Electronic Supplementary Material (ESI) for Dalton Transactions.

Supplementary Information

Mechanistic Studies on the Palladium-Catalyzed Cross-Dehydrogenative Coupling of 4-Phenoxy-2-Coumarins: Experimental and Computational Insights

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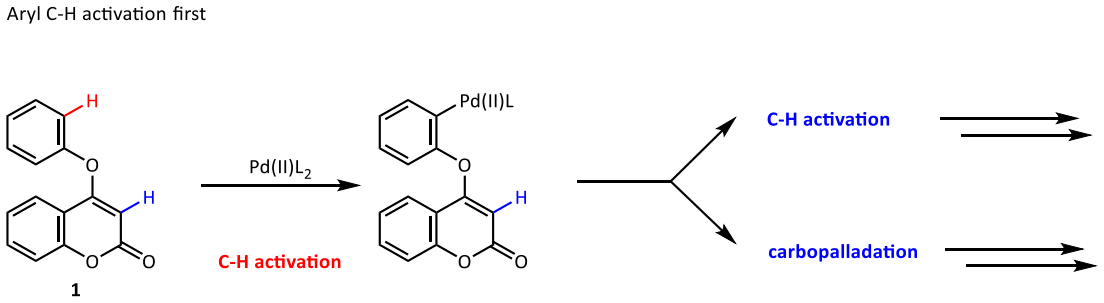
Other pathways for the CDC of 4-phenoxy-2-coumarins

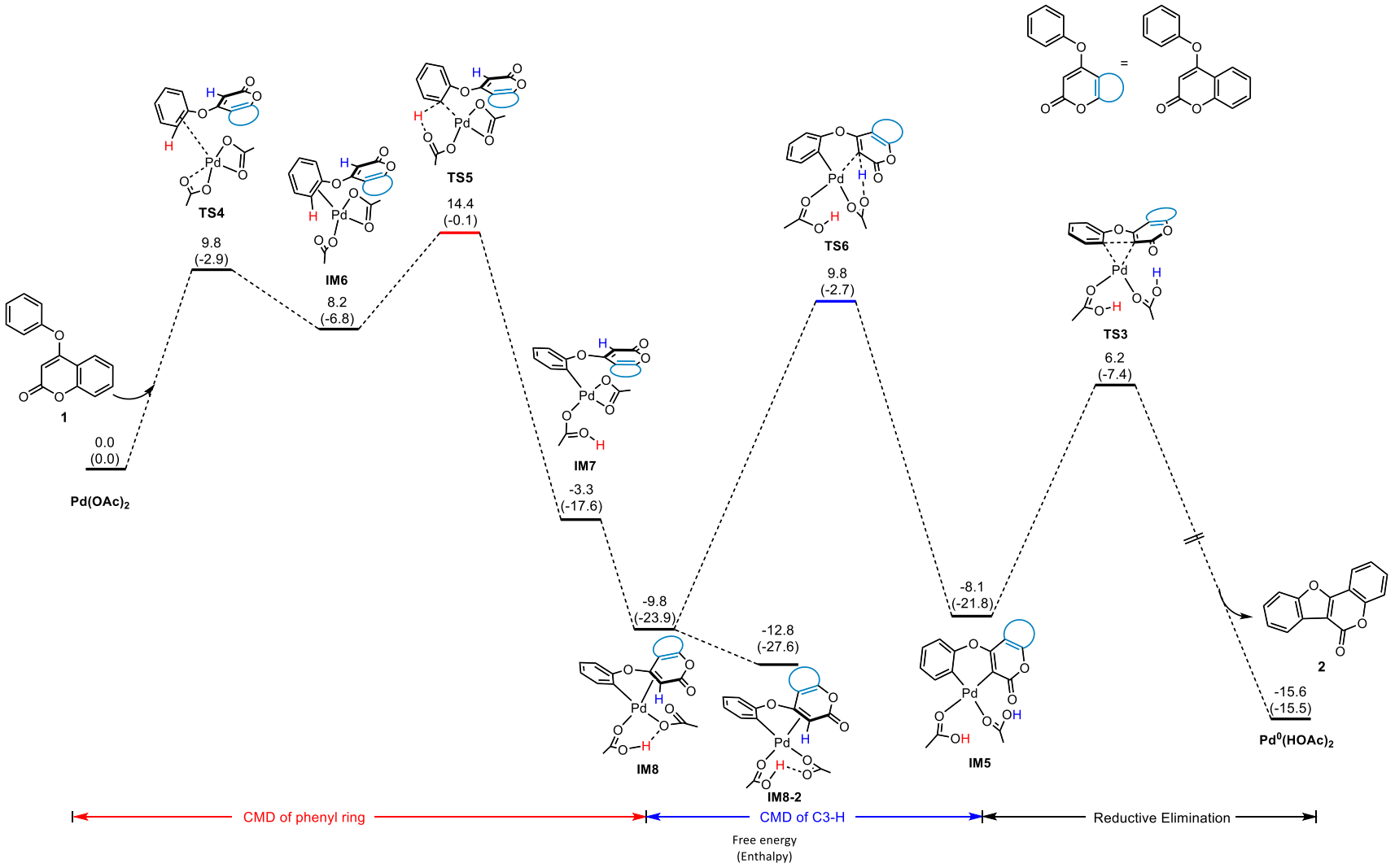
Several mechanistic modes of action were considered possible for the CDC of 4-phenoxy-2-coumarins. The most likely mechanistic pathway is discussed in the manuscript. In addition to that pathway, other pathways were considered but discounted. It is these pathways which are discussed in here.

The activation of the aryl C–H bond could occur before coumarin C–3–H activation, as in **Scheme S1**. A CMD pathway[1] and a carbopalladation pathway[2] were both considered as possibilities for this sequence of activation.



Scheme S1. Mechanistic possibilities investigated for Pd-catalysed CDC of 4-phenoxy-2-coumarin.

The CMD pathway was calculated using DFT (**Scheme S2**).



Scheme S2. DFT calculations for the direct arylation of **1** to **2** *via* double CMD C–H activation. Activation of aryl C–H bond first.

This pathway was calculated to begin with an κ^2-κ^1 displacement of an acetate ligand (**TS4**, $\Delta G^{\ddagger}$ = 9.8 kcal mol^{-1}) to give a π-complex **IM6**. The structure of this intermediate only shows small distortion, which cannot be regarded as Wheland intermediate, thus ruling out an S_EAr mechanism.[1, 3, 4] **IM6** is followed by a CMD[5] transition state **TS5** ($\Delta G^{\ddagger}$ = 6.2 kcal mol^{-1}) which generates **IM7**. **TS5** represents the summit of the potential energy surface for this pathway, which is consistent with the observed primary positive KIE of 3 for the cleavage of the aryl C–H bond.

After interconversion from **IM7** to the π-complex **IM8**, the acetate ligand could rotate to coordinate to the hydrogen of the other acetate acid ligand to generate **IM3-2** (ΔG = -12.8 kcal mol^{-1}) *via* a stronger intramolecular hydrogen bond which confers additional stability.[6] An acetate ligand abstracts the C-3 proton from the 2-coumarin (**Scheme S2**, blue hydrogen) *via* a second CMD transition state **TS6** ($\Delta G^{\ddagger}$ = 22.6 kcal mol^{-1}) to generate **IM5**. **IM5** is also calculated to exist in the DFT calculation shown in **Scheme 4** in the manuscript.

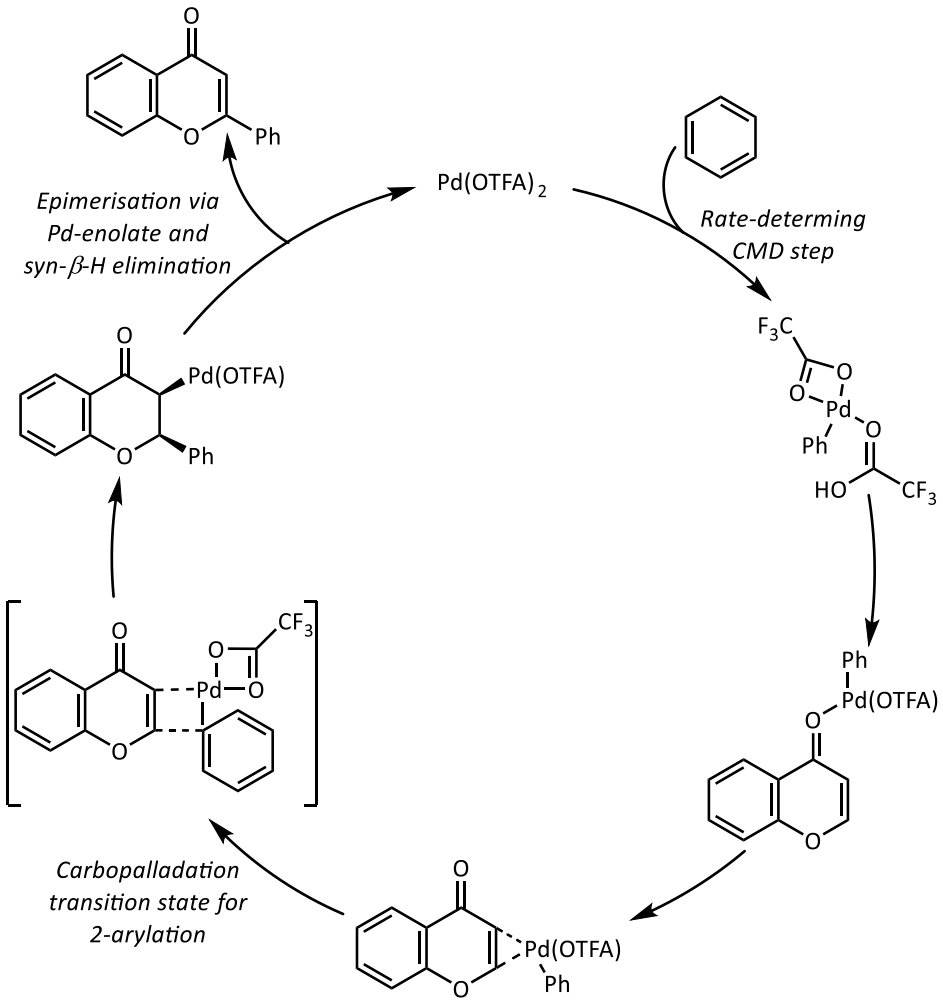
The palladation and C–H cleavage at the C-3 position is not calculated to be reversible in this pathway due to the energy barrier between intermediates **IM8** and **IM5**. Additionally, the relatively facile reductive elimination (**TS7**, $\Delta G^{\ddagger}$ = 21.8 kcal mol^{-1}) is likely irreversible. This conflicts with the experimental evidence which shows that palladium-mediated H/D exchange is reversible at the C–3 position (**Scheme 2** of the manuscript).

The reductive elimination (**TS7**, $\Delta G^{\ddagger}$ = 21.8 kcal mol^{-1}) releases product **2** and the palladium complex Pd(0)$(HOAc)_2$. The proton on the acetic acid ligand could transfer to a Brønsted base such as tert-butoxide ($tBuO^-$) or pivalate ($PivO^-$), while Pd(0) is likely oxidised to Pd(II) by Ag_2O. It is difficult to study the oxidation step in a meaningful way as there are no reasonable structural models for Ag_2O at this time.

The summit of the potential energy surfaces for both DFT calculations can be compared. The summit of the potential energy surface for the pathway shown in **Scheme 4** is **TS2** (ΔG = 12.2 kcal mol^{-1}) which is lower than the summit of the other pathway (**Scheme S2**, **TS5,** ΔG = 14.4 kcal mol^{-1}). The pathway in **Scheme 4** is therefore more favourable by 2.2 kcal mol (in the free energy barrier).

In general, it would seem unlikely that the pathway in **Scheme S2** is the operative mechanism due to the conflicts between the experimental evidence and the computational data.

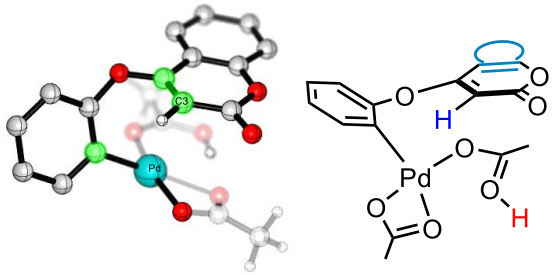
Next, it was important to consider carbopalladation (**Scheme S1**) as a possible mechanism for the CDC of 4-phenoxy-2-coumarins due to the similarities between 2-coumarins and 4-chromones. A carbopalladation pathway has been reported for the arylation of 4-chromones by Choi *et al.* (**Scheme S3**).[2] The objective of their computational work was to explain the experimentally observed regioselectivity of 4-chromone arylation, in favour of 2-arylation.



Scheme S3. Mechanism of chromone arylation proposed by Choi *et al.*[2]

The C–H activation of benzene was computed to occur more quickly than the C–H activation at either the C-2 or C-3 position of chromone. Additionally, the resultant phenylpalladium species is more stable than the analogous intermediate at either position of chromone. Since arylpalladium species were known experimentally to add across the π-bonds of enones, a carbopalladation of the phenylpalladium intermediate across the isolated π-bond of chromone was investigated by Choi et al.[2] Two carbopalladation transition states were identified (one for the 2-arylated product (**Scheme S3**) and one for the 3-arylated product) and it was confirmed that there was no feasible means of interconversion between the two adducts, meaning that carbopalladation was the regioselective step. The greater π-electron density at the C-3 position of chromone favours the delivery of the electrophilic Pd(OTFA) centre to this position, which leads to the C-2 delivery of the phenyl group in the carbopalladation step (**Scheme S3**). The experimentally observed KIE of 2.90 for benzene-h_6/d_6 agrees with the computed turnover-limiting C–H cleavage of benzene. These carbopalladation transition states were found to lie much lower in energy (>7 kcal mol^{-1}) than the structures obtained for a sequential CMD pathway, lending support for a carbopalladation pathway. The calculations showed that the steps following carbopalladation were relatively facile, rendering carbopalladation irreversible and therefore the regiodetermining step in chromone arylation.

In our case, the electrophilic Pd species also prefers to approach the C-3 position due to the greater π-electron density, consistent with the calculations described by Choi et al.[2] This electronic preference of Pd for the C-3 position restricts the ability of the aryl ring to approach the C-3 position to give the observed product **2**. In order to achieve our observed product **2**, Pd would need to approach either C-2 or C-4. Since the phenyl ring of the arylpalladium intermediate **IM7** is connected to the 2-coumarin through an oxygen atom, a conformation to fulfil a carbopalladation-type addition could not be found (**Chart S1**). This is in contast to Choi et al.'s report which describes an intermolecular reaction.[2]



IM7 **IM7**

Chart S1. The optimised structure **IM7**. Some hydrogen atoms are omitted for clarity.

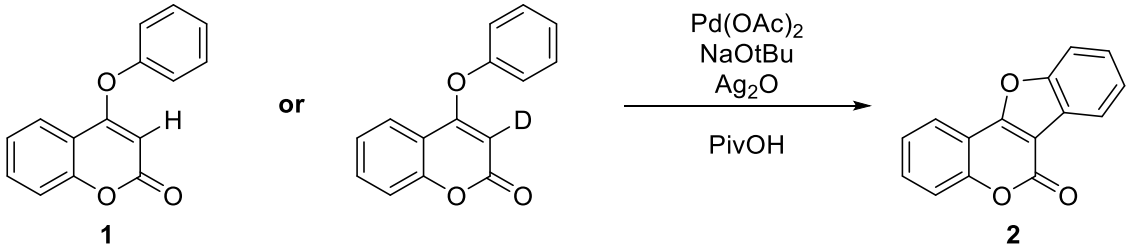
Overall, this data seems to render a carbopalladation mechanism for the CDC of 4-phenoxy-2-coumarin (**1**) unlikely.

Having identified conflicts between the experimental observations and the computational data for both of the mechanistic modes shown in **Scheme S1**, these mechanisms were considered unlikely. The available experimental and computational evidence at this time indicates that the mechanistic proposal shown in **Scheme 4** in the manuscript is most likely to be operative.

Determination of kinetic isotope effects

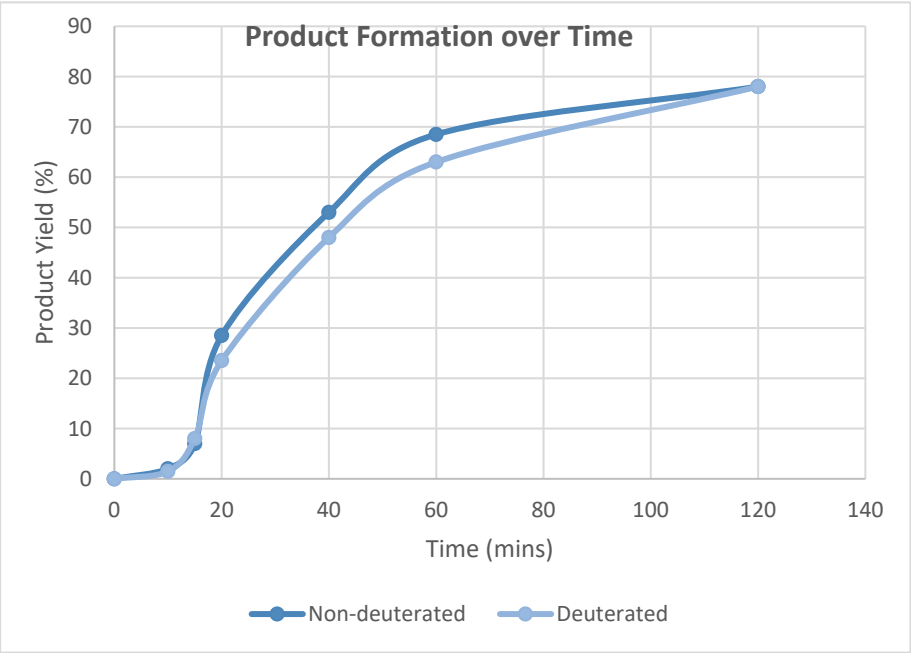
Determination of kinetic isotope effect at 2-coumarin C3–H bond

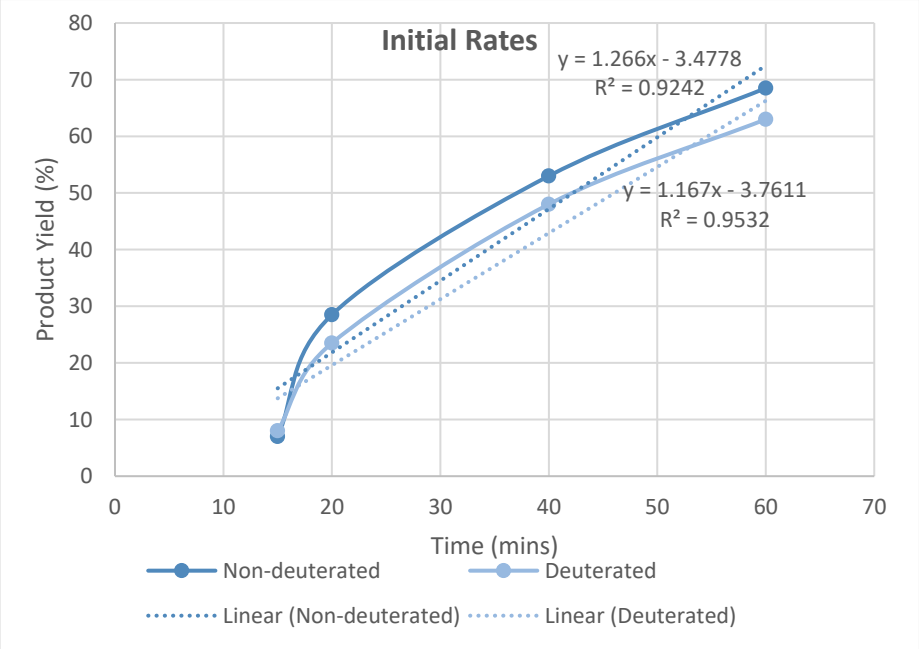
We have previously disclosed this experiment.[7] The procedures and data are reported again here for completeness.



