89
PMI total ($g \cdot g^{-1}$)	13,44	14,49
PMI Reaction ($g \cdot g^{-1}$)	13,44	14,49
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	1,77	1,97

	Mass	MW	Mol
Product	9,00	94,11	0,0956
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
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	HOAc
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	

Experimental:
M. S. Kharasch, A. Fono, W. Nudenberg *J. Org. Chem.* **1950**, *15*, 748.

Decomposition of α-cumyl hydroperoxide in the presence of acetic acid and catalytic quantities of perchloric acid. α-Cumyl hydroperoxide (15.2 g., 0.1 mole), dissolved in 100 cc. of glacial acetic acid was treated with 0.1 cc. of a 5% solution of 70% perchloric acid in acetic acid. The temperature of the reaction mixture was kept below 22°. The peroxide titre of the mixture fell to zero after 5 minutes. *Phenol* (9 g., 95% yield) was isolated in crystalline form. *Acetone* was identified and estimated by means of its dinitrophenylhydrazone. An unidentified neutral oil (amounting to less than 3% of the starting material) was also obtained.

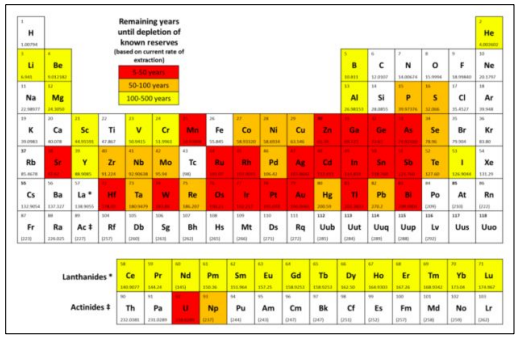
Catalyst/enzyme (First Pass)

		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	
+500 years	Green Flag	X



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 pressure)	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

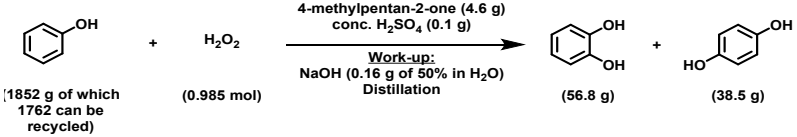
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			$HClO_4$ HOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	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	

- Step 4

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)
Phenol	90,00	94,11	0,9563	H_2SO_4	0,10			H_2O (H_2O_2)	22,32	1,00	22,32	NaOH	0,08	H_2O (NaOH)	0,08	1,00	0,08
H_2O_2	33,48	34,01	0,9844	MIBK	4,60			H_2O (H_2SO_4)	0,004	1,00	0,004						
Total	123,48	128,12			4,70		0,00				22,32		0,08				0,08



	STEP	CUMULATIVE
Yield (%)	53,95	44,16
Conversion (%)	100,00	/
Selectivity (%)	53,95	/
AE (%)	85,94	59,13
RME (%)	46,00	27,89
PMI total ($g \cdot g^{-1}$)	2,65	24,02
PMI Reaction ($g \cdot g^{-1}$)	2,65	24,02
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	2,26	3,80

	Mass	MW	Mol
Product	56,80	110,10	0,5159
	mass		
reactant			

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	

Experimental:

S. Umemura, N. Takamitsu, T. Hamamoto, N. Kuroda *Ube Industries Ltd* **1978**, US4078006A.

EXAMPLE 37

In the same reaction vessel as in Example 34, 1852 g. of phenol (19.68), 4.6 g. of 4-methyl-2-pentanone (0.046), 55.8 g. of 60 percent hydrogen peroxide (0.985 mole), and 0.10 g. of concentrated sulfuric acid were placed. The mixture was stirred at 50° C. in an oil bath for 10 minutes. After neutralization of sulfuric acid by adding 0.16 g. of 50 percent aqueous sodium hydroxide, the mixture was subjected to distillation under reduced perssure to fraction water, 3.7 g. of 4-methyl-2-pentanone, 1762 g. of phenol (18.72 moles), 56.8 g. of catechol (0.516 mole) and 38.5 g. of hydroquinone (0.350 mole). The total yield of the dihydric phenols based on hydrogen peroxide was 88.0 percent, and that based on phenol was 90.2 percent.

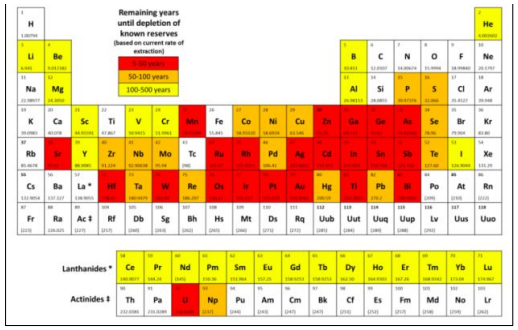
Catalyst/enzyme (First Pass)

		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	
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 pressure)	Green Flag	Distillation Neutralization
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

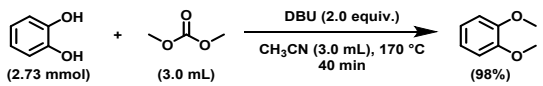
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O_2 H_2O MIBK $KHSO_4$
Explosive thermal runaway	H230, H240, H250	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	

- Step 5

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)
Catechol	0,30	110,00	0,0027			DBU	0,83	CH_3CN	3,00	0,79	2,36	HCl	0,27	H_2O (HCl)	7,50	1,00	7,50
Dimethyl carbonate (DMC)	0,49	90,10	0,0055					DMC	2,54	1,07	2,72	$MgCl_2{\cdot}6H_2O$	11,74	H_2O ($MgCl_2{\cdot}6H_2O$)	7,50	1,00	7,50
												Na_2SO_4	2,73	EtOAc	20,00	0,90	18,04
Total	0,79	200,10			0,00		0,83				5,08		14,74				33,04



	STEP	CUMULATIVE
Yield (%)	97,66	43,13
Conversion (%)	100,00	/
Selectivity (%)	97,66	/
AE (%)	69,05	50,04
RME (%)	46,50	23,48
PMI total ($g{\cdot}g^{-1}$)	148,04	166,81
PMI Reaction ($g{\cdot}g^{-1}$)	18,20	36,97
PMI Workup ($g{\cdot}g^{-1}$)	129,84	129,84
PMI RRC ($g{\cdot}g^{-1}$)	4,41	6,69

	Mass	MW	Mol
Product	0,37	138,16	0,0027
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	EtOAc 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	

Experimental:
M. Y. Lui, K. S. Lokare, E. Hemming, J. N. G. Stanley, A. Perosa, M. Selva, A. F. Masters, T. Maschmeyer *RSC Adv.* **2016**, *6*, 58443.

A solution of catechol (2.73 mmol), a catalytic amount of DBU (1 equiv. per OH), DMC (3 mL) and MeCN (3 mL) was heated in a 30 mL air tight glass vessel in an Anton Paar Monowave 300 microwave synthesis reactor at 170 °C with a stirring rate of 600 rpm. After 40 minutes, the reaction vial was removed from the microwave reactor and cooled to room temperature. The mixture was concentrated at 40 °C and 98 mbar, and mesitylene (200 µL) added as an external standard. The mixture was then combined with 1M HCl (7.5 mL) and magnesium chloride hexahydrate (7.7 M, 7.5 mL). The organic layer was subsequently extracted with ethyl acetate (10 × 2 mL), dried over anhydrous sodium sulfate and filtered. The sample was then analyzed by 1H NMR, GC-FID and GC-MS. Veratrole was obtained in 97.6% yield, no guaiacol, 100% conversion of catechol.

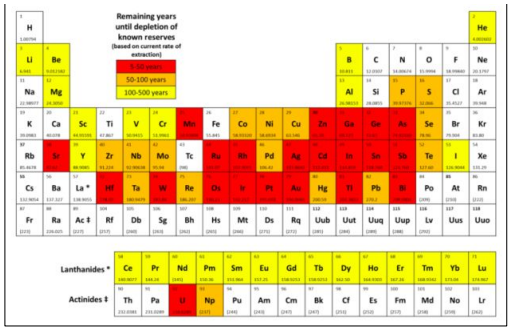
Catalyst/enzyme (First Pass)

		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	X

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+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 pressure)	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			Catechol Dimethylcarbonate Acetonitril HCl $MgCl_2.6H_2O$ Na_2SO_4 H_2O EtOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			DBU: H301	
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	

- Step 6

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)
Veratrole	50,00	138,07	0,3621					H_2O	16,80	1,00	16,80	Charcoal	724,27	EtOH	600,00	0,79	473,40
HNO_3	39,20	63,01	0,6221					H_2O	40,00	1,00	40,00			H_2O	200,00	1,00	200,00
														Et_2O	50,00	0,71	35,65
														ice	500,00	1,00	500,00
Total	89,20	201,08			0,00		0,00				56,80		724,27				1209,05

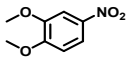
(50 g, 362 mmol)

+ HNO_3 (40 mL, 70%)

Reaction
H_2O (from HNO_3), H_2O (40 mL)
0°C, 30 min

ice (500 g)
0 °C to r.t., overnight

Workup
EtOH (600 mL)
H_2O (200 mL)
Charcoal, filtration
Et_2O (50 mL)



(55.3 g, 83%)