Following the reported methodology,[8, 9] six identical reactions were set side-by-side. Each reaction tube was charged with 4-phenoxy-2-coumarin **1** (50 mg, 0.21 mmol), $Pd(OAc)_2$ (4.7 mg, 0.02 mmol), NaOtBu (4.0 mg, 0.04 mmol), Ag_2O (73 mg, 0.31 mmol) and PivOH (0.5 M). The reactions were stirred at 120 °C in air and stopped at 5, 10, 20, 40, 60 and 120 min, respectively. In a parallel experiment, six reactions were performed using 3-deuterio-4-phenoxy-2-coumarin (50 mg, 0.21 mmol) as a substrate under otherwise identical conditions. Each of the reactions was worked up by diluting the mixture with dichloromethane (DCM) and filtering through a pad of celite. The organic layers were washed with aqueous NaOH solution (10% w/v), dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was analysed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard for quantification. The yields of 6*H*-benzofuro[3,2-*c*]chromen-6-one **2** from the 12 reactions were plotted against reaction time. The ratio of product formation was determined to be 1.08 by comparing the slopes (data averaged from two runs).

We also observed that the integral of the C-3 proton was increasing over time during the conversion of 3-deuterio-4-phenoxy-2-coumarin to **2**. This was not observed in the absence of the palladium source. This allowed us to conclude that deuterium at the C-3 position was being exchanged for hydrogen, i.e. scrambled, during the reaction, indicating that the C-H activation of this C-H bond is palladium-mediated and reversible.

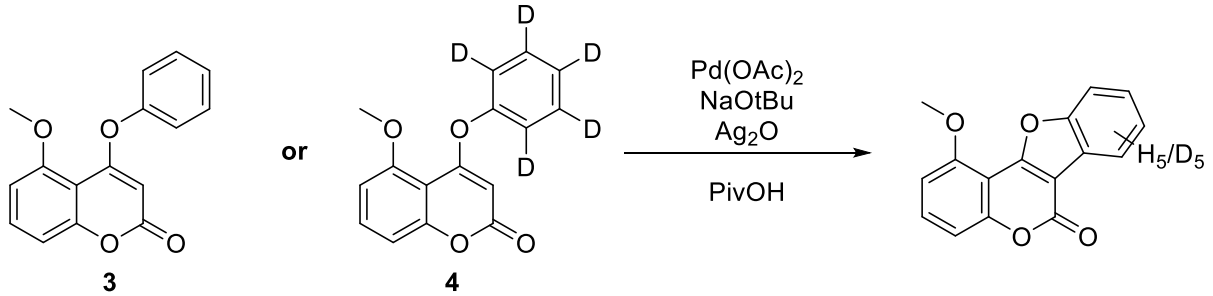




KIE = 1.266/1.167 = 1.08 (data shown is the average of two runs)

Determination of kinetic isotope effect at aryl C–H bond

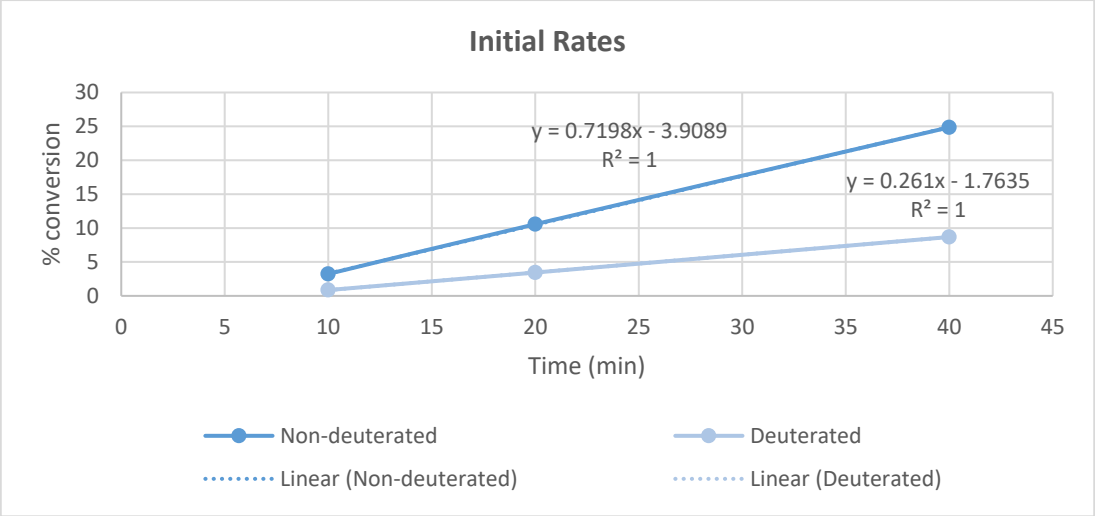
Experiment 1



3 **4**

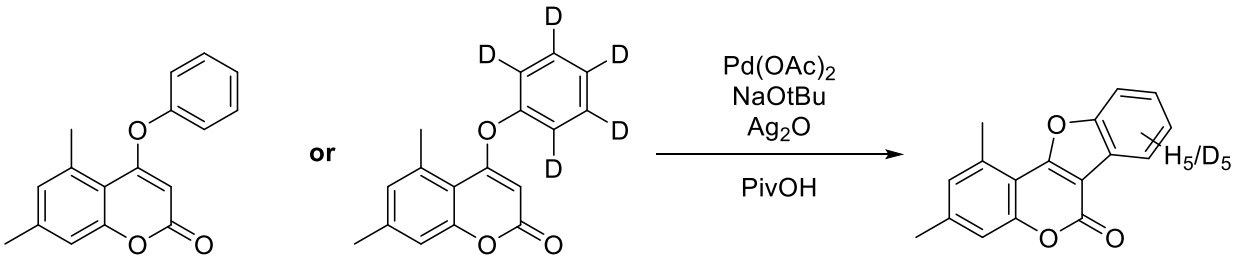
A reaction tube was charged with 5-methoxy-4-phenoxy-2-coumarin **3** (40 mg, 0.150 mmol), $Pd(OAc)_2$ (3.4 mg, 0.0150 mmol), NaOtBu (2.9 mg, 0.030 mmol), Ag_2O (52.1 mg, 0.225 mmol) and PivOH (889 mg, 1 mL). The reaction was stirred at 120 °C in air. In a parallel experiment, a reaction was performed using 5-methoxy-4-(phenoxy-d_5)-2-coumarin **4** (41 mg, 0.150 mmol) as a substrate under otherwise identical conditions. After 5, 10, 20 and 40 mins, a sample was simultaneously removed from both reactions. The sample was diluted with DCM and filtered through a pad of celite. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

The crude reaction mixture was analysed by ^{1}H NMR. The % conversion to 1-methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one for each sample was plotted against reaction time.



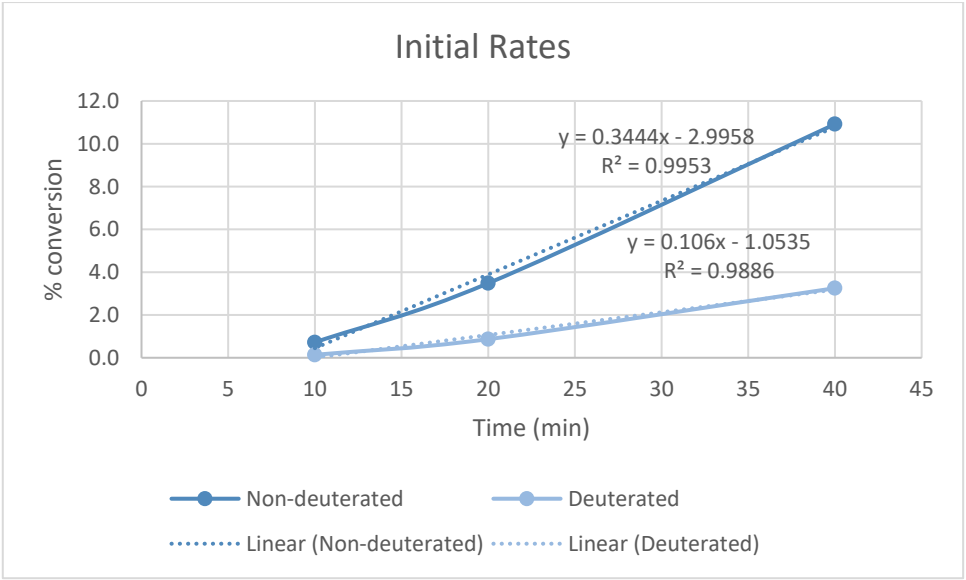
KIE = 0.7198/0.261 = 2.76 (data shown is the average of two runs)

Experiment 2



A reaction tube was charged with 5,7-dimethyl-4-phenoxy-2-coumarin (26.6 mg, 0.10 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), NaOtBu (1.9 mg, 0.02 mmol), Ag_2O (34.8 mg, 0.15 mmol) and PivOH (889 mg, 1 mL). The reaction was stirred at 120 °C in air. In a parallel experiment, a reaction was performed using 5,7-dimethyl-4-(phenoxy-d_5)-2-coumarin (27.1 mg, 0.10 mmol) as a substrate under otherwise identical conditions. After 5, 10, 20 and 40 mins, a sample was simultaneously removed from both reactions. The sample was diluted with DCM and filtered through a pad of celite. The organic layers were concentrated under reduced pressure.

The crude reaction mixture was analysed by ^{1}H NMR. The % conversion to 1,3-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one for each sample was plotted against reaction time.

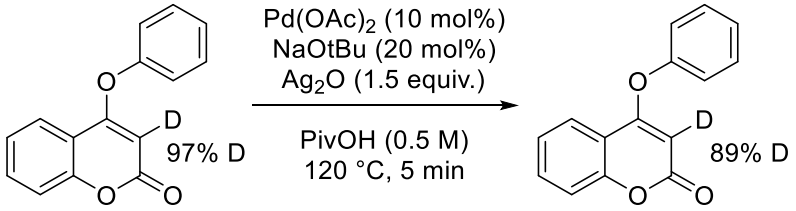


KIE = 0.3444/0.106 = 3.25 (data shown was obtained from one run)

Reversibility studies

Reaction of 3-deuterio-4-phenoxy-2-coumarin in PivOH

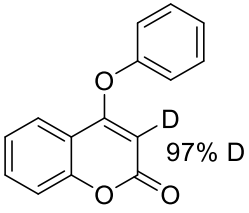
We have previously disclosed this experiment.[7] The procedures and data are reported again here for completeness.

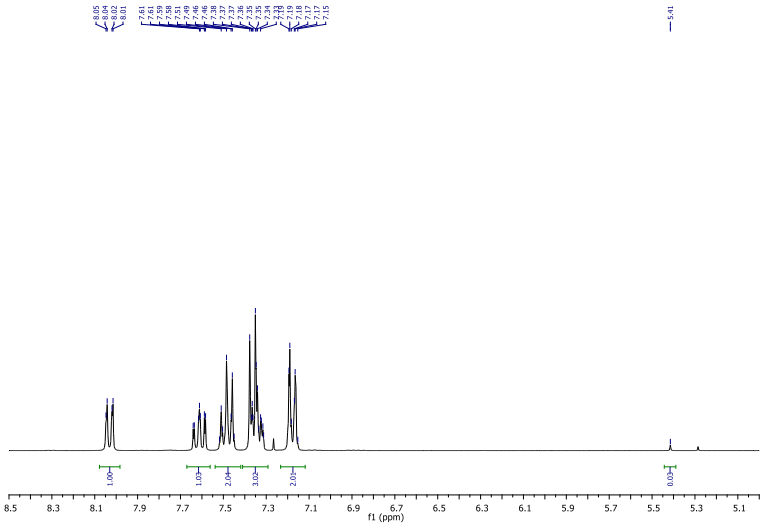


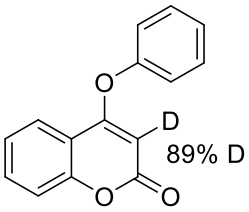
A reaction tube was charged with 3-deuterio-4-phenoxy-2-coumarin (50 mg, 0.21 mmol), $Pd(OAc)_2$ (4.7 mg, 0.02 mmol), NaOtBu (4.0 mg, 0.04 mmol), Ag_2O (73 mg, 0.31 mmol) and PivOH (0.5 M). The reaction was stirred at 120 °C in air for 5 min, then cooled to ambient temperature, diluted with dichloromethane (DCM) and filtered through a pad of celite. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was analysed by ^1H NMR.

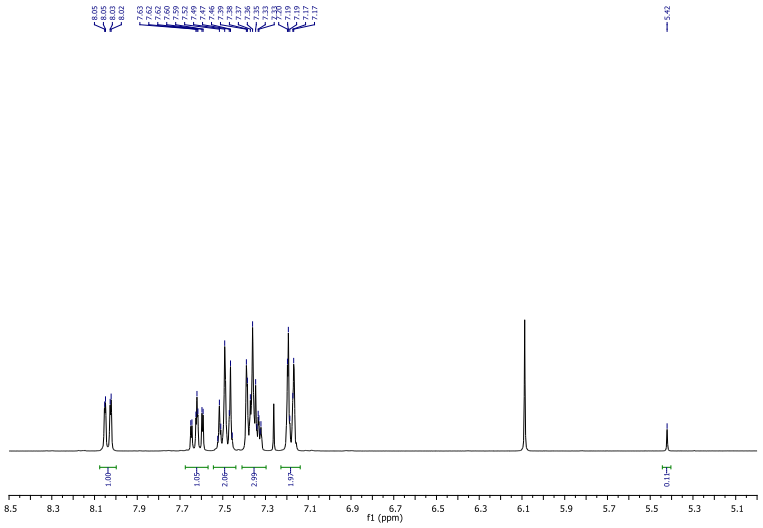
The extent of deuterium incorporation at C-3 was found to be 89%, a decrease of 8%. This indicates that C-3 palladation is reversible.

As a control, using 3-deuterio-4-phenoxy-2-coumarin in PivOH in the absence of palladium gave no significant hydrogen incorporation in the starting material at any position.


O
D
97% D
O
O

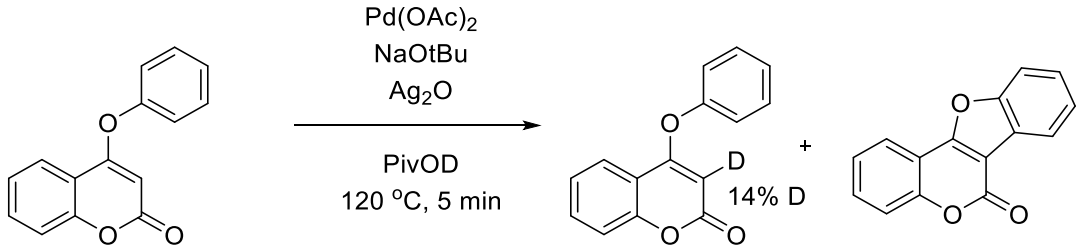

8.05
8.04
8.02
8.01
7.61
7.61
7.59
7.58
7.51
7.49
7.48
7.46
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.19
7.18
7.17
7.17
7.15
5.41
1.00
1.05
2.04
3.05
2.00
0.03
8.5
8.3
8.1
7.9
7.7
7.5
7.3
7.1
6.9
6.7
6.5
6.3
6.1
5.9
5.7
5.5
5.3
5.1
f1 (ppm)


O
D
89% D
O
O


8.05
8.05
8.03
8.02
7.63
7.62
7.62
7.60
7.59
7.53
7.50
7.47
7.46
7.39
7.38
7.37
7.36
7.35
7.33
7.33
7.19
7.19
7.17
7.17
5.42
1.00
1.05
2.09
2.09
1.07
0.11
8.5
8.3
8.1
7.9
7.7
7.5
7.3
7.1
6.9
6.7
6.5
6.3
6.1
5.9
5.7
5.5
5.3
5.1
f1 (ppm)

Reaction of 4-phenoxy-2-coumarin (1) in PivOD

We have previously disclosed this experiment.[7] The procedures and data are reported again here for completeness.

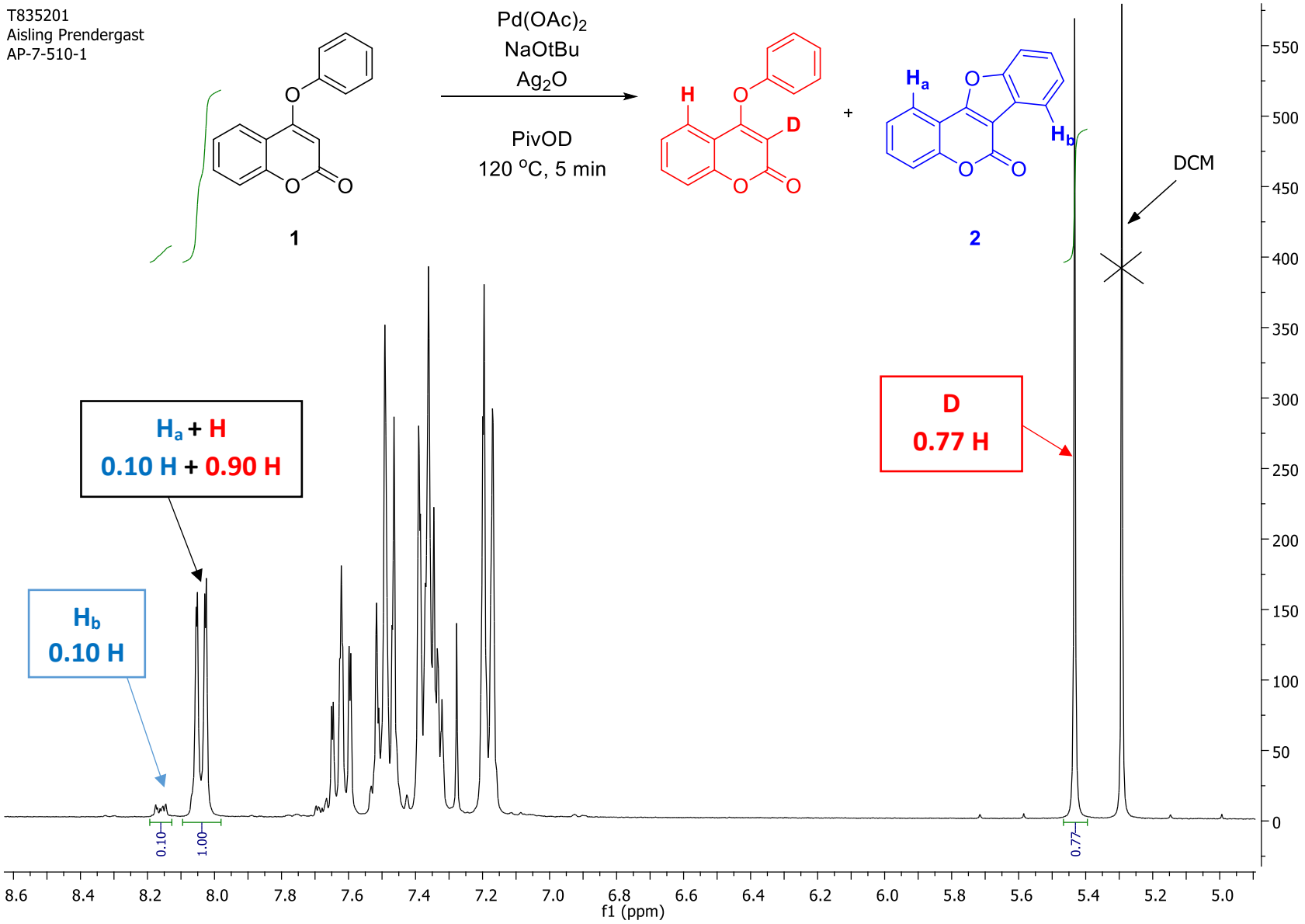


1 **2**

A reaction tube was charged with 4-phenoxy-2-coumarin **1** (30 mg, 0.13 mmol), $Pd(OAc)_2$ (2.9 mg, 0.01 mmol), NaOtBu (2.4 mg, 0.03 mmol), Ag_2O (43.6 mg, 0.19 mmol) and PivOD (0.5 M). The reaction was stirred at 120 °C in air for 5 min, then cooled to ambient temperature, diluted with dichloromethane (DCM) and filtered through a pad of celite. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was analysed by ^1H NMR.