	STEP	CUMULATIVE
Yield (%)	83,42	35,98
Conversion (%)	100,00	/
Selectivity (%)	83,42	/
AE (%)	91,03	54,00
RME (%)	62,00	21,93
PMI total ($g \cdot g^{-1}$)	37,60	187,52
PMI Reaction ($g \cdot g^{-1}$)	2,64	35,16
PMI Workup ($g \cdot g^{-1}$)	34,96	152,36
PMI RRC ($g \cdot g^{-1}$)	1,61	6,76

	Mass	MW	Mol
Product	55,30	183,05	0,3021
	mass		
reactant	0,00		

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 EtOH
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

Experimental:

J. G. Stuart, S. Khora, J. D. McKenney, R. N. Castle *J. Heterocycl. Chem.* **1987**, *24*, 1589.

The title compound was prepared according to the procedure described by Cardwell and Robinson [14]. Veratrole (50 g, 362 mmoles) was added dropwise to a stirred solution of nitric acid (40 ml, d 1.40) and water (40 ml) at ice bath temperatures. After the addition was complete, the ice bath was removed and the mixture manually stirred periodically over 30 minutes then transferred to crushed ice (*ca* 500 g). After standing at room temperature overnight, the yellow precipitate was collected by filtration. This solid was dissolved in hot ethanol (*ca* 600 ml), diluted with water (200 ml), treated with charcoal then allowed to cool and stand at room temperature for 12 hours. The precipitate was collected by filtration, washed with anhydrous ether (50 ml) then dried to give 55.3 g (83%) of **10** as thick yellow irregular plates, mp 95-97° (lit [15] mp 97.5°);

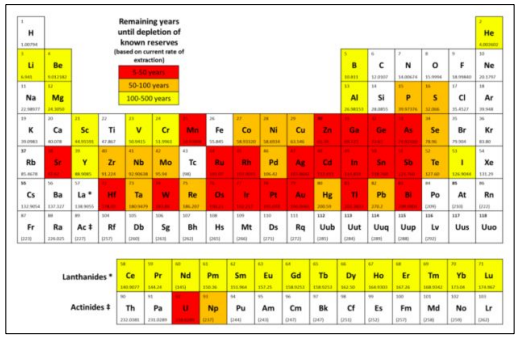
Catalyst/enzyme (First Pass)

		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	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 pressure)	Green Flag	filtration washing
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

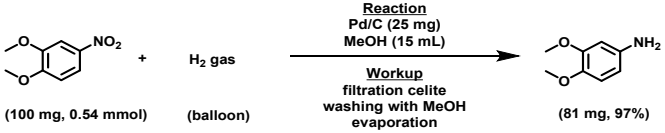
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Et_2O: H224	veratrole 4-nitroveratrole EtOH
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			HNO_3: 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	

- Step 7

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-nitroveratrole	0,10	183,050	0,0005	Pd/C	0,025			MeOH	15,00	0,79	11,88	Celite	1,09	MeOH	2,73	0,79	2,16
H_2 gas	0,33	2,020	0,1635														
Total	0,43	185,07			0,03		0,00				11,88		1,09				2,16



	STEP	CUMULATIVE
Yield (%)	97,55	35,09
Conversion (%)	100,00	/
Selectivity (%)	97,55	/
AE (%)	82,13	44,58
RME (%)	18,83	10,30
PMI total ($g \cdot g^{-1}$)	192,48	422,76
PMI Reaction ($g \cdot g^{-1}$)	152,29	194,46
PMI Workup ($g \cdot g^{-1}$)	40,20	228,29
PMI RRC ($g \cdot g^{-1}$)	5,62	12,73

	Mass	MW	Mol
Product	0,08	152,00	0,0005
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	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	

Experimental:
L. D. Arnold, K. W. Foreman, D. S. Werner *Coferon, Inc., USA* . **2013**, WO2013033270A2.

[00579] A solution of 3,4-dimethoxy nitrobenzene (100 mg, 0.54 mmol) in methanol (15 mL) was charged with 10% Pd/C (25 mg) under inert atmosphere then charged with H_2 gas at atmospheric pressure (balloon pressure) for 3 h. The reaction mixture was filtered through a pad of c*elite* and the pad was washed with methanol and the filtrate was concentrated *in vacuo* to afford 3,4-dimethoxy aniline (81 mg, Yield: 97%).

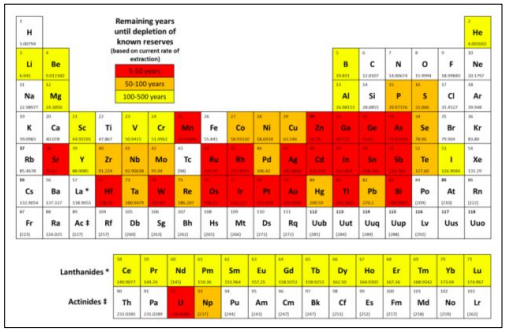
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any**	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	Pd
50-500 years	Amber Flag	
+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 pressure)	Green Flag	filtration
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_2 gas: H220	4-nitroveratrole Pd/c 4-aminoveratrole
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			MeOH: H301, H311, H331	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		MeOH: H370		
Environmental implications	H400, H410, H411, H420	H401, H412				

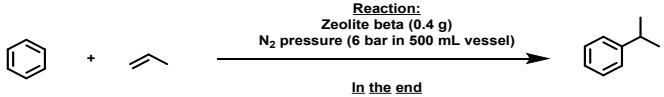
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

22.2 Classical synthesis of 2-Bromo-4,5-dimethoxyaniline (7)

- Step 1

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)
Benzene	352,00	78,11	4,51	Zeoite beta	0,40			N_2			3,39						
Propylene	208,00	42,08	4,94														
			#DIV/0!														
			#DIV/0!														
			#DIV/0!														
			#DIV/0!														
			#DIV/0!														
Total	560,00	120,19			0,40		0,00				3,39		0,00				0,00



(4.51 mol, 3.52 g) (0.62 mol, 26 g)

Reaction:
Zeolite beta (0.4 g)
N_2 pressure (6 bar in 500 mL vessel)

In the end
13% conversion

Work-up:
distillation
recycling of benzene

91.3% yield (after recycling of benzene)

	STEP	CUMULATIVE
Yield (%)	91,30	91,30
Conversion (%)	100,00	/
Selectivity (%)	91,30	/
AE (%)	99,92	99,92
RME (%)	88,23	88,23
PMI total ($g \cdot g^{-1}$)	1,14	1,14
PMI Reaction ($g \cdot g^{-1}$)	1,14	1,14
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	1,13	1,13

	Mass	MW	Mol
Product	4,94E+02	120,09	4,11E+00
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
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	

Experimental:
G. Spano, S. Ramello, G. Girotti, F. Rivetti, A. Carati *Polimeri Europa S.p.A., Italy; Enitecnologie S.p.A.* . **2006**, WO2006002805A1.

5 :Example nr. 5; 0.4 g of beta zeolite prepared according to what is described in example I, previously dried to 120°C for 16 hours, are charged into an electrically heated autoclave with an internal volume equal to 0.5 litres, equipped with a mechanical stirrer and with all the necessary devices forthe feeding of the benzene and propylene reagents.The autoclave is closed, put under vacuum by suction with a pump connected externally, and 352 g of benzene are .bul. then charged by suction. The autoclave is pressurized with nitrogen until a pressure of about 6 bar is reached and the heating is initiated to the programmed temperature of 150°C. When the temperature inside the autoclave has stably reached the pre-selected value, 26 g of propylene are rap-idly fed, by means of a pressure tank, and the mixture i s left to react for a time of exactly I hour, calculated starting from the end of the propylene feeding.At the end of the reaction, the product is discharged and analyzed by gas chromatography. The following products are present in the mixture at the end of the reaction: benzene, cumene, C_6 and C_9 ofIgomers of propylene, diisopropyl benzenes, other diisopropyl benzene isomers (C_9-phenyl = aromatic products generally indicated with the formula Ci_2Hi_8) / triisqpropyl benzenes, other triisopropyl benzene isomers (Cg-phenyl = aromatic products generally indicated with the formula $Ci_3H_2$4) , polyalkylated products with a mo-lecular weight higher than triisopropyl benzene (heavy polyalkylated products).The propylene conversion proves to be higher than97.0percent, the selectivity to mono-alkylated product (cumene)with respect to the converted propylene is equal to 91.3percentand the selectivity to (cumene + diisopropyl benzenes + triisopropyl benzenes) with respect to the converted pro-pylene is equal to 97.5percent.The weight ratio, called R, between the sum of (diisopropyl benzenes + triisopropyl benzenes + C_9-phenyl + C_9-phenyl + heavy polyalkylated products) and the sum of (cumene + diisopropyl benzenes + triisopropyl benzenes + C_9-phenyl + C_9-phenyl + heavy polyalkylated products) proves to be equal to 0.052.This ratio R is a measurement of the total quantity ofthe polyalkylated by-products alone with respect to the to- tal products and alkylated by-products formed during thereaction.

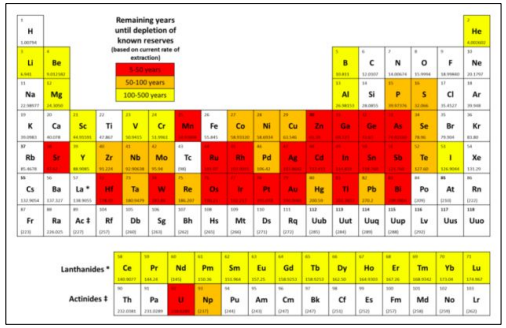
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any**	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	Al
+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	
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 pressure)	Green Flag	X
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

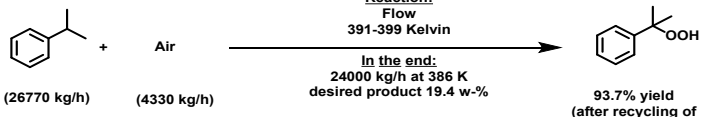
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Propylene: H220	
Explosive thermal runaway	H230, H240, H250	H241				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

- Step 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 (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Cumene	2,68E+07	120,09	2,23E+05					N_2 from air			1,57E+07						
O_2 from air	5,22E+06	31,99	1,63E+05														
Total	3,20E+07	152,08			0,00		0,00				1,57E+07		0,00				0,00



(26770 kg/h) (4330 kg/h)

Reaction:
Flow
391-399 Kelvin

In the end:
24000 kg/h at 386 K
desired product 19.4 w-%

Work-up:
condensation
distillation
recycling of cumene

93.7% yield
(after recycling of cumene)

	STEP	CUMULATIVE
Yield (%)	93,70	85,55
Conversion (%)	100,00	/
Selectivity (%)	93,70	/
AE (%)	100,00	99,94
RME (%)	99,30	89,33
PMI total ($g \cdot g^{-1}$)	1,50	1,62
PMI Reaction ($g \cdot g^{-1}$)	1,50	1,62
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	1,01	1,12

	Mass	MW	Mol
Product	3,18E+07	152,08	2,09E+05
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
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	

Experimental:

H. Bartkowiak, B. Haase, R. Hofmann, H. J. Naumann, B. Raue *VEB Leuna-Werke "Walter Ulbricht", Ger. Dem. Rep.* **1988**, DD258531A3.

Beispiel 1

Die Oxidation des Cumens zu Cumenhydroperoxid erfolgt in einem stehenden 62 m^3 großen Reaktor, der durch Siebbodenelemente in vier Reaktionsabschnitte geteilt ist, deren Reaktionsvolumen von oben nach unten 21, 21, 13 und 7 m^3 beinhalten. Dem Reaktor werden stündlich 26770 kg Cumen mit einer Temperatur von 388 K, das 1,8 Ma.-% Cumenhydroperoxid enthält, zugeführt. Unten werden 4330 kg/h Luft mit einer Temperatur von 298 K in den Reaktor eingeleitet. Oben verlassen den Reaktor 7100 kg/h Abgas, bestehend aus Stickstoff, Sauerstoff, Cumen und Cumenhydroperoxid mit einer Temperatur von 398 K. Mittels eines Kühlkreislaufes werden die Temperaturen in den einzelnen Reaktionsstufen zwischen 399 K oben und 391 K unten gehalten. Den Reaktor verlassen 24000 kg/h Oxidat mit einer Temperatur von 386 K und einem Gehalt an Cumenhydroperoxid von 19,4 Ma.-%. Das im Abgas enthaltene Cumen und Cumenhydroperoxid wird mittels Kühlwasser auskondensiert. Gleichfalls mittels Kühlwasser wird dem Kühlkreislauf die im Reaktor aufgenommene Wärme entzogen. Die Erwärmung des Cumens auf die Eintrittstemperatur von 388 K erfolgt zunächst in einem Wärmeaustauschapparat mittels des den Reaktor verlassenden Oxidats, wobei sich das Cumen von 303 K auf 349 K erwärmt und dann in einem weiteren Wärmeaustauscher mittels Heizdampf. Das Oxidat wird dabei innerhalb von 15 Minuten auf eine Temperatur von 346 K abgekühlt und gelangt danach in eine unterteilte, bei Drücken von 4 kPa und 1 kPa arbeitende Verdampferstufe, in der das Oxidat auf 89 Ma.-% Cumenhydroperoxid aufkonzentriert wird. Die Ausbeute an nutzbarem Cumenhydroperoxid beträgt bezüglich Cumen 93,7 Ma.-%. Der Verbrauch an Heizdampf zur Erzeugung des 89%igen Cumenhydroperoxids beträgt 4970 kg/h.

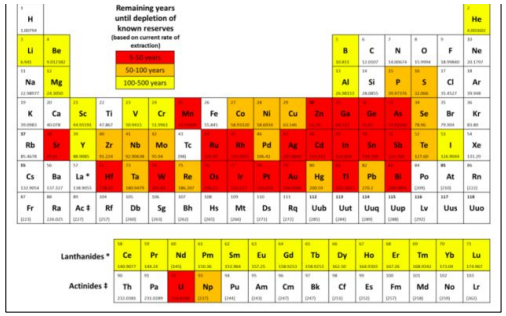
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any**	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	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	X
Batch	Amber Flag	

Work Up

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

Health & safety

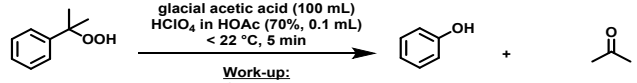
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			air
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, 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		Cumene (H411)		

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	

- Step 3

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)
Cumene hydroperoxide	15,20	152,08	0,0999	$HClO_4$	0,74			HOAc	100,00	1,05	104,92						
								HOAc	0,10	1,05	0,10						
Total	15,20	152,08			0,74		0,00				105,02		0,00				0,00



(15.2 g, 0.1 mol) (9.0 g, 95%) (estimated by means of its dinitrophenylhydrazone)

	STEP	CUMULATIVE
Yield (%)	95,69	81,85
Conversion (%)	100,00	/
Selectivity (%)	95,69	/
AE (%)	61,88	61,84
RME (%)	59,21	52,89
PMI total ($g \cdot g^{-1}$)	13,44	14,49
PMI Reaction ($g \cdot g^{-1}$)	13,44	14,49
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	1,77	1,97

	Mass	MW	Mol
Product	9,00	94,11	0,0956
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
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	HOAc
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	

Experimental:
M. S. Kharasch, A. Fono, W. Nudenberg *J. Org. Chem.* **1950**, *15*, 748.

Decomposition of α-cumyl hydroperoxide in the presence of acetic acid and catalytic quantities of perchloric acid. α-Cumyl hydroperoxide (15.2 g., 0.1 mole), dissolved in 100 cc. of glacial acetic acid was treated with 0.1 cc. of a 5% solution of 70% perchloric acid in acetic acid. The temperature of the reaction mixture was kept below 22°. The peroxide titre of the mixture fell to zero after 5 minutes. *Phenol* (9 g., 95% yield) was isolated in crystalline form. *Acetone* was identified and estimated by means of its dinitrophenylhydrazone. An unidentified neutral oil (amounting to less than 3% of the starting material) was also obtained.

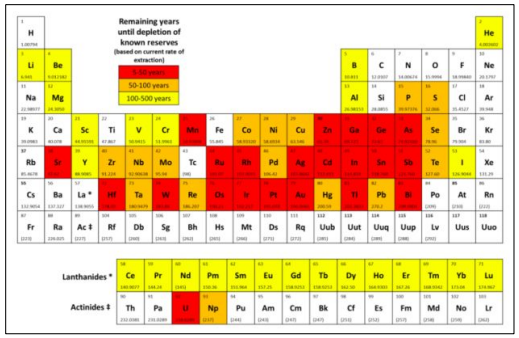
Catalyst/enzyme (First Pass)

		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	
+500 years	Green Flag	X



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 pressure)	Green Flag	Filtration
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

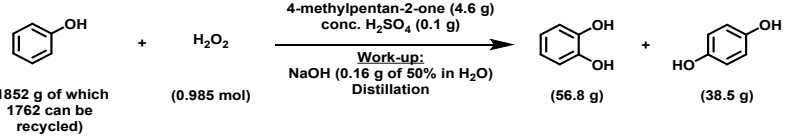
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			$HClO_4$ HOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	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	

- Step 4

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)
Phenol	90,00	94,11	0,9563	H_2SO_4	0,10			H_2O (H_2O_2)	22,32	1,00	22,32	NaOH	0,08	H_2O (NaOH)	0,08	1,00	0,08
H_2O_2	33,48	34,01	0,9844	MIBK	4,60			H_2O (H_2SO_4)	0,004	1,00	0,004						
Total	123,48	128,12			4,70		0,00				22,32		0,08				0,08



	STEP	CUMULATIVE
Yield (%)	53,95	44,16
Conversion (%)	100,00	/
Selectivity (%)	53,95	/
AE (%)	85,94	59,13
RME (%)	46,00	27,89
PMI total ($g \cdot g^{-1}$)	2,65	24,02
PMI Reaction ($g \cdot g^{-1}$)	2,65	24,02
PMI Workup ($g \cdot g^{-1}$)	0,00	0,00
PMI RRC ($g \cdot g^{-1}$)	2,26	3,80

	Mass	MW	Mol
Product	56,80	110,10	0,5159
	mass		
reactant			

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	

Experimental:

S. Umemura, N. Takamitsu, T. Hamamoto, N. Kuroda *Ube Industries Ltd* **1978**, US4078006A.

EXAMPLE 37

In the same reaction vessel as in Example 34, 1852 g. of phenol (19.68), 4.6 g. of 4-methyl-2-pentanone (0.046), 55.8 g. of 60 percent hydrogen peroxide (0.985 mole), and 0.10 g. of concentrated sulfuric acid were placed. The mixture was stirred at 50° C. in an oil bath for 10 minutes. After neutralization of sulfuric acid by adding 0.16 g. of 50 percent aqueous sodium hydroxide, the mixture was subjected to distillation under reduced perssure to fraction water, 3.7 g. of 4-methyl-2-pentanone, 1762 g. of phenol (18.72 moles), 56.8 g. of catechol (0.516 mole) and 38.5 g. of hydroquinone (0.350 mole). The total yield of the dihydric phenols based on hydrogen peroxide was 88.0 percent, and that based on phenol was 90.2 percent.