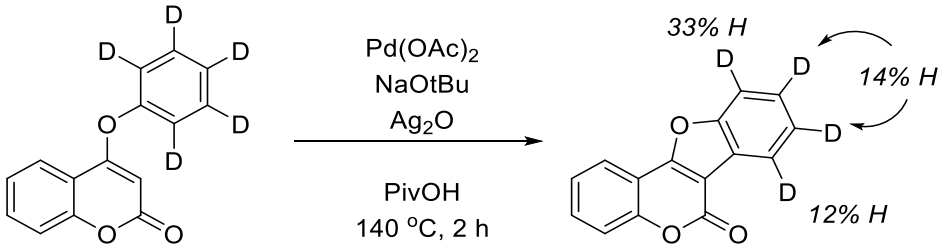
The extent of deuterium incorporation at C-3 was found to be 14%. This indicates that C-3 palladation is reversible.

When the reaction was performed a second time and allowed progress to completion, deuterium incorporation on the aryl ring was observed, but only in the product **2** and not in the starting material **1**. Since no deuterium incorporation was observed on the aryl ring of the starting material, we have concluded that palladation of the aryl can be considered irreversible in these reactions.


T835201
Aisling Prendergast
AP-7-510-1
Pd(OAc)2
NaOtBu
Ag2O
PivOD
120 °C, 5 min
1
2
Ha + H
0.10 H + 0.90 H
Hb
0.10 H
D
0.77 H
DCM
0.10
1.00
0.77
f1 (ppm)

Scrambling experiment – reaction of 4-(phenoxy-d_5)-2-coumarin

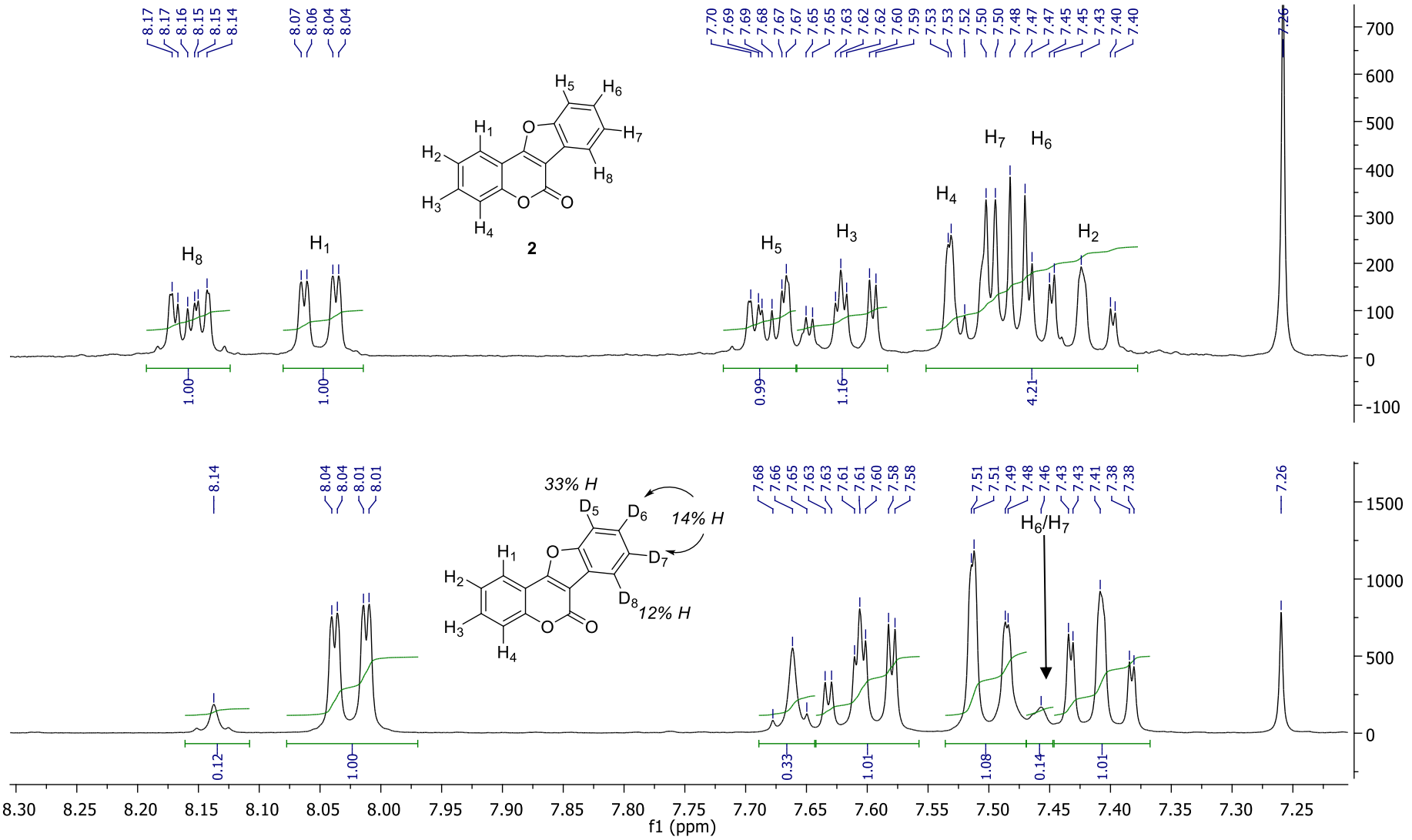
We have previously disclosed this experiment.[7] The procedures and data are reported again here for completeness.



A reaction tube was charged with 4-phenoxy-2-coumarin (50 mg, 0.21 mmol), $Pd(OAc)_2$ (4.7 mg, 0.02 mmol), NaOtBu (4.0 mg, 0.04 mmol), Ag_2O (73 mg, 0.31 mmol) and PivOH (0.5 M). The reaction was stirred at 140 °C in air for 2 h, then cooled to ambient temperature, diluted with dichloromethane (DCM) and filtered through a pad of celite. The organic layers were washed with aqueous NaOH solution (10% w/v), dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was analysed by ^{1}H NMR.

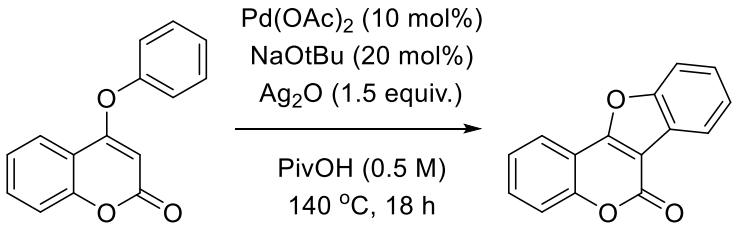
During the analysis of the experiment, some unexpected peaks were identified in the ^{1}H NMR. The signals for each proton were assigned with the aid of 2D-NMR experiments (COSY, HSQC and HMBC). This allowed us to conclude that deuterium on the aryl ring was being exchanged for hydrogen, i.e. scrambled, apparently after the product was formed. When the reaction was halted early, H/D exchange was not observed on the aryl ring of the pentadeuterated starting material (in a series of parallel experiments), indicating palladation of the aryl ring can be considered irreversible. This scrambling was not observed in the absence of the palladium source.

The levels of newly incorporated hydrogen in the product increased if the reaction was left on longer.


8.17
8.17
8.16
8.15
8.15
8.14
8.07
8.06
8.04
8.04
7.70
7.69
7.69
7.68
7.67
7.67
7.65
7.65
7.63
7.62
7.62
7.60
7.59
7.53
7.53
7.52
7.50
7.50
7.48
7.47
7.47
7.45
7.45
7.43
7.40
7.40
7.26
H5
H6
H1
O
H7
H2
H8
H3
O
O
H4
2
H8
H1
H5
H3
H4
H7
H6
H2
1.00
1.00
0.99
1.16
4.21
700
600
500
400
300
200
100
0
-100
8.14
8.04
8.04
8.01
8.01
33% H
D5
D6
14% H
D7
H1
O
H2
D8
12% H
H3
O
O
H4
7.68
7.66
7.65
7.63
7.63
7.61
7.61
7.60
7.58
7.58
7.51
7.51
7.49
7.48
7.46
7.43
7.43
7.41
7.38
7.38
7.26
H6/H7
0.12
1.00
0.33
1.01
1.08
0.14
1.01
1500
1000
500
0
8.30
8.25
8.20
8.15
8.10
8.05
8.00
7.95
7.90
7.85
7.80
7.75
7.70
7.65
7.60
7.55
7.50
7.45
7.40
7.35
7.30
7.25
f1 (ppm)

Temperature effects

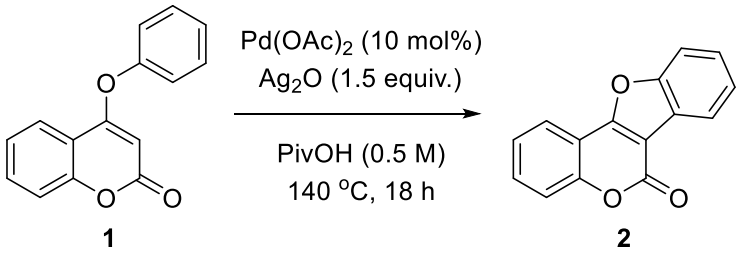
Table S1. Investigation of effect of lower temperature on double C–H activation reaction.



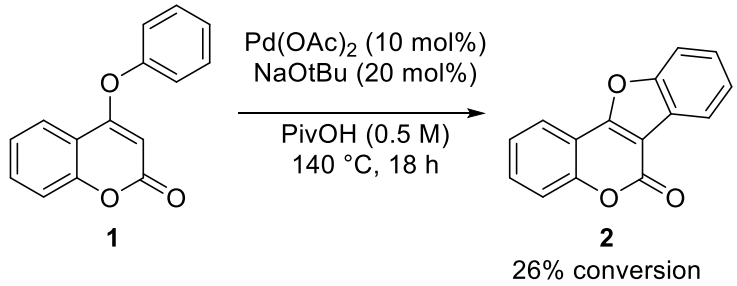
Reaction Temperature (°C)	Conversion (%)
40	0
60	4
80	65

These results revealed that the reaction does not progress at temperatures below 60 °C.

Effect of the base and the oxidant



The reaction proceeded to 100% conversion in the absence of NaOtBu, and a 63% yield was determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification. It would appear that the addition of 20 mol% of NaOtBu is crucial for yield but not for conversion. Fagnou also observed that the addition of small amounts of base resulted in enhanced yields.[10] It may be that NaOtBu has a role in the activation of the catalyst, as was recently reported by Docherty *et al.* for the activation of earth-abundant metals.[11] Alternatively, NaOtBu may participate in equilibria reactions with Ag_2O and PivOH to generate basic silver species[12] which could act as insoluble proton sinks.



It was found that the reaction proceeds to 26% conversion in the absence of Ag_2O, which is slightly more than two turnovers of the catalyst. This shows that at least some of the catalyst is oxidised back to Pd(II) before being deactivated, possibility by air or some other internal oxidant. This could prove useful in further development of this reaction, as the use of stoichiometric silver salts to oxidise the catalyst is not cost-effective.

Experimental Details

General Information

Melting point determinations were performed by the open capillary method and are reported uncorrected. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 25 ºC in $CDCl_3$ at 300 and 75 MHz spectrometer unless otherwise specified, with TMS as the internal standard. Chemical shifts (δH and δC) were expressed as parts per million (ppm) positive shift being downfield from TMS; coupling constants (*J*) are expressed in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a TOF MS instrument with ESI source. High-resolution mass spectra were recorded only for new compounds. Literature citations are provided for known compounds and representative characterisation data. IR spectra were recorded on an FT-IR spectrometer as a thin film (liquid samples) or applied as a solution in chloroform, and the chloroform was allowed to evaporate (solid samples). Column chromatography was carried out using 60 Å (35-70 μm) silica.

Preparation of 4-hydroxy-5-methoxy-2-coumarin[13] Based on a modification of the literature procedures,[14, 15] a 100 mL, 2-neck round-bottomed flask was heated under vacuum and refilled with N_2. 2'-Hydroxy-6'-methoxyacetophenone (4.5 g, 27.08 mmol) and toluene (30 mL) were added. A 500 mL, 3-neck round-bottomed flask was heated under vacuum and refilled with N_2. NaH (11.8 g, 55% dispersion in mineral oil, 10.0 equiv.) and toluene (60 mL) were added. The acetophenone solution was added dropwise to the stirring suspension of NaH over 15 min. The mixture was stirred until hydrogen evolution ceased (about 10 min). A solution of diethyl carbonate (4.4 mL, 36.11 mmol) in toluene (10 mL) was added to the reaction mixture over 5 min. The reaction mixture was stirred at ambient temperature for 15 min., then heated to 110 °C using an oil bath. The reaction was stirred at this temperature for 21 h, then cooled to ambient temperature. The mixture was concentrated under reduced pressure to obtain a yellow solid which was slowly added to 100 mL of ice water. The mixture was acidified with aqueous HCl (36.5-38.5%) until no further precipitate was formed. The precipitate was isolated by suction filtration, and washed with H_2O. The resulting solid was recrystallised from EtOH to yield a cream solid (1.2265 g, 24%); m.p. 153–154 °C (lit.[16] 152–153 °C); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 11.32 (br s, 1H), 7.55 (t, *J* = 8.4, 1H), 7.10 – 6.66 (m, 2H), 5.51 (s, 1H), 3.90 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $(CD_3)_2SO$) δ 167.7, 161.9, 157.8, 155.6, 133.5, 109.7, 107.2, 105.5, 91.3, 57.0; *m/z* (ES+) 193 ($(M+H)^+$ 100%).

Preparation of 4-hydroxy-5,7-dimethyl-2-coumarin[17] Based on a modification of the literature procedure,[18] a mixture of 3,5-dimethylphenol (1.0 g, 8.19 mmol) and Meldrum's acid (1.2 g, 8.19 mmol) was stirred at 100 °C for 3 h. The small remaining amount of acetone was removed by vacuum. Eaton's reagent (25 mL, 129.8 mmol) was added to the mixture and was stirred at 70 °C for 4 h. Water (25 mL) was then added to this mixture while stirring vigorously. The precipitate was filtered by suction, washed with water and dried. This solid was then purified by recrystallization from EtOH to give the product as a pale yellow solid (1.2183 g, 78 %); m.p. >250 °C (lit.[17] 219–220 °C); IR ν_{max} (film) 1644, 1604, 1550, 1345, 1271; ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 12.21 (s, 1H), 6.97 (d, *J* = 0.6, 1H), 6.89 (d, *J* = 0.7, 1H), 5.48 (s, 1H), 2.60 (s, 3H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $(CD_3)_2SO$) δ 169.2, 162.1, 155.6, 142.7, 137.1, 128.7, 115.2, 112.2, 90.8, 22.9, 21.2; *m/z* (ES+) 191 ($(M+H)^+$ 6%).

General Procedure for the synthesis of 4-bromo-2-coumarins

A solution of the 4-hydroxy-2-coumarin (1.0 equiv.), TBAB (1.5 equiv.), and P_2O_5 (2.4 equiv.) in toluene (4.0 mL/mmol starting material) was stirred at 94 °C for 1.5 h. Upon cooling, the reaction mixture was washed with toluene (2 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was isolated as a solid and purified by recrystallization from EtOH.

4-Bromo-2-coumarin Prepared according to literature procedure and data were comparable.[19]

4-Bromo-5-methoxy-2-coumarin Yellow solid (0.314 g, 31%); m.p. >250 °C; IR ν_{max} (film) 1651, 1072, 981, 666; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, *J* = 8.4, 1H), 6.92 (dd, *J* = 8.4, 0.8, 1H), 6.78 (d, *J* = 8.4, 1H), 6.74 (s, 1H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.5, 157.0, 154.1, 136.5, 133.1, 120.1, 109.6, 108.6, 107.1, 56.0; *m/z* (ES+): 255 (^{79}Br $(M+H)^+$ 100%), 257 (^{81}Br $(M+H)^+$ 98%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_8O_3Br$ 254.9657; Found 254.9646.

4-Bromo-5,7-dimethyl-2-coumarin[20] Orange solid (0.4373 g, 33%); m.p. 160–163 °C (lit.[20] 125–127 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.94 (s, 1H), 6.80 (s, 1H), 2.86 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.6, 154.1, 143.4, 139.7, 137.4, 130.4, 120.4, 116.3, 114.8, 24.4, 21.3; *m/z* (ES+): 252 (^{79}Br $(M+H)^+$ 42%), 254 (^{81}Br $(M+H)^+$ 38%).

General Procedure for the synthesis of 4-phenoxy-2-coumarins

A solution of the 4-bromo-2-coumarin (1.0 equiv.), the phenol (1.5 equiv.), and K_2CO_3 (1.8 equiv.) in acetone (4.0 mL/mmol starting material) was heated to 65 °C and stirred for 16 h. Upon cooling, the reaction was diluted with H_2O (10 mL) and EtOAc (20 mL). The mixture was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with aqueous NaOH (10% w/v, 2 x 20 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure.

4-Phenoxy-2-coumarin (1) Prepared according to literature procedure and data were comparable.[19]

4-(Phenoxy-d_5)-2-coumarin[7] Light brown solid (0.9282 g, 86%); m.p. 131–133 °C; IR ν_{max} (film) 1725, 1625, 1568, 1371, 1224, 790; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.9, 1.2, 1H), 7.62 (ddd, *J* = 8.6, 7.3, 1.6, 1H), 7.42 – 7.29 (m, 2H), 5.42 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.4, 162.6, 153.7, 152.4, 132.8, 129.9 (t, *J* = 25), 126.3 (t, *J* = 25), 124.1, 123.1, 120.9 (t, *J* = 25), 116.9, 115.5, 93.6; *m/z* (ES+): 244 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_6D_5O_3$ 244.1022; Found 244.1022.