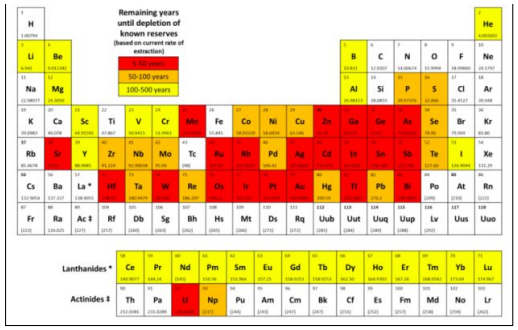
Catalyst/enzyme (First Pass)

		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	
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 pressure)	Green Flag	Distillation Neutralization
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

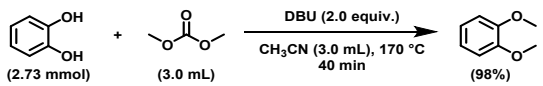
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H_2O_2 H_2O MIBK $KHSO_4$
Explosive thermal runaway	H230, H240, H250	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	

- Step 5

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)
Catechol	0,30	110,00	0,0027			DBU	0,83	CH_3CN	3,00	0,79	2,36	HCl	0,27	H_2O (HCl)	7,50	1,00	7,50
Dimethyl carbonate (DMC)	0,49	90,10	0,0055					DMC	2,54	1,07	2,72	$MgCl_2{\cdot}6H_2O$	11,74	H_2O ($MgCl_2{\cdot}6H_2O$)	7,50	1,00	7,50
												Na_2SO_4	2,73	EtOAc	20,00	0,90	18,04
Total	0,79	200,10			0,00		0,83				5,08		14,74				33,04



	STEP	CUMULATIVE
Yield (%)	97,66	43,13
Conversion (%)	100,00	/
Selectivity (%)	97,66	/
AE (%)	69,05	50,04
RME (%)	46,50	23,48
PMI total ($g{\cdot}g^{-1}$)	148,04	166,81
PMI Reaction ($g{\cdot}g^{-1}$)	18,20	36,97
PMI Workup ($g{\cdot}g^{-1}$)	129,84	129,84
PMI RRC ($g{\cdot}g^{-1}$)	4,41	6,69

	Mass	MW	Mol
Product	0,37	138,16	0,0027
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	EtOAc 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	

Experimental:
M. Y. Lui, K. S. Lokare, E. Hemming, J. N. G. Stanley, A. Perosa, M. Selva, A. F. Masters, T. Maschmeyer *RSC Adv.* **2016**, *6*, 58443.

A solution of catechol (2.73 mmol), a catalytic amount of DBU (1 equiv. per OH), DMC (3 mL) and MeCN (3 mL) was heated in a 30 mL air tight glass vessel in an Anton Paar Monowave 300 microwave synthesis reactor at 170 °C with a stirring rate of 600 rpm. After 40 minutes, the reaction vial was removed from the microwave reactor and cooled to room temperature. The mixture was concentrated at 40 °C and 98 mbar, and mesitylene (200 µL) added as an external standard. The mixture was then combined with 1M HCl (7.5 mL) and magnesium chloride hexahydrate (7.7 M, 7.5 mL). The organic layer was subsequently extracted with ethyl acetate (10 × 2 mL), dried over anhydrous sodium sulfate and filtered. The sample was then analyzed by 1H NMR, GC-FID and GC-MS. Veratrole was obtained in 97.6% yield, no guaiacol, 100% conversion of catechol.

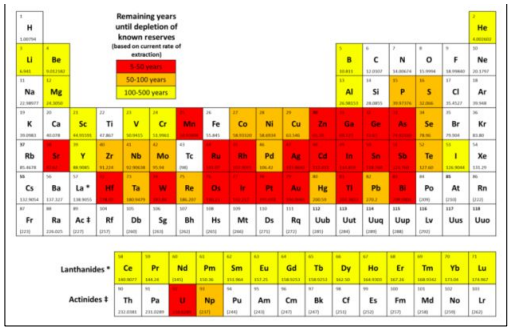
Catalyst/enzyme (First Pass)

		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	X

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+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 pressure)	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			Catechol Dimethylcarbonate Acetonitril HCl $MgCl_2.6H_2O$ Na_2SO_4 H_2O EtOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			DBU: H301	
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	

- Step 6

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)
Veratrole	50,00	138,07	0,3621					H_2O	16,80	1,00	16,80	Charcoal	724,27	EtOH	600,00	0,79	473,40
HNO_3	39,20	63,01	0,6221					H_2O	40,00	1,00	40,00			H_2O	200,00	1,00	200,00
														Et_2O	50,00	0,71	35,65
														ice	500,00	1,00	500,00
Total	89,20	201,08			0,00		0,00				56,80		724,27				1209,05

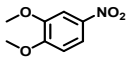
(50 g, 362 mmol)

+ HNO_3 (40 mL, 70%)

Reaction
H_2O (from HNO_3),
H_2O (40 mL)
0°C, 30 min

ice (500 g)
0 °C to r.t., overnight

Workup
EtOH (600 mL)
H_2O (200 mL)
Charcoal, filtration
Et_2O (50 mL)



(55.3 g, 83%)

	STEP	CUMULATIVE
Yield (%)	83,42	35,98
Conversion (%)	100,00	/
Selectivity (%)	83,42	/
AE (%)	91,03	54,00
RME (%)	62,00	21,93
PMI total ($g \cdot g^{-1}$)	37,60	187,52
PMI Reaction ($g \cdot g^{-1}$)	2,64	35,16
PMI Workup ($g \cdot g^{-1}$)	34,96	152,36
PMI RRC ($g \cdot g^{-1}$)	1,61	6,76

	Mass	MW	Mol
Product	55,30	183,05	0,3021
	mass		
reactant	0,00		

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 EtOH
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

Experimental:

J. G. Stuart, S. Khora, J. D. McKenney, R. N. Castle *J. Heterocycl. Chem.* **1987**, *24*, 1589.

The title compound was prepared according to the procedure described by Cardwell and Robinson [14]. Veratrole (50 g, 362 mmoles) was added dropwise to a stirred solution of nitric acid (40 ml, d 1.40) and water (40 ml) at ice bath temperatures. After the addition was complete, the ice bath was removed and the mixture manually stirred periodically over 30 minutes then transferred to crushed ice (*ca* 500 g). After standing at room temperature overnight, the yellow precipitate was collected by filtration. This solid was dissolved in hot ethanol (*ca* 600 ml), diluted with water (200 ml), treated with charcoal then allowed to cool and stand at room temperature for 12 hours. The precipitate was collected by filtration, washed with anhydrous ether (50 ml) then dried to give 55.3 g (83%) of **10** as thick yellow irregular plates, mp 95-97° (lit [15] mp 97.5°);

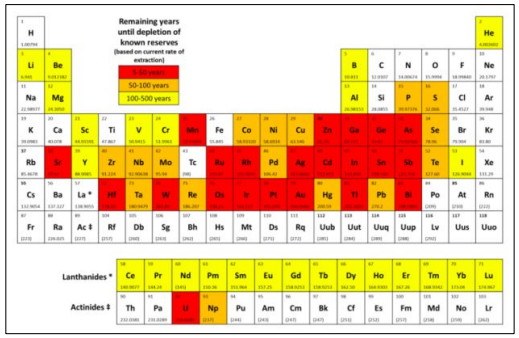
Catalyst/enzyme (First Pass)

		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	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 pressure)	Green Flag	filtration washing
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

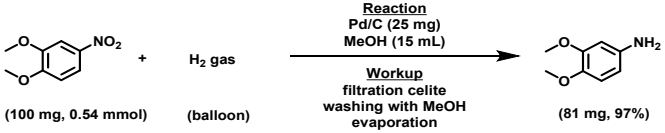
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Et_2O: H224	veratrole 4-nitroveratrole EtOH
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			HNO_3: 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	

- Step 7

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-nitroveratrole	0,10	183,050	0,0005	Pd/C	0,025			MeOH	15,00	0,79	11,88	Celite	1,09	MeOH	2,73	0,79	2,16
H_2 gas	0,33	2,020	0,1635														
Total	0,43	185,07			0,03		0,00				11,88		1,09				2,16



	STEP	CUMULATIVE
Yield (%)	97,55	35,09
Conversion (%)	100,00	/
Selectivity (%)	97,55	/
AE (%)	82,13	44,58
RME (%)	18,83	10,30
PMI total ($g \cdot g^{-1}$)	192,48	422,76
PMI Reaction ($g \cdot g^{-1}$)	152,29	194,46
PMI Workup ($g \cdot g^{-1}$)	40,20	228,29
PMI RRC ($g \cdot g^{-1}$)	5,62	12,73

	Mass	MW	Mol
Product	0,08	152,00	0,0005
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	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	

Experimental:
L. D. Arnold, K. W. Foreman, D. S. Werner *Coferon, Inc., USA* . **2013**, WO2013033270A2.

[00579] A solution of 3,4-dimethoxy nitrobenzene (100 mg, 0.54 mmol) in methanol (15 mL) was charged with 10% Pd/C (25 mg) under inert atmosphere then charged with H_2 gas at atmospheric pressure (balloon pressure) for 3 h. The reaction mixture was filtered through a pad of c*elite* and the pad was washed with methanol and the filtrate was concentrated *in vacuo* to afford 3,4-dimethoxy aniline (81 mg, Yield: 97%).

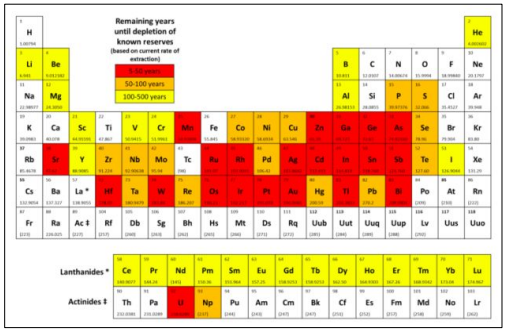
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any**	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	Pd
50-500 years	Amber Flag	
+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 pressure)	Green Flag	filtration
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_2 gas: H220	4-nitroveratrole Pd/c 4-aminoveratrole
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			MeOH: H301, H311, H331	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		MeOH: H370		
Environmental implications	H400, H410, H411, H420	H401, H412				

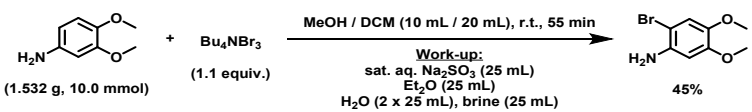
Use of chemicals of environmental concern

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

- Step 8

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)
3,4-dimethoxyaniline	1,53	153,00	0,0100					MeOH	10,00	0,79	7,92	Na_2SO_3	5,50	H_2O (Na_2SO_3)	25,00	1,00	25,00
Bu_4NBr_3	5,55	482,18	0,0115					CH_2Cl_2	20,00	1,33	26,60	NaCl	9,00	H_2O	50,00	1,00	50,00
												$MgSO_4$	10,01	H_2O (brine)	25,00	1,00	25,00
												SiO_2	80,10	Heptane	675,00	0,68	461,70
												SiO_2 plug	2,00	EtOAc	75,00	0,90	67,65
														Et_2O	25,00	0,71	17,83
Total	7,08	635,18			0,00		0,00				34,52		106,62				647,18



	STEP	CUMULATIVE
Yield (%)	44,90	15,76
Conversion (%)	100,00	/
Selectivity (%)	44,90	/
AE (%)	36,21	27,87
RME (%)	14,60	5,06
PMI total ($g \cdot g^{-1}$)	769,24	1394,13
PMI Reaction ($g \cdot g^{-1}$)	40,23	326,88
PMI Workup ($g \cdot g^{-1}$)	729,01	1067,25
PMI RRC ($g \cdot g^{-1}$)	6,85	24,23

	Mass	MW	Mol
Product	1,03	230,00	0,0045
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	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	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	Et_2O

Experimental:
P. Mampuys, H. Neumann, S. Sergeyev, R. V. A. Orru, H. Jiao, A. Spannenberg, B. U. W. Maes, M. Beller *ACS Catal.* **2017**, *7*, 5549.

In a roundbottom flask was added 3,4-dimethoxyaniline (1.532 g, 10.0 mmol, 1.0 equiv), MeOH (10 mL) and CH_2Cl_2 (20 mL) and the solution was stirred at room temperature. Tetrabutylammonium tribromide (5.550 g, 11.5 mmol, 1.1 equiv) was added in one portion, causing the reaction mixture to turn purple. The resulting mixture was allowed to stir for 55 minutes before it was poured into a separatory funnel containing saturated aqueous Na_2SO_3 (25 mL) and diethyl ether (25 mL). The organic layer was collected, washed with water (2 x 25 mL) and brine (25 mL) and dried over anhydrous $MgSO_4$. After filtration through a short plug of silica, the solvents were removed in vacuo and the product was purified by an automated flash chromatography system using silica cartridges and a heptane / EtOAc gradient (from 100% heptane to 20% ethyl acetate in 30 minutes, 25 mL/min). 2-Bromo-4,5-dimethoxyaniline was obtained in 45% (1.034 g) yield.

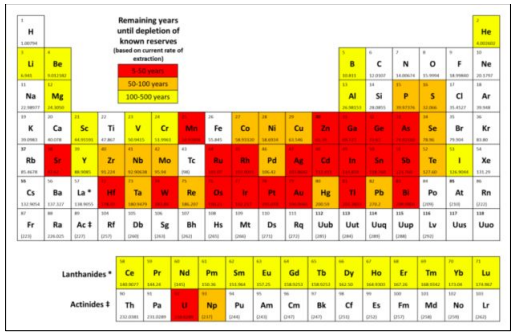
Catalyst/enzyme (First Pass)

		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	
+500 years	Green Flag	X



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 pressure)	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		Et_2O: H224	4-nitroveratrole Bu_4NBr_3 Na_2SO_3 $MgSO_4$ SiO_2 EtOAc
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			Methanol: H301, H311, H331	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		Methanol: H370	CH_2Cl_2: H351, H373	
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H400		

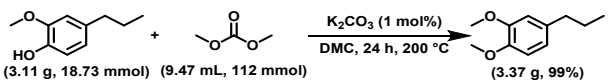
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

22.3 New synthesis of 3,4-dimethoxyaniline (5a)

- Step 1

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	3,11	166,00	0,0187	K_2CO_3	0,026			DMC	7,89	1,07	8,45			EtOAc	10,00	0,90	9,02
Dimethylcarbonate (DMC)	1,69	90,08	0,0187														
Total	4,80	256,08			0,03		0,00				8,45		0,00				9,02



	STEP	CUMULATIVE
Yield (%)	99,93	99,93
Conversion (%)	100,00	100,00
Selectivity (%)	99,93	99,93
AE (%)	70,29	70,29
RME (%)	70,24	70,24
PMI total ($g \cdot g^{-1}$)	6,61	6,61
PMI Reaction ($g \cdot g^{-1}$)	3,94	3,94
PMI Workup ($g \cdot g^{-1}$)	2,68	2,68
PMI RRC ($g \cdot g^{-1}$)	1,43	1,43

	Mass	MW	Mol
Product	3,37	180,00	0,01872
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	Dimethyl carbonate 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	

Experimental: ***[MS-538]***

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with potassium carbonate (26 mg, 0.187 mmol, 0.01 eq.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 3.00 mL, 18.7 mmol, 1 eq.) and dimethyl carbonate (10.13 g, 112 mmol, 6.0 eq.) (9.47 mL). The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to room temperature. The contents of the pressure tube was transferred with EtOAc (5 mL), filtered through cotton-wool into the round-bottom flask and the precipitate was washed with EtOAc (5 mL). The solvent was evaporated in order to afford 1,2-dimethoxy-4-propylbenzene (**2a)** as a pale yellow oil (3.39 g, 18.81 mmol, >99%).

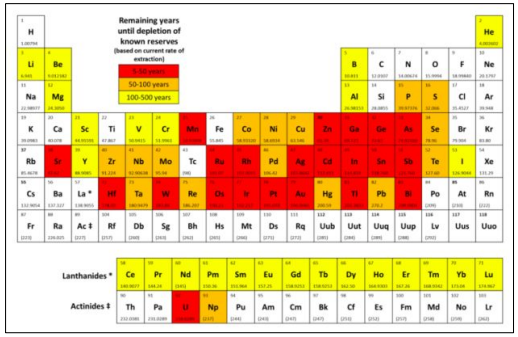
Catalyst/enzyme (First Pass)

		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	
+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	X

Work Up

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

Health & safety

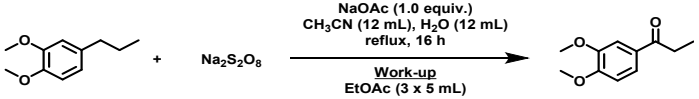
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			Dimethyl carbonate K_2CO_3 EtOAc
Explosive thermal runaway	H230, H240, 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	

- Step 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)
1,2-dimethoxy-4-propylbenzene	0,51	180,00	0,0028			NaOAc	0,23	CH_3CN	12,00	0,79	9,43			EtOAc	15,00	0,90	13,53
$Na_2S_2O_8$	1,60	238,00	0,0067					H_2O	12,00	1,00	12,00						
Total	2,11	418,00			0,00		0,23				21,43		0,00				13,53



	STEP	CUMULATIVE
Yield (%)	60,08	60,04
Conversion (%)	100,00	/
Selectivity (%)	60,08	/
AE (%)	46,41	39,26
RME (%)	15,53	8,43
PMI total ($g \cdot g^{-1}$)	114,06	122,73
PMI Reaction ($g \cdot g^{-1}$)	72,69	77,22
PMI Workup ($g \cdot g^{-1}$)	41,38	45,51
PMI RRC ($g \cdot g^{-1}$)	7,14	7,81

	Mass	MW	Mol
Product	0,33	194,00	0,0017
	mass		
reactant	0,00		

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
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	

Experimental: ***[JBO-1364]***

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-dimethoxy-4-propylbenzene (**2a**, 505 mg, 2.80 mmol, 1.0 eq.), CH_3CN (12 mL) and H_2O (12 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