5-Methoxy-4-phenoxy-2-coumarin (3) Purified by silica gel chromatography (EtOAc:hexanes 70:30) to give an off-white solid (0.020 g, 13%); m.p. 213–215 °C; IR ν_{max} (film) 1705, 1614, 1255, 1095; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.41 (m, 3H), 7.36 – 7.27 (m, 1H), 7.22 – 7.09 (m, 2H), 6.98 (dd, *J* = 8.4, 0.9, 1H), 6.81 (d, *J* = 8.4, 1H), 5.33 (s, 1H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.7, 162.5, 158.0, 155.7, 152.8, 132.8, 130.4, 126.4, 121.4, 109.8, 106.7, 105.8, 93.4, 56.5; *m/z* (ES+): 269 ($(M+H)^+$ 58%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}O_4$ 269.0814; Found 269.0814.

5-Methoxy-4-(phenoxy-d_5)-2-coumarin (4) Purified by silica gel chromatography (EtOAc:hexanes 20:80) to give a white solid (0.116 g, 28%); m.p. 212–217 °C; IR ν_{max} (film) 1704, 1612, 1471, 1255, 1189, 1094; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, *J* = 8.4, 1H), 6.97 (dd, *J* = 8.4, 0.9, 1H), 6.80 (d, *J* = 8.4, 1H), 5.33 (s, 1H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.6, 162.4, 158.0, 155.7, 152.8, 132.8, 129.8 (t, *J* = 25), 125.9 (t, *J* = 24), 120.9 (t, *J* = 25), 109.7, 106.8, 105.8, 93.5, 56.5; *m/z* (ES+): 274 ($(M+H)^+$ 70%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_8D_5O_4$ 274.1128; Found 274.1118.

5,7-Dimethyl-4-phenoxy-2-coumarin Purified by silica gel chromatography (EtOAc:hexanes 10:90) to give a white solid (0.036 g, 17%); m.p. 130–133 °C; IR ν_{max} (film) 1718, 1611, 1369, 1194; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, *J* = 7.8, 2H), 7.33 (t, *J* = 7.4, 1H), 7.15 (d, *J* = 7.8, 2H), 7.03 (s, 1H), 6.94 (s, 1H), 5.33 (s, 1H), 2.76 (s, 3H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.4, 162.8, 155.3, 152.2, 143.1, 136.7, 130.5, 129.0, 126.7, 121.4, 115.5, 111.7, 93.0, 23.3, 21.5; *m/z* (ES+): 267 ($(M+H)^+$ 8%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{15}O_3$ 267.1021; Found 267.1034.

5,7-Dimethyl-4-(phenoxy-d_5)-2-coumarin Purified by silica gel chromatography (EtOAc:hexanes 10:90) to give a white solid (0.036 g, 17%); m.p. 129–132 °C; IR ν_{max} (film) 1715, 1613, 1366, 1232; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.94 (s, 1H), 5.33 (s, 1H), 2.76 (s, 3H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 162.8, 155.3, 152.2, 143.0, 136.7, 130.0 (t, *J* = 25), 129.0, 126.2 (t, *J* = 24), 121.0 (t, *J* = 25), 115.5, 111.7, 93.0, 23.3, 21.5; *m/z* (ES+): 272 ($(M+H)^+$ 10%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{10}D_5O_3$ 272.1335; Found 272.1336.

Preparation of 3-deuterio-4-phenoxy-2-coumarin A Schlenk tube was heated under vacuum and refilled with N_2 three times. 3-Iodo-4-phenoxy-2-coumarin[21] (1.20 g, 4.12 mmol) and zinc dust (1.1 g, 20.60 mmol) were added to the Schlenk tube. The Schlenk tube was evacuated and refilled with N_2 three times. Monodeuterioacetic acid (AcOD) (10 mL) was added and the mixture was stirred at ambient temperature for 17 h. A saturated solution of K_2CO_3 in D_2O (2 mL) was slowly added, evolving gas and forming a precipitate. The mixture was stirred at ambient temperature for 30 min. The mixture was diluted with DCM (25 mL), dissolving the precipitate, and the zinc metal was removed by gravity filtration. The layers in the filtrate were separated and the aqueous layer was washed with DCM (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude yellow residue was purified by silica gel chromatography (DCM) to yield the product as a pale yellow solid (0.680 g, 86%, 97% D); m.p. 134–135 °C; IR ν_{max} (film); 1726, 1619, 1368, 1190, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.3, 1.5, 1H), 7.67 – 7.56 (m, 1H), 7.54 – 7.42 (m, 2H), 7.42 – 7.29 (m, 3H), 7.18 (dd, *J* = 7.5, 1.1, 2H), 5.41 (s, 0.03H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.3, 162.5, 153.7, 152.5, 132.8, 130.4, 126.8, 124.1, 123.1, 121.3, 116.8, 115.4, 93.3 (t, *J* = 25); *m/z* (ES+): 240 ($(M+H)^+$ 74%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{10}DO_3$ 240.0771; Found 240.0771; Anal. Calcd. for $C_{15}H_9DO_3$: C, 75.30; H, 4.63; Found: C, 75.10; H, 4.37.

General Procedure for the cross-dehydrogenative coupling of 4-phenoxy-2-coumarins

2-Coumarin (1 equiv.), $Pd(OAc)_2$ (10 mol%), Ag_2O (1.5 equiv.), NaOtBu (0.2 equiv.) and pivalic acid (PivOH) (0.5 M) were stirred at 140 ºC under air atmosphere for 16 h. Upon cooling, the reaction was diluted with DCM (15 mL) and washed with aqueous NaOH (10% w/v, 2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residues were then purified using silica gel chromatography with DCM as the eluent to afford the title products.

6*H*-Benzofuro[3,2-*c*]chromen-6-one (2) Prepared according to literature procedure and data were comparable.[7]

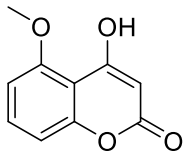
1-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one White solid (0.006 g, 47%); m.p. 205–206 °C; IR ν_{max} (film) 1742, 1617, 1596, 1286, 1083; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.04 (m, 1H), 7.80 – 7.66 (m, 1H), 7.59 – 7.38 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.4, 1H), 4.11 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.8, 158.2, 156.0, 155.6, 154.9, 132.1, 126.4, 125.1, 123.0, 121.5, 111.9, 110.0, 106.1, 105.3, 103.8, 56.5; *m/z* (ES+): 267 ($(M+H)^+$ 10%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{11}O_4$ 267.0657; Found 267.0650.

Computational Details

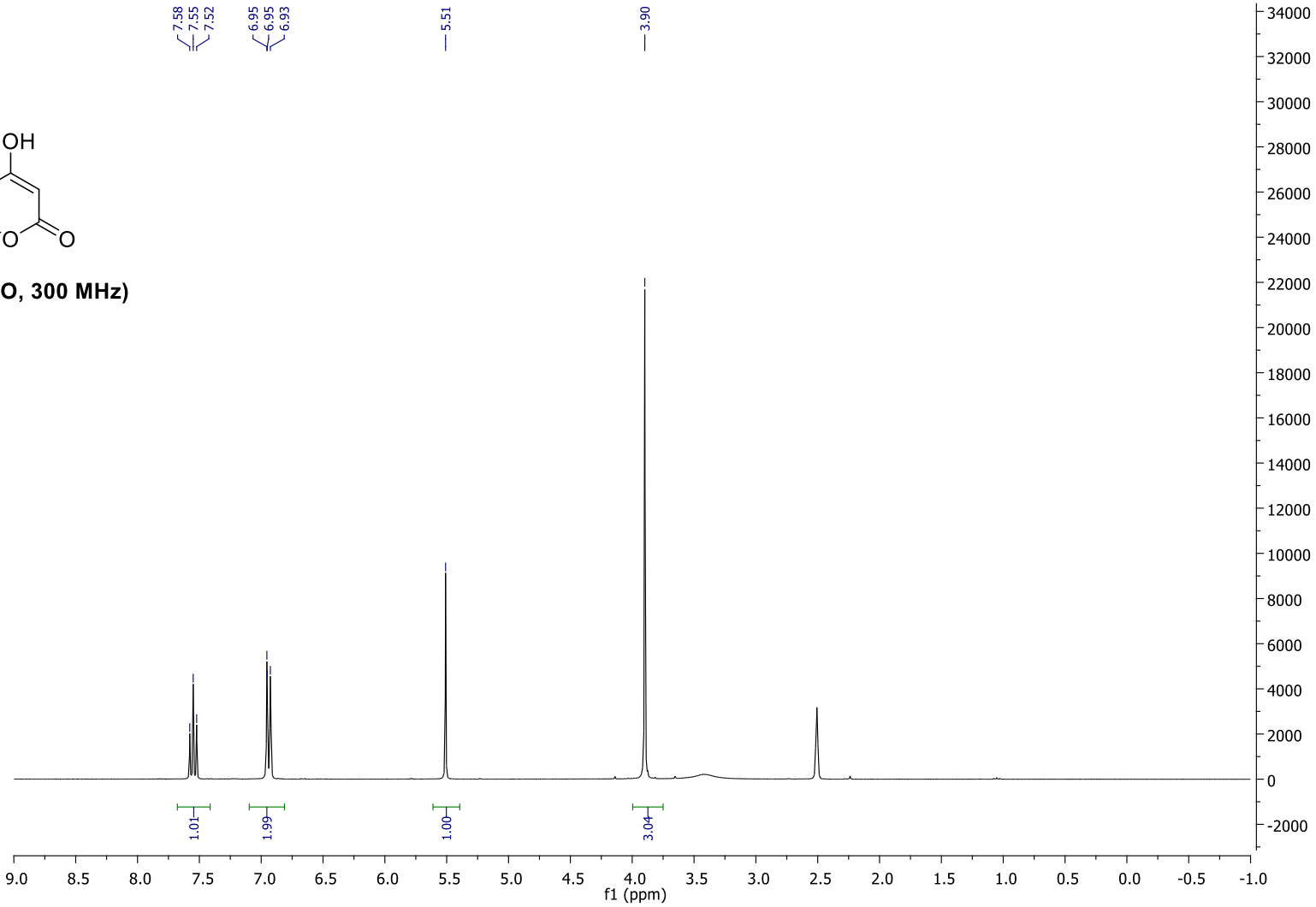
Density Functional Theory (DFT) calculations were performed using Gaussian 09 D.01 program.[22] The geometries were fully optimized at solvent phase with SMD solvation model[23] (we choose propanoic acid as solvent because its structure is similar to pivalic acid and its dielectric constant is of a similar magnitude) using M. Head-Gordon's long-range corrected (LC) hybrid density functional ωB97X-D[24] which has been reported to take noncovalent interactions into consideration and worked well for similar systems.[25-27] The effective core potentials (ECPs) of Hay and Wadt with a double-ζ valence basis set (LanL2DZ)[28] were used to describe Pd atom. Polarization functions were added for Pd (ζ_f=1.472)[29]. The 6-31G(d,p) Pople basis set were used for all other atoms. Frequency calculations were carried out to confirm the characteristics of all of the optimized structures as minima or transition states. Calculations of intrinsic reaction coordinates (IRC)[30] were also performed to confirm that transition states connect two relevant minima. In order to obtain more accurate free energy in solution, we further carried out single point calculations at basis set II level (LanL2DZ(f) for Pd and 6-311++G(d, p) for all other atoms) and solvation effect of propanoic acid was simulated by the SMD continuum solvent model. All natural bond orbital (NBO) analysis were performed using the NBO 3.0 package.[22]

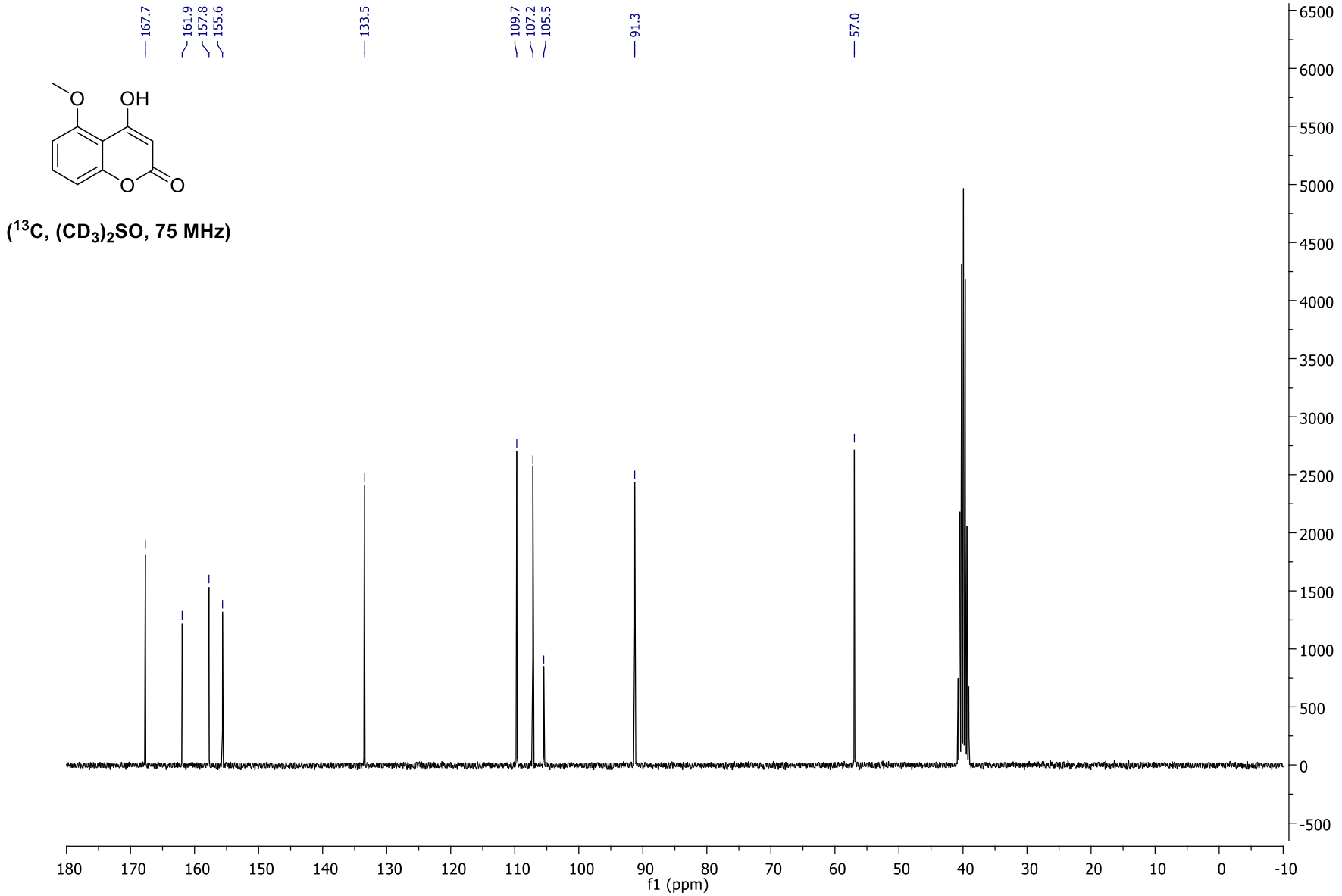
Spectra

4-hydroxy-5-methoxy-2-coumarin

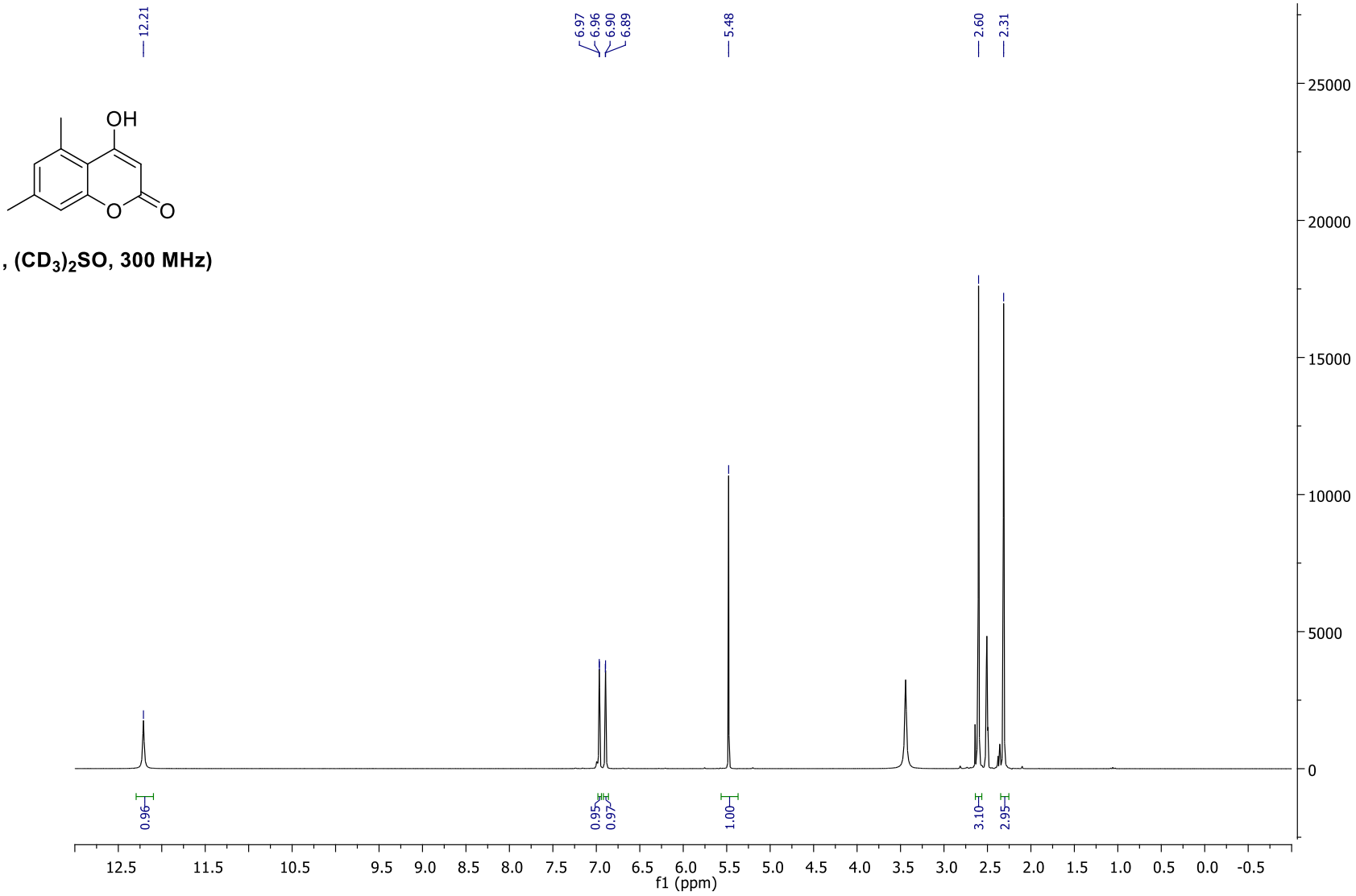


(^{1}H, $(CD_3)_2SO$, 300 MHz)

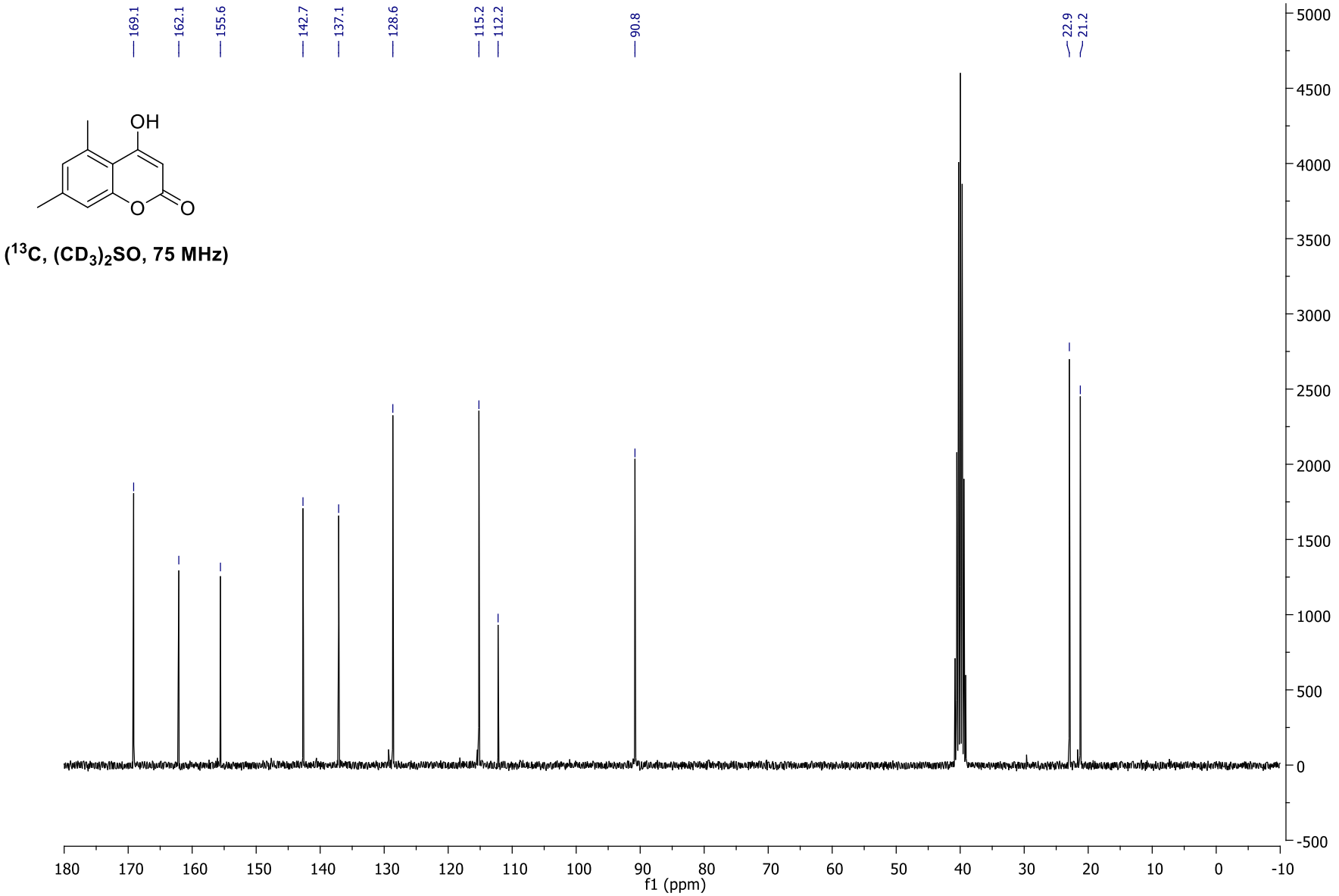



167.7
161.9
157.8
155.6
133.5
109.7
107.2
105.5
91.3
57.0
O
OH
O
O
(^{13}C, (CD$_3$)$_2$SO, 75 MHz)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

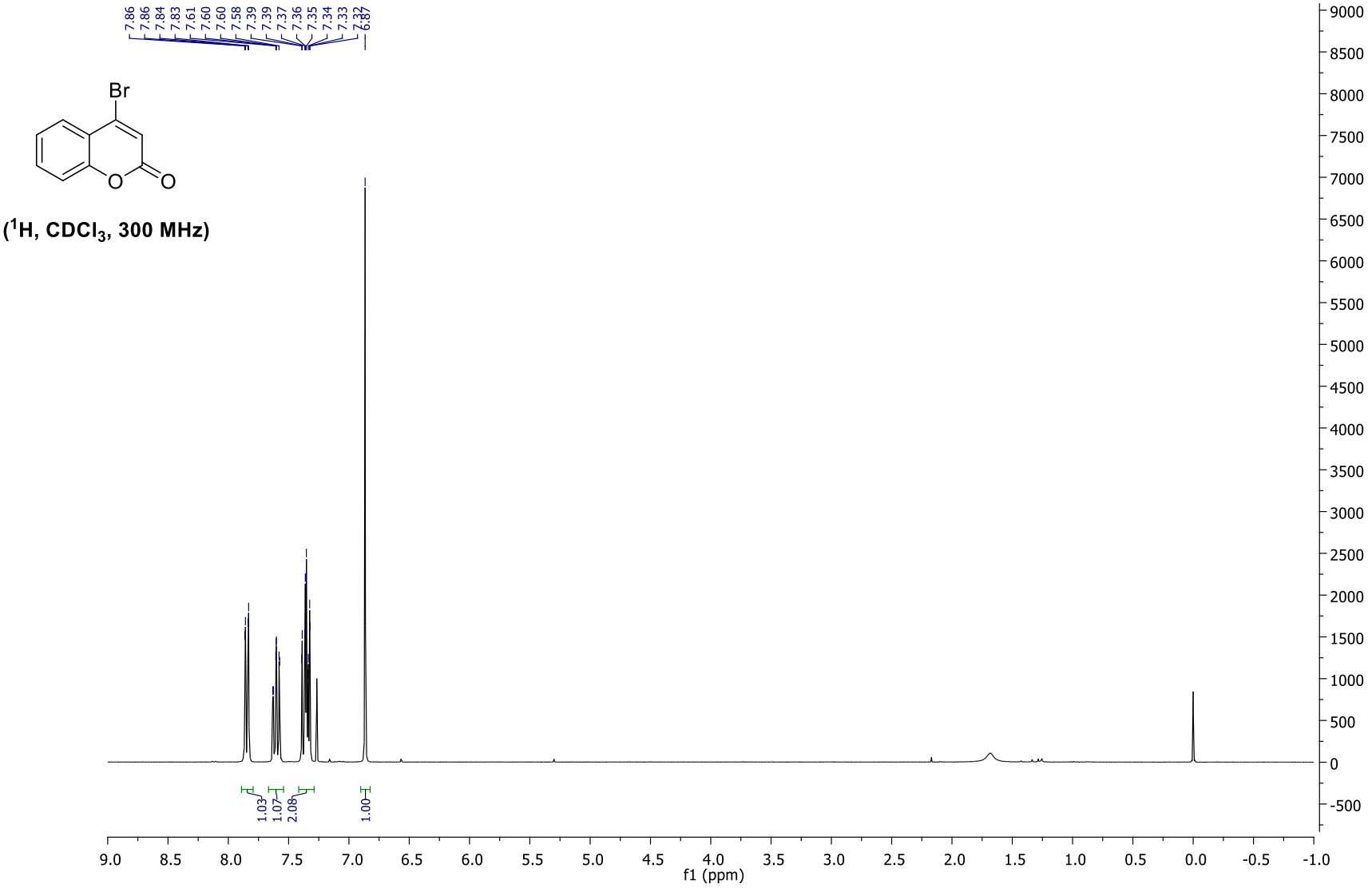
4-Hydroxy-5,7-dimethyl-2-coumarin



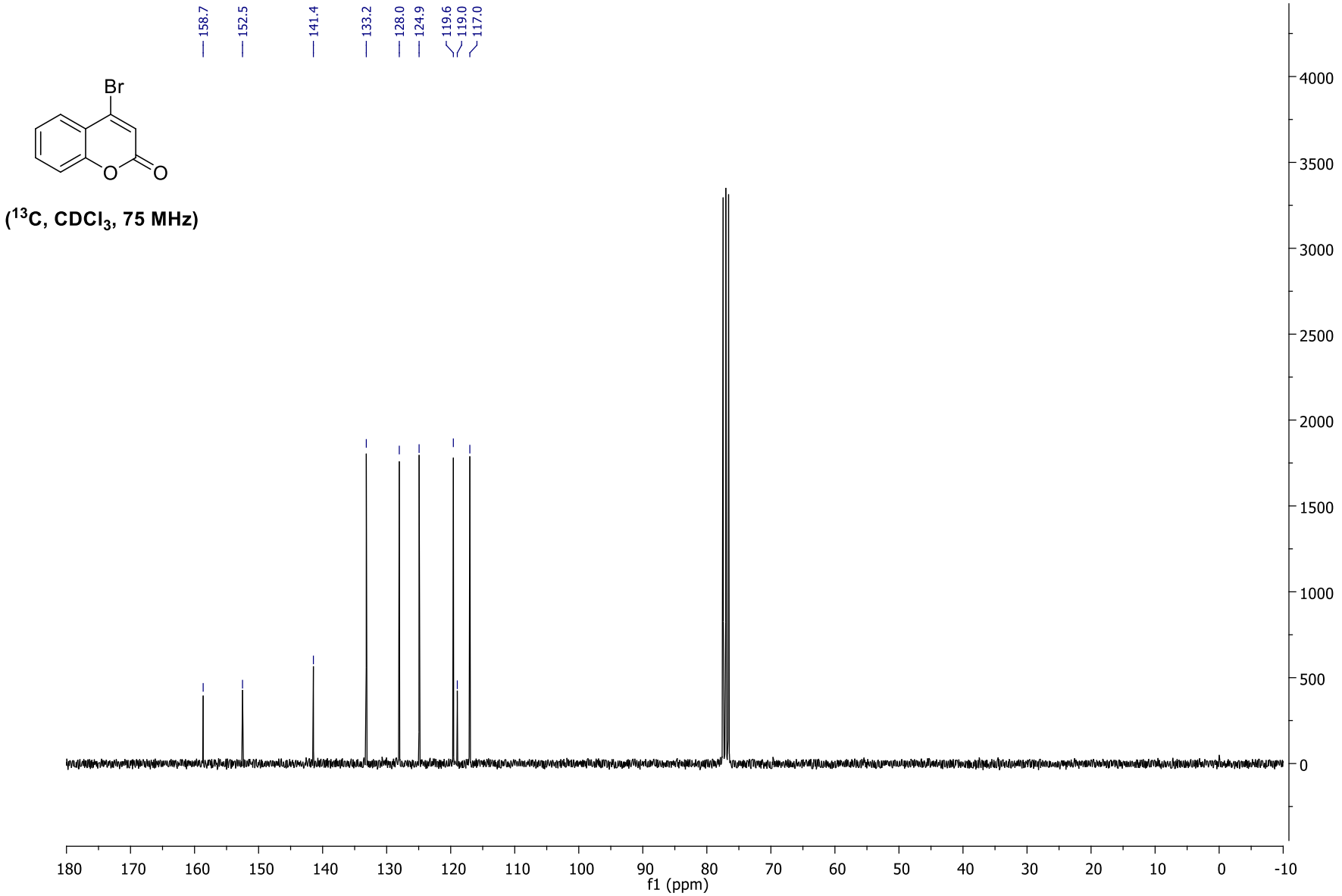
(^{1}H, $(CD_3)_2SO$, 300 MHz)


169.1
162.1
155.6
142.7
137.1
128.6
115.2
112.2
90.8
22.9
21.2
OH
O
O
(^{13}C, (CD$_3$)$_2$SO, 75 MHz)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

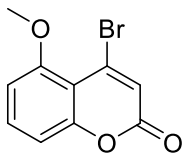
4-Bromo-2-coumarin



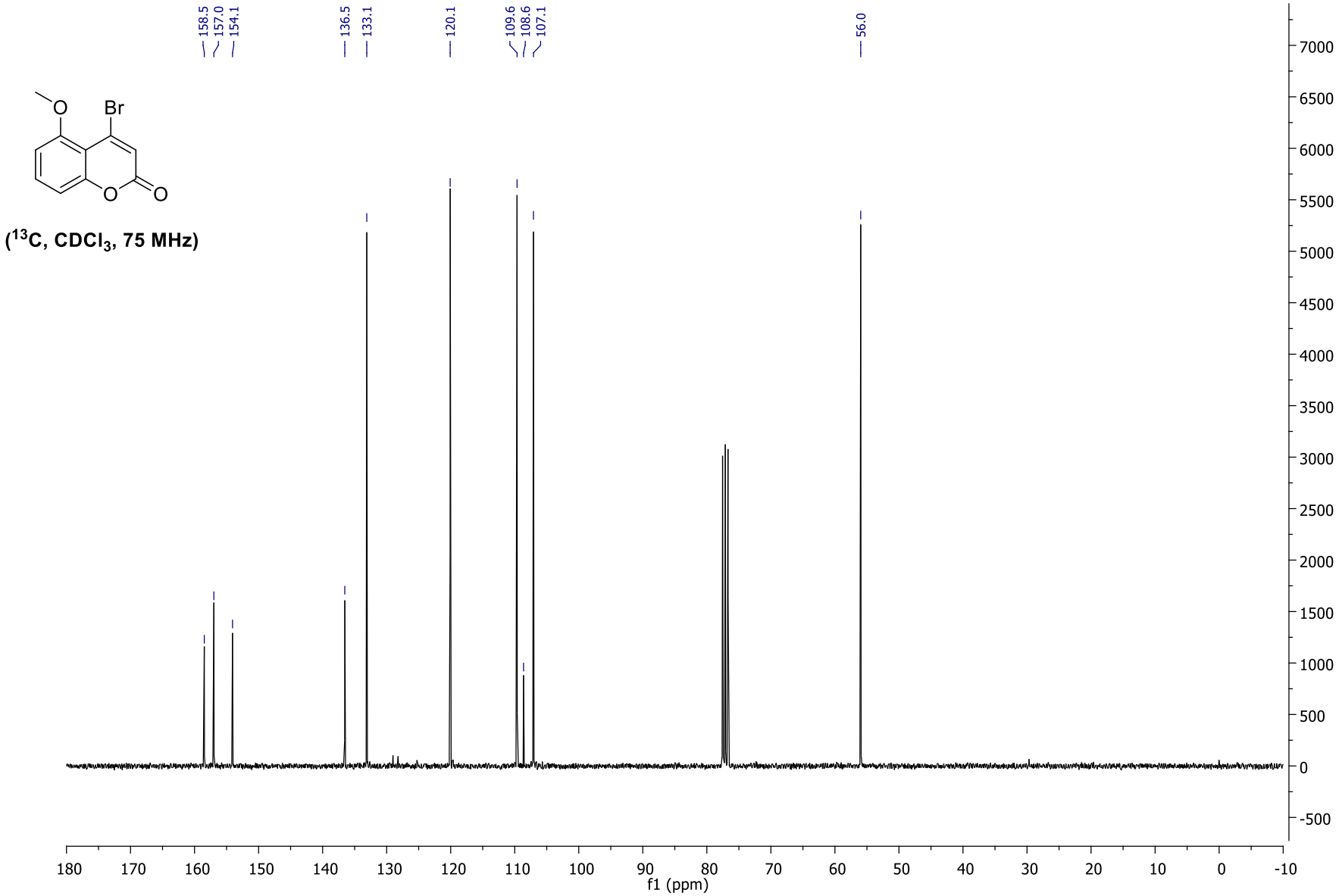
(^{1}H, $CDCl_3$, 300 MHz)


158.7
152.5
141.4
133.2
128.0
124.9
119.6
119.0
117.0
Br
O
O
(13C, CDCl3, 75 MHz)
4000
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

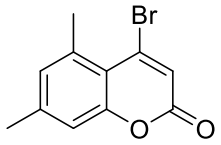
4-Bromo-5-methoxy-2-coumarin



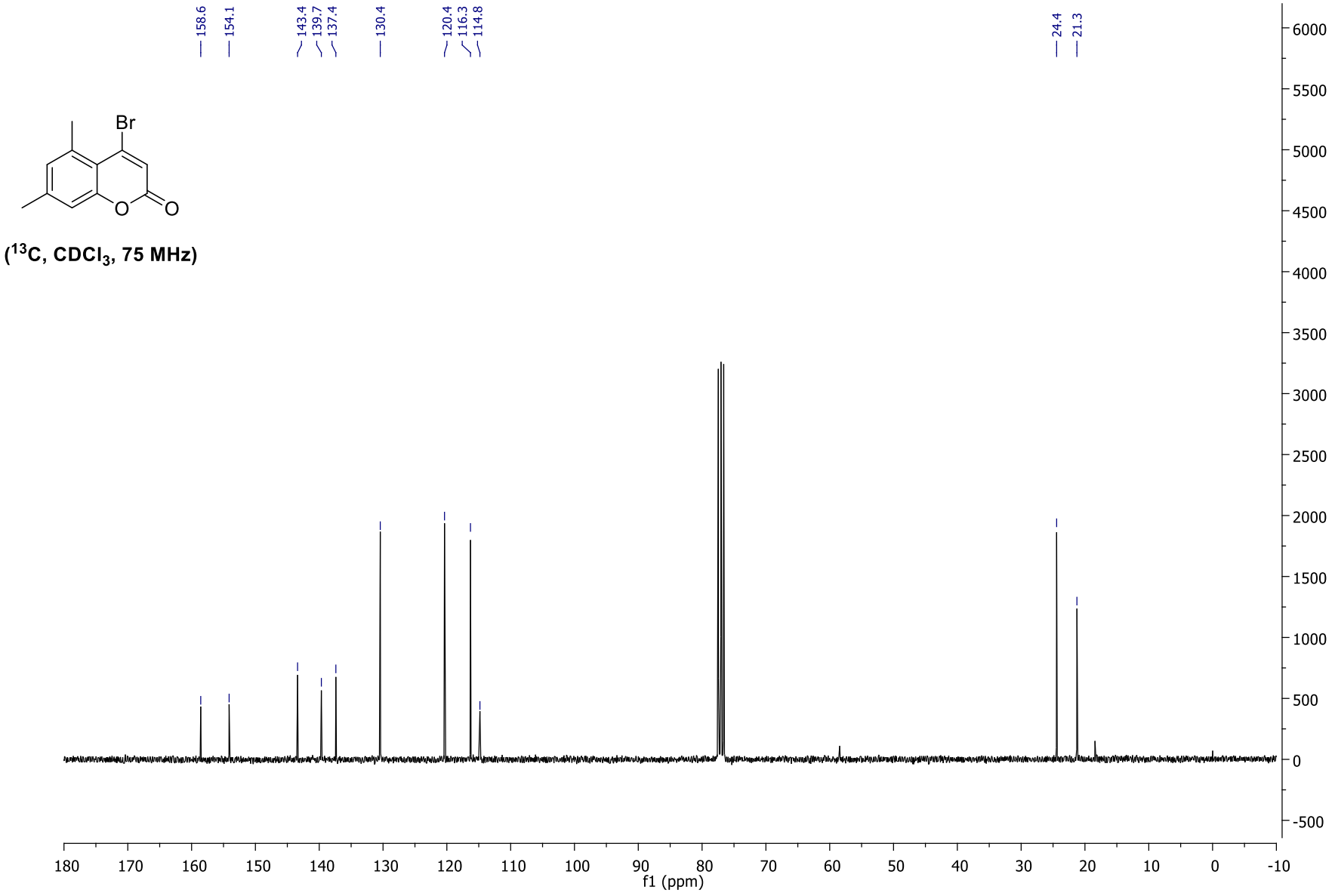
(^{1}H, $CDCl_3$, 300 MHz)