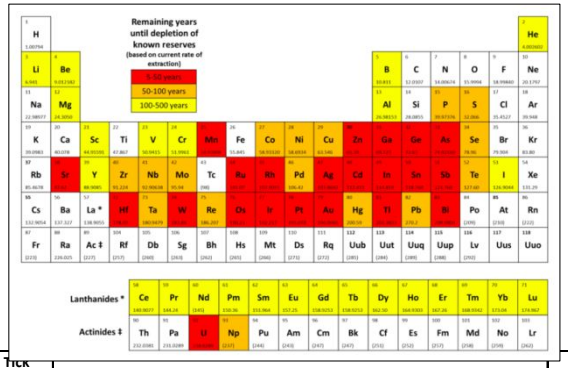
Catalyst/enzyme (First Pass)

		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	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	
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 pressure)	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

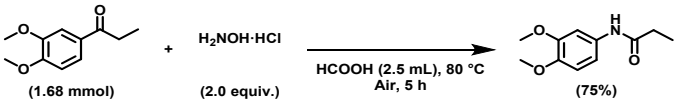
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			CH_3CN NaOAC
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			$Na_2S_2O_8$: H371	
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	

- Step 3

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)
1-(3,4-dimethoxyphenyl)propan-1-one	0,326	194,00	0,0017					Formic acid	2,50	1,22	3,05			H_2O	5,00	1,00	5,00
$NH_2OH{\cdot}HCl$	0,233	69,00	0,0034											MTBE	30,00	0,74	22,20
Total	0,56	263,00			0,00		0,00				3,05		0,00				27,20



	STEP	CUMULATIVE
Yield (%)	74,88	44,96
Conversion (%)	100,00	/
Selectivity (%)	74,88	/
AE (%)	79,47	37,12
RME (%)	47,05	6,41
PMI total ($g{\cdot}g^{-1}$)	117,14	268,04
PMI Reaction ($g{\cdot}g^{-1}$)	13,72	108,20
PMI Workup ($g{\cdot}g^{-1}$)	103,42	159,83
PMI RRC ($g{\cdot}g^{-1}$)	2,13	10,57

	Mass	MW	Mol
Product	0,263	209,00	0,0013
	mass		
reactant	0,00		

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	Formic acid 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	

Experimental: ***[JBO-1365]***

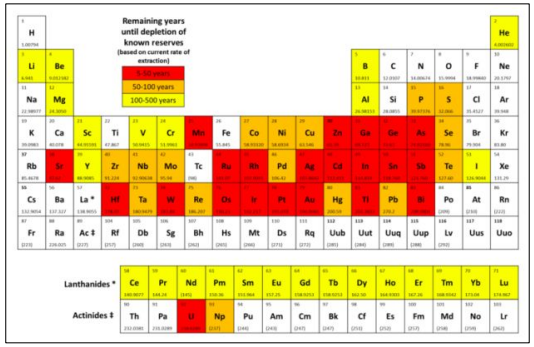
A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 2, containing 1-(3,4-dimethoxyphenyl)propan-1-one (**3a**) (around 1.68 mmol, 1.0 eq.), hydroxylammonium chloride (233 mg, 3.36 mmol, 2.0 eq.) and formic acid (2.5 mL). The reaction mixture was stirred at 80 °C for 6 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers are combined and concentrated under reduced pressure in order to afford a black oil.

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	
+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	
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 pressure)	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

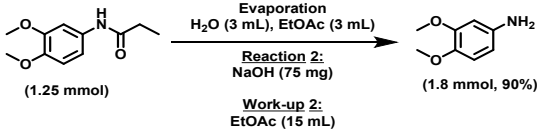
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			$NH_2OH{\cdot}HCl$: H351, H373 CH_2Cl_2: H351	
Environmental implications	H400, H410, H411, H420	H401, H412		$NH_2OH{\cdot}HCl$: 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	

- Step 4

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)
N-(3,4-dimethoxyphenyl)propionamide	0,263	209,00	0,0013			NaOH	0,08	EtOH	1,97	0,79	1,56	$MgSO_4$	1,26	EtOAc	3,00	0,90	2,71
HCl	0,092	36,46	0,0025					H_2O	3,00	1,00	3,00			EtOAc	15,00	0,90	13,53
Total	0,35	245,46			0,00		0,08				4,56		1,26				16,24



	STEP	CUMULATIVE
Yield (%)	91,93	41,33
Conversion (%)	100,00	/
Selectivity (%)	91,93	/
AE (%)	62,33	25,52
RME (%)	49,89	4,22
PMI total ($g \cdot g^{-1}$)	127,02	523,80
PMI Reaction ($g \cdot g^{-1}$)	28,18	187,47
PMI Workup ($g \cdot g^{-1}$)	98,84	336,33
PMI RRC ($g \cdot g^{-1}$)	2,43	16,64

	Mass	MW	Mol
Product	0,177	153,00	0,0012
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	EtOH 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	

Experimental: ***[JBO-1366]***

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture obtained in step 2, containing *N*-(3,4-dimethoxyphenyl)propionamide (**4a**) (around 1.26 mmol, 1.0 eq.), and a 1.25 M HCl solution in ethanol (2.0 mL, 2.50 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture, containing 3,4-dimethoxyaniline (**5a**) as a hydrochloride, was diluted with water (5 mL), washed with EtOAc (5 mL) in order to remove organic by-products. To the aqueous phase was added solid NaOH (75 mg, 1.5 eq.) and the product was extracted with EtOAc (3×5 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure in order to afford **5a** as a light brown powder (177 mg, 1.16 mmol, 41% over 4 steps).

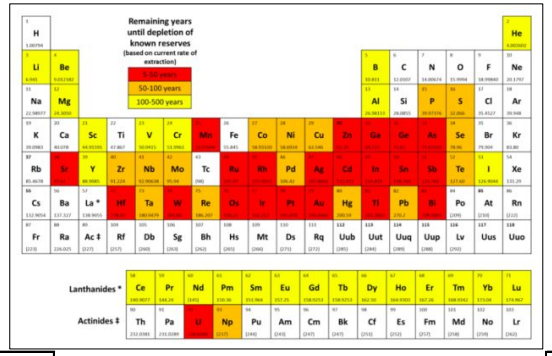
Catalyst/enzyme (First Pass)

		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	
+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	
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 pressure)	Green Flag	Quenching
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 EtOH NaOH HCl
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				

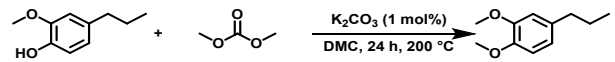
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

22.4 New synthesis of 2-bromo-4,5-dimethoxyaniline (7)

- Step 1

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	3,11	166,00	0,0187	K_2CO_3	0,026			DMC	7,89	1,07	8,45			EtOAc	10,00	0,90	9,02
Dimethyl carbonate (DMC)	1,69	90,08	0,0187														
Total	4,80	256,08			0,03		0,00				8,45		0,00				9,02



(3.11 g, 18.73 mmol) (9.47 mL, 112 mmol) (3.37 g, 99%)

	STEP	CUMULATIVE
Yield (%)	99,93	99,93
Conversion (%)	100,00	100,00
Selectivity (%)	99,93	99,93
AE (%)	70,29	70,29
RME (%)	70,24	70,24
PMI total ($g \cdot g^{-1}$)	6,61	6,61
PMI Reaction ($g \cdot g^{-1}$)	3,94	3,94
PMI Workup ($g \cdot g^{-1}$)	2,68	2,68
PMI RRC ($g \cdot g^{-1}$)	1,43	1,43

	Mass	MW	Mol
Product	3,37	180,00	0,0187
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	Dimethyl carbonate 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	

Experimental: ***[MS-538]***

A 100 mL pressure tube, equipped with a magnetic stirring bar, was charged with potassium carbonate (26 mg, 0.187 mmol, 0.01 eq.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 3.00 mL, 18.7 mmol, 1 eq.) and dimethyl carbonate (10.13 g, 112 mmol, 6.0 eq.) (9.47 mL). The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to room temperature. The contents of the pressure tube was transferred with EtOAc (5 mL), filtered through cotton-wool into the round-bottom flask and the precipitate was washed with EtOAc (5 mL). The solvent was evaporated in order to afford 1,2-dimethoxy-4-propylbenzene (**2a)** as a pale yellow oil (3.37 g, 18.81 mmol, >99%).

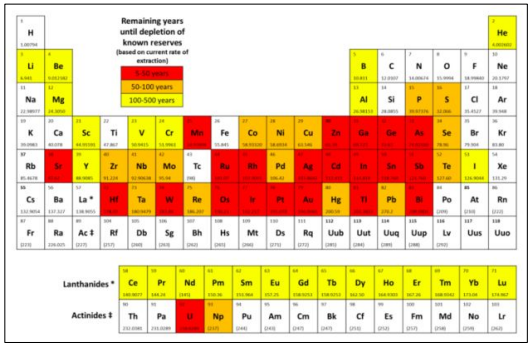
Catalyst/enzyme (First Pass)

		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	
+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	X

Work Up

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

Health & safety

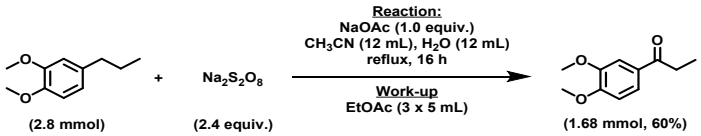
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			Dimethyl carbonate K_2CO_3 EtOAc
Explosive thermal runaway	H230, H240, 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	

- Step 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)
1,2-dimethoxy-4-propylbenzene	0,51	180,00	0,0028			NaOAc	0,23	CH_3CN	12,00	0,79	9,43			EtOAc	15,00	0,90	13,53
$Na_2S_2O_8$	1,60	238,00	0,0067					H_2O	12,00	1,00	12,00						
Total	2,11	418,00			0,00		0,23				21,43		0,00				13,53



	STEP	CUMULATIVE
Yield (%)	60,08	60,04
Conversion (%)	100,00	/
Selectivity (%)	60,08	/
AE (%)	46,41	39,26
RME (%)	15,53	14,10
PMI total ($g \cdot g^{-1}$)	114,06	122,73
PMI Reaction ($g \cdot g^{-1}$)	72,69	77,22
PMI Workup ($g \cdot g^{-1}$)	41,38	45,51
PMI RRC ($g \cdot g^{-1}$)	7,14	7,81

	Mass	MW	Mol
Product	0,33	194,00	0,0017
	mass		
reactant	0,00		

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
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	

Experimental: ***[JBO-1371]***

A 100 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with sodium persulfate (1.60 g, 6.72 mmol, 2.4 eq.), sodium acetate (230 mg, 2.80 mmol, 1.0 eq.), 1,2-dimethoxy-4-propylbenzene (**2a**, 505 mg, 2.80 mmol, 1.0 eq.), CH_3CN (12 mL) and H_2O (12 mL). The reaction mixture was stirred under reflux for 16 h, cooled down to room temperature, and extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a brown oil.