158.5
157.0
154.1
136.5
133.1
120.1
109.6
108.6
107.1
56.0
O
Br
O
O
(13C, CDCl3, 75 MHz)
f1 (ppm)

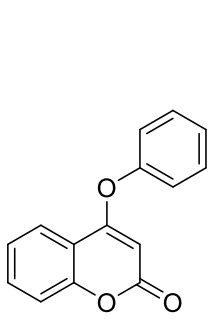
4-Bromo-5,7-dimethyl-2-coumarin



(^{1}H, $CDCl_3$, 300 MHz)

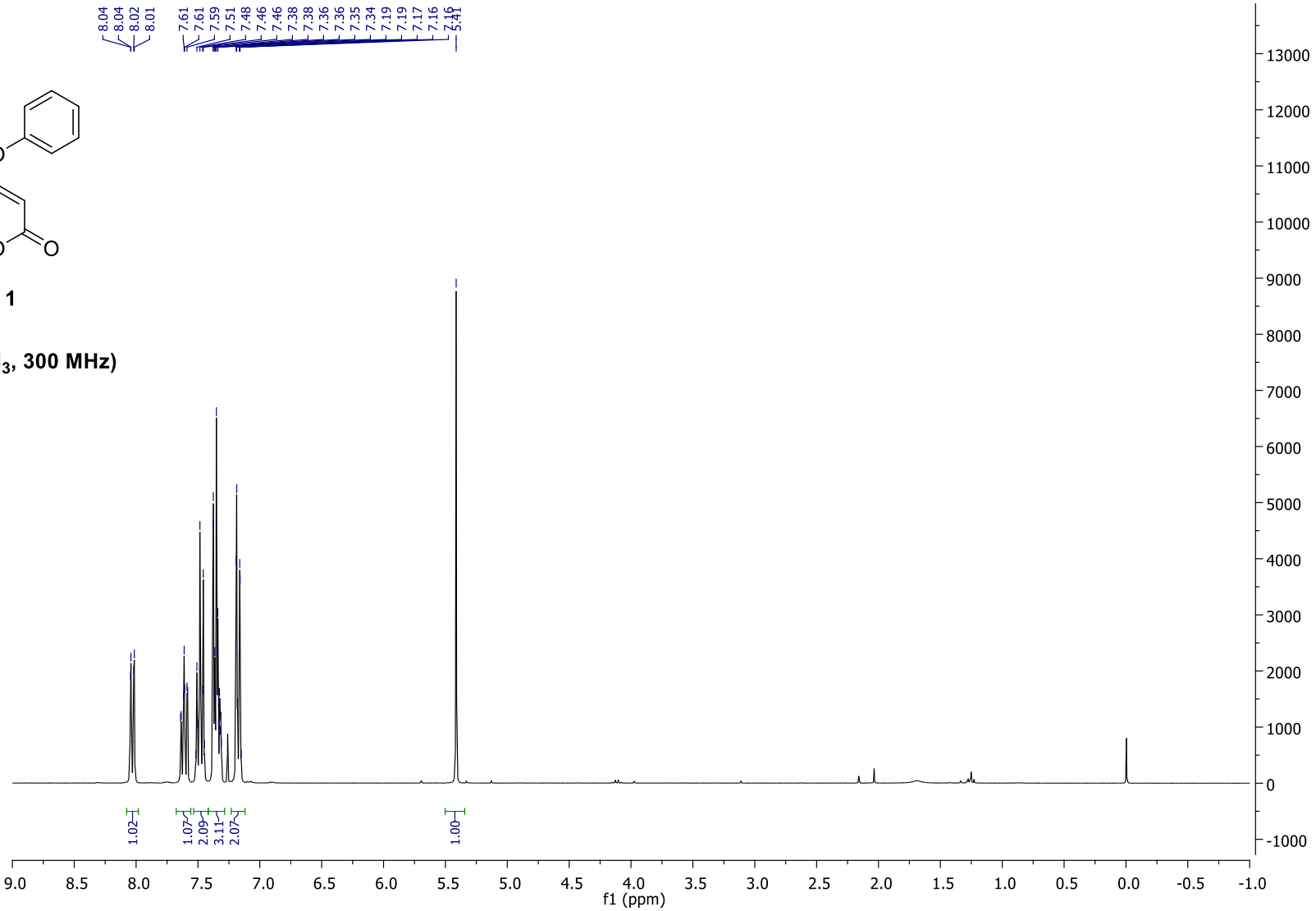

158.6
154.1
143.4
139.7
137.4
130.4
120.4
116.3
114.8
24.4
21.3
Br
O
O
(^{13}C, CDCl$_3$, 75 MHz)
f1 (ppm)

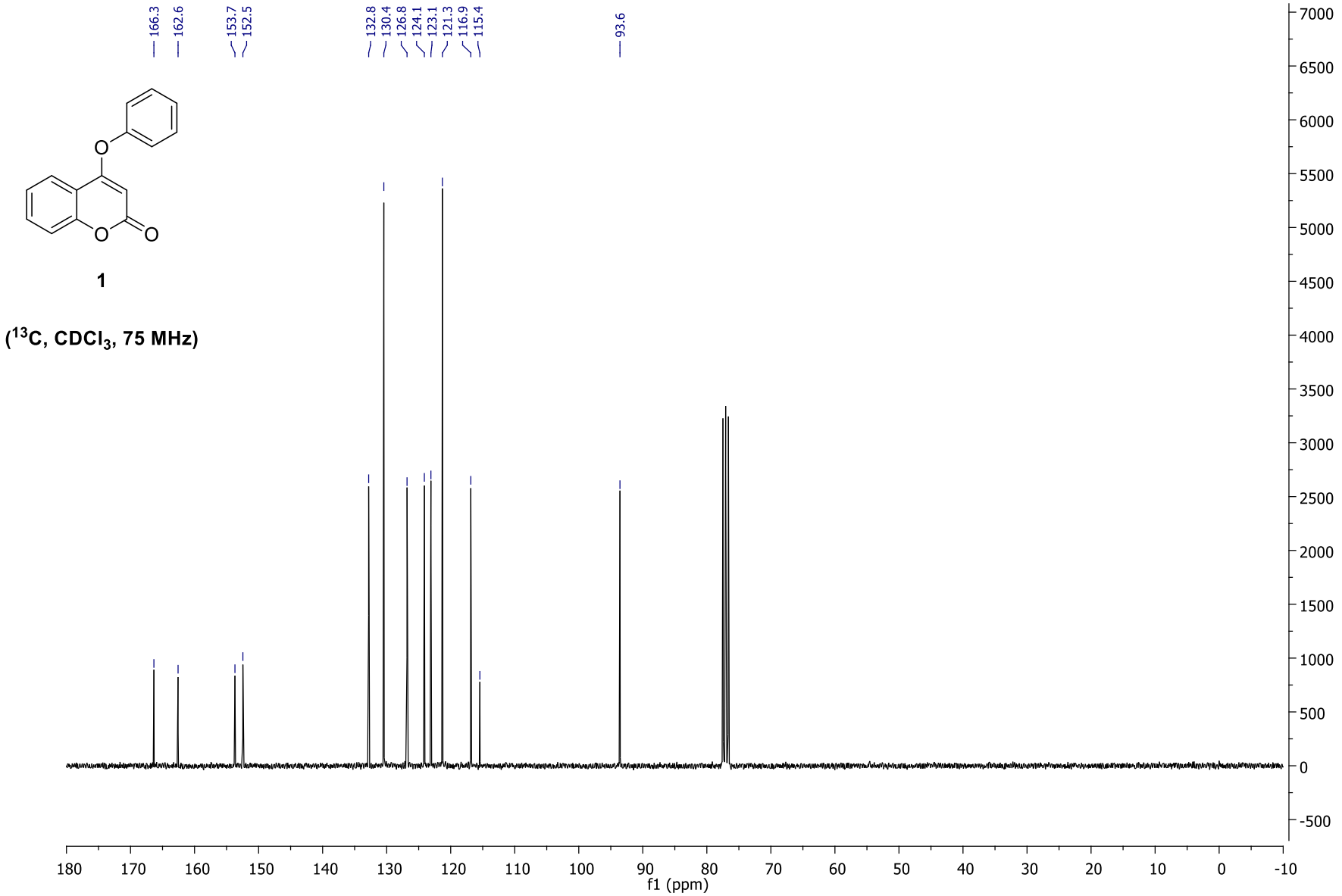
4-Phenoxy-2-coumarin (1)



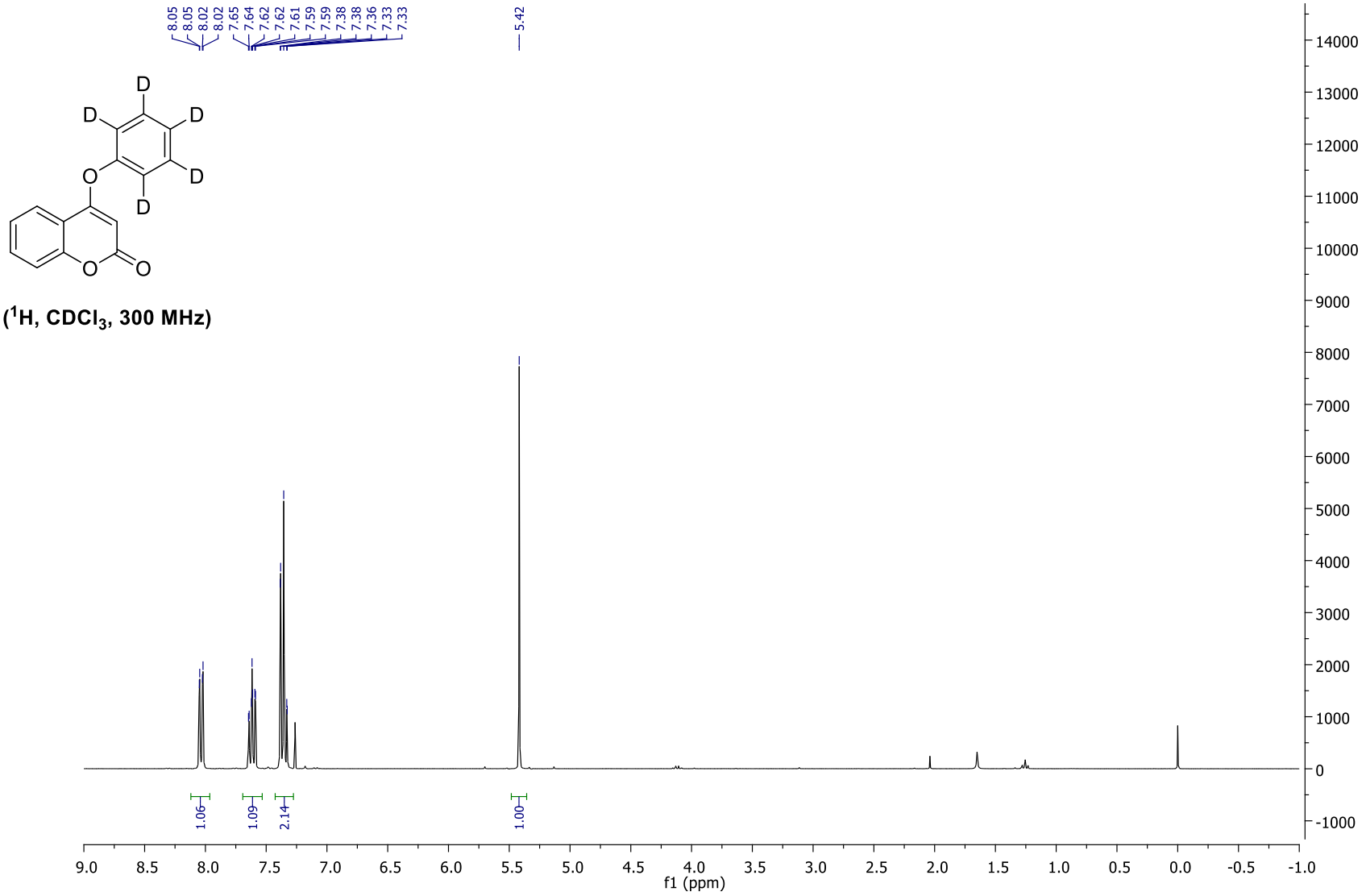
1

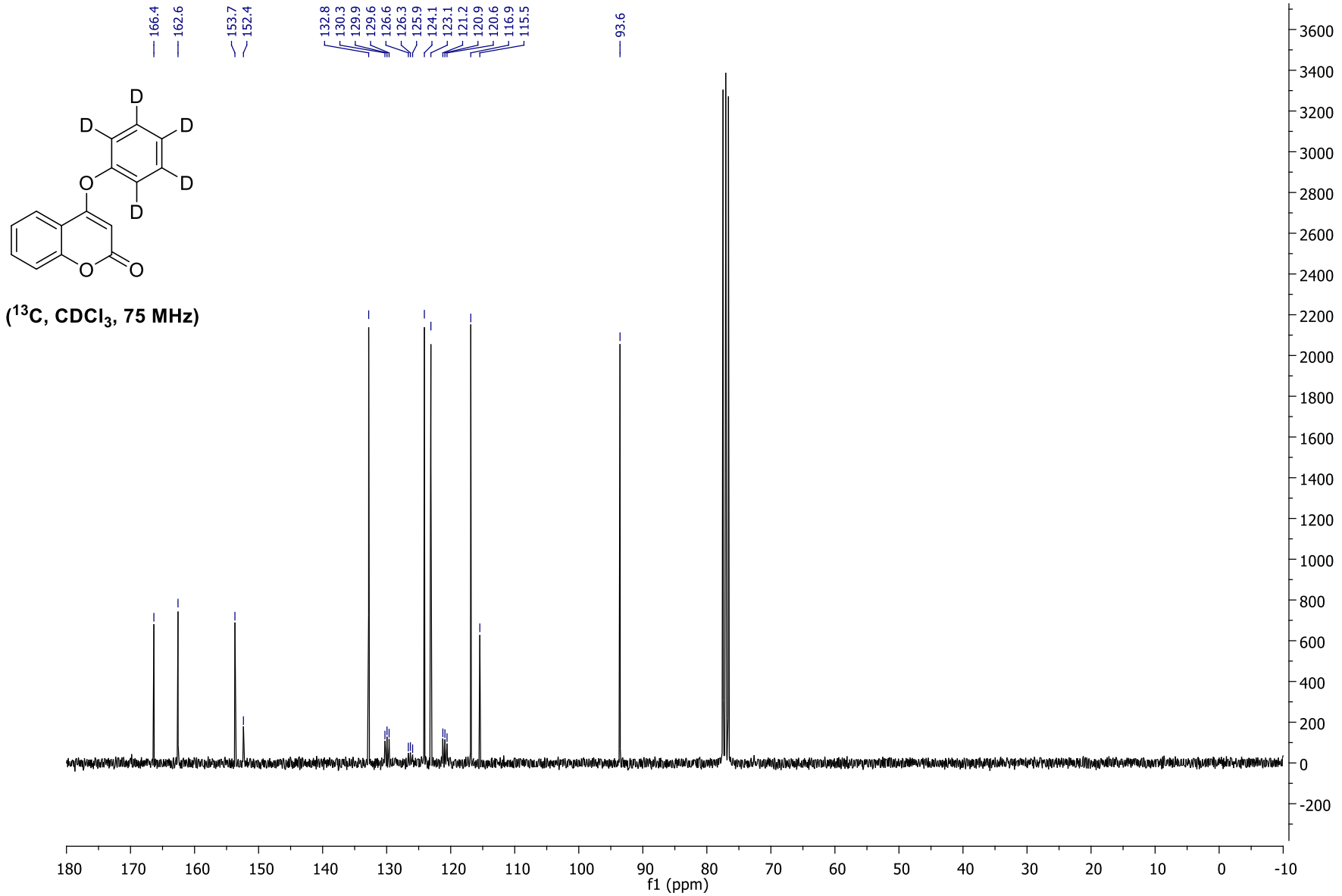
(^{1}H, $CDCl_3$, 300 MHz)



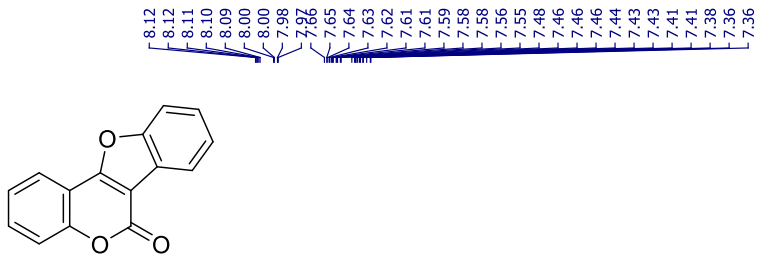

166.3
162.6
153.7
152.5
132.8
130.4
126.8
124.1
123.1
121.3
116.9
115.4
93.6
O
O
O
1
(13C, CDCl3, 75 MHz)
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

4-(Phenoxy-d_5)-2-coumarin



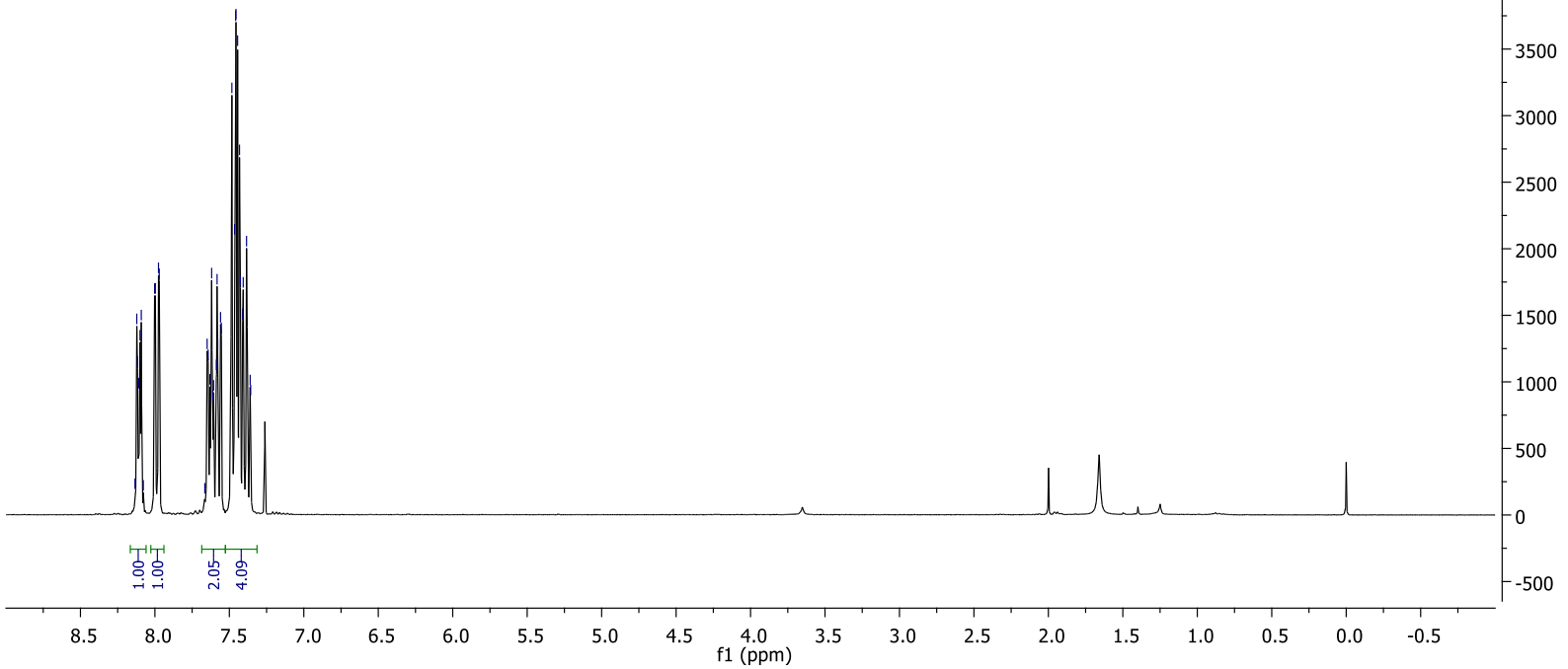

166.4
162.6
153.7
152.4
132.8
130.3
129.9
129.6
126.6
126.3
125.9
124.1
123.1
121.2
120.9
120.6
116.9
115.5
93.6
D
D
D
D
D
O
O
O
(13C, CDCl3, 75 MHz)
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

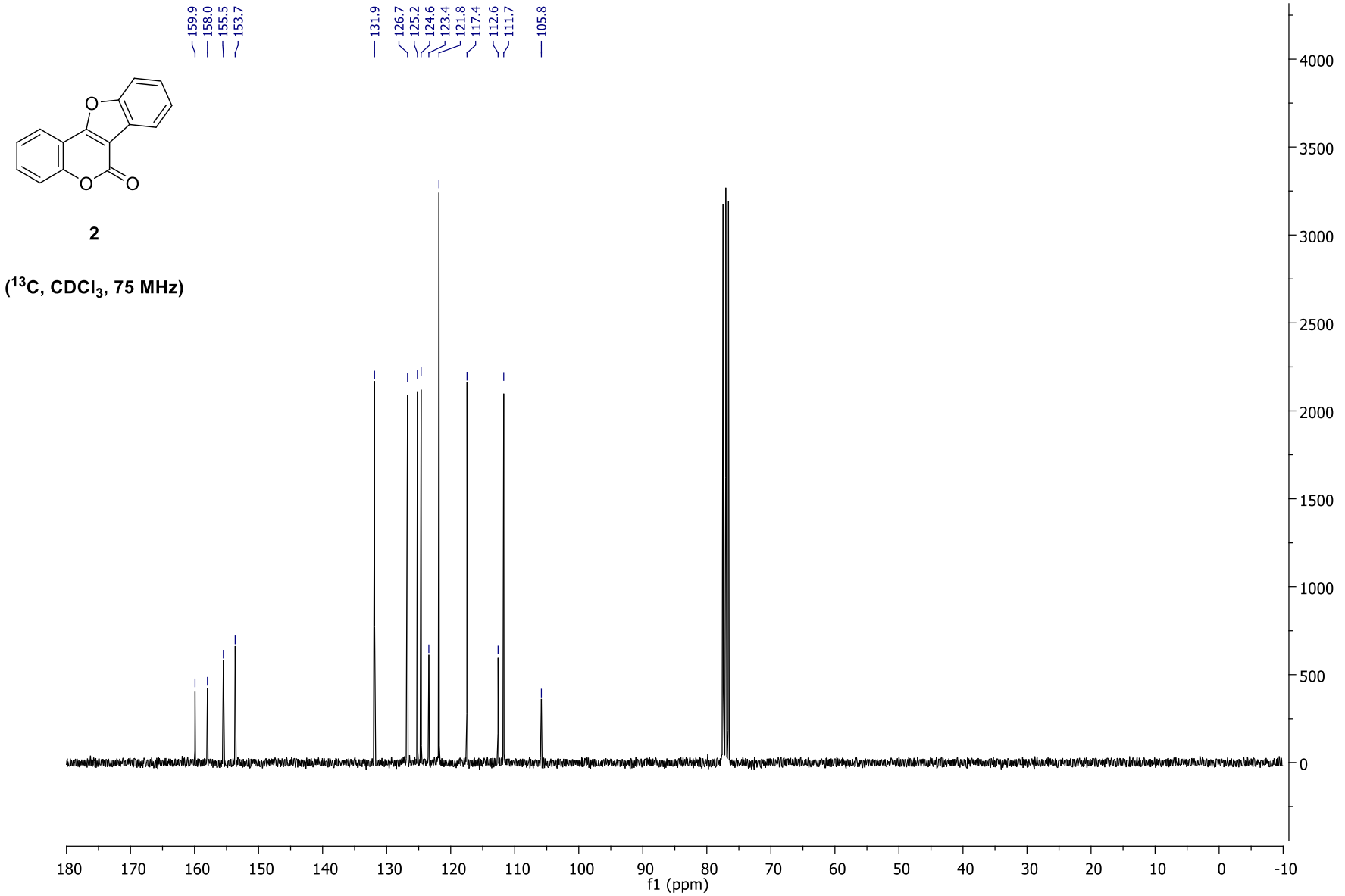
6*H*-Benzofuro[3,2-*c*]chromen-6-one (2)



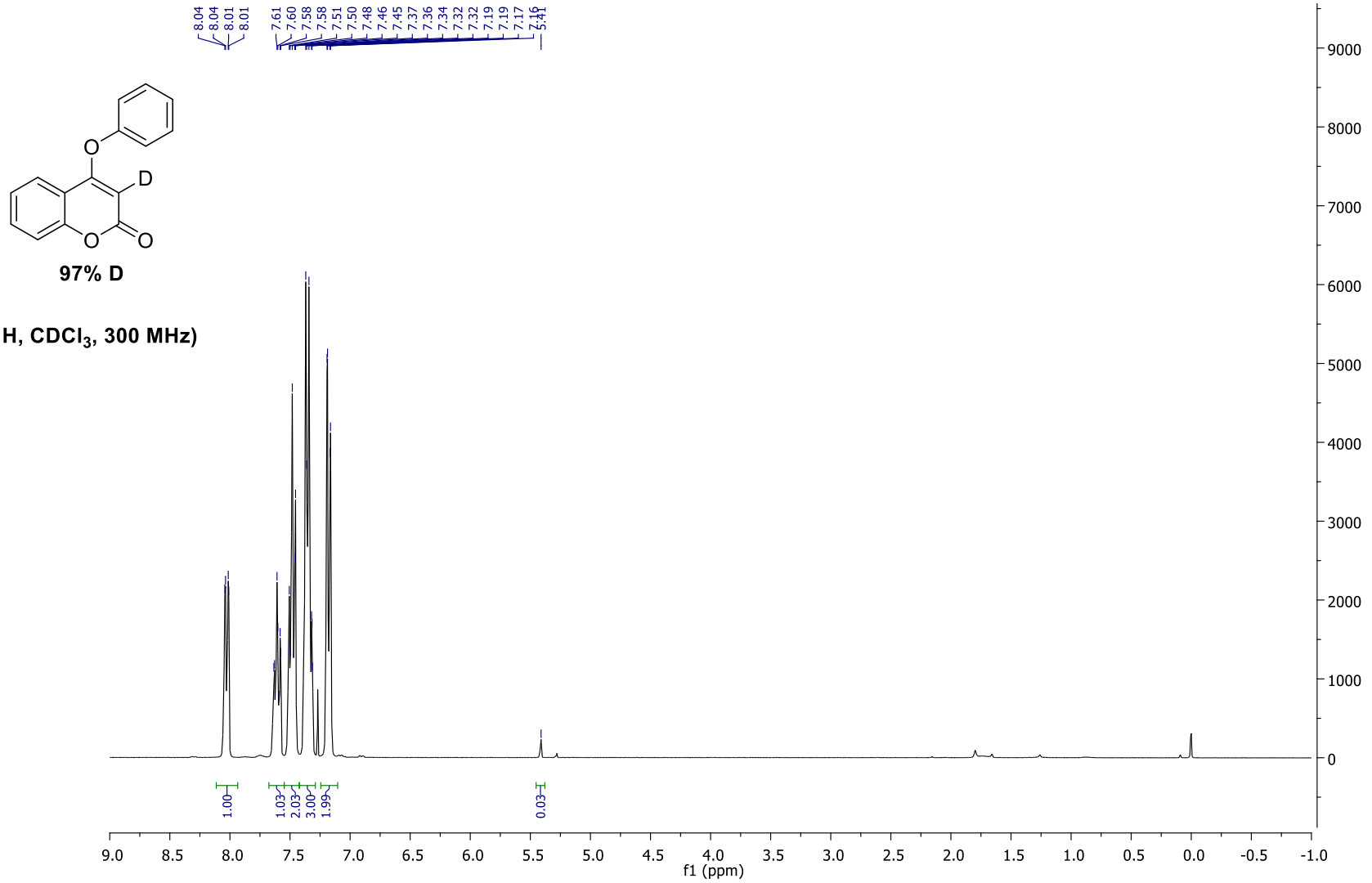
2

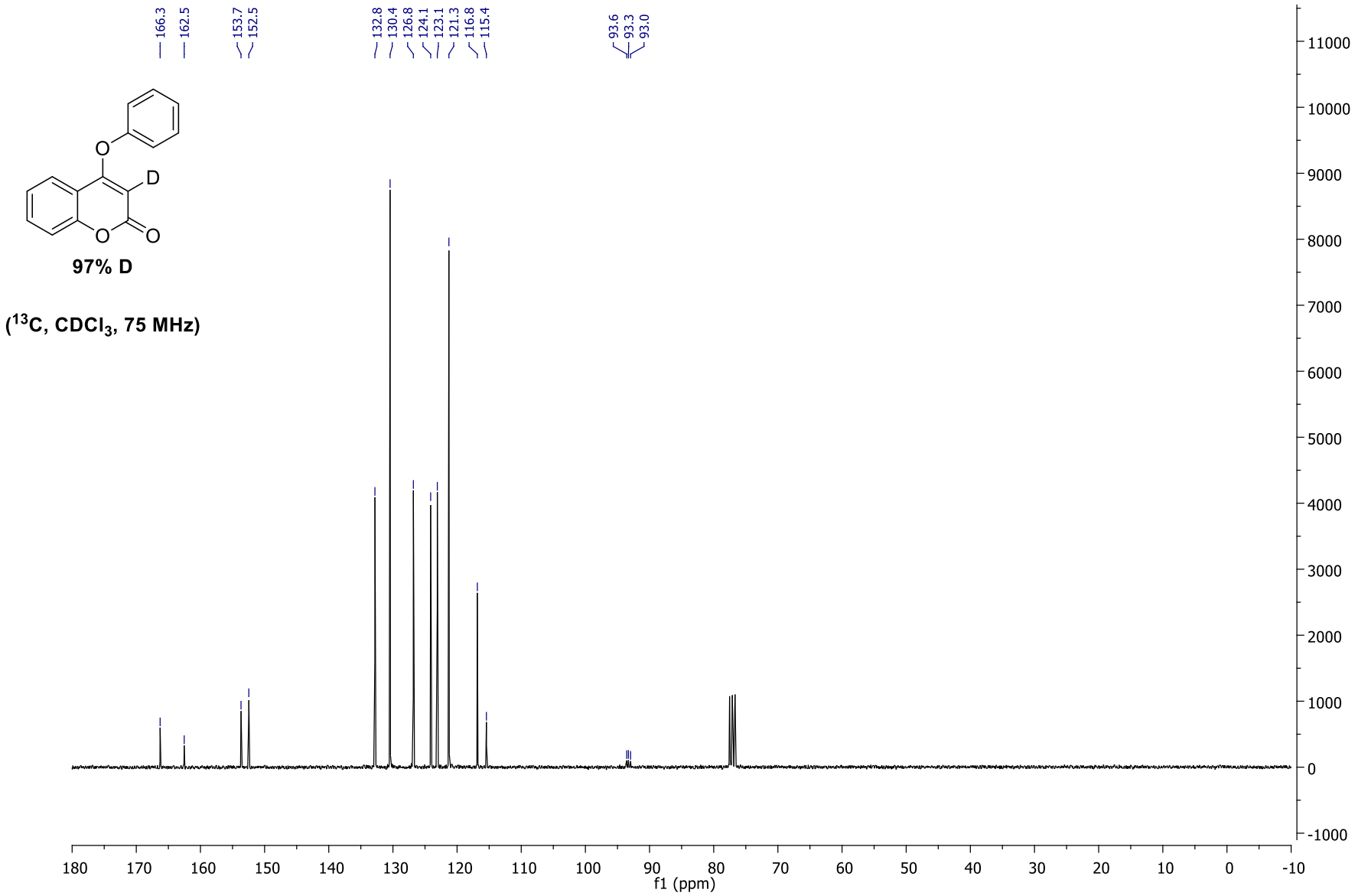
(^{1}H, $CDCl_3$, 300 MHz)



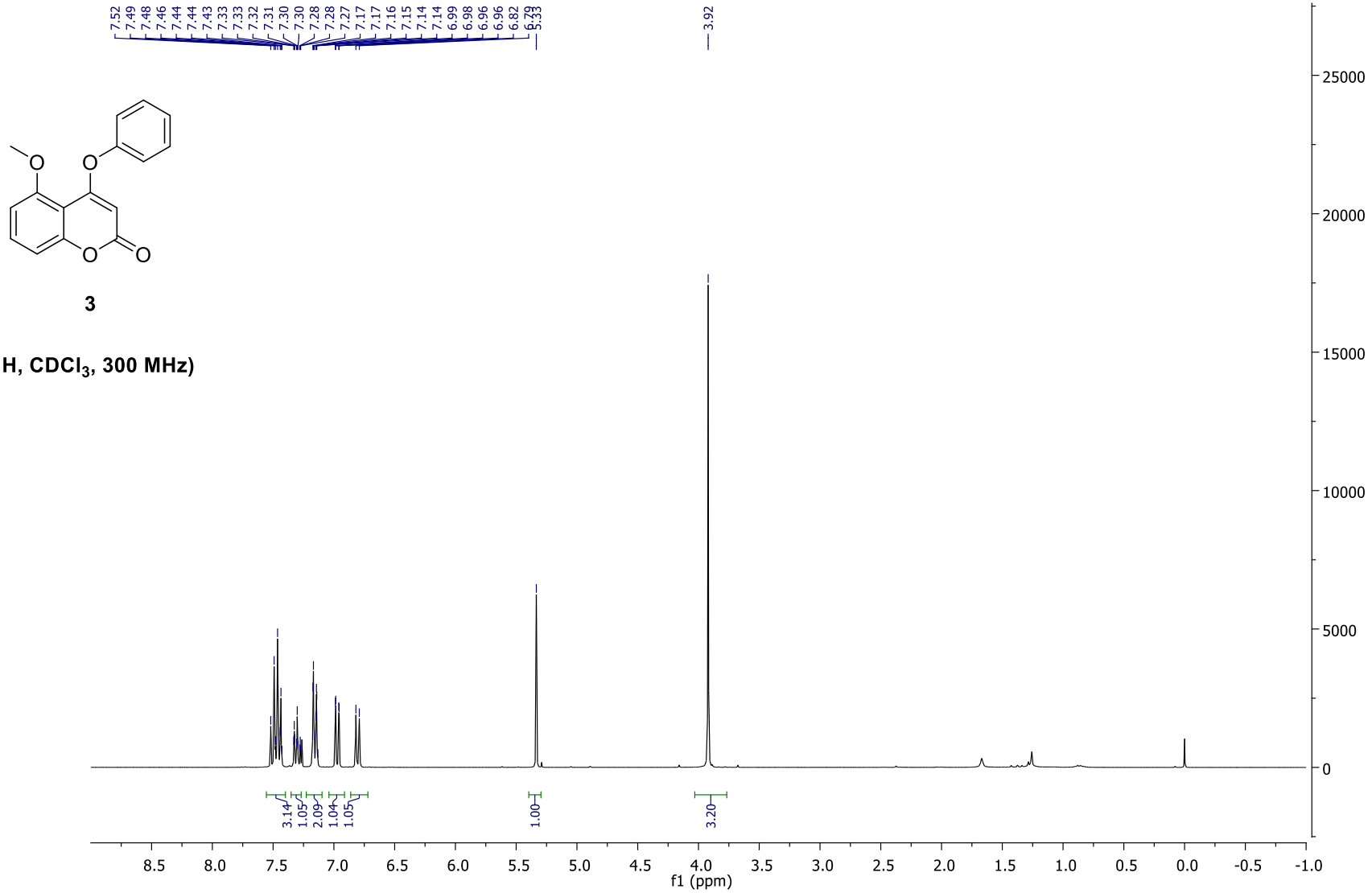

159.9
158.0
155.5
153.7
131.9
126.7
125.2
124.6
123.4
121.8
117.4
112.6
111.7
105.8
O
O
O
2
(13C, CDCl3, 75 MHz)
4000
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

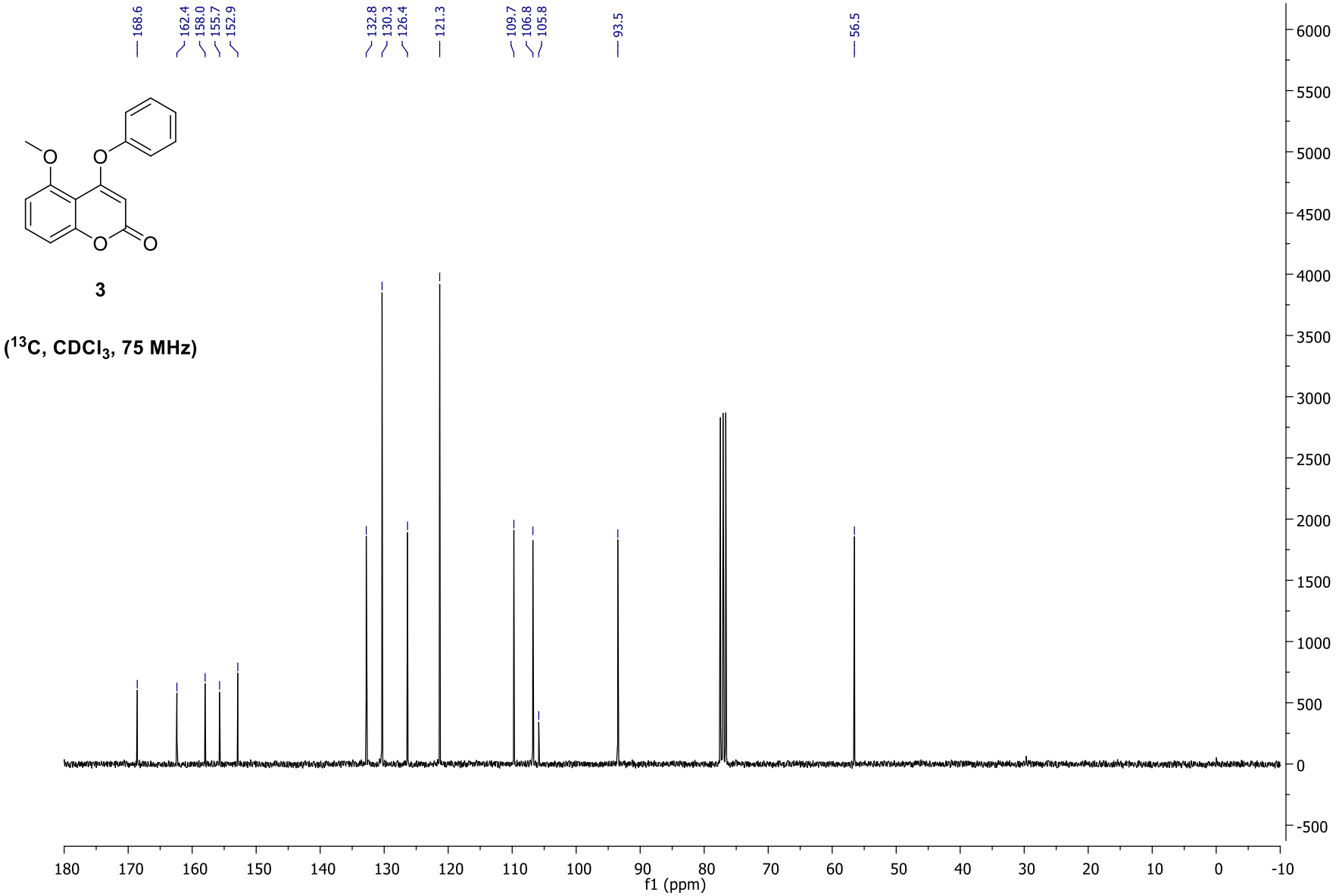
3-Deuterio-4-phenoxy-2-coumarin



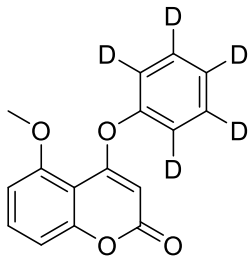

166.3
162.5
153.7
152.5
132.8
130.4
126.8
124.1
123.1
121.3
116.8
115.4
93.6
93.3
93.0
O
D
O
O
97% D
(13C, CDCl3, 75 MHz)
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