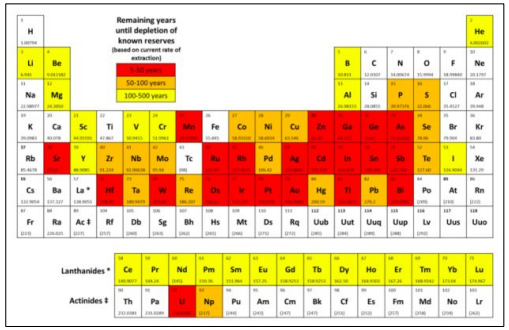
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	S
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	
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 pressure)	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

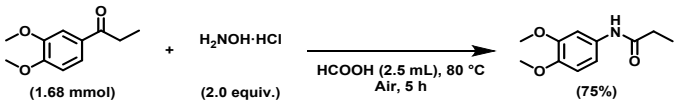
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			CH_3CN NaOAC
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			$Na_2S_2O_8$: H371	
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	

- Step 3

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)
1-(3,4-dimethoxyphenyl)propan-1-one	0,33	194,00	0,0017					Formic acid	2,60	1,22	3,17			H_2O	5,00	1,00	5,00
$NH_2OH{\cdot}HCl$	0,23	69,00	0,0034								0,00			MTBE	30,00	0,74	22,20
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
			#DIV/0!								0,00						0,00
Total	0,56	263,00			0,00		0,00				3,17		0,00				27,20



	STEP	CUMULATIVE
Yield (%)	74,88	44,96
Conversion (%)	100,00	/
Selectivity (%)	74,88	/
AE (%)	79,47	37,12
RME (%)	47,05	10,33
PMI total ($g{\cdot}g^{-1}$)	117,61	268,50
PMI Reaction ($g{\cdot}g^{-1}$)	14,19	108,67
PMI Workup ($g{\cdot}g^{-1}$)	103,42	159,83
PMI RRC ($g{\cdot}g^{-1}$)	2,13	10,57

	Mass	MW	Mol
Product	0,263	209,00	0,0013
	mass		
reactant	0,00		

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	Formic acid 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	

Experimental: ***[JBO-1372]***

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 2 containing 1-(3,4-dimethoxyphenyl)propan-1-one (**3a**, around 1.68 mmol, 1.0 eq.), hydroxylammonium chloride (234 mg, 3.37 mmol, 2.0 eq.) and formic acid (2.6 mL). The reaction mixture was stirred at 80 °C for 6 h, cooled down to room temperature, diluted with H_2O (5 mL) and extracted with MTBE (3×10 mL). The organic layers were combined and concentrated under reduced pressure in order to afford a black oil.

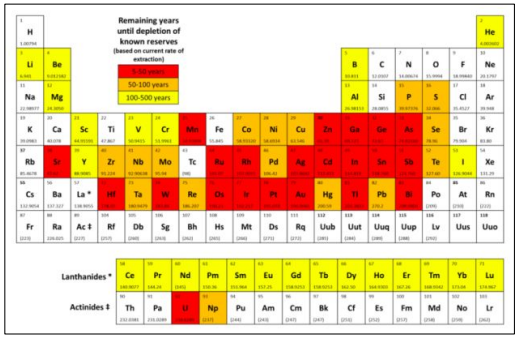
Catalyst/enzyme (First Pass)

		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	X

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	
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 pressure)	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

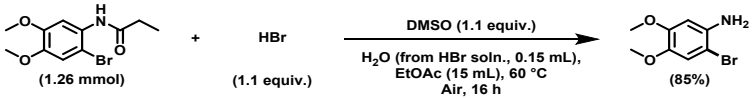
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			$NH_2OH{\cdot}HCl$: H351, H373 CH_2Cl_2: H351	
Environmental implications	H400, H410, H411, H420	H401, H412		$NH_2OH{\cdot}HCl$: 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	

- Step 4

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)
N-(3,4-dimethoxyphenyl)propionamide	0,263	209,11	0,0013			DMSO	0,11	H_2O (HBr)	0,12	1,00	0,12	$MgSO_4$	1,26	H_2O	15,00	1,00	15,00
HBr	0,112	80,91	0,0014					EtOAc	5,00	0,90	4,51						
Total	0,38	290,02			0,00		0,11				4,63		1,26				15,00



	STEP	CUMULATIVE
Yield (%)	94,57	42,52
Conversion (%)	100,00	/
Selectivity (%)	94,57	/
AE (%)	98,97	44,55
RME (%)	91,09	12,85
PMI total ($g \cdot g^{-1}$)	62,50	268,58
PMI Reaction ($g \cdot g^{-1}$)	14,96	97,90
PMI Workup ($g \cdot g^{-1}$)	47,54	170,68
PMI RRC ($g \cdot g^{-1}$)	1,42	8,79

	Mass	MW	Mol
Product	0,342	287,02	0,0012
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	EtOAc 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	

Experimental: ***[JBO-1373]***

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 3 containing *N*-(3,4-dimethoxyphenyl)propionamide (**4a**, around 1.26 mmol, 1.0 eq.), DMSO (99 µL, 1.39 mmol, 1.1 eq.), aqueous solution of HBr 48% (156 µL, 1.39 mmol, 1.1 eq.) and EtOAc (5 mL). The reaction mixture was stirred at 60 °C for 16 h , cooled down to room temperature and washed with water (3×5 mL). The organic layer is dried with $MgSO_4$, filtered and concentrated under reduced pressure in order to afford a black oil.

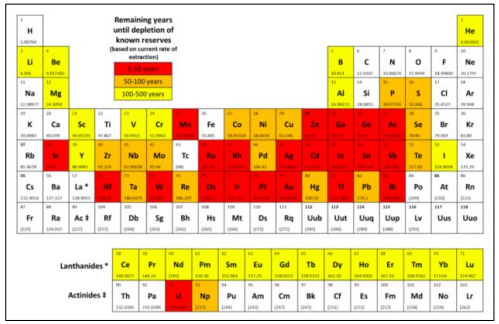
Catalyst/enzyme (First Pass)

		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 pressure)	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	Extraction
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

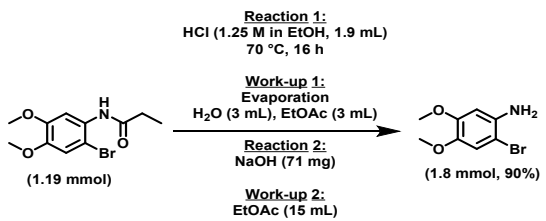
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			DMSO EtOAc HBr
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	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	

- Step 5

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)
N-(2-bromo-4,5-dimethoxyphenyl)propionamid	0,342	287,02	0,0012			NaOH	0,07		1,79	0,79	1,42	$MgSO_4$	1,19	EtOAc	3,00	0,90	2,71
HCl	0,087	36,46	0,0024					H_2O	3,00	1,00	3,00			EtOAc	15,00	0,90	13,53
Total	0,43	323,48			0,00		0,07				4,42		1,19				16,24



	STEP	CUMULATIVE
Yield (%)	61,40	26,11
Conversion (%)	100,00	/
Selectivity (%)	61,40	/
AE (%)	71,41	33,93
RME (%)	39,40	6,15
PMI total ($g \cdot g^{-1}$)	132,21	673,71
PMI Reaction ($g \cdot g^{-1}$)	29,09	225,19
PMI Workup ($g \cdot g^{-1}$)	103,12	448,52
PMI RRC ($g \cdot g^{-1}$)	2,96	18,71

	Mass	MW	Mol
Product	0,169	230,99	0,0007
	mass		
reactant	0,00		

Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	EtOH 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	

Experimental: ***[JBO-1374]***

A 50 mL round bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with the crude mixture from Step 4 containing *N*-(2-bromo-4,5-dimethoxyphenyl)propionamide (**10**, around 1.19 mmol, 1.0 eq.) and a 1.25 M HCl solution in ethanol (1.90 mL, 2.37 mmol, 2.0 eq.). The reaction mixture was stirred at 70 °C for 24 h, cooled down to room temperature and concentrated under reduced pressure. The crude mixture containing 2-bromo-3,4-dimethoxyaniline as a hydrochloride (**7**·HCl) was diluted with H_2O (3 mL), washed with EtOAc (3 mL) in order to remove organic by-products. NaOH (71 mg, 1.78 mol, 1.5 eq.) was added to the aqueous layer and this layer was extracted with EtOAc (3×5 mL). The organic layers were combined and concentrated under reduced pressure in order to afford 2-bromo-4,5-dimethoxyaniline (**7**) as a brown powder (169 mg, 0.73 mmol, 26% over 5 steps).