5-Methoxy-4-phenoxy-2-coumarin (3)



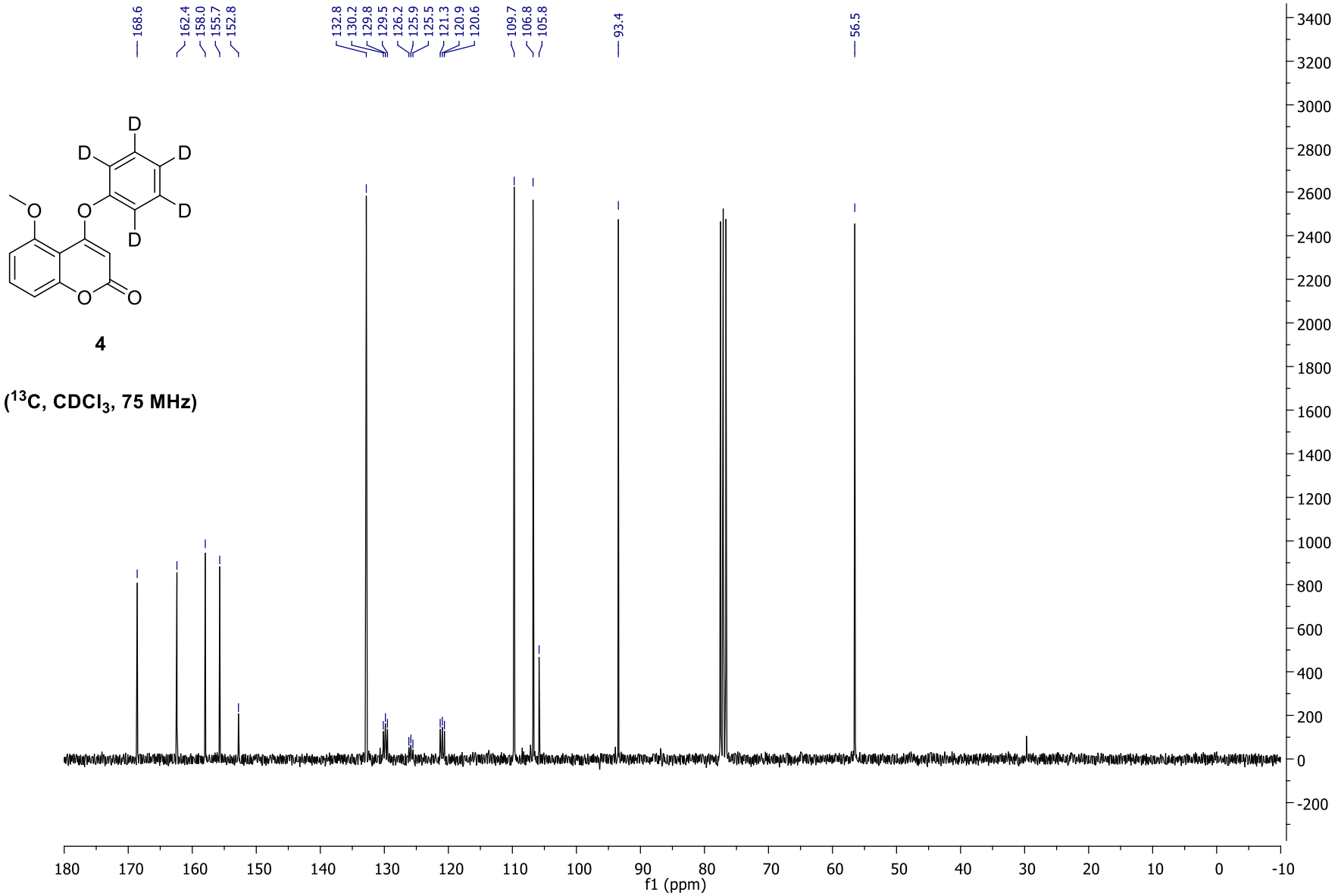

168.6
162.4
158.0
155.7
152.9
132.8
130.3
126.4
121.3
109.7
106.8
105.8
93.5
56.5
O
O
O
O
3
(13C, CDCl3, 75 MHz)
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

5-Methoxy-4-(phenoxy-d_5)-2-coumarin (4)

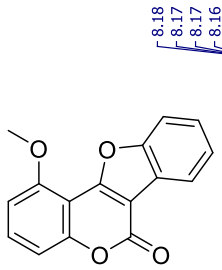


4

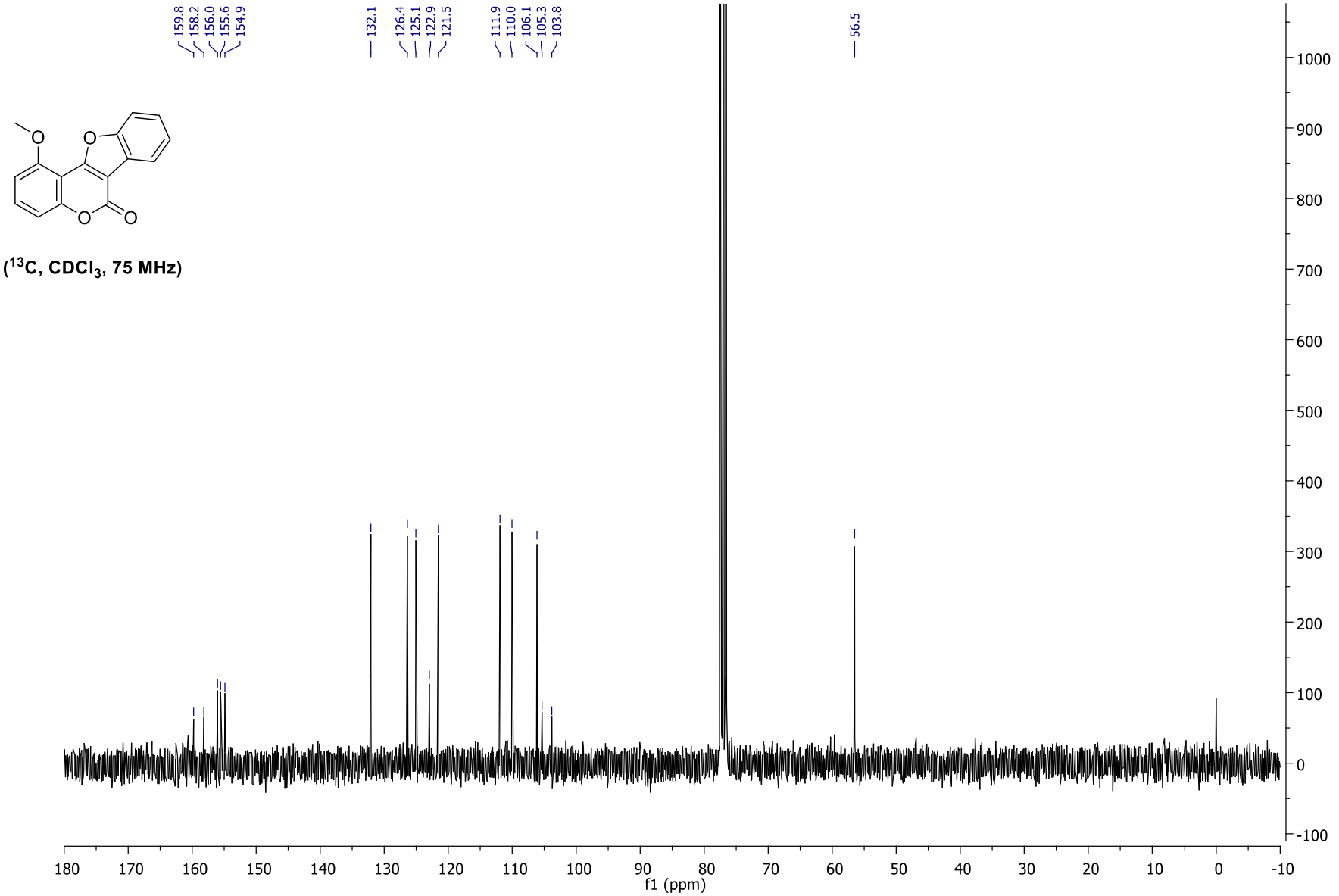
(^{1}H, $CDCl_3$, 300 MHz)


168.6
162.4
158.0
155.7
152.8
132.8
130.2
129.8
129.5
126.2
125.9
125.5
121.3
120.9
120.6
109.7
106.8
105.8
93.4
56.5
D
D
D
D
D
O
O
O
O
4
(13C, CDCl3, 75 MHz)
f1 (ppm)

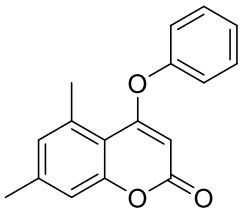
1-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one



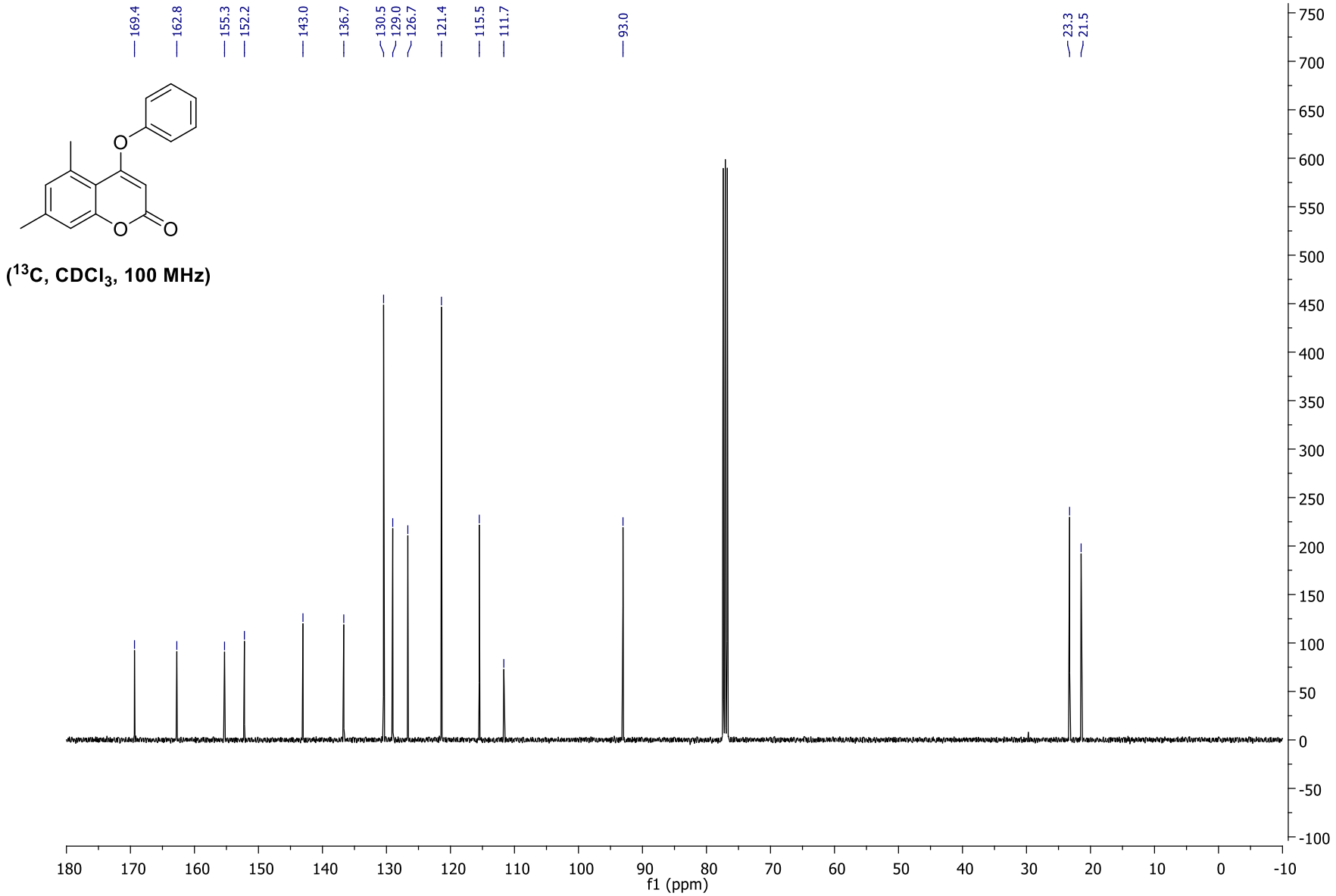
(^{1}H, $CDCl_3$, 300 MHz)


159.8
158.2
156.0
155.6
154.9
132.1
126.4
125.1
122.9
121.5
111.9
110.0
106.1
105.3
103.8
56.5
O
O
O
O
(^{13}C, CDCl$_3$, 75 MHz)
1000
900
800
700
600
500
400
300
200
100
0
-100
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

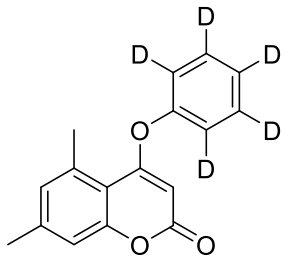
5,7-Dimethyl-4-phenoxy-2-coumarin



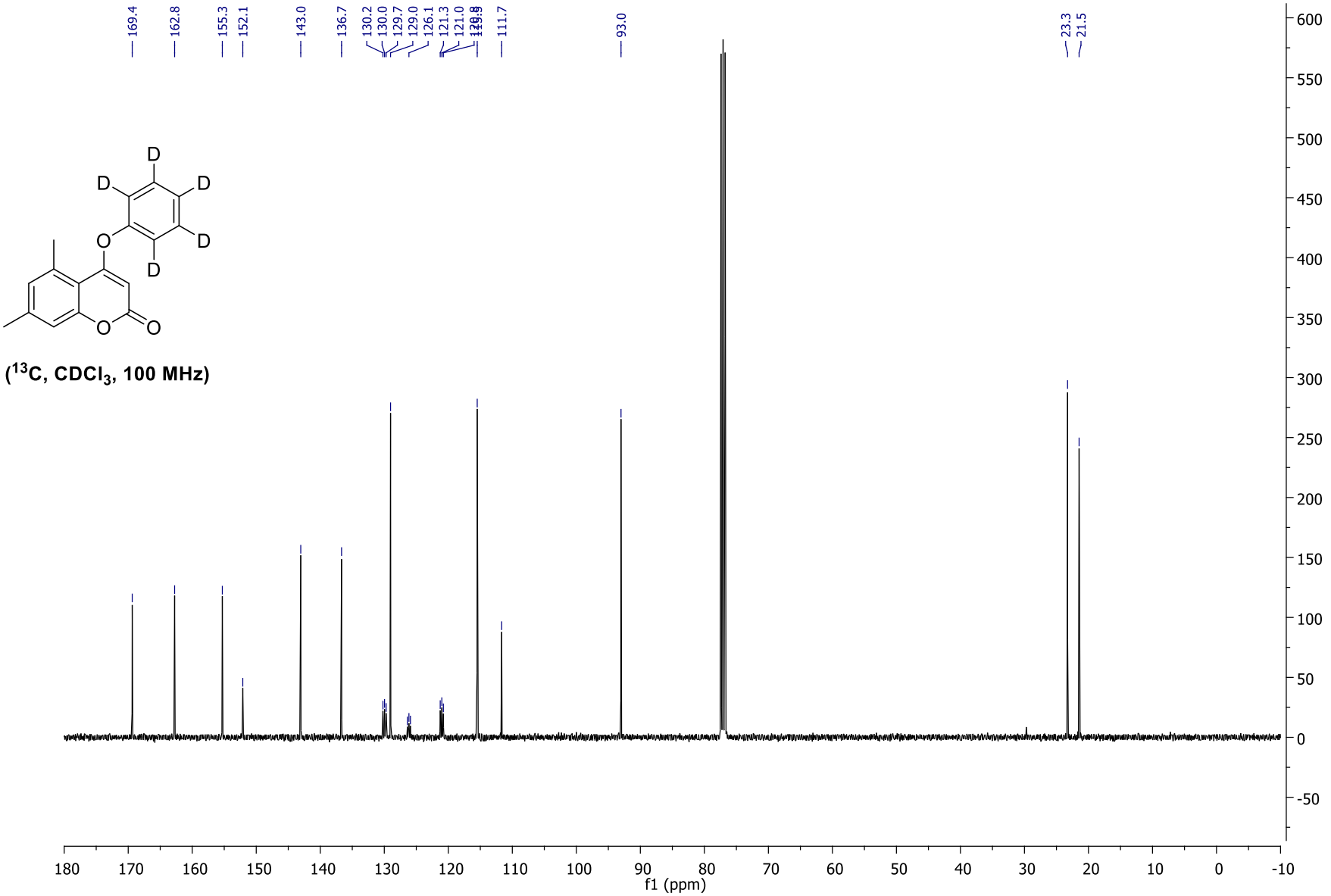
(¹H, $CDCl_3$, 400 MHz)


169.4
162.8
155.3
152.2
143.0
136.7
130.5
129.0
126.7
121.4
115.5
111.7
93.0
23.3
21.5
O
O
O
(^{13}C, CDCl$_3$, 100 MHz)
f1 (ppm)

5,7-Dimethyl-4-(phenoxy-d_5)-2-coumarin



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


169.4
162.8
155.3
152.1
143.0
136.7
130.2
130.0
129.7
129.0
126.1
121.3
121.0
111.7
93.0
23.3
21.5
D
D
D
D
D
O
O
O
(^{13}C, CDCl$_3$, 100 MHz)
f1 (ppm)

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