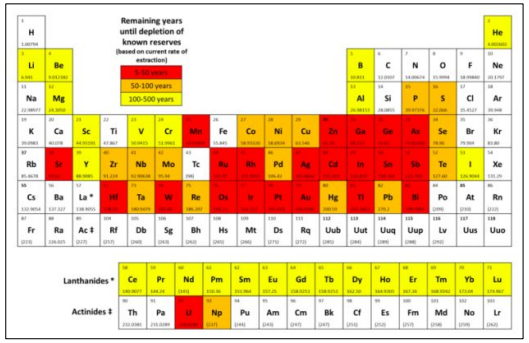
Catalyst/enzyme (First Pass)

		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	
+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	
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 pressure)	Green Flag	Quenching
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 EtOH NaOH HCl
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			CH_2Cl_2: H351	
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	

23 References

1. Zhao, S.; Abu-Omar, M. M., Biobased Epoxy Nanocomposites Derived from Lignin-Based Monomers. *Biomacromolecules* **2015,** *16* (7), 2025-31, DOI 10.1021/acs.biomac.5b00670.

2. Lee, M.; Sanford, M. S., Remote C(sp^3)–H Oxygenation of Protonated Aliphatic Amines with Potassium Persulfate. *Org. Lett.* **2017,** *19* (3), 572-575, DOI 10.1021/acs.orglett.6b03731.

3. Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L., Copper-Catalyzed Cross-Coupling Reaction of Organoboron Compounds with Primary Alkyl Halides and Pseudohalides. *Angewandte Chemie International Edition* **2011,** *50* (17), 3904-3907, DOI 10.1002/anie.201008007.

4. Joshi, B. P.; Sharma, A.; Sinha, A. K., Microwave- and ultrasound-assisted semisynthesis of natural methoxylated propiophenones from isomeric mixture of phenylpropenes in minutes. *Can. J. Chem.* **2005,** *83* (10), 1826-1832, DOI 10.1139/V05-185.

5. Aksenov, A. V.; Aksenov, N. A.; Nadein, O. N.; Aksenova, I. V., Nitroethane in Polyphosphoric Acid: A New Reagent for Acetamidation and Amination of Aromatic Compounds. *Synlett* **2010,** *2010* (17), 2628-2630, DOI 10.1055/s-0030-1258767.

6. Patel, B. K.; Ghosh, H.; Baneerjee, A.; Rout, S. K., A convenient one-pot synthesis of amines from aldoximes mediated by Koser's reagent. *Arkivoc* **2011,** *2011* (2), 209, DOI 10.3998/ark.5550190.0012.216.

7. Bourguignon, J.-J.; Lagouge, Y.; Lugnier, C.; Klotz, E.; Macher, J.-P.; Raboisson, P.; Schultz, D. Preparation of benzodiazepinones as cyclic nucleotide phosphodiesterase (particularly PDE4) inhibitors useful as antiinflammatories. WO2002098865A2, 2002.

8. Marzaro, G.; Guiotto, A.; Pastorini, G.; Chilin, A., A novel approach to quinazolin-4(3*H*)-one via quinazoline oxidation: an improved synthesis of 4-anilinoquinazolines. *Tetrahedron* **2010,** *66* (4), 962-968, DOI 10.1016/j.tet.2009.11.091.

9. Liu, J.; Wu, K.; Shen, T.; Liang, Y.; Zou, M.; Zhu, Y.; Li, X.; Li, X.; Jiao, N., Fe-Catalyzed Amination of (Hetero)Arenes with a Redox-Active Aminating Reagent under Mild Conditions. *Chemistry – A European Journal* **2017,** *23* (3), 563-567, DOI 10.1002/chem.201605476.

10. Mampuys, P.; Neumann, H.; Sergeyev, S.; Orru, R. V. A.; Jiao, H.; Spannenberg, A.; Maes, B. U. W.; Beller, M., Combining Isocyanides with Carbon Dioxide in Palladium-Catalyzed Heterocycle Synthesis: *N*3-Substituted Quinazoline-2,4(1*H*,3*H*)-diones via a Three-Component Reaction. *ACS Catal.* **2017,** *7* (8), 5549-5556, DOI 10.1021/acscatal.7b01503.

11. McElroy, C. R.; Constantinou, A.; Jones, L. C.; Summerton, L.; Clark, J. H., Towards a holistic approach to metrics for the 21st century pharmaceutical industry. *Green Chem.* **2015,** *17* (5), 3111-3121, DOI 10.1039/c5gc00340g.

12. Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J., CHEM21 selection guide of classical- and less classical-solvents. *Green Chem.* **2016,** *18* (1), 288-296, DOI 10.1039/c5gc01008j.

13. CHEM21 Metrics Toolkit. https://www.chem21.eu/project/metrics-toolkit/ (accessed November 2018).

14. Van den Bosch, S.; Schutyser, W.; Vanholme, R.; Driessen, T.; Koelewijn, S. F.; Renders, T.; De Meester, B.; Huijgen, W. J. J.; Dehaen, W.; Courtin, C. M.; Lagrain, B.; Boerjan, W.; Sels, B. F., Reductive lignocellulose fractionation into soluble lignin-derived phenolic monomers and dimers and processable carbohydrate pulps. *Energy Environ. Sci.* **2015,** *8* (6), 1748-1763, DOI 10.1039/C5EE00204D.

15. Spano, G.; Ramello, S.; Girotti, G.; Rivetti, F.; Carati, A. Catalysts for alkylated aromatic hydrocarbon preparation through alkylation and/or transalkylation of aromatic compounds. WO2006002805A1, 2006.

16. Hock, H.; Lang, S., Autoxydation von Kohlenwasserstoffen, IX. Mitteil.: Über Peroxyde von Benzol-Derivaten. *Chem. Ber.* **1944,** *77* (3-4), 257-264, DOI 10.1002/cber.19440770321.

17. Bartkowiak, H.; Haase, B.; Hofmann, R.; Naumann, H. J.; Raue, B. Process for cumene hydroperoxide manufacture by cumene oxidation with reduced energy consumption by efficient heat of formation exchange. DD258531A3, 1988.

18. Kharasch, M. S.; Fono, A.; Nudenberg, W., The Chemistry of Hydroperoxides I. The Acid-Catalyzed Decomposition of α,α-Dimethylbenzyl (α-Cumyl) Hydroperoxide. *J. Org. Chem.* **1950,** *15* (4), 748-752, DOI 10.1021/jo01150a005.

19. Umemura, S.; Takamitsu, N.; Hamamoto, T.; Kuroda, N. Process for preparing dihydric phenol derivatives. US4078006A, 1978.

20. Fiege, H.; Voges, H.-W.; Hamamoto, T.; Umemura, S.; Iwata, T.; Miki, H.; Fujita, Y.; Buysch, H.-J.; Garbe, D.; Paulus, W., Phenol Derivatives. In *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA: 2000, DOI 10.1002/14356007.a19_313.

21. Lui, M. Y.; Lokare, K. S.; Hemming, E.; Stanley, J. N. G.; Perosa, A.; Selva, M.; Masters, A. F.; Maschmeyer, T., Microwave-assisted methylation of dihydroxybenzene derivatives with dimethyl carbonate. *RSC Adv.* **2016,** *6* (63), 58443-58451, DOI 10.1039/c6ra09841j.

22. Stuart, J. G.; Khora, S.; McKenney, J. D.; Castle, R. N., The synthesis of dimethoxy- and trimethoxy[1]benzothieno[2,3-*c*]quinolines. *J. Heterocycl. Chem.* **1987,** *24* (6), 1589-1594, DOI 10.1002/jhet.5570240617.

23. Arnold, L. D.; Foreman, K. W.; Werner, D. S. Preparation of 4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine derivatives as bromodomain ligands capable of dimerizing in an aqueous solution, and methods of using same. WO2013033270A2, 2013.

24. Lopez-Tapia, F.; Walker, K. A.; Brotherton-Pleiss, C.; Caroon, J.; Nitzan, D.; Lowrie, L.; Gleason, S.; Zhao, S. H.; Berger, J.; Cockayne, D.; Phippard, D.; Suttmann, R.; Fitch, W. L.; Bourdet, D.; Rege, P.; Huang, X.; Broadbent, S.; Dvorak, C.; Zhu, J.; Wagner, P.; Padilla, F.; Loe, B.; Jahangir, A.; Alker, A., Novel Series of Dihydropyridinone P2X7 Receptor Antagonists. *J. Med. Chem.* **2015,** *58* (21), 8413-26, DOI 10.1021/acs.jmedchem.5b00365.

25. Samel, U.-R.; Kohler, W.; Gamer, A. O.; Keuser, U., Propionic acid and derivatives. In *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH: 2011, DOI 10.1002/14356007.a22_223.pub2.

26. ChemSec SIN LIST. http://sinlist.chemsec.org/ (accessed November 15, 2018).

27. Kreye, O.; Over, L. C.; Nitsche, T.; Lange, R. Z.; Meier, M. A. R., Organic carbonates: sustainable and environmentally-friendly ethylation, allylation, and benzylation reagents. *Tetrahedron* **2015,** *71* (2), 293-300, DOI 10.1016/j.tet.2014.11.053